TITLE PAGE

Protocol Title:

A Phase 2, Open-label Study to Assess Copper and Molybdenum Balance in Participants with Wilson Disease Treated with ALXN1840

Protocol Number: ALXN1840-WD-204

Amendment Number: 3.1 (US)

Compound: ALXN1840 (bis-choline tetrathiomolybdate)

Study Phase: 2

Short Title: Copper and Molybdenum Balance in Participants with Wilson Disease Treated with ALXN1840

Sponsor Name: Alexion Pharmaceuticals, Inc.

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Original Protocol	**12 May 2020**
Amendment 1	**18 Aug 2020**
Amendment 2	**19 Mar 2021**
Amendment 3	**31 Aug 2021**
Amendment 3.1 (US)	**18 Mar 2022**

Sponsor Signatory:

[redacted]

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 3.1 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

Amendment 3.1 (US), 18 Mar 2022

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, the US Food and Drug Administration's (FDA) regulation at 21 CFR part 312.30(b), and any applicable local regulations.

Overall Rationale for the Amendment

The main reason for preparation of this amendment was to clarify study procedures occurring across different sites in the US, so as to facilitate participant recruitment across different regions of the US, and to lessen inconvenience for participants without compromising the quality of the study.

Changes to the Protocol

Section # and Name	Description of Change	Brief Rationale and/or Clarifications
Section 1.3 Schedule of Activities (SoA), Table 1	Addition of text to the footnote to state that procedures specific to screening sites (only in the US) detailed in Section 8	As per Section 8 (below).
4.2 Scientific Rationale for Study Design	Number of days changed from 30 days to 21 days in the following sentence: • However, the physiologic turnover of human gastrointestinal epithelial cells is 3 - 5 days (Darwich, 2014); therefore, the inhibitory effect of zinc on intestinal copper absorption is expected to be minimal ~~30~~ **21** days after discontinuation of zinc.	To align the number of days with the mention of zinc discontinuation elsewhere in the protocol.
Section 8 Study Assessments and Procedures	Addition of text applicable only to the US that details the possibility for sites in the US to only perform screening procedures and not any of the remaining study procedures.	To facilitate participant recruitment across different regions of the US and to lessen inconvenience for participants without compromising the quality of the study.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 2, Open-label Study to Assess Copper and Molybdenum Balance in Participants with Wilson Disease Treated with ALXN1840

Short Title: Copper and Molybdenum Balance in Participants with Wilson Disease Treated with ALXN1840

Rationale:

The principal aim of this exploratory study is to investigate the effects of ALXN1840 on copper balance in participants with Wilson disease (WD). The study will specifically evaluate the effects of 2 different ALXN1840 doses as well as the duration of treatment on copper balance to further elucidate the dose response of "decoppering" versus "maintenance" dose in participants with WD.

The secondary aim of the study is to characterize the steady-state absorption, distribution, metabolism, and excretion (ADME; mass balance) of total molybdenum which is a surrogate measure of ALXN1840 disposition in participants with WD.

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

Depletion of copper by ALXN1840 has been shown to occur primarily through fecal elimination in both healthy and WD animal models. In this study, copper balance will be calculated as the difference between measured copper input in food and drink and measured copper output in urine and feces. This method is classically considered the most objective measure of decoppering ability with a decoppering agent able to drive a net negative copper balance.

As part of the secondary objective, to confirm that ALXN1840 steady state is adequately characterized by the plasma pharmacokinetics (PK), a molybdenum mass balance assessment will be performed at predicted steady state for the 15 mg/day and 30 mg/day doses: if steady state is achieved, molybdenum(out) will equal molybdenum(in). This approach may also detect potential accumulation in the liver or other tissues of participants with WD.

Objectives and Endpoints

Objectives	Endpoints
Primary Assess net copper balance with daily repeat-dose ALXN1840 treatment (15 mg and 30 mg) in participants with Wilson disease (WD)	Mean daily copper balance where copper balance is measured by the calculated difference between copper intake (in food and drink) and copper output (in feces and urine) during ALXN1840 accumulation and steady-state periods for each dose
Secondary Assess change in copper balance in response to ALXN1840 15 mg/day and 30 mg/day during ALXN1840 accumulation and at steady state periods versus the pretreatment baseline in participants with WD	Change in mean daily copper balance as measured by the calculated difference between copper intake (in food and drink) and copper output (in feces and urine) from pretreatment baseline (Days -4 through -1) and ALXN1840 accumulation and steady-state periods for each dose
Investigate the effect of ALXN1840 (15 mg/day and 30 mg/day) on the disposition of copper in participants with WD	Copper quantified in food, drink, feces, and urine, including plasma total and labile bound copper (LBC) during ALXN1840 accumulation and steady-state periods for each dose
Investigate the effect of ALXN1840 on the disposition of molybdenum at steady state at 15 mg/day and 30 mg/day in participants with WD	Molybdenum quantified in food, drink, feces, and urine, plasma total molybdenum at ALXN1840 steady state
Assess steady-state total molybdenum balance as a measure of ALXN1840 15 mg/day and 30 mg/day in participants with WD	Mean daily molybdenum balance as demonstrated through measurement of molybdenum intake (in food, drink and ALXN1840), and molybdenum output (feces and urine) representing ALXN1840 steady state
Assess accumulation of molybdenum with ALXN1840 treatment at 15 mg/day and 30 mg/day in participants with WD	Accumulation of molybdenum as determined by molybdenum balance
Determine the steady-state plasma pharmacokinetic (PK) of total molybdenum and plasma ultrafiltrate (PUF) molybdenum (as surrogate measures of ALXN1840, 15 mg and 30 mg) in participants with WD	PK parameters for plasma total and PUF-molybdenum
Safety Evaluate the safety and tolerability of repeated-dose administration of ALXN1840 15 mg/day and 30 mg/day in participants with WD	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 electrocardiogram (ECG) findings as determined by triplicate 12-lead ECG • Vital sign assessments (blood pressure and heart rate)
Exploratory Determine dose response of ALXN1840 15 mg/day and 30 mg/day for copper balance in participants with WD	Assess dose response of ALXN1840 on copper balance focusing on copper balance
Determine the effect of treatment duration on copper balance in participants with WD	Determine the effect of time following initiation of ALXN1840 treatment on copper balance
Assess the effects of ALXN1840 on ceruloplasmin, ceruloplasmin-bound copper LBC profiles in plasma in participants with WD	Ceruloplasmin, ceruloplasmin-bound copper, and LBC: Change in ceruloplasmin at Days 1, 8, 25, 29, 36, and Day 39 compared with predose

Objectives	Endpoints
Assess dose proportionality at steady state of doses of ALXN1840 15 mg/day and 30 mg/day in participants with WD	Based on PK parameters
Assess effects ALXN1840 on copper:molybdenum ratio in plasma at steady state in participants with WD	Measure plasma copper:molybdenum ratios at steady state compared with predose
Assess the effects of repeat-dose ALXN1840 on copper:molybdenum ratio in urine and feces in participants with WD	Mean daily copper:molybdenum ratio in urine and feces at steady state compared with predose baseline

Note: The accumulation period refers to time from initiation of ALXN1840 (Day 1) to expected steady state at Day 10, based on 5 times the half-life of 2 days.

Overall Design

This is a single-arm, open-label, repeat-dose study to evaluate the effects of ALXN1840 administration on copper balance in participants with WD. The safety and tolerability of ALXN1840 in participants with WD will also be assessed. ALXN1840 PK in plasma as measured via total molybdenum and plasma ultrafiltrate (PUF) molybdenum will be determined after repeated dosing along with total molybdenum mass balance at steady state.

Disclosure Statement: This is an open-label, 3-period study with 1 arm.

Number of Participants:

The sample size will be approximately 10 participants which will allow a general characterization of copper balance in response to ALXN1840.

Note: "Enrolled" means all participants who sign the informed consent form (ICF), are eligible for the study, and are registered on Day -7 when participants are assigned a participant number.

Intervention Groups and Duration:

Treatment-experienced (which includes standard of care therapies or ALXN1840) and treatment-naïve participants are eligible for this 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 copper and molybdenum balance (Day -4 through Day -1). Following the Run-in Period, participants will be administered ALXN1840 at 15 mg/day for a treatment period of approximately 28 days followed by titration up to 30 mg/day on Day 29. Before titration to 30 mg/day, the Safety Review Committee (SRC) will review available safety data through Day 23 for each participant.

Participants will have intake and output collection periods from Day -4 through Day -1, from Day 1 through Day 8 (initial 15 mg/day collection period), and Day 25 through Day 39. The collection periods will support an assessment of both copper and molybdenum balance (as a measure of ALXN1840 ADME) at the 15 mg/day and 30 mg/day doses and will allow assessment of the effects of duration of treatment on copper elimination and copper balance.

Participants may be discharged from the clinical research unit (CRU) on Day 9 to return on Day 22 or Day 23 (predose); all procedures will start on Day 23. To ensure flexibility, the Outpatient Period during Treatment Period 1 may be extended up to an additional 14 days with Investigator approval. In this situation, participants will be given additional investigational product to support daily dosing throughout the Outpatient Period. In such cases, the actual Outpatient Period

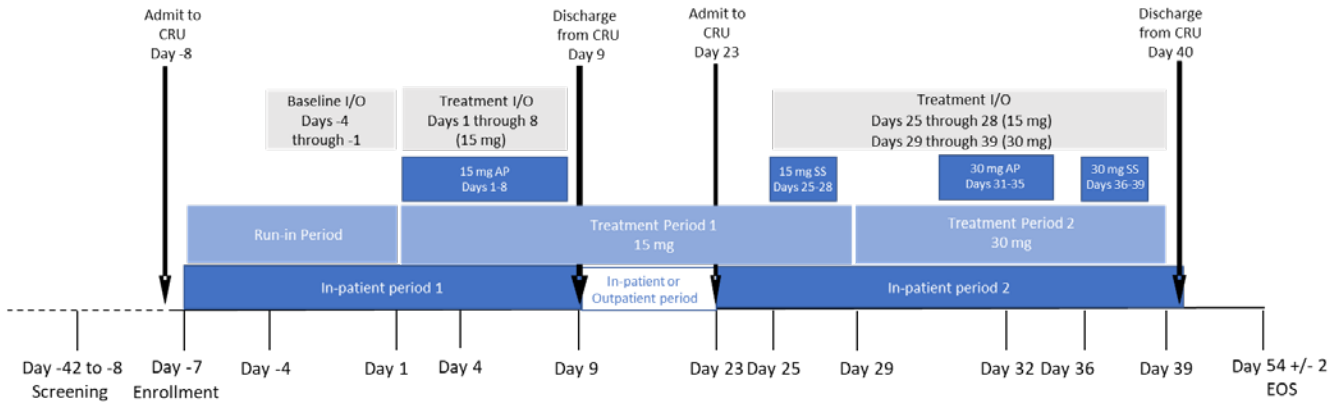
duration will be recorded and the participant will continue Inpatient Period 2 at Day 23. During the Outpatient Period, participants will use SMS text messaging to confirm study intervention administration. At the CRU's discretion, participants may remain in the CRU during the outpatient period for safety or to maintain the integrity of the conduct of the study.

Safety Review Committee:

A Safety Review Committee (SRC), composed of a minimum of the Investigator, Alexion Medical Monitor, and Alexion Safety Physician, will meet at the end of 15 mg/day dosing to confirm proceeding to 30 mg/day and as necessary based on any emerging safety concerns.

1.2. Schema

Figure 1: Study Schematic



1. Participants eligible for the study will be enrolled on Day -7 and initiated on a copper- and molybdenum-controlled diet, which will be continued during Treatment Period 1 and Treatment Period 2 when in the CRU, through Day 39.
2. Participants will be admitted to the CRU for Treatment Period 1 on Day -8 and may be discharged on Day 9 or remain in the CRU for their own safety or to maintain the integrity of the conduct of the study. Participants who are discharged will be re-admitted on Day 22 or Day 23 for Treatment Period 2 and will remain in house until Day 40. To ensure flexibility, the Outpatient Period may be extended up to an additional 14 days with Investigator approval. In this situation, participants will be given additional investigational product to support daily dosing throughout the Outpatient Period. In such cases, the actual Outpatient Period duration will be recorded and the participant will continue Inpatient Period 2 at Day 23.
3. Participants will be administered ALXN1840 at a dose of 15 mg/day on Day 1 through Day 28 and then increase to 30 mg/day on Day 29 through Day 39. During the Outpatient Period, participants will use SMS text messaging to confirm study intervention administration.
4. Participants will have 3 intake and output collection periods including:
    - Baseline Day -4 through Day -1
    - Day 1 through Day 8 (I/O for 15 mg)
    - Day 25 through Day 39 (Days 25 through 28, I/O for 15 mg; Days 29 through 39, I/O for 30 mg)
5. During these periods all intake (including food and drink) and output (including urine and feces) will be collected and assessed for copper and molybdenum.
6. Blood sampling for PK/PD will be as follows:
    - PK/PD collection (24-hour): Days 1, 25, 29, and 39
    - Predose PK/PD sampling days: Days 4 - 7, Days 26 - 28, Days 30 - 38
    - End of Study Visit Day 54 +/- 2 days

Abbreviations: AP = accumulation period; CRU = clinical research unit; EOS = End of Study; I/O = input/output; PD = pharmacodynamic; PK = pharmacokinetic; SS = steady state.

1.3. Schedule of Activities (SoA)

Table 1: Schedule of Activities

Study Procedures	Screening[a]		C-I[b]																				UNS[d]	EOS or ET[e]
	Screening		C-I	Inpatient Period 1								OP[c]		Inpatient Period 2										
Days	-42 to -9	-21	-8	-7	-6 through -5	-4 through -1	1	2-3	4-7	8	9	10-22	23	24	25	26-28	29	30-35	36	37-38	39	40		EOS Day 54+/-2
Eligibility																								
Informed consent	X																							
Admit to unit			X										X											
Discharge from unit[f]											X											X		
Outpatient visit or phone call												X[g]												
Inclusion/exclusion	X		X				X																	
Discuss/document contraception	X		X								X													X
Follicle-stimulating hormone (post-menopausal females only[h])	X																							
Alcohol test	X		X																					
Urine drug screen	X		X																					
HIV, hepatitis B and C screen	X																							
Study Administration																								
Medical history/demographics[i]	X																							
WD history[j]	X																							
Prior WD treatment[j]	X						X																	
Physical examination[k]	X		X										X											X
Height[l], weight, and BMI	X		X										X									X		
Enrollment																								
Enrollment/inclusion				X																				
Discontinue chelation therapy						X →	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→		
Discontinue zinc therapy		X →	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→		
Administration of Study Intervention[m]																								
ALXN1840 15 mg/day							X	X	X	X	X	X	X	X	X	X								
ALXN1840 30 mg/day																	X	X	X	X	X			
Study intervention compliance												X[n]	X											
PK/PD Analyses[o]																								
Blood sampling for PK: Plasma total Mo and PUF-Mo							X[p]		X						X[p]	X	X[p]	X	X	X	X[p]	X		

Study Procedures	Screening[a]		C-I[b]																			UNS[d]	EOS or ET[e]
	Screening		C-I	Inpatient Period 1								OP[c]		Inpatient Period 2									
Days	**-42 to -9**	**-21**	**-8**	**-7**	**-6 through -5**	**-4 through -1**	**1**	**2-3**	**4-7**	**8**	**9**	**10-22**	**23**	**24**	**25**	**26-28**	**29**	**30-35**	**36**	**37-38**	**39**	**40**		**EOS Day 54+/-2**
PD: Plasma total and PUF-Cu, LBC, ceruloplasmin, ceruloplasmin-bound Cu																							
Safety Assessments / Laboratory Analyses																							
Chemistry[q], hematology, Coagulation	X		X			X[r]				X		X[g]	X			X[r]		X				X	X
Urinalysis	X		X							X		X[g]	X			X						X	X
Urine/serum pregnancy test[s]	X		X										X										X
Retained serum sample (safety)[t]				X																			
Vitals sign measurements[u]	X			X			X				X		X									X	X
12-lead ECG (triplicate)	X			X			X				X		X								X		X
Adverse events	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Balance assessments																							
Cu/Mo-controlled meals[v]				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		
Urination and bowel movement monitoring, menstruation check[s]						X	X	X	X	X					X	X	X	X	X	X	X		
24-hour urine for Cu and Mo[w]						X	X	X	X	X					X	X	X	X	X	X	X		
Feces for Cu and Mo[x]						X	X	X	X	X					X	X	X	X	X	X	X		
Other																							
Concomitant medication and non-pharmacologic therapy/procedure	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[a] Within 42 days of ALXN1840 administration. Details of procedures that may be performed by sites designated as "screening sites" (only in the US) are detailed in Section 8.

[b] Participants will be admitted to the clinical research unit (CRU) at least 10 hours prior to enrollment and initiation of copper- and molybdenum-controlled diet.

[c] At the CRU's discretion, participants may remain in the CRU or be readmitted on Day 22 with all procedures starting on Day 23.

[d] Unscheduled study visits may occur at any time during the study and may include any study procedure as deemed necessary by the Investigator.

[e] Participants are required to return to the CRU Day 54+/-2; participants will be discontinued from ALXN1840 medication by their physician at the latest by the Day 54 follow-up.

[f] Discharge from the unit may occur after completion of all procedures on Day 9 and on Day 40 and after the Investigator has reviewed all safety assessment (including safety laboratory tests) and confirmed that the participant is appropriate for discharge.

[g] A single outpatient visit or phone call and safety laboratory assessment should occur between Day 14 and Day 18. A phone call may take place on a different day than the blood draw within the Day 14 through Day 18 period.

[h] If needed to confirm menopause.

[i] Parameters include age and sex. Race and ethnicity will be collected where permitted by local regulations.
[j] Wilson disease history will include diagnosis date, method of diagnosis, history of cirrhosis, details of any previous liver biopsies performed, and treatment received.
[k] A full physical examination will be performed at Screening, at check-in for the study, and at the End of the study/Early Termination Visit. A physical examination should also be performed on any participants with ongoing adverse events prior to discharge from the unit. Otherwise, a symptom-driven physical examination may be performed at other times, at the Principal Investigator's discretion.
[l] Height at screening only.
[m] While in the CRU, study intervention will be administered after an overnight fast (ie, at least 10 hours) at the same time every morning; drug is to be administered with 240 mL of water and meals should be delayed a minimum of 2 hours after dosing. As an outpatient, participants are expected to take ALXN1840 at approximately the same time daily (+/-1 hour). Participants should take the medication with a glass of water on an empty stomach; meals should be delayed a minimum of 2 hours after dosing.
[n] During the outpatient period, participants will use SMS text messaging to confirm study intervention administration.
[o] Blood sampling for PK/PD will occur before ALXN1840 administration and represents a predose trough. See Table 2 for PK/PD sampling on Days 1, 25, 29, and 39.
[p] PK/PD collection will include timepoints described in the schedule of PK/PD assessment for Days 1, 25, 29, and 39 (Table 2).
[q] Samples for serum chemistry will be obtained following a fast of at least 8 hours at the Screening Visit and at check-in. In case of rechecks, and postdose serum chemistry, participants may not have fasted for 6 or 8 hours before the serum chemistry sample is taken.
[r] Laboratory assessment including chemistry, hematology, and coagulation parameters should be performed on Days -8, -1, 8, 23, and 28 only.
[s] 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 Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) (Section 10.2). In addition to pregnancy tests detailed at the visits in the SoA, females of childbearing potential will be required to perform urine pregnancy tests at least every 4 weeks at their home or the study site throughout their time in the study.
[t] 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.
[u] 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.
[v] Copper- and molybdenum-controlled diet will be initiated after registration/inclusion. Participants will remain on a copper/molybdenum controlled diet throughout both the inpatient Period 1 (Day -8 to Day 9) and inpatient Period 2 (Day 23 to Day 40); during this time participants will be strongly encouraged to complete all meals. While not in the CRU, participants will be encouraged to adhere to their usual copper-controlled diet.
[w] For each input/output balance period, 24-hour urine samples are to be collected for measurement of copper and molybdenum.
[x] 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; C-I = check-in; Cu = copper; D = day; ECG = electrocardiogram; EOS/ET = End of Study or Early Termination; HIV = human immunodeficiency virus; HR = heart rate; LBC = labile bound copper; Mo = molybdenum; OP = outpatient; PD = pharmacodynamic; PK = pharmacokinetics; PUF = plasma ultrafiltrate; UNS = unscheduled; WD = Wilson disease.

Table 2: Schedule of Pharmacokinetic and Pharmacodynamic Assessments on Days 1, 25, 29, and 39

Time point (hours)[a]	−0.5	0	1	2	3	4	5	6	8	12	24
Blood sampling for PK: Plasma total Mo and PUF-Mo PD: Plasma total and PUF-Cu, LBC, ceruloplasmin, ceruloplasmin-bound Cu	X			X		X	X	X	X	X	X[b]

Note: Windows for PK/PD time points will be defined as ±10% of the nominal time point. On Days 1 and 39, triplicate 12-lead ECG will be collected at 4 hours postdose. 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 (eg, for PK/PD), study intervention administration, and meal.

[a] Time points are relative to dosing (0 hours).

[b] Hour 24 PK/PD sampling is to occur just prior to the next-day dose of ALXN1840.

Abbreviations: Cu = copper; LBC = labile bound copper; Mo = molybdenum; PD = pharmacodynamic; PK = pharmacokinetic; PUF = plasma ultrafiltrate.

2. INTRODUCTION

ALXN1840 (bis-choline tetrathiomolybdate; formerly known as WTX101) is a novel copper binding agent in development for the treatment of WD.

2.1. Study Rationale

The principal aim of this exploratory study is to investigate the effects of ALXN1840 on copper balance in participants with WD. The study will specifically evaluate the effects of 2 different ALXN1840 dose levels as well as the duration of treatment on copper balance to further elucidate the dose response of "decoppering" versus "maintenance" dose in participants with WD.

ALXN1840 contains the active anion tetrathiomolybdate and has been shown to cause negative copper balance 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 participants with WD, ALXN1840 demonstrated enhanced copper control as measured by reduced plasma $NCC_{corrected}$ for the stable tetrathiomolybdate-copper-albumin TPC (Weiss, 2017).

Depletion of copper 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 copper 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, when Long-Evans Cinnamon (LEC) WD model rats were injected intraperitoneally with a saline solution of tetrathiomolybdate at a dose of 10 mg/kg body weight for 8 consecutive days, the amounts of both copper and molybdenum excreted into the feces increased significantly (Ogra, 2000), which may suggest that copper is excreted in a complex with tetrathiomolybdate into the feces. While fecal copper increases with tetrathiomolybdate, the amount of copper excreted into the urine decreased and that of molybdenum increased significantly during treatment with tetrathiomolybdate. Molybdenum in the urine was molybdate which does not bind copper (data on file). These findings are in line with other studies showing enhanced biliary and/or fecal excretion of copper and molybdenum upon administration of tetrathiomolybdate in rats and sheep (Komatsu, 2000; Ogra, 1995; Mason, 1988).

We hypothesize that repeated doses of ALXN1840 may drive a net negative copper balance in participants with WD by increasing fecal excretion of copper. In this study, copper balance will be calculated as the difference between measured copper input in food and drink and measured copper output in urine and feces. This method is classically considered the most objective measure of decoppering ability with a decoppering agent able to drive a net negative copper balance (Hill,1986; Strickland, 1971; Walshe, 1973). The purpose of this study is to provide additional descriptive characterization of the effect of ALXN1840 on copper balance in participants with WD. Further data obtained may help support characterization of a "decoppering" versus "maintenance" dose of ALXN1840, where a decoppering dose would be a dose sufficient to drive a net negative copper balance and maintenance would support a more neutral copper balance.

The secondary aim of the study is to characterize the steady-state ADME (mass balance) of total molybdenum as a surrogate measure of ALXN1840 disposition in participants with WD. To confirm that steady state is adequately characterized by the plasma PK, a molybdenum mass balance assessment will be performed on Day 25 through Day 28 for the 15 mg/day dose and Day 36 through Day 39 for the 30 mg/day dose: if steady state is achieved, molybdenum(out) will equal molybdenum(in).

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 participants with WD and other indications. Ammonium tetrathiomolybdate and bis-choline tetrathiomolybdate nonclinical and clinical data reported to date support the efficacy and safety of ALXN1840.

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

Studies in both healthy and WD animal models showed that treatment with tetrathiomolybdate results in removal of copper from the liver. Tetrathiomolybdate administered to healthy mice by intraperitoneal injection resulted in a dose-dependent reduction in liver copper 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 copper 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 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 copper concentration. Because ALXN1840 has been shown to have a similar mechanism of action in healthy and WD animal models, a mechanism of action study in healthy participants is being performed (Study ALXN1840-HV-108) to demonstrate that ALXN1840 can result in a change from baseline in copper balance with repeat-dose ALXN1840 (30 mg/day) treatment.

In the Phase 2 proof-of-concept Study WTX101-201 in participants with WD, ALXN1840 demonstrated a sustained control of free copper as measured by $NCC_{corrected}$. Importantly, ALXN1840 treatment resulted in improvements in disability and neurologic symptoms as measured by the Unified Wilson 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 participant titration of dose based on safety, $NCC_{corrected}$, and symptoms.

Following single-dose administration of 60 mg ALXN1840, total molybdenum peaked at approximately 4.54 hours with a terminal elimination half-life measured at approximately 51 hours. In Study WTX101-201, the PK of ALXN1840, based on total molybdenum, indicated that exposure in participants with WD at a dose of 30 mg appeared consistent with previous results from healthy participants. The half-life was estimated to be approximately 24 hours at steady state on Days 84 and 168 and was shorter than estimated in previous studies. Based on a total molybdenum PK half-life of approximately 24 - 51 hours, total molybdenum steady state may conservatively be reached within approximately 10 - 12 days. Nevertheless, results (as

measured by total molybdenum) obtained from the ALXN1840 balance study in the LEC WD rat model suggested that approximately 30% of a single dose of ALXN1840 remained in the liver by Day 7, indicating the possibility of tissue accumulation, particularly in the setting of high liver copper concentration (Plitz, 2019).

If the half-life of ALXN1840 in liver were longer than that of the systemic compartment, the accumulation may not be readily detected in the absence of a longer treatment period and with characterization of the terminal elimination period. An alternative approach to assessing steady state using total molybdenum PK is to assess whether the total molybdenum intake is equal to the total molybdenum output; this approach may detect any significant ongoing accumulation in the liver or other tissues.

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 are presented in the IB. Information about the known or potential risks and benefits are detailed in the following sections.

2.3.1. Risk Assessment

Details of the potential risks and mitigation strategy are provided in Table 3.

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 participants with WD; see the IB.	Regular monitoring of liver function tests. Dose modification or discontinuation (Section 6.6).
Anemia	Anemia has been observed in participants with WD, attributed to overtreatment and resultant copper 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 participants with WD, attributed to overtreatment and resultant copper depletion. Results obtained from studies of ALXN1840 and ammonium tetrathiomolybdate in participants 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 copper mobilization. Peripheral neuropathy may be seen with over decoppering; however, symptoms such as myelosuppression is typically seen earlier.	Regular monitoring for neurologic adverse events. Dose modification or discontinuation (Section 6.6).
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; IB = Investigator's Brochure; PK = pharmacokinetics; WD = Wilson disease.

2.3.1.1. Coronavirus (SARS-CoV-2) Disease 2019

The COVID-19 pandemic is active at the time of this protocol amendment. Given this unique circumstance, specific consideration has been given to the potential risks and mitigation measures due to COVID-19 vaccine (see Section 10.5).

2.3.2. Benefit Assessment

The main objective of effective WD treatment is to provide:

- Rapid and sustained control of copper and mitigation of clinical symptoms of WD through the formation of a stable tetrathiomolybdate-copper-albumin TPC. Copper control may prevent tissue toxicity, including neurological deterioration that has been reported at the initiation of treatment with chelators. This hypothesis is supported by results from Study WTX101-201 in participants with WD (Weiss, 2017).
- Improved compliance over current chelator therapy through improved tolerability and the convenience of a simplified dosing regimen (once daily) compared to current therapeutic options (multiple daily dosing).

Potential benefits of study participation for participants include:

- Participation in a clinical study increases the participant's understanding of the pathophysiology and treatment of WD.
- Removal of total body copper as a definitive treatment for WD.
- Participants in the study will contribute to improved care for other participants with WD in the future.

2.3.3. Overall Benefit-Risk Conclusion

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

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary Assess net copper balance with daily repeat-dose ALXN1840 treatment (15 mg and 30 mg) in participants with Wilson disease (WD)	Mean daily copper balance where copper balance is measured by the calculated difference between copper intake (in food and drink) and copper output (in feces and urine) during ALXN1840 accumulation and steady-state periods for each dose
Secondary Assess change in copper balance in response to ALXN1840 15 mg/day and 30 mg/day during ALXN1840 accumulation and at steady state periods versus the pretreatment baseline in participants with WD	Change in mean daily copper balance as measured by the calculated difference between copper intake (in food and drink) and copper output (in feces and urine) from pretreatment baseline (Days -4 through -1) and ALXN1840 accumulation and steady-state periods for each dose
Investigate the effect of ALXN1840 (15 mg/day and 30 mg/day) on the disposition of copper in participants with WD	Copper quantified in food, drink, feces, and urine, including plasma total and labile bound copper (LBC) during ALXN1840 accumulation and steady-state periods for each dose
Investigate the effect of ALXN1840 on the disposition of molybdenum at steady state at 15 mg/day and 30 mg/day in participants with WD	Molybdenum quantified in food, drink, feces, and urine, plasma total molybdenum at ALXN1840 steady state
Assess steady-state total molybdenum balance as a measure of ALXN1840 15 mg/day and 30 mg/day in participants with WD	Mean daily molybdenum balance as demonstrated through measurement of molybdenum intake (in food, drink, and ALXN1840), and molybdenum output (feces and urine) representing ALXN1840 steady state
Assess accumulation of molybdenum with ALXN1840 treatment at 15 mg/day and 30 mg/day in participants with WD	Accumulation of molybdenum as determined by molybdenum balance
Determine the steady-state plasma pharmacokinetic (PK) of total molybdenum and plasma ultrafiltrate (PUF) molybdenum (as surrogate measures of ALXN1840, 15 mg and 30 mg) in participants with WD	PK parameters for plasma total and PUF-molybdenum
Safety Evaluate the safety and tolerability of repeated-dose administration of ALXN1840 15 mg/day and 30 mg/day in participants with WD	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 electrocardiogram (ECG) findings as determined by triplicate 12-lead ECG • Vital sign assessments (blood pressure and heart rate)
Exploratory Determine dose response of ALXN1840 15 mg/day and 30 mg/day for copper balance in participants with WD	Assess dose response of ALXN1840 on copper balance focusing on copper balance
Determine the effect of treatment duration on copper balance in participants with WD	Determine the effect of time following initiation of ALXN1840 treatment on copper balance
Assess the effects of ALXN1840 on ceruloplasmin, ceruloplasmin-bound copper, LBC profiles in plasma in participants with WD	Ceruloplasmin, ceruloplasmin-bound copper, and LBC: Change in ceruloplasmin at Days 1, 8, 25, 29, 36, and Day 39 compared with predose

Objectives	Endpoints
Assess dose proportionality at steady state of doses of ALXN1840 15 mg/day and 30 mg/day in participants with WD	Based on PK parameters
Assess effects ALXN1840 on copper:molybdenum ratio in plasma at steady state in participants with WD	Measure plasma copper:molybdenum ratios at steady state compared with predose
Assess the effects of repeat-dose ALXN1840 on copper:molybdenum ratio in urine and feces in participants with WD	Mean daily copper:molybdenum ratio in urine and feces at steady state compared with predose baseline

Note: The accumulation period refers to time from initiation of ALXN1840 (Day 1) to expected steady state at Day 10, based on 5 times the half-life of 2 days.

4. STUDY DESIGN

4.1. Overall Design

This study will be conducted as an open-label, repeat-dose study to evaluate the effects of ALXN1840 on copper balance in participants with WD.

Treatment-experienced (which includes standard of care therapies or ALXN1840) and treatment-naïve participants are eligible for this study. Eligible patients will be classified into one of two cohorts:

- Cohort 1 (treatment experienced): Patients who have received WD therapy for > 28 days
- Cohort 2 (treatment naïve): Patients who have received WD therapy for ≤ 28 days

Following screening and enrollment, participants will check-in to the CRU on Day -8 for the Run-in Period. The purpose of the Run-in Period is to support diet equilibration (Day -7 through Day -5) and measure pretreatment copper and molybdenum balance (Day -4 through Day -1). Participants will remain on a copper/molybdenum-controlled diet throughout both the Inpatient Period 1 (Day -8 to Day 9) and Inpatient Period 2 (Day 23 to Day 40). While not in the CRU, participants will be encouraged to adhere to their usual copper-controlled diet.

Participants who are taking copper-chelating therapies (penicillamine or trientine) at the time of enrollment will be discontinued from their decoppering therapies starting on Day -4 to allow a baseline assessment of copper/molybdenum balance prior to ALXN1840 treatment. On Day 1, participants will be initiated on 15 mg/day of ALXN1840 for a treatment period of approximately 28 days followed by titration up to 30 mg/day on Day 29. Before titration to 30 mg/day, the SRC will review available safety data through Day 23 for each participant.

Participants will have intake and output collection periods from Day -4 through Day -1, from Day 1 through Day 8, and Day 25 through Day 39. The collection periods will support an assessment of both copper and molybdenum balance (as a measure of ALXN1840 ADME) at the 15 mg and 30 mg doses and will allow assessment of the effects of duration of treatment on copper elimination and copper balance.

Collection periods for feces and urine will vary in duration from 3 to 15 days to support assessment of both copper and molybdenum balance before and at steady state for both 15 mg and 30 mg. Equilibration periods on copper/molybdenum-controlled diets will be a minimum of 48 hours. Copper balance will be calculated as the mean daily copper balance over each of the 4 collection periods. The interpretation of copper balance will be based on the criteria established by Hill,1986 when undertaking copper balance studies with zinc treatment. For assessment of ALXN1840 effect on copper 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).

Throughout the inpatient periods, participants will remain on a copper-controlled diet. Meal portions will be weighed, and meal sizes will be appropriate to support male and female caloric consumption. Participants will be encouraged to complete 100% of all meals throughout the inpatient period to support quantification of copper and molybdenum intake. If participants are unable to complete the full meal, the uneaten portion will be weighed to allow calculation of meal fraction, and copper and molybdenum intake will be adjusted based on the fractional intake

of the meal. In addition to food, fluid intake and type will be measured and recorded each day. Samples of all meals and fluids will be sent for bioanalysis to support accurate quantification of copper and molybdenum in fluids. In the event that items cannot be accurately quantified, items may be balanced during pretreatment period and post-treatment period to support the change from baseline assessment.

During the inpatient collection periods, daily urine will be pooled (24-hour collection) with volumes recorded for each 24-hour period; participants will be strongly encouraged to void within 2 hours of completion of each 24-hour period (ie, dosing time). Stool samples will be individually collected and each sample will include a collection date, time, and weight.

Participants may be discharged from the CRU on Day 9 and return on Day 22 or Day 23 (predose); all procedures will start on Day 23. To ensure flexibility, the Outpatient Period during Treatment Period 1 may be extended up to an additional 14 days with Investigator approval. In this situation, participants will be given additional investigational product to support daily dosing throughout the Outpatient Period. In such cases, the actual Outpatient Period duration will be recorded and the participant will continue Inpatient Period 2 at Day 23. During the Outpatient Period, participants will use SMS text messaging to confirm study intervention administration. At the CRU's discretion, participants may remain in the CRU during the outpatient period for safety or to maintain the integrity of the conduct of the study.

Blood sampling for PK/pharmacodynamic (PD) will occur over the 24-hour dosing period on Days 1, 25, 29, and 39. Predose PK samples will be collected at all time points during the intake and output collection period to help characterize PK during accumulation (Days 1 through 9 for 15 mg and Days 31 through 35 for 30 mg) and at steady state (Days 25 through 28 for 15 mg and Days 36 through 39 for 30 mg).

This study incorporates the use of an adaptive design. Adaptive features may be implemented at the discretion of the Investigator to support conduct of the study. Such adaptive features do not require amendment of the protocol. Adaptive features and their limits are described in Table 4.

Table 4. Adaptive Protocol Features

Features	Limits
1. Outpatient Period (Day 9 to Day 23) may be extended up to an additional 14 days with Investigator approval with adequate supply of study intervention to support daily dosing can be provided, and with record of exact duration of Outpatient Period is recorded; participants will reinitiate the study on Day 23.	• Not >14 days
2. Participants may be checked in on Day 22 rather than Day 23 at the Investigator discretion.	• Check-in to clinical research unit allowed 1 day prior
3. In this study, dosing for ALXN1840 will be initiated at 15 mg once daily for a minimum of 4 weeks, with an increase to 30 mg after 4 weeks, unless there are safety concerns that, in the opinion of the Investigator(s) and/or Alexion, may place participants at undue risk, in which case, patients may remain on the 15 mg/day dose for the duration of the study.	• Dose range limit 15 mg every other day to 30 mg/day
4. The dose should be decreased or interrupted if any of the relevant Dose Modification criteria are met (Table 7).	• Dose range limit 15 mg every other day to 30 mg/day

4.2. Scientific Rationale for Study Design

The study is designed as an open-label exploratory study to provide a descriptive assessment of copper balance in participants with WD, the target population for ALXN1840 therapy. The study is being conducted as a repeat-dose study to assess the effect of duration of ALXN1840 treatment and the effects of intra-patient dose increase on copper and molybdenum balance in participants with WD. The intra-patient dose escalation schedule is similar to that employed in the current Phase 3 Study WTX101-301. The similar schedule was chosen to characterize the decoppering effects expected early with treatment. This study is designed to supplement the mechanism of action study in healthy participants (Study ALXN1840-HV-108). While healthy participants are expected to be adequate to assess the mechanism of action of ALXN1840, characterization of copper balance in the WD population will help to understand if there are differences in the magnitude of effect between the 2 populations as this may be important to understand the doses that may support a net neutral versus a net negative copper balance. Limited nonclinical data on copper elimination with tetrathiomolybdate suggested copper excretion may be at least maintained or increased with repeated dosing (refer to the current IB).

Therefore, the duration of the study and multiple collection periods will better characterize the pattern of copper elimination over time. Such information may be helpful in understanding the decoppering and maintenance phases.

As the study involves intensive diet control and sampling, the study is planned to be conducted in a small number of participants with WD who will be admitted to a CRU for 2 inpatient periods. Inpatient Period 1 includes a baseline and initial 15 mg/day collection period during the accumulation phase followed by an Outpatient Period; Inpatient Period 2 with a second collection period to support analysis of copper balance at 15 mg/day steady state and a 30 mg/day accumulation and steady state.

During the Outpatient Period, participants will be encouraged to remain on a copper-controlled diet; however, to avoid confounding, a diet equilibration period is included in each study period. Overall, collection periods are a minimum of 3 days and as long as 15 days (which will be subdivided for analyses). Collection periods of at least 3 days were used to help minimize the impact of day-to-day variability on measurements. In addition, 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). Because the periods are of different lengths, the study will calculate mean daily copper balance.

While the primary endpoint for the study is an assessment of net copper balance, measurement of a pretreatment copper baseline will be helpful to understand the magnitude of effect of ALXN1840. To assess the copper baseline during the Inpatient Run-in Period, participants will be discontinued from their chelator therapy for approximately 4 days prior to initiating ALXN1840. During this period, participants will be maintained on a copper-controlled diet to minimize risk to the participants. In the Phase 3 study ALXN1840-WD-301, participants discontinue their chelator approximately 48 hours prior to initiation of ALXN1840 without reported complications. Among participants who discontinue chelator due to intolerance or noncompliance, the time from chelator discontinuation to the onset or worsening of symptoms varies from as little as 1 or 2 weeks to as long as months or years (Scheinberg, 1987). To prevent confounding of the study results, participants must be off zinc therapy for a minimum of 21 days prior to Day 1 because zinc works through upregulation of metallothionein (MT) in enterocytes resulting in elevation of fecal copper excretion. Previously, reports in the literature suggest that it can take up to 3 weeks or longer for zinc treatment to have an efficacious effect on copper balance (Brewer, 1983), so a delayed time to reversal of this effect could also occur. However, the physiologic turnover of human gastrointestinal epithelial cells is 3 - 5 days (Darwich, 2014); therefore, the inhibitory effect of zinc on intestinal copper absorption is expected to be minimal 21 days after discontinuation of zinc.

Following ALXN1840 administration, the active drug moiety tetrathiomolybdate rapidly binds copper to form TPC, mostly 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 molybdenum, and is excreted in the urine. Total molybdenum concentration has been measured as a surrogate of ALXN1840 PK; however, total molybdenum concentration cannot distinguish whether the molybdenum is protein bound (mostly as TPC), free active drug as ALXN1840, intermediate hydrolysis products, or molybdate. To better characterize the amount of non-TPC-bound drug and its unbound degradation products, plasma PUF-molybdenum has also been measured, which

represents the free parent drug (ALXN1840), short-lived intermediate hydrolysis products, and molybdate, which may have originated from the tetrathiomolybdate or from food intake as a micronutrient. Total molybdenum PK and free molybdenum PK serve as surrogate measures of ALXN1840 PK. To better characterize the ADME of ALXN1840, the PK of both total molybdenum and PUF-molybdenum will be characterized and described.

This study is designed to provide an extensive assessment of copper and molybdenum balance over the first 40 days of treatment with ALXN1840 and support a more robust understanding of the effects of duration of treatment and dose of ALXN1840 on copper balance. Half-life estimates for total molybdenum in Study WTX101-201 were reported to be approximately 24 hours at steady state on Days 84 and 168, while in healthy participants, total molybdenum half-life was measured closer to 51 hours. With a half-life within this range, the sample collection periods include assessment of copper and molybdenum balance both during accumulation and at steady state for both the 15 mg/day and 30 mg/day doses. The study will include both intake and output collection as well as PK and copper assessments (ie, ceruloplasmin-bound copper and labile bound copper [LBC]) to inform the relationship between balance measurements and copper and molybdenum levels in the blood.

Finally, preclinical data from ALXN1840 ADME study suggest the potential for molybdenum accumulation in the liver of participants with WD; therefore, an assessment of molybdenum balance will help determine whether steady state has been reached as defined by a molybdenum balance of neutral during the collection period. Because molybdenum is a necessary micronutrient and serves as a cofactor for a number of enzymes and may exist in intracellular stores, small variations in molybdenum balance could be due to molybdate rather than ALXN1840.

4.2.1. Participant Input into Design

Not applicable.

4.3. Justification for Dose

ALXN1840 at 60 mg single dose has been shown to have an adequate safety profile and be well-tolerated in healthy male and female participants in the Phase 1 bioavailability Studies WTX101-101 and WTX101-102. In addition, preliminary data from Study WTX101-106 have also shown ALXN1840 to be well tolerated in healthy Japanese and non-Japanese male and female participants at a single dose of 15 mg or 60 mg. While no repeat-dose studies have been performed in healthy participants, bis-choline tetrathiomolybdate (ALXN1840) has been tested in a range of oncologic indications with a maximum tolerated dose of 300 mg/day (Lowndes, 2008).

In the Phase 2 Study WTX101-201 conducted in participants with WD, the daily ALXN1840 doses were 15 mg for 6 (21%) participants, 30 mg for 13 (46%) participants, and 60 mg (32%) for 9 participants at Week 24 when the primary endpoint assessment was conducted, or at the last dose received for participants with early discontinuation. The 15 to 60 mg/day dose range has been demonstrated to be efficacious with a favorable safety profile in treating participants with WD (Weiss, 2017). Based on these Phase 2 study results, the ongoing Phase 3 Study WTX101-301 in participants with WD has been testing the efficacy and safety of ALXN1840 at

a dose titration range from 15 mg to 60 mg daily with data to date supporting an acceptable safety profile.

Similar to the Phase 2 study, in Study WTX101-301, participants are started at a dose of 15 mg/day and, after review of all safety information, participants may be titrated up to 30 mg/day after approximately 4 weeks. Based on the results of Study WTX101-201, doses ranging from 15 mg/day to 60 mg/day were adequate to significantly decrease non-ceruloplasmin corrected copper concentrations corrected for TPC ($NCC_{corrected}$) and, in many cases, return the NCC to normal concentrations of copper control. Given the robust improvement in copper control, it is hypothesized that doses within the 15 to 30 mg/day range will be adequate to drive a net negative copper balance. The current study will explore copper balance in response to treatment with ALXN1840, with the purpose of informing the dose and dosing duration required to result in adequate copper elimination to drive a measurable net negative copper balance. Copper balance will be assessed for the 15 mg/day dose at the beginning and end of the 15 mg/day treatment period, and at the beginning of the 30 mg/day treatment period. Copper balance will be assessed for the 30 mg/day dose at Days 31 through 35 and Days 36 through 39. The multiple collection periods will support assessment of duration of treatment and dose on copper elimination and overall copper balance.

In this study, dosing for ALXN1840 will be initiated at 15 mg once daily for a minimum of 4 weeks, with an increase to 30 mg after 4 weeks, unless there are safety concerns that, in the opinion of the Investigator(s) and/or Alexion, may place participants at undue risk, in which case, participants may remain on the 15 mg/day dose for the duration of the study. Further dose adjustments will be made as appropriate.

The dose should be decreased or interrupted if any of the relevant Dose Modification Criteria are met. Deviation from the dose modification guidelines must be agreed with the Alexion Medical Monitor.

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 (Section 1.3).

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

Age

1. Participants aged ≥18 at the time of signing the ICF.

Type of Participants and Disease Characteristics

2. Diagnosis of WD by Leipzig Criteria ≥ 4 documented by testing as outlined in the 2012 European Association for the Study of Liver WD Clinical Practice Guidelines (Ferenci, 2003; EASL, 2012) or by historical test results for WD including some or all of the following:
   - Presence of Kayser Fleischer rings,
   - Neurological symptoms,
   - Serum ceruloplasmin below reference range,
   - Coombs-negative hemolytic anemia,
   - Elevated liver or urinary copper,
   - Presence of mutations in the ATP7B gene, or
   - Other, as considered appropriate, may be used instead to confirm the diagnosis of WD.
3. Participants who in the opinion of the referring Investigator may benefit from decoppering therapy.
4. Participants must be able to comply with all study-related procedures.
5. Participants must be able to reside in the CRU for intensive metabolic monitoring of copper and molybdenum.
6. Participants willing to discontinue chelator therapy for approximately 4 days prior to initiation of ALXN1840 to allow a baseline assessment of copper balance.
7. Participants with adequate venous access to allow collection of required blood samples.
8. Participants must be able to swallow intact ALXN1840 tablets.
9. Participants willing to avoid use of minerals containing copper, zinc, or molybdenum throughout the study duration.
10. Participants willing to adhere to copper/molybdenum-controlled diet during inpatient periods and willing to comply with a low copper dietary requirement during the Outpatient Period.

Sex

11. 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. Male

participants must not donate sperm for at least 3 months after the end of systemic exposure of the study intervention.

- 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.
- Barrier contraception (male condom) 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 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. Female participants must not donate ova for at least 3 months after the end of systemic exposure of the study intervention.
- 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

12. Participants capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2. Exclusion Criteria

Medical Conditions

1. Decompensated cirrhosis or model for end-stage liver disease (MELD) score > 13.
2. Modified Nazer score > 7 (Dhawan, 2005).
3. Clinically significant gastrointestinal bleed within past 3 months.
4. Alanine aminotransferase (ALT) > 2 × upper limit of normal (ULN).
5. Marked neurological disease requiring assistance with self-care or activities of daily life.
6. Hemoglobin less than lower limit of the reference range for age and sex.
7. Active infection with hepatitis B virus (positive hepatitis B surface antigen) or C virus (participants with positive hepatitis C antibody result would require confirmation of active disease with a positive hepatitis C polymerase chain reaction test), or seropositivity for human immunodeficiency virus (HIV).

8. History or presence of/significant history of or current cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrinological, hematological, or neurological disorders, or psychiatric disorder that in the opinion of the Investigator may constitute a risk when taking the study intervention; or may interfere with the interpretation of data.

Prior/Concomitant Therapy

9. Previous treatment with ALXN1840 or other form of tetrathiomolybdate within 1 year prior to dosing.
10. Previous treatment with zinc within 21 days prior to Day 1.

Prior/Concurrent Clinical Study Experience

11. The use of an experimental or unapproved/unlicensed therapy at the same time or within 90 days or 5 half-lives, whichever is longer, prior to the Screening Visit.

Diagnostic Assessments

12. Participants in renal failure, defined as in end-stage renal disease on dialysis (chronic kidney disease [CKD] stage 5) or creatinine clearance < 30 mL/min (Levey, 2006).

Other Exclusions

13. Pregnant (or females who are planning to become pregnant) or breastfeeding females (women of childbearing potential must have a negative serum pregnancy test result at screening).
14. Known sensitivity to ALXN1840, ALXN1840 excipients (anhydrous dicalcium phosphate, anhydrous sodium carbonate), or any of the ingredients contained in ALXN1840 or related compounds.
15. In the opinion of the Investigator, the participant and/or their legal guardian is likely to be non-compliant or uncooperative during the study.
16. History of illicit drug abuse, 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 National Health Service (NHS) alcohol tracker http://www.nhs.uk/Tools/Pages/drinks-tracker.aspx.
17. Positive urine drug toxicology screen at Screening or on Day -8 (cannabinoids will not be tested).
18. Alcohol consumption within 48 hours prior to study intervention administration or positive alcohol breath test at screening or on Day -8.
19. Participants unwilling to consistently complete every meal and tolerate a controlled, limited menu for the duration of the study.

5.3. Lifestyle Considerations

Participants must be able and willing to adhere to the lifestyle restrictions detailed in Table 5.

Table 5: Participant Lifestyle Considerations

Restrictions	Timeframe Restriction Applies	Restrictions End
Food Participants will remain on a copper/molybdenum-controlled diet. Standardized copper- and molybdenum-controlled meals will be provided. 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 copper/molybdenum determination as a fraction of the total meal. Participants will be expected to fast overnight. During the dosing period, participants will be administered ALXN1840 with 240 mL of water each morning; participants must remain fasted for a least 2 hours after dose administration.	Dietary restrictions will remain in place during Inpatient Periods 1 and 2.	Participants may return to routine diet after completion of Day 40.
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 during Inpatient Periods 1 and 2.	Participants may return to routine fluid intake after completion of Day 40.
Alcohol	48 hours before check-in to the CRU (Day -8 and Day 22/23) and until discharge on Day 40, and 48 hours before each study Outpatient/Follow-up Visit.	Discharge from the CRU 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 for 24 hours prior to each study visit for the duration of the study.	48 hours prior to check-in to the CRU (Day -8 and Day 22/23) and until discharge on Day 40.	Restrictions end after completion of EOS Visit.
Concomitant medication Concomitant medication guidelines are as per Section 6.5. Note: If participants have a medical need to take any new medication(s) prescribed to them by a doctor, they should follow the medical advice but inform the Investigator as soon as possible afterwards. Investigator in consultation with Alexion should determine participant's continued suitability to remain in the study.	Signing of informed consent until EOS Visit.	Restrictions ends after completion of EOS Visit.

Restrictions	Timeframe Restriction Applies	Restrictions End
Nonprescription/over-the-counter medication Any nonprescription/over-the-counter medication may be taken under the direction of the Investigator. Over-the-counter medications may be given if they are not expected to impact the outcome of the study. Acetaminophen should be limited to 1000 mg/day. Herbal remedies must be discontinued at least 7 days prior to first admission until study completion.	Allowed under direction of Investigator.	After the EOS Visit.
St John's wort 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 Section 5.1 [inclusion criteria]).	See Section 10.4.

Abbreviations: CRF = case report form; CRU = clinical research unit; EOS = End of Study; SoA = Schedule of Activities.

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. Rescreened participants are not required to reconsent as long as they have signed the latest version of the ICF.

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(s) Administered

Details of ALXN1840 administered in the study are provided in Table 6.

Table 6: Study Intervention Dosage and Mode of Administration

Drug 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 doses of 15 mg/day or 30 mg/day (administered as 2 × 15 mg ALXN1840 tablets) for 40 days
Route of administration	Oral
Use	Experimental/study intervention
IMP and NIMP	IMP
Sourcing	Provided by Alexion
Packaging and labeling	ALXN1840 will be provided in treatment kits that will each have a unique identification number and be packaged and labelled in accordance with all applicable regulatory requirements. At a minimum, the treatment kit label will provide the following information: Alexion study identification, batch number, directions for use, required storage conditions, caution statements (including "New Drug-Limited by Federal Law to Investigational Use" language), study identification, and expiry date.
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. Authorized site staff will instruct participants on study intervention storage and how to correctly dose themselves during the Outpatient Period. A sufficient number of kits should be dispensed to the participant to cover the need until check-in for Treatment Period 2. Participants will return all unused study intervention and empty kits so that study drug compliance may be calculated.

4. 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 [redacted] 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 study 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.
5. 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 ALXN1840.

6.4. Study Intervention Compliance

While in the CRU, 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 case report form (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.

During the Outpatient Period, participants will use SMS text messaging to confirm study intervention administration. Compliance with ALXN1840 during the Outpatient Period will be assessed by means of tablet counts of used and partially used treatment kits returned to the site by the participant. Any deviation from the prescribed dosing regimen including extra doses, missed doses, and drug interruptions will be documented in the source documents and CRF.

Reasons for not following study intervention administration as described in the protocol should be clearly recorded in the source documents.

A record of the number of ALXN1840 tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Study intervention start and stop dates, including dates for drug delays and/or dose reductions will also be recorded in the CRF.

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 EOS 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 or prior therapy.

Medications specific for WD taken at any time prior to the study will also be recorded, including ALXN1840 received in a previous clinical study (clinical study number and subject ID should be noted).

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 coadministration 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 delegate.
- 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

Participants will be initiated on ALXN1840 at 15 mg once daily and increased to 30 mg once daily on Day 29. Specific criteria for dose reduction, temporary interruption of dosing, or restriction of dose increases of ALXN1840 are detailed in Table 7. Repeat testing of parameters meeting dose modification criteria should follow the instructions in Table 7. 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, electrocardiogram (ECG) abnormality, or AE that are considered of clinical concern by the Investigator. Investigators must notify Alexion immediately of study intervention discontinuation. The decision to discontinue study intervention should not be delayed for causality assessment.

Table 7: ALXN1840 Dose Modifications for Individual Participants

Test	Result	Conditions	Action with ALXN1840 Dosing	Changes in Safety Monitoring[a]	Rechallenge[b,c,d]
ALT	> 5 × ↑ from baseline	ALT above reference range at baseline	Temporary interruption	Contact participant within 48 hours to arrange repeat testing (weekly repeat testing)	At 15 mg QOD when ALT < 2 × ↑ from baseline.
	> 5 × ULN	ALT within reference range at baseline	Temporary interruption	Contact participant within 48 hours to arrange repeat testing (weekly repeat testing)	At 15 mg QOD when ALT < 2 × ULN.
	> 2 × ↑ from baseline	ALT above reference range at baseline	Reduce dose to previous dose level if up-titration has occurred or reduce dose to 15 mg QOD if on 15 mg QD. No further dose ↑ until resolution of abnormality.	Weekly repeat testing	Not applicable.
	> 2 × ULN	ALT within reference range at baseline	Reduce dose to previous dose level if up-titration has occurred or reduce dose to 15 mg QOD if on 15 mg QD. No further dose ↑ until resolution of abnormality.	Weekly repeat testing	Not applicable.
Hemoglobin	< 8 g/dL in the absence of bleeding	None	Temporary interruption	Weekly repeat testing	At 15 mg QOD when hemoglobin and other hematology parameters (neutrophils and platelets) are at baseline concentration.
	> 30% ↓ from baseline	None	Reduce dose to previous dose level if up-titration has occurred or reduce dose to 15 mg QOD if on 15 mg QD. No further dose ↑ until resolution of abnormality.	Weekly repeat testing	Not applicable.
Platelets	< 30,000 µL	None	Temporary interruption	Weekly repeat testing	At 15 mg QOD when platelets and other hematology parameters (neutrophils and hemoglobin) are at baseline concentration.
	> 30% ↓ from baseline	Platelets below reference range at baseline	Reduce dose to previous dose level if up-titration has occurred or reduce dose to 15 mg QOD if on 15 mg QD. No further dose ↑ until resolution of abnormality.	Weekly repeat testing	Not applicable.
Neutrophils	< 1.0 × 10^3/µL	None	Temporary interruption	Weekly repeat testing	At 15 mg QOD when neutrophils and other hematology parameters

Test	Result	Conditions	Action with ALXN1840 Dosing	Changes in Safety Monitoring[a]	Rechallenge[b,c,d]
					(hemoglobin and platelets) are at baseline concentration.
	> 30% ↓ from baseline	Neutrophils below reference range at baseline	Reduce dose to previous dose level if up-titration has occurred or reduce dose to 15 mg QOD if on 15 mg QD. No further dose ↑ until resolution of abnormality.	Weekly repeat testing	Not applicable.
Bilirubin	> 2 × ULN	Accompanied by ALT > 3 × ULN, indicative of liver injury	Temporary interruption	Weekly repeat testing	At 15 mg QOD or less frequent, when bilirubin is below ULN. Rechallenge under these conditions requires approval of the Alexion Medical Monitor.
Neurological assessment	Evidence of neurologic worsening by AEs or by neurologic physical exam assessment		Investigator and Alexion Medical Monitor will evaluate the need for dose modification (interruption, increase or decrease) based on copper control parameters and relevant clinical data. Rationale for dosing decision must be documented in study record and re-evaluated at the next study visit.	All neurologic worsening should be documented as AEs and followed up until study completion or resolution of symptoms.	Discuss with the Alexion Medical Monitor.
Psychiatric assessment	Evidence of clinically significant acute psychiatric worsening which may include but not limited to suicidality, acute depression, or psychosis.		Investigator and Alexion Medical Monitor will evaluate the need for dose modification (interruption, increase or decrease) based on copper control parameters and relevant clinical data. Rationale for dosing decision must be documented in study record and re-evaluated at the next study visit.	Worsening psychiatric symptoms will be documented as adverse events in the eCRF and will be followed until completion of the study or resolution of symptoms.	Discuss with the Alexion Medical Monitor.

[a] For changes in safety monitoring, weekly repeat testing for laboratory parameters can be completed by a home healthcare nurse if a routine study visit is not scheduled during this time period.

[b] A maximum of 3 rechallenges will be allowed.

[c] For rechallenges, participants who were on 15 mg QOD should be rechallenged at the 15 mg QOD dose.

[d] The Investigator, in consultation with the Medical Monitor, may change dose and dose frequency in participants who require rechallenge.

Abbreviations: AEs = adverse event; ALT = alanine aminotransferase; eCRF = electronic case report form; QD = once daily; QOD = every other day; ULN = upper limit of normal.

6.7. Intervention After the End of the Study

Following completion of both inpatient periods of the study (ie, Day 40), participants will either:

- transition to therapy that was discontinued before enrollment, or
- transition to other standard of care therapy as directed by the treating physician, or
- at the discretion of the treating physician, consider and request continuation of ALXN1840 treatment permissible under local regulations for preapproval access.

All participants should return to the CRU for the EOS Visit on Day 54 (+/- 2 days).

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 Schedule of Activities (SoA, Section 1.3) 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 study 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.
- At the time of discontinuation from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See 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.
- The following only applies to sites in the US.
  - In the US only, it is permissible for study visits for individual participants to occur at more than 1 site. Some sites may perform screening procedures only and not any of the remaining study procedures. These sites will be known as "screening sites". The procedures performed at screening sites are defined in the Screening column (Study Days -42 to -9 and -21) of the SoA (Section 1.3). Following the completion of screening procedures at a screening site, eligible participants will be transferred to the CRU, where the remaining study procedures and visits will occur. Site-to-site transfer of the participant will be documented accordingly.

8.1. Efficacy Assessments

8.1.1. Copper and Molybdenum Balance Measurements

Copper and molybdenum 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 copper and molybdenum concentration of each sample will be determined by inductively coupled plasma mass spectrometry (ICP-MS). Copper and molybdenum 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.

8.1.1.1. Food and Fluid Collection for Copper and Molybdenum Concentrations

Samples of all meal and fluid batches will be collected and analyzed for measurement of copper and molybdenum 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 copper and molybdenum content.

Samples will be collected, stored and shipped as detailed in the Laboratory Manual. All sample handling procedures will be documented in detail in the Laboratory Manual. Copper and

molybdenum concentration of each food sample (ng/g) and each fluid sample (ng/mL) sample will be determined by ICP-MS.

8.1.1.2. Urine Collection for Measurement of Copper and Molybdenum content

Urine samples to measure copper and molybdenum content will be collected periodically 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 will be documented in detail as described in the Laboratory Manual. Copper and molybdenum concentration (ng/mL) of each 24-hour urine sample will be determined by ICP-MS.

8.1.1.3. Fecal Collection for Measurement of Copper and Molybdenum Content

Fecal samples to measure copper and molybdenum content will be collected periodically 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 will be documented in detail in the Laboratory Manual. Copper and molybdenum concentration (ng/g) of each stool sample will be determined by ICP-MS; each sample will be analyzed using a minimum of technical triplicates.

8.2. 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.

Pharmacokinetic 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 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 participant 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 triplicate will be performed 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 tests with values considered abnormal and clinically significant during participation in the study or 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

Participant's bowel movements and urination will be monitored by the clinical staff. The clinical staff will record in the CRF each time a fecal and urine sample is collected. All urine and feces must be collected from Day -4 through Day -1, Day 1 through Day 8, Day 25 through Day 39.

8.2.4.2. Intake Monitoring

To support accurate quantification of copper/molybdenum 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 copper/molybdenum 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

Suicidal ideation and behavioral changes will be recorded as adverse events and may, at the discretion of the Investigator, result in withdrawal of the participation from the study and urgent referral for psychiatric treatment.

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 and 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 for 3 months postpartum.
- 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 the 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 toward 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, Institutional Review Boards (IRBs)/ Independent Ethics Committees (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. The sample will not be used for genetic testing (see Section 8.7).

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/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 molybdenum and PUF-molybdenum as specified in the SoA (Table 1) via ICP-MS. Samples collected within ± 10% or 30 min, whichever is less, of the scheduled time will not be considered a protocol deviation.

- 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.
- Total molybdenum and PUF-molybdenum are surrogate measures of ALXN1840 and concentrations 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 8.1.1 for details of molybdenum measured in food, drinks, urine, and feces.

8.6. Pharmacodynamics

Plasma total and PUF-copper, ceruloplasmin, ceruloplasmin-bound copper, 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. Plasma samples will be used for ICP-MS measurement of total copper and PUF-copper, ceruloplasmin, ceruloplasmin-bound copper, and non-ceruloplasmin-bound copper measured via PUF-copper, and/or LBC, or assessed via NCC/$NCC_{corrected}$ methods at the time points indicated in the SoA (Table 1).

8.7. Genetics

Genetics will not be evaluated in this study.

8.8. Biomarkers

Please see Section 8.6 for details of total copper and PUF-copper, ceruloplasmin, ceruloplasmin-bound copper, and non-ceruloplasmin-bound copper as measured via PUF-copper, and/or LBC, or assessed via NCC/$NCC_{corrected}$ methods, and Section 8.1.1 for details of copper measured in food, drink, urine, and feces.

8.9. Immunogenicity Assessments

Not applicable.

8.10. 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

As this study is an exploratory study, no formal hypothesis testing is being conducted. Study results will be summarized using descriptive statistics.

9.2. Sample Size Determination

The sample size will be approximately 10 participants which will allow a general characterization of copper balance in response to ALXN1840.

9.3. Populations for Analyses

The population sets used for analysis are defined Table 8.

Table 8: Populations for Analysis

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 when participants are assigned a participant number.
Safety Analysis Set	All participants who receive at least 1 dose of ALXN1840 treatment.
Full Analysis Set	All participants who receive at least 1 dose of ALXN1840 treatment.
Per Protocol Set	All participants who received at least 1 dose of ALXN1840, had Baseline and all post Baseline values of copper intake (in food and drink) and copper output (in feces and urine), and were 100% compliant with study drug dosing. Participants with major protocol deviations that are likely to impact the primary endpoint analysis will be excluded from the Per Protocol (PP) Set. Major protocol deviations, and the PP Set, will be defined, documented, and agreed within Alexion prior to database lock.
Pharmacokinetic/Pharmacodynamic Analysis Set	All participants who have sufficient plasma samples to enable the calculation of PK parameters and provide PK/PD profiles.

Abbreviations: ICF = informed consent form; PD = pharmacodynamic; PK = pharmacokinetic.

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 visit where applicable and will be presented by cohort (treatment experienced/treatment naïve), and overall Descriptive statistics for continuous variables will minimally include the number of participants, mean, standard deviation, 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. Primary Analysis

The primary objective of this study is to demonstrate a net negative copper balance with daily repeat-dose ALXN1840 treatment (15 mg and 30 mg) in participants with WD.

The primary analysis will be performed using the Full Analysis Set. Average daily copper balance and molybdenum balance will be calculated over the following periods:

1. Day -4 through Day -1 representing predose baseline
2. Days 1 through 8 representing the ALXN1840 15 mg/day accumulation period
3. Days 25 through 28 representing the ALXN1840 15 mg/day steady-state period
4. Days 31 through 35, representing the ALXN1840 30 mg/day accumulation period
5. Days 36 through 39 representing the ALXN1840 30 mg/day steady-state period

As ALXN1840 is expected to increase copper excretion through fecal excretion, copper in stool will be critical for determining copper balance. Because stools can be irregular, assessment of copper and molybdenum balance will only include data up to the day of the final bowel movement. For example, for the period Day 1 through Day 8, if the final bowel movement occurs on Day 7, average daily copper balance for the Day 1 through Day 8 period will only include data from Day 1 through Day 7.

In the case of the 15 mg/day steady-state period (ie, Day 25 through Day 28), stool data collected on Days 29 - 30 samples may be used if needed to support assessments for the 15 mg/day dose. Use of these stool data (as needed) are consistent with an approximately 2-day gastrointestinal transit time.

In the case of stool irregularity, and to support assessment of copper output over time, bowel movement copper and molybdenum outputs may be averaged over the days between bowel movement (or start of study) to ensure an approximate value for each 24-hour period.

9.4.2. Secondary Analyses

Secondary analyses will be performed using the Full Analysis Set. The secondary continuous endpoints (including copper balance, molybdenum balance, and 24-hour urine excretion of copper and molybdenum) will be analyzed using the same methods described for the primary analysis.

9.4.3. Safety Analysis

Safety analyses will be performed using the Safety Analysis 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, hematology, coagulation, and urinalysis) will be summarized by treatment. Laboratory parameter values will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (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.

Electrocardiogram 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.

9.4.4. Pharmacokinetic, Pharmacodynamic, and Biomarker Analyses

For PK, PD, and biomarker endpoints, analyses will be performed using the PK/PD Analysis Set. The following plasma PK parameters will be calculated for total molybdenum and PUF molybdenum (as surrogate measures of ALXN1840 PK) using noncompartmental methods with Phoenix® WinNonlin® (Certara USA Inc., Princeton, New Jersey) Version 8.0 or higher or SAS Version 9.3 or higher (SAS Institute Inc., Cary, North Carolina), as applicable. Calculations will be based on the actual sampling times recorded during the study.

- Time delay between the time of dosing and time of appearance of molybdenum concentration (T_{lag}) in plasma
- Maximum observed concentration (C_{max})
- Time to maximum concentration (t_{max})
- Trough (predose) concentration observed at the start of the dosing interval (C_{trough})
- Area under the plasma concentration versus time curve (AUC) from time 0 to the last quantifiable concentration (AUC_t)
- AUC over the dosing interval (AUC_{tau})
- Accumulation ratio (AR) calculated as:

  For 15 mg/day:

  - $C_{max,Day25}/C_{max,Day1}$
  - $C_{trough,Day26}/C_{trough,Day2}$
  - $AUC_{tau,Day25}/AUC_{tau,Day1}$

  For 30 mg/day:

  - $C_{max,Day39}/C_{max,Day29,adjusted}$
  - $C_{trough,Day40}/C_{trough,Day30,adjusted}$
  - $AUC_{tau,Day39}/AUC_{tau,Day29,adjusted}$

  Note: total molybdenum and PUF molybdenum concentration-time profiles on Day 28 after the last 15 mg ALXN1840 dose will be extrapolated to Day 29 (0-24 hr) and subtracted from the observed Day 29 concentration-time profiles after the first 30 mg

ALXN1840 dose for the estimation of the $C_{max,Day29,adjusted}$, $C_{trough,Day30,adjusted}$, and $AUC_{tau,Day29,adjusted}$.

- Apparent terminal phase elimination rate constant (λ_z)
- Terminal elimination half-life ($t_{½}$)
- Apparent total body clearance (CL/F) of ALXN1840 from plasma
- Apparent volume of distribution (V_d/F).

Additional plasma PK parameters may be calculated if deemed appropriate.

Plasma concentrations of total molybdenum and PUF molybdenum vs. time data will be presented in a data listing by participant. Plasma concentration data will be summarized separately by analyte and time point for each treatment by day using the following descriptive statistics: number of participants, arithmetic mean, geometric mean (GM), SD, coefficient of variation (CV), GMCV, median, minimum, and maximum. Mean plasma concentration versus scheduled time profiles will be presented in figures on both linear and semilogarithmic scales. Individual plasma concentration versus actual time profiles will be presented similarly.

Pharmacokinetic parameters derived from plasma concentrations of total molybdenum and PUF molybdenum will be presented in data listings and summarized separately using the following descriptive statistics: number of participants, arithmetic mean, GM, SD, arithmetic CV, GMCV, median, minimum, and maximum. Geometric mean and geometric CV will be presented for C_{max} and AUCs only.

For PD (total and PUF copper and LBC) and biomarker endpoints (ceruloplasmin, ceruloplasmin-bound copper), 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

Marketing Authorisation Application(s) may be submitted before all patients complete the Treatment Periods; therefore, interim analyses of safety and efficacy data may be performed to support these submissions. These analyses will be descriptive only; they will not include formal hypothesis testing and will not be used to adapt the study. Full details will be provided in the SAP.

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 (SRC)

A SRC, composed of a minimum of the Investigator, Alexion Medical Monitor, and Alexion Safety Physician, will meet at the end of 15 mg/day dosing to confirm proceeding to 30 mg/day and as necessary based on any emerging safety concerns as described in Section 6.6.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. 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 International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol substantial 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 substantial 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 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, Directive 2001/20/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and Subinvestigators 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) informed consent 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/ICFs.
- Participants must be reconsented to the most current version of the ICF/ICFs 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.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorized designee will explain to each participant or their legally authorized representative the objectives of the exploratory research. If sharing exploratory research results with the Investigator is not planned, the ICF should mention it. Participants or their legally authorized representative will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

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, appropriate IRB/IEC members, and 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

The full terms regarding publication of the results of this study are outlined in the applicable Clinical Study Agreement.

10.2. Clinical Laboratory Tests

- The tests detailed in Table 9 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Pregnancy testing: 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 IRB/IEC 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 9: Protocol-Required Safety Laboratory Assessments

Clinical Chemistry	
Blood urea nitrogen (BUN)	Alanine aminotransferase
Potassium	Alkaline phosphatase
Creatinine	Urea
Creatine kinase	Magnesium
Sodium	Iron
Chloride	Zinc
Potassium	Total and direct bilirubin
Glucose	Total protein
Total carbon dioxide	Albumin
Aspartate aminotransferase	Calcium
Gamma glutamyltransferase	Phosphate
Hematology	
Hematocrit	Red blood cell count[a]
Platelets	Mean corpuscular volume
White blood cell count	Mean cell hemoglobin concentration
Mean cell hemoglobin	Lymphocytes
Neutrophils	Eosinophils
Monocytes	Prothrombin time
Basophils	International normalized ratio
Hemoglobin	Partial thromboplastin time
Urinalysis	
Bilirubin	Blood
Glucose	Ketones
Leukocytes	Microscopy
Nitrite	pH
Protein	Specific gravity
Urobilinogen	Red blood cells
Bacteria	
Other Tests	
HIV, hepatitis B, and hepatitis C screen	Total copper and total molybdenum
Ceruloplasmin (serum and plasma)	PUF-molybdenum and PUF-copper
Ceruloplasmin-bound copper	Labile bound copper
24-hour urine copper and molybdenum	Serum and urine pregnancy test
Urine drug screen	

[a] Including nucleated red blood cells.

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. All events of alanine aminotransferase (ALT) ≥ 3 × upper limit of normal (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: HIV= human immunodeficiency virus; PUF = plasma ultrafiltrate; SAE = serious adverse event.

Investigators must document their review of each laboratory safety report.

10.3. 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 (ie, not related to progression of underlying disease).
- 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.
- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- 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.

A suspected unexpected serious adverse reaction (SUSAR) is defined as:

A serious event that is not listed in the Reference Safety Information of the Investigator's Brochure and that the Investigator or Sponsor identifies as related to investigational product or procedure. United States Title 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Alexion has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances. Suspected unexpected serious adverse reactions will be reported to the national competent authority and IRBs/IECs where applicable.

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.

Recording of AE and/or SAE

- 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 participant 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 Severity

The Investigator will make an assessment of severity for each AE and SAE reported during the study and assign it to one of the following categories from National Cancer Institute CTCAE v5.0, 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.

Assessment of Causality

- 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 Alexion via Paper Safety Reporting Form

- All SAEs will be recorded and reported to Alexion or designee immediately and within 24 hours awareness.
- All 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: [redacted] or Fax: [redacted]
- 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. Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Definitions and Contraceptive Guidance

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 copper-containing IUD are excluded from study
• Intrauterine hormone-releasing system (IUS)[c]
• Bilateral tubal occlusion
• Vasectomized partner o Vasectomy 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 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.
Female participants of non-childbearing potential are exempt from contraception requirements. Non-childbearing potential for female participants 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 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

Note: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea 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).

[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.

10.4.2. Collection of Pregnancy Information

If a female participant or a male participant's female spouse/partner becomes pregnant after the first dose of ALXN1840 through 3 months after the end of systemic exposure of the study intervention, 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.

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. COVID-19 Vaccine Risk Assessment

To date, following a review of the limited available COVID-19 vaccine data (eg, Pfizer/BioNTech, Moderna, AstraZeneca), it is unlikely that the immune response to a COVID-19 vaccine will be diminished with concomitant ALXN1840 administration, based on ALXN1840's mechanism of action. There is currently no information available evaluating the safety or efficacy of COVID-19 vaccines in participants treated with ALXN1840.

Local and national guidelines should be consulted for recommendations related to COVID-19 vaccination. Alexion suggests that participants complete vaccination series before study participation, if feasible. The decision to allow COVID-19 vaccinated participants to continue in the study should be made by the investigator on a participant-by-participant basis.

The potential risks identified and mitigation measures put in place in light of the COVID-19 vaccination rollout are provided in Table 10.

Table 10: Potential Risks and Mitigation Measures due to COVID-19 Vaccine

Risks category	Summary of Data/ Rationale for Risk	Mitigation Strategy
Potential risks		
Data quality and integrity	Missing data due to appointments for COVID-19 vaccination or side effects of COVID-19 vaccine may impact study visit schedules and increase missed visits and/or participant study discontinuations, inadvertently resulting in missing data (eg, for protocol-specified procedures).	It will be important to capture specific information in the eCRF that explains the reason the data is missing (eg, missed study visits due to appointments for COVID-19 vaccination or side effects of COVID-19 vaccine).

Abbreviation: COVID-19 = coronavirus disease 2019.

10.6. Abbreviations

A list of abbreviations and terms used in this study protocol is provided in Table 11.

Table 11: 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
BSA	body surface area
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CKD	chronic kidney disease
CL/F	apparent total body clearance
C_{max}	maximum observed concentration
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	Coronavirus disease
CRF	case report form
CRU	clinical research unit
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
CYP2C9/2B6	cytochromes 2C9 and 2B6
EDC	electronic data capture
EOS	End of Study
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GDS	Global Drug Safety
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
ICP-MS	inductively coupled plasma mass spectrometry
IEC	Independent Ethics Committee
IRB	Institutional Review Board

IUD	intrauterine device
IUS	intrauterine hormone-releasing system
LBC	labile bound copper
LEC	Long-Evans Cinnamon
MELD	model for end-stage liver disease
MT	metallothionein
NCC	non-ceruloplasmin-bound copper
$NCC_{corrected}$	corrected NCC
NHS	National Health Service
PD	pharmacodynamic
PK	pharmacokinetic(s)
PUF	plasma ultrafiltrate
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	serious adverse event
SAP	Statistical Analysis Plan
SoA	Schedule of Activities
SRC	Safety Review Committee
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
$t_{½}$	terminal elimination half-life
T_{lag}	time delay between the time of dosing and time of appearance of molybdenum concentration
t_{max}	time to maximum concentration
TPC	tripartite complex
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

10.7. 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**
Original Protocol	12 May 2020
Amendment 1	18 Aug 2020
Amendment 2	19 Mar 2021
Amendment 3	31 Aug 2021
Amendment 3.1 (US)	18 Mar 2022

Amendment 1 (18 Aug 2020)

This amendment was 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 update procedures outlined in the Schedule of Activities, remove contradictory text on the reporting of serious adverse events, and add details of an interim analysis. Additional, minor changes are included in the table below.

Changes to the Protocol

Section # and Name	Description of Change	Brief Rationale and/or Clarifications
Section 1.3, Schedule of Activities, Section 4.1, Overall Design, Section 6.4, Study Intervention Compliance	Procedures updated include Wilson disease history and treatment; study intervention compliance during outpatient period captured with study dosing diary; light exercise.	Data collected for analysis of patient population and study intervention compliance, and to compare endpoints with other ALXN1840 studies.
Section 2, Introduction Section 2.2, Background	Removal of text relating to primary biliary cholangitis.	To reflect that development of ALXN1840 is for Wilson disease.
Section 6.7, Intervention After the End of Study	Text updated regarding access to study intervention after the end of study.	To clarify the option for study intervention access at the end of study.
Section 9.3, Populations for Analysis	Definition of the Per Protocol set was updated.	To align the definition with the Statistical Analysis Plan.
Section 9.5, Interim Analyses	Text pertaining to an interim analysis was added.	Interim data may support Marketing Authorisation Application(s).
Section 10.3.2, Definition of SAE	Definition of SUSAR was added.	To align with current Alexion approved language
Section 10.3.4, Reporting of SAEs	Removal of contradictory text on SAE reporting via an electronic data collection tool.	SAE reporting will be via a paper safety reporting form.
All	Minor editorial updates and corrections	For clarification, and to ensure accuracy and consistency throughout the protocol

Amendment 2 (19 Mar 2021)

This amendment was 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 revise the exclusion criterion for a urine drug screen. Changes implemented via Administrative Letter 1 and Administrative Letter 2, as well as COVID vaccination guidance, have also been incorporated.

Changes to the Protocol

Section # and Name	Description of Change	Brief Rationale and/or Clarifications
Section 1.1, Synopsis; Section 9.2, Sample Size Determination	The number of participants changed from "up to 10" to "approximately 10".	Clarification of sample size.
Section 1.1, Synopsis; Section 1.2, Schema; Section 1.3, Schedule of Activities; Section 4.1, Overall Design; Section 6.4, Study Intervention Compliance	SMS text messaging will replace the dosing diary as the method of confirming treatment compliance during the outpatient period.	Site processes does not allow use of paper diary.
Section 2.3.1.1, Coronavirus Disease 2019; Section 10.5, COVID-19 Vaccine Risk Assessment	COVID-19 vaccination guidance added.	To provide guidance on potential risks identified and mitigation measures put in place regarding the COVID-19 vaccination rollout.
Section 5.1, Inclusion criteria	Inclusion criterion for confirmation of diagnosis of WD changed to Leipzig score ≥ 4 and expanded to include historical test results.	To clarify the process for confirming the score for patients who were diagnosed prior to the establishment of the 2012 European Association for the Study of Liver WD Clinical Practice Guidelines.
Section 5.2, Exclusion criteria	Exclusion criterion for drug screen revised to state that cannabinoids will not be tested.	• To align with other ALXN1840 Phase 2 and Phase 3 study protocols which did not reference this criterion • Recreational use of cannabis use is being decriminalized in many countries • Medicinal use of cannabis would potentially relieve symptoms of WD • Recent use of cannabis is not expected to alter copper or molybdenum balance
Section 5.2, Exclusion criteria	Exclusion criterion 11 revised to "The use of an experimental or unapproved/unlicensed therapy at the same time or within 90 days or 5 half-lives, whichever is longer, prior to the Screening Visit."	For consistency across all ALXN1840 protocols.
Section 10.1.1, Regulatory and Ethical Considerations	Added: "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."	To align with UK legislation
All sections	Minor editorial updates and corrections	For clarification, and to ensure accuracy and consistency throughout the protocol

Amendment 3 (31 Aug 2021)

This amendment was 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, the US Food and Drug Administration's (FDA) regulation at 21 CFR part 312.30(b), and any applicable local regulations.

Overall Rationale for the Amendment

The main reason for preparation of this amendment was to update the washout period for zinc. Additional changes are listed below.

Changes to the Protocol

Section # and Name	Description of Change	Brief Rationale and/or Clarifications
Section 1.3, Schedule of Activities; Section 4.2, Scientific Rationale for Study Design; Section 5.2, Exclusion Criteria	Previous treatment with zinc changed to 21 days prior to Day 1.	To align with feasibility of study participation.
Section 4.1, Overall Design, Table 4	Deleted the Adaptive Protocol Feature 1 that allowed enrollment of participants who had completed other ALXN1840 studies.	To remove contradiction of the exclusion for previous treatment with ALXN1840.
Section 6.7 Intervention after the End of Study	Updated the options for intervention after study completion to include both therapy that was discontinued before enrollment and other standard of care therapy.	To clarify treatment options at end of study.

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