A Phase 1, Randomized, 2-Period, 2-Sequence, Crossover with Parallel-group Extension, Open-label Study to Compare the Relative Bioavailability of 2 Oral Formulations of ALXN1840 in Healthy Adult Participants

Unique Protocol ID:	ALXN1840-HV-109
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TITLE PAGE

Protocol Title:

A Phase 1, randomized, 2-period, 2-sequence, crossover with parallel-group extension, open label- study to compare the relative bioavailability of 2 oral formulations of ALXN1840 in healthy adult participants

Protocol Number: ALXN1840-HV-109

Amendment Number: 2

Compound: ALXN1840 (bis-choline tetrathiomolybdate)

Study Phase: 1

Short Title: Phase 1, bioavailability study of 2 oral formulations of ALXN1840

Sponsor Name: Alexion Pharmaceuticals, Inc.

Legal Registered Address:

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Boston, MA 02210
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Regulatory Agency Identifier Number(s): IND 119006

Approval:

Original Protocol	**10 Jul 2020**
Amendment 1	**16 Sep 2020**
Amendment 2	**18 Dec 2020**

Sponsor Signatory:

PPD

21-Dec-2020 | 11:49:18 EST

Date

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

INVESTIGATOR'S AGREEMENT

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

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Original Protocol	10 Jul 2020
Amendment 1	16 Sep 2020
Amendment 2	18 Dec 2020

Amendment 2 (18 Dec 2020)

Overall Rationale for the Amendment

This amendment has been prepared to remove mention of biomarkers from the exploratory endpoint, and non-ceruloplasmin-bound copper (NCC), $NCC_{corrected}$, labile bound copper (LBC), ceruloplasmin, and ceruloplasmin-bound copper from the exploratory endpoints because, although these samples will be collected, they will not be analyzed immediately but retained for potential future analysis. Minor edits for consistency and accuracy have also been made.

Details of the changes are presented in the table below.

Changes to the Protocol

Section # and Name	Description of Change	Brief Rationale and/or Clarifications
1.1 Synopsis 3 Objectives, Table 4	Removal of biomarkers from the exploratory objective and corresponding removal of NCC, $NCC_{corrected}$, LBC, ceruloplasmin, and ceruloplasmin-bound copper from the exploratory endpoints	It is not currently planned to analyze these samples at time of study completion. The samples will be retained and may be used for diagnostic biomarker development and research to better understand how ALXN1840 exerts its effects in the body.
1.2 Schema	Removal of crossover lines between Dosing Periods 1 and 2	The lines have been removed to clarify that each subject will receive Treatment A and Treatment B sequentially. The order of Treatment A and Treatment B will be randomized.
1.3 Schedule of Activities, Table 1	Removal of requirement for PK/PD/biomarker samples during Screening	PK/PD/biomarker samples are not required during Screening.
1.3 Schedule of Activities, Table 1 8.2.1 Physical Examinations	Removal of requirement to assess height, weight, and BMI at EOS/EOT; these assessments will only be performed at Screening	Height, weight, and BMI will only be assessed at Screening.
1.3 Schedule of Activities, Table 1 10.2, Clinical Laboratory Tests, Table 6	Clarification added that a sample for HbA1c is only required during the Screening Period.	A sample for HbA1c is only required during the Screening Period, and not at every time point where samples for hematology, chemistry, urinalysis, and coagulation are required.
8.6 Pharmacodynamics 8.8 Biomarkers 9.4.3 Pharmacokinetics/ Pharmacodynamics Analysis	Text amended regarding the analysis of LBC, NCC, $NCC_{corrected}$, ceruloplasmin, and ceruloplasmin-bound copper	As mentioned above, it is not currently planned to analyze these samples at time of study completion.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 1, randomized, 2-period, 2-sequence, crossover with parallel-group extension, open -label study to compare the relative bioavailability of 2 oral formulations of ALXN1840 in healthy adult participants

Short Title: Phase 1, bioavailability study of 2 oral formulations of ALXN1840

Rationale:

The purpose of this study is to assess relative bioavailability of the 1.25 mg enteric-coated (EC) mini-tablet formulation of ALXN1840 compared with the 15 mg EC tablet that is currently used in clinical studies and to assess dose proportionality between 2.5 mg (2 × 1.25 mg), 5 mg (4 × 1.25 mg), 10 mg (8 × 1.25 mg), 15 mg (12 × 1.25 mg), and 30 mg (24 × 1.25 mg) EC mini-tablet doses.

The 1.25 mg EC mini-tablet is in development for treating patients with Wilson disease (WD) who may require a lower dose and/or who may have difficulty swallowing the 15 mg EC tablet (eg, pediatric patients with WD). Several of the 1.25 mg EC mini-tablets could be administered together with acidic soft foods to protect the enteric coating through to the site of absorption in the gastrointestinal tract. To support this alternative administration method, further investigation of the formulation stability of the 1.25 mg EC mini-tablets in acidic soft foods is also planned.

Objectives and Endpoints

Objective	Endpoints/Estimands
Primary	
To assess the relative bioavailability of equal doses of ALXN1840 administered as 1.25 mg EC mini-tablets versus a single 15 mg EC tablet	PK parameters for plasma total Mo and PUF Mo (C_{max}, AUC_t, and AUC_∞)
Secondary	
To assess dose-proportionality between 2.5 mg (2 × 1.25 mg), 5 mg (4 × 1.25 mg), 10 mg (8 × 1.25 mg), 15 mg (12 × 1.25 mg), and 30 mg (24 × 1.25 mg) EC mini-tablet doses	Dose-normalized PK parameters for plasma total Mo and PUF Mo (C_{max_n}, AUC_{t_n}, and AUC_{∞_n})
Safety	
To assess the overall safety and tolerability of ALXN1840, administered as 1.25 mg EC mini-tablets and as a single 15 mg EC tablet	Incidence of TEAEs and TESAEs, physical examination, vital signs measurements, clinical laboratory, and 12-lead ECG results
Exploratory	
To explore relationships between total Mo and PUF Mo clearance and body size — body weight (kg) and BMI (kg/m^2)	CL/F, body weight, and BMI
To explore PD of ALXN1840 either as a single 15 mg EC tablet or EC mini-tablets of 1.25 mg at different total dose strengths	Absolute and percent changes from pre-dose baseline of plasma Cu concentrations: total Cu and PUF Cu

Abbreviations: AUC_∞ = area under the plasma concentration versus time curve from time 0 to infinity; AUC_t = area under the plasma concentration versus time curve from time 0 to the last quantifiable concentration; BMI = body mass index; CL/F = apparent oral clearance; C_{max} = maximum observed concentration; Cu = copper; EC = enteric-coated; ECG = electrocardiogram; Mo = molybdenum; n = dose-normalized; PD = pharmacodynamic(s); PK = pharmacokinetic(s); PUF = plasma ultrafiltrate; TEAE = treatment-emergent adverse events; TESAE = treatment-emergent serious adverse event.

Overall Design

This is a 2-period, 2-sequence crossover study with parallel group extension designed to assess the relative bioavailability of equal doses of ALXN1840 administered as 1.25 mg EC mini-tablets versus a single 15 mg EC tablet, and to assess dose-proportionality between 2.5 mg (2 × 1.25 mg), 5 mg (4 × 1.25 mg), 10 mg (8 × 1.25 mg), 15 mg (12 × 1.25 mg), and 30 mg (24 × 1.25 mg) EC mini-tablet doses in the Dose-Proportionality Extension Period. The safety and tolerability of the 2 formulations of ALXN1840 in healthy participants will also be assessed. ALXN1840 pharmacokinetics (PK) in plasma as measured via total molybdenum (Mo) and plasma ultrafiltrate (PUF) Mo will be determined.

Disclosure Statement: This is a randomized, 2-period, 2-sequence, open-label crossover study with parallel group extension. There are 2 treatment arms in the first and second periods, and 4 treatment arms in the Dose-Proportionality Extension period.

Number of Participants:

Approximately 48 male or female participants will be enrolled and randomly assigned to 1 of 2 treatment sequences (24 participants in each sequence) to ensure a minimum of 40 participants complete the study.

Note: "Enrolled" means a participant's agreement to participate in a clinical study following completion of the informed consent process and satisfying inclusion/exclusion criteria. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled, unless otherwise specified by the protocol.

Intervention Groups and Duration:

The study has a Screening Period (Days -28 to -2), the Two-way Crossover Period, consisting of 2 dosing periods (Day 1 to Day 11 each), and a Dose-Proportionality Extension Period. After completing the Screening Period, enrolled participants will be admitted to the clinical research unit (CRU) on Day -1 for dosing on Day 1 in Dosing Period 1. If discharged after Dosing Period 1, participants will be readmitted to the CRU for Dosing Period 2 following a minimum washout of 14 days after the previous dose, and again for the Dose-Proportionality Extension Period after a minimum washout of 14 days. The end of study (EOS) visit will take place 14 days (± 2 days) after the dose of ALXN1840 in the Dose-Proportionality Extension Period.

Two-way Crossover Period

The Two-way Crossover Period is a randomized, open-label, 2-way (2-period, 2-sequence), crossover design to assess the relative bioavailability of 12 × 1.25 mg EC mini-tablets compared with the 15 mg EC tablet currently used in clinical studies. Participants will be randomized to one of the two treatments sequences. Randomized treatment assignment will be based on Baseline body mass index (BMI). Two strata for BMI (< 25, 25 to < 32 kg/m^2) will be used:

- Treatment A: ALXN1840 12 × 1.25 mg EC mini-tablets
- Treatment B: ALXN1840 single 15 mg EC tablet (reference tablet, currently being tested in the Phase 3 Study WTX101-301)

Sequence Number	Treatment Sequence		Total
	Period 1	Period 2	
1	A	B	24
2	B	A	24
Total			48

Blood samples for PK analysis of total and PUF Mo (as surrogate measures of ALXN1840 PK) and pharmacodynamic (PD)/biomarkers will be collected in each dosing period on Day 1 at pre-dose, and postdose at 1, 2, 3, 4, 5, 6, 8, 12 and 24 hours (Day 2) and then at 24 hour intervals on Days 3, 4, 5, 6, 7, 8, 9, 10, and 11.

The 336-hour sample for Dosing Period 1 will be collected predose in Dosing Period 2. Participants may be discharged on Day 11 of each dosing period after completion of all procedures and review of all safety data. The end of Dosing Period 2 will occur on Day 15 ± 2 of Dosing Period 2, with the collection of the 336-hour PK sample for Dosing Period 2.

Dose-Proportionality Extension Period

The Dose-Proportionality Extension Period is a re-randomized, open-label, parallel group design to assess the dose-proportionality between 2.5 mg (2 × 1.25 mg), 5 mg (4 × 1.25 mg), 10 mg (8 × 1.25 mg), and 30 mg (24 × 1.25 mg) EC mini-tablet doses. The 15 mg (12 × 1.25 mg) dose will not be repeated during the Dose-Proportionality Extension Period.

The Dose-Proportionality Extension Period will be conducted following completion of the Two-way Crossover Period of the study and after an at least 14-day washout period. Participants will be re-randomized as follows:

- Treatment C (N=10-12): ALXN1840 2.5 mg (2 × 1.25 mg EC mini-tablets)
- Treatment D (N=10-12): ALXN1840 5 mg (4 × 1.25 mg EC mini-tablets)
- Treatment E (N=10-12): ALXN1840 10 mg (8 × 1.25 mg EC mini-tablets)
- Treatment F (N=10-12): ALXN1840 30 mg (24 × 1.25 mg EC mini-tablets)

The dose-proportionality evaluation will include data obtained from Treatment A of the Two-way Crossover Period (12 × 1.25 mg EC mini-tablets) to represent a dose of 15 mg.

Re-randomized treatment assignment will be based on Baseline body mass index (BMI). Two strata for Baseline BMI (< 25, 25 to < 32 kg/m^2)will be used. Block randomization will be used to equally randomly assign participants to each treatment.

Participants may be discharged on Day 11 of the Dose-Proportionality Extension Period after completion of all procedures and review of all safety data.

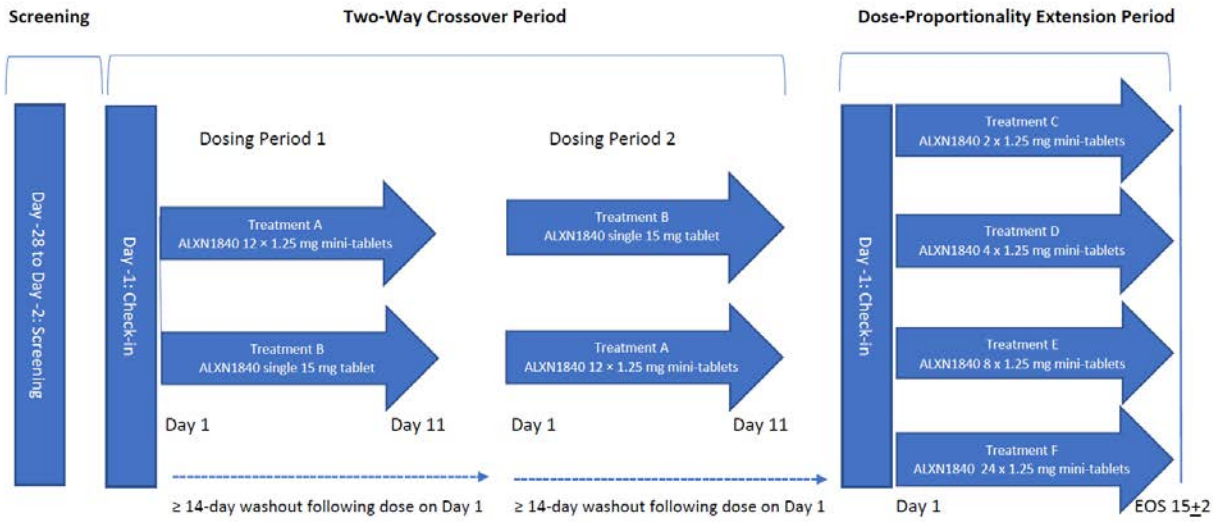
Participants may be asked or required to stay in the CRU during the Two-way Crossover Period, and/or at the end of the Dose-Proportionality Extension Period before the end of study (EOS) visit, for their own safety, and also to maintain the integrity of the conduct of the study.

Data Monitoring Committee: There will not be a Data Monitoring Committee, but provision is included for an ad hoc Safety Review Committee, if needed.

1.2. Schema

The study design is presented in Figure 1.

Figure 1: Study Design Schematic



Two-way Crossover Period
Participants will be admitted to the CRU on Day -1 for check-in procedures. Eligible participants will be randomized on Day 1 immediately prior to dosing in Dosing Period 1.
Participants will receive treatment (A [12 × 1.25 mg EC mini-tablets] or B [single 15 mg EC tablet]) based on randomization on Day 1 of each dosing period.
There will be at least 14 days washout following the dose in Dosing Period 1 before the participant is readmitted to the CRU for Dosing Period 2 (if discharged after Dosing Period 1) and also at least 14 days washout following the dose in Dosing Period 2 before the participant is readmitted to the CRU for the Dose-Proportionality Extension Period (again, if discharged after Dosing Period 2).

Dose-Proportionality Extension Period
Participants will be block randomized by BMI and receive one of the Treatments C to F (C = 2.5 mg, D = 5 mg, E = 10 mg, F = 30 mg) in a parallel-group design in the Dose-Proportionality Extension Period. The PK/PD/biomarker samples will be collected at the same time points as stated above for Dosing Period 2 of the Two-way Crossover Period.
The EOS visit will take place 14 days (± 2 days) after the dose of ALXN1840 in the Dose-Proportionality Extension Period.

Discharge from the CRU
It is planned that participants will be discharged from the CRU on Day 11 of each Dosing Period and on Day 11 of the Dose-Proportionality Extension Period. However, participants may be asked or required to stay in the CRU during the Two-way Crossover Period, and/or at the end of the Dose-Proportionality Extension Period before the EOS visit, for their own safety, and also to maintain the integrity of the conduct of the study.

Abbreviations: BMI = body mass index; CRU = clinical research unit; EC = enteric-coated; EOS = End of Study; PD = pharmacodynamics; PK = pharmacokinetics.

1.3. Schedule of Activities

The Schedule of Activities (SoA) is presented in Table 1. Detailed timing of assessments on Day 1 of each Dosing Period and on Day 1 of the Dose-Proportionality Extension Period is presented in Table 2.

Table 1: Schedule of Activities

	Screening[a]	Each Dosing Period of the Two-way Crossover Period[b]												Dose-Proportionality Extension Period												EOS or ET[c]
Dosing Period: Days/ Hours	-28 to -2	-1[d]	1/ 0	2/ 24	3/ 48	4/ 72	5/ 96	6/ 120	7/ 144	8/ 168	9/ 192	10/ 216	11/ 240	-1	1/ 0	2/ 24	3/ 48	4/ 72	5/ 96	6/ 120	7/ 144	8/ 168	9/ 192	10/ 216	11/ 240	15 ± 2/ 336
Informed consent	x																									
Admit to unit		x												x[b]												
Discharge from unit[d]													x												x	
Inclusion/exclusion criteria[e]	x	x												x												
Medical history	x																									
Randomization			x[f]																							
Re-randomization															x[f]											
Physical examination[g]	x	x												x												x
Height, weight, and BMI	x																									
12-Lead ECG[h]	x		x[i]												x[i]											
Vital signs (heart rate, BP, RR & T)[j]	x		x[i]	x			x						x		x	x			x						x	x
Hematology, chemistry, urinalysis, and coagulation	x[k]		x	x			x					x[k]			x	x			x					x[k]		x
Serum ceruloplasmin and copper	x																									
Pregnancy test (females only)[l]	x	x												x												x
FSH (postmenopausal females only)	x																									
Alcohol breath test and urine drug screen	x	x												x												
HIV antibody/hepatitis B and C screen	x																									
AE monitoring	◄	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	►
Concomitant medications	◄	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	►
ALXN1840 administration[m]			x												x											
Plasma PK/PD biomarker samples[n]			x[i]	x	x	x	x	x	x	x	x	x	x		x[i]	x	x	x	x	x	x	x	x	x	x	x	x

[a] Within 28 days prior to Day 1 of the first dose of ALXN1840 in Dosing Period 1. Note that Screening only occurs once.

[b] After completion of Dosing Period 1, if discharged after Dosing Period 1, participants will be readmitted to the CRU for Dosing Period 2 following a minimum of 14 days post dose. The assessments listed will be repeated in Dosing Period 2. After completion of Dosing Period 2, if discharged after Dosing Period 2, participants will be readmitted to the CRU for the Dose-Proportionality Extension Period, again following a minimum of 14 days post dose.

[c] Participants will return to the CRU 14 days (± 2 days) following the final dose of ALXN1840 in the Dose-Proportionality Extension Period for an EOS evaluation. In the event of ET, the procedures listed at the EOS are performed prior to participant discharge.

[d] Participants may be asked or required to stay in the CRU during the Two-way Crossover Period, and/or at the end of the Dose-Proportionality Extension Period before the EOS Visit, for their own safety, and also to maintain the integrity of the conduct of the study.

[e] Full eligibility criteria will be assessed only for Dosing Period 1 (ie, on Day -1). On the first day of Dosing Period 2, the Investigator will confirm the participant is able to continue in the study.

[f] Randomization is to occur after the participant has met all inclusion and no exclusion criteria on Day 1 in Dosing Period 1 with treatment assignment based on Baseline BMI. Re-randomization of patients will occur on Day 1 of the Dose-Proportionality Extension Period, with treatment assignment again based on Baseline BMI.

[g] A full physical examination will be performed at Screening and on Day -1 of the 2 dosing periods. A symptom-driven physical examination of relevant body systems may be performed at other times, at the Investigator's discretion.

[h] 12-lead ECGs in triplicate will be taken 0.5 hours pre-dose and at 6 hours post-dose on Day 1 of the first dosing period and Day 1 of the Dose-Proportionality Extension Period (see Table 2). 12-Lead ECGs in triplicate will be conducted before PK/PD/biomarker blood sampling if these 2 events occur at the same time. 12-lead ECGs should be measured after a minimum of 5 minutes in supine position.

[i] See Table 2 for details.

[j] At Screening, supine blood pressures will be performed to exclude volunteers with orthostatic hypotension. Supine blood pressure should be taken after a minimum of 5 minutes in supine position. Supine blood pressure ≤ 90/60 mmHg or > 140/90 mmHg at Screening; systolic or diastolic components outside of range should result in exclusion. If vital sign results are abnormal, 2 additional readings will be taken. The mean of the 3 replicates will be recorded in the case report form and used to determine inclusion.

[k] A sample for HbA1c is only required during the Screening Period, and not at every time point where samples for hematology, chemistry, urinalysis, and coagulation are required. Samples for urinalysis and coagulation will not be obtained on Day 10 of each Dosing Period.

[l] A serum pregnancy test will be performed at Screening and urine pregnancy tests will be performed at subsequent visits. A serum pregnancy test is not required if the participant is confirmed to be postmenopausal.

[m] ALXN1840 dosing will occur with the participant after an overnight fast of at least 10 hours.

[n] Blood samples for the measurement of plasma total Mo and PUF Mo (PK) and total Cu, PUF Cu, LBC (PD), ceruloplasmin, and ceruloplasmin-bound Cu (biomarkers). In the Two-way Crossover Period, the 336-hour sample for Dosing Period 1 will be collected pre-dose in Dosing Period 2. Upon study completion, LBC, ceruloplasmin, and ceruloplasmin-bound Cu samples will be retained and potentially analyzed in the future.

Abbreviations: AE = adverse event; BMI = body mass index; BP = blood pressure; CRU = clinical research unit; Cu = copper; ECG = electrocardiogram; EOS/ET = End of Study or Early Termination; FSH = follicle stimulating hormone; HbA1c = glycated hemoglobin; LBC = labile bound copper; Mo = molybdenum; PD = pharmacodynamics; PK = pharmacokinetics; PUF = plasma ultrafiltrate; RR = respiration rate; T = temperature.

Table 2: Detailed Timing of Assessments on Day 1 of Each Dosing Period and on Day 1 of the Dose-Proportionality Extension Period

Time point (h)	Pre-dose -0.5	0[a]	1	2	3	4	5	6	8	12
ALXN1840 (total Mo and PUF Mo) PK	X		X	X	X	X	X	X	X	X
Plasma total and PUF Cu and LBC (PD); ceruloplasmin, and ceruloplasmin-bound Cu (biomarkers)[b]	X		X	X	X	X	X	X	X	X
ECG (triplicate)[c]	X							X[d]		
Vital signs	X							X		X

[a] Hour 0 corresponds to the time of ALXN1840 administration. Unless stated otherwise, times listed are in relation to ALXN1840 dosing.

[b] LBC, ceruloplasmin, and ceruloplasmin-bound Cu samples will be retained and potentially analyzed in the future.

[c] 12-lead ECGs in triplicate will be conducted before PK/PD/biomarker blood sampling if these 2 events occur at the same time. Note that ECGs will only be conducted on Day 1 of the first dosing period of the Two-way Crossover Period and on Day 1 of the Dose-Proportionality Extension Period.

[d] 12-lead ECGs in triplicate at 6 hours post-dose.

Abbreviations: Cu = copper; ECG = electrocardiogram; LBC = labile bound copper; Mo = molybdenum; PD = pharmacodynamic(s); PK = pharmacokinetic(s); PUF = plasma ultrafiltrate.

2. INTRODUCTION

ALXN1840 (bis-choline tetrathiomolybdate; formerly known as WTX101) is a novel, copper (Cu)-protein binding agent in development for the treatment of Wilson disease (WD). ALXN1840 directly targets and removes Cu from intracellular Cu stores, rapidly forms stable Cu-protein complexes, and promotes biliary excretion of Cu to reduce Cu overload.

2.1. Study Rationale

The purpose of this study is to assess relative bioavailability of the 1.25 mg enteric-coated (EC) mini-tablet formulation of ALXN1840 compared with the 15 mg EC tablet that is currently used in clinical studies and to assess dose proportionality between 2.5 mg (2 × 1.25 mg), 5 mg (4 × 1.25 mg), 10 mg (8 × 1.25 mg), 15 mg (12 × 1.25 mg), and 30 mg (24 × 1.25 mg) EC minitablet doses.

The 1.25 mg EC mini-tablet is in development for treating patients with WD who may require a lower dose and/or who may have difficulty swallowing the 15 mg EC tablet (eg, pediatric patients with WD). Several of the 1.25 mg EC mini-tablets could be administered together with acidic soft foods to protect the enteric coating through to the site of absorption in the gastrointestinal tract. To support this alternative administration method, further investigation of the formulation stability of the 1.25 mg EC mini-tablets in acidic soft foods is also planned.

Following completion of this study, the safety, efficacy, and pharmacokinetics (PK)/pharmacodynamics (PD) of the 1.25 mg EC minitablet are planned to be assessed in pediatric patients with WD.

2.2. Background

ALXN1840 has been selected for development in WD due to its improved stability properties over ammonium tetrathiomolybdate, which has previously been studied in patients with WD and other indications. Ammonium tetrathiomolybdate as well as bis-choline tetrathiomolybdate non-clinical and clinical data reported to date support the efficacy and safety of ALXN1840.

ALXN1840 rapidly forms irreversible tetrathiomolybdate-Cu-albumin tripartite complexes (TPCs), which stabilize free Cu leading to a reduction in the non-ceruloplasmin-bound Cu (NCC) concentrations after correction for Cu bound to TPC ($NCC_{corrected}$). Alexion is developing a novel bioanalytical method to directly measure NCC/$NCC_{corrected}$, defined as labile bound Cu (LBC). PD assessments may be explored to further characterize the dynamic relationship between Cu and ALXN1840.

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

ALXN1840 is currently being evaluated in a Phase 3 multicenter, randomized study to assess the efficacy and safety of ALXN1840 compared with standard of care on plasma toxic Cu control as

measured by $NCC_{corrected}$. Toxic Cu in this study is to be measured via assays for plasma ultrafiltrate (PUF) Cu.

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

2.3. Benefit/Risk Assessment

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

2.3.1. Risk Assessment

Table 3: Potential Risks and Mitigation Strategy

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

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

2.3.2. Benefit Assessment

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

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 patients with WD.

3. OBJECTIVES AND ENDPOINTS

Table 4: Mapping Objectives to Endpoints/Estimands

Objective	Endpoints/Estimands
Primary	
To assess the relative bioavailability of equal doses of ALXN1840 administered as 1.25 mg EC mini-tablets versus a single 15 mg EC tablet	PK parameters for plasma total Mo and PUF Mo (C_{max}, AUC_t, and AUC_∞)
Secondary	
To assess dose-proportionality between 2.5 mg (2 × 1.25 mg), 5 mg (4 × 1.25 mg), 10 mg (8 × 1.25 mg), 15 mg (12 × 1.25 mg), and 30 mg (24 × 1.25 mg) EC mini-tablet doses	Dose-normalized PK parameters for plasma total Mo and PUF Mo (C_{max_n}, AUC_{t_n}, and AUC_{∞_n})
Safety	
To assess the overall safety and tolerability of ALXN1840, administered as 1.25 mg EC mini-tablets and as a single 15 mg EC tablet	Incidence of TEAEs and TESAEs, physical examination, vital signs measurements, clinical laboratory, and 12-lead ECG results
Exploratory	
To explore relationships between total and PUF Mo clearance and body size — body weight (kg) and BMI (kg/m^2)	CL/F, body weight, and BMI
To explore PD of ALXN1840 either as a single 15 mg EC tablet or EC mini-tablets of 1.25 mg at different total dose strengths	Absolute and percent changes from pre-dose baseline of plasma Cu concentrations: total and PUF Cu

Abbreviations: AUC_∞ = area under the plasma concentration versus time curve from time 0 to infinity; AUC_t = area under the plasma concentration versus time curve from time 0 to the last quantifiable concentration; BMI = body mass index; CL/F = apparent oral clearance; C_{max} = maximum observed concentration; Cu = copper; EC = enteric-coated; ECG = electrocardiogram; Mo = molybdenum; n = dose-normalized; PD = pharmacodynamic(s); PK = pharmacokinetic(s); PUF = plasma ultrafiltrate; TEAE = treatment emergent adverse events; TESAE = treatment emergent serious adverse event.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 1 study to compare the relative bioavailability of 2 formulations of ALXN1840 in healthy participants. Equal doses of the 1.25 mg EC mini-tablet will be compared with a single 15 mg EC tablet (12 × 1.25 mg and 1 × 15 mg, respectively). The study will be conducted in 2 periods. The study will also assess dose-proportionality between 2.5 mg (2 × 1.25 mg), 5 mg (4 × 1.25 mg), 10 mg (8 × 1.25 mg), 15 mg (12 × 1.25 mg), and 30 mg (24 × 1.25 mg) EC minitablet doses in the Dose-Proportionality Extension Period.

The study has a Screening Period (Days -28 to -2), the Two-way Crossover Period, consisting of 2 dosing periods (Day 1 to Day 11 each), and a Dose-Proportionality Extension Period of 14 days. After completing the Screening Period, enrolled participants will be admitted to the clinical research unit (CRU) on Day -1 for dosing on Day 1 in Dosing Period 1. If discharged after Dosing Period 1, participants will be readmitted to the CRU for Dosing Period 2 following a minimum washout of 14 days after the previous dose, and again for the Dose-Proportionality Extension Period after a minimum washout of 14 days.

This study will be conducted with approximately 48 healthy participants enrolled to allow for a minimum of 40 participants to complete the Dose-Proportionality Extension Period of the study.

Two-way Crossover Period

The Two-way Crossover Period is a randomized, open-label, two-way (2-period, 2-sequence) crossover design to assess the relative bioavailability of 12 × 1.25 mg EC mini-tablets compared with the 15 mg EC tablet currently used in clinical studies. Participants will be randomized to one of the 2 treatments sequences. Randomized treatment assignment will be based on Baseline body mass index (BMI). Two strata for Baseline BMI (< 25, 25 to < 32 kg/m^2) will be used:

- Treatment A: ALXN1840 12 × 1.25 mg EC mini-tablets
- Treatment B: ALXN1840 single 15 mg EC tablet (reference tablet, currently being tested in the Phase 3 Study WTX101-301)

Blood samples for PK analysis of total and PUF molybdenum (Mo) (as surrogate measures of ALXN1840 PK) and PD/biomarkers will be collected in each dosing period on Day 1 at pre-dose, and postdose at 1, 2, 3, 4, 5, 6, 8, 12 and 24 hours (Day 2) and then at 24 hour intervals on Days 3, 4, 5, 6, 7, 8, 9, 10, and 11.

The 336-hour sample for Dosing Period 1 will be collected predose in Dosing Period 2. Participants may be discharged on Day 11 of each dosing period after completion of all procedures and review of all safety data. The end of Dosing Period 2 will occur on Day 15 ± 2 of Dosing Period 2, with the collection of the 336-hour PK sample for Dosing Period 2.

Participants may be asked or required to stay in the CRU during the Two-way Crossover Period, and/or at the end of the Dose-Proportionality Extension Period before the End of Study (EOS) Visit, for their own safety, and also to maintain the integrity of the conduct of the study.

Dose-Proportionality Extension Period

The Dose-Proportionality Extension Period is a re-randomized, open-label, parallel group design to assess the dose-proportionality between 2.5 mg (2 × 1.25 mg), 5 mg (4 × 1.25 mg), 10 mg (8 × 1.25 mg), and 30 mg (24 × 1.25 mg) EC mini-tablet doses.

The Dose-Proportionality Extension Period will be conducted following completion of the Two-way Crossover Period of the study and after an at least 14-day washout period. Participants will be re-randomized as follows:

- Treatment C (N=10-12): ALXN1840 2.5 mg (2 × 1.25 mg EC mini-tablets)
- Treatment D (N=10-12): ALXN1840 5 mg (4 × 1.25 mg EC mini-tablets)
- Treatment E (N=10-12): ALXN1840 10 mg (8 × 1.25 mg EC mini-tablets)
- Treatment F (N=10-12): ALXN1840 30 mg (24 × 1.25 mg EC mini-tablets)

The 15 mg dose will not be repeated during the Dose-Proportionality Extension Period. For the purpose of evaluating dose-proportionality of the EC mini-tablet, data obtained from Treatment A of the Two-way Crossover Period (12 × 1.25 mg EC tablets) will be included to represent a dose of 15 mg.

Re-randomized treatment assignment will be based on body mass index (BMI). Two strata for BMI (< 25, 25 to < 3Baseline BMI (< 25, 25 to < 32 kg/m^2) will be used. Block randomization will be used to equally randomly assign participants to each treatment.

4.2. Scientific Rationale for Study Design

This study is being conducted in healthy participants so that the assessments are not confounded by disease activity, comorbidities, or concomitant medications. The inclusion and exclusion criteria for this study are consistent with Phase 1 clinical pharmacology studies that assess the medication of interest and to minimize assignment bias. As the key objectives of the study are assessments of bioavailability and dose-exposure proportionality, a blinded design is not necessary.

The Two-way Crossover Period was adopted to control the variability within and between participants. A minimum of 14 days between dose administration is considered sufficient to eliminate, on average, approximately more than 99.2% of the plasma total Mo.

Following ALXN1840 administration, the active drug moiety tetrathiomolybdate rapidly binds Cu to form the TPC in the liver and blood and presents as such in the systemic circulation. If TPC is not rapidly formed, tetrathiomolybdate spontaneously undergoes serial hydrolysis to form molybdate, the most common form of nutrient Mo, and is excreted in the urine. Total Mo concentration has been measured as a surrogate of ALXN1840 PK; however, total Mo concentration cannot distinguish whether the Mo is complexed with Cu and albumin (as in TPC), free active ALXN1840 drug, intermediate hydrolysis products, or molybdate which may be from ALXN1840 hydrolysis. To better characterize the amount of non-TPC bound ALXN1840 and its degradation products, PUF Mo, which represents the free parent drug (ALXN1840), short-lived intermediate hydrolysis products, and molybdate, will be measured. Total Mo and PUF Mo concentrations also include physiologic molybdate concentrations from dietary micronutrient molybdate intake. While it is not feasible to separate and quantify ALXN1840 directly in the

plasma, total Mo PK and PUF Mo PK provide surrogate measures to characterize ALXN1840 exposure. To better characterize the absorption, distribution, metabolism, and excretion (ADME) of ALXN1840, the PK of both total Mo and PUF Mo will be characterized and described. The primary PK measure is total Mo, whereas PUF Mo is an exploratory measure.

4.2.1. Participant Input into Design

Not applicable as this is a study in healthy participants.

4.3. Justification for Dose

The 15 mg dose to be used in the Two-way Crossover Period of the study has been chosen because it is the dose most commonly used in the ongoing Phase 3 Study WTX101-301 and is expected to be the prescribed starting dose in adult and adolescent patients with WD aged 12 years and older.

The 15 mg tablet is the only dose strength currently available as a reference dose for the relative bioavailability test. If a dose of 30 mg or greater is required, a patient with WD will be administered 2 or more 15 mg EC tablets, rather than ≥ 24 EC mini-tablets.

The EC mini-tablet doses of 2.5, 5, 10, and 30 mg to be tested in the Dose-Proportionality Extension Period of the study, in addition to the 15 mg dose to be tested in the Two-way Crossover Period, will cover the entire anticipated dose range recommended in the planned study in the pediatric population. Selection of the starting and maximum doses for the planned study in the pediatric population aged 3 to < 12 years is based on a combination of standard body weight based allometric principles and age-based changes in liver volume. To support the dose selection, PK simulations were conducted based on the allometric scaling of population PK model using PK data (ie, total Mo) from Study WTX101-201 in patients with WD and Study WTX101-102 in healthy participants who were administered the EC tablet. The general approach of dose selection for pediatric investigation used here is consistent with the United States Food and Drug Administration guidance (https://www.fda.gov/media/90358/download) as well as European Medicines Agency (EMA) guidance ICH E11(R1) (EMA, 2017).

For patients aged 3 to < 12 years, a lower starting dose of 2.5 mg/day will be administered for 4 weeks based on scaling of the starting dose of 15 mg/day in patients with WD aged 12 years and above in the ongoing Phase 3 Study WTX101-301. After 4 weeks, up titration to 5 mg once daily may be performed at the discretion of the Investigator, if the disease is not adequately controlled, taking into account the patient's clinical status and free blood Cu concentration based on pre-defined criteria, as measured by LBC, and provided none of the dose modification criteria apply. Further dose increases up to a maximum dose of 30 mg/day in 5 mg increments at least 4 weeks apart are possible at the discretion of the Investigator following the same aforementioned criteria.

For patients aged 3 to < 6 years, the population PK modeling results showed that a 5 mg dose has comparable exposure to 15 mg administered to adult patients, and that a 15 mg dose has a higher exposure than 30 mg, but a lower exposure than 60 mg administered to adult patients. Hence, the predicted dose range for patients aged 3 to < 6 years is 5 mg to 15 mg, which is anticipated to provide comparable safety and efficacy outcomes to those in adolescent and adult patients over 12 years of age with a dose range of 15 mg to 60 mg currently allowed in the ongoing Phase 3

Study WTX101-301. Therefore, the EC mini-tablet doses of 2.5, 5, 10, 15, and 30 mg will be tested in this study, which covers the entire anticipated dose range recommended in the planned study in the pediatric population.

An inductively coupled plasma-mass spectroscopy (ICP-MS) method, with a lower limit of quantification (LLOQ) of 1.00 ng/mL and 0.25 ng/mL for the assays of total Mo and PUF Mo, respectively, has been previously implemented for analyzing plasma samples from Study WTX101-HV-106. In that study, for the 15 mg and 60 mg doses, $\%AUC_{extrap}$ ranged from 1.3% - 12.2% (all were less than 20%). In the current study, a maximum observed concentration (C_{max}) for total Mo of approximately 40 ng/mL is anticipated after the lowest ALXN1840 dose of 2.5 mg and with an assay LLOQ of 1.00 ng/mL, it would be possible to detect measurable total Mo concentrations at a mean of 1.25 ng/mL for approximately 5 half-lives with reasonably low expectation for excess AUC extrapolation of over 20% for AUC_{∞} estimation. A C_{max} for PUF Mo of approximately 2 ng/mL is anticipated after the lowest ALXN1840 dose of 2.5 mg and with an assay LLOQ of 0.25 ng/mL, it would be possible to detect measurable PUF Mo concentrations at a mean of 0.25 ng/mL for approximately 3 half-lives with possibility of AUC extrapolation of over 20% for AUC_{∞} estimation.

4.4. End of Study Definition

The planned study duration is approximately 10 weeks, which includes an up to 28-day Screening period, 2 periods of approximately 11 days in the Two-way Crossover Period (with at least 14 days from the previous dose of ALXN1840 before the next dose is administered), plus a 14 -day period in the Dose--Proportionality Extension Period (again, 11 days in the CRU with at least 14 days from the previous dose before the next dose is administered).

The EOS for each participant is defined as completion of the EOS Visit on Day 15 ± 2 days of the Dose-Proportionality Extension Period.

The EOS is defined as the date of the last participant's last scheduled visit (ie, the last visit as scheduled/foreseen by the protocol, including the scheduled Follow-up Visit).

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

Male and female participants are eligible to be included in the study only if all of the following criteria apply:

Age

1. Participants must be ≥ 18 to 55 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who are healthy as determined by medical evaluation with no clinically significant or relevant abnormalities as determined by medical history, physical examination, vital signs, 12-lead electrocardiogram (ECG), and clinical laboratory evaluation (hematology, biochemistry, coagulation, and urinalysis) that are reasonably likely to interfere with the participant's participation in or ability to complete the study, or to potentially confound interpretation of study results, as assessed by the Investigator.
3. Adequate venous access in the left or right arm to allow collection of study-required blood samples.

Weight

4. Body weight ≥ 50 to ≤ 100 kg and BMI within the range 18 to < 32 kg/m^2 for all participants.

Sex

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

    a. Male participants:

    - Male participants, if heterosexually active and with a female spouse or partner of childbearing potential or a pregnant or breastfeeding spouse or partner, must agree to use barrier contraception (male condom) for the duration of the study and for at least 3 months after the end of systemic exposure of the study intervention (ie, 3 months after the EOS Visit). Male participants must not donate sperm for at least 3 months after the end of systemic exposure of the study intervention (ie, 3 months after the EOS Visit).
    - Female spouses or partners of male participants who are of childbearing potential must use highly effective contraception as defined in Section 10.4 starting at least 6 weeks before (the male participant's) first study intervention administration and continuing until at least 3 months after the end of their male partner's systemic exposure to the study intervention (ie, 3 months after the EOS Visit).

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

b. Female participants:

- Female participants or female partners of male participants of childbearing potential (including breastfeeding females), if heterosexually active, must be willing to follow protocol specified contraception guidance starting at least 6 weeks before first study intervention administration and continuing for at least 3 months after the end of systemic exposure of the study intervention (ie, 3 months after the EOS Visit). Female participants must not donate ova for at least 3 months after the EOS (ie. 3 months after the EOS Visit).
- Female participants who are documented as being of non-childbearing potential as defined in Section 10.4 are exempt from contraception requirements.
- Highly effective contraceptive methods for female participants and female partners of male participants are detailed in Section 10.4.

Informed Consent

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

5.2. Exclusion Criteria

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

1. History or presence of/significant history of or current cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrinological, hematological, or neurological disorders, or psychiatric disorder. Any surgical or medical history which may significantly alter the absorption, metabolism, or elimination of drugs or constitute a risk when taking the study intervention; or interfering with the interpretation of data (eg, gastric bypass, cyclical vomiting, etc).
2. Supine blood pressure ≤ 90/60 mmHg or > 140/90 mmHg at Screening; systolic or diastolic components outside of range should result in exclusion. Supine blood pressure should be taken after a minimum of 5 minutes in supine position. If vital signs are abnormal, 2 additional readings will be taken. The mean of the 3 replicates will be recorded in the case report form (CRF) and used to determine inclusion.
3. Lymphoma, leukemia, or any malignancy within 5 years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years.
4. Alanine aminotransferase (ALT), aspartate aminotransferase (AST) or total bilirubin > upper limit of normal (ULN) of laboratory reference range at Screening. At the

discretion of the Investigator, a single repeat analysis may be performed to assess eligibility during the Screening period.

5. Serum Cu or serum ceruloplasmin below lower limit of normal on laboratory reference range at Screening.
6. History of anemia or hemoglobin < 130 g/L for men and hemoglobin < 115 g/L for women at Screening. At the discretion of the Investigator, a single repeat analysis may be performed to assess eligibility, with the agreement of the Medical Monitor.
7. History of benign ethnic neutropenia or absolute neutrophil count < 1500/μL; lymphocyte <1000/μL.
8. Blood donation or blood loss in excess of 500 mL in the 60 days prior to Screening.
9. QT interval corrected using Fridericia's formula (QTcF) > 450 ms for male participants; QTcF > 470 ms for female participants.
10. Current or chronic history of liver disease or known hepatic or biliary abnormalities (except for asymptomatic gallstones). Participants with elevated total bilirubin or history of Gilbert's will be excluded from the study.
11. Any other significant disease or disorder which, in the opinion of the Investigator, may put the participant at risk or confound the interpretation of the results.
12. History of hypersensitivity to ALXN1840 or its excipients or any significant allergic reaction (eg, anaphylaxis or angioedema) to any product (eg, food, pharmaceutical).

Prior/Concomitant Therapy

13. Use or intended use of prescription medications (excluding oral contraceptives) within 21 days or 5 half-lives of the drug (whichever is longer) prior to Day -1, and/or intended use at any point over the duration of the study except with prior approval of Alexion.
14. Use of nonprescription/ over-the-counter medications, including herbal remedies and supplements, within 7 days or 5 half-lives of the drug (whichever is longer) prior to Day -1 and/or intended use at any point over the duration of the study.

Prior/Concurrent Clinical Study Experience

15. Current enrollment or past participation, within the last 90 days, before signing of consent in this or any other clinical study involving an investigational study intervention or any other type of medical research. Participants, involved in intervention studies using investigation or non-investigational drug with prolonged half-lives, are not eligible unless the time since last treatment has exceeded 90 days or 5 half-lives of the study intervention, whichever is longer.

Diagnostic Assessments

16. Presence of hepatitis B surface antigen or positive hepatitis C antibody or RNA test result at Screening. NOTE: participants with positive hepatitis C antibody due to prior resolved disease can be enrolled if a confirmatory negative hepatitis C RNA test result is obtained. NOTE: The RNA test is optional and participants with negative hepatitis C antibody test are not required to also undergo hepatitis C RNA testing.

17. Positive human immunodeficiency virus (HIV) antibody test.

Other Exclusions

18. Female participants who are pregnant, as evidenced by a positive serum pregnancy test result at Screening, or breastfeeding.
19. Prior exposure to ALXN1840.
20. Major surgery or hospitalization within 90 days prior to dosing on Day 1.
21. Use of tobacco in any form (eg, smoking, chewing or vaping), other nicotine-containing products in any form (eg, gum, patch, electronic cigarettes, or vapes), or any recreational inhalational product within 6 months prior to the planned first day of dosing.
22. Use of known drugs of abuse within 6 months prior to the planned first day of dosing.
23. Regular alcohol consumption within 6 months prior to the study defined as: an average weekly intake of > 14 units/week for males or > 7 units/week for females. One unit is equivalent to 8 g of alcohol: a half pint (~240 mL) of beer, one ~4 oz glass (125 mL) of wine or 1 (25 mL) measure of spirits.
24. Positive urine drug toxicology screen at Screening or check-in (Day -1).
25. Alcohol consumption within 24 hours prior to study intervention administration or positive alcohol breath test at Screening or check-in (Day -1).
26. Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the Investigator or Medical Monitor, contraindicates participation in the study.

5.3. Lifestyle Considerations

Participants must be able and willing to adhere to the lifestyle restrictions detailed in the exclusion criteria (Section 5.2).

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly 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 Alexion Medical Monitor.

6. STUDY INTERVENTION

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

6.1. Study Intervention Administered

Details of ALXN1840 administered in the study are provided in Table 5. ALXN1840 will be administered with up to 240 mL (8 fluid ounces) of water after an overnight fast of at least 10 hours, as per FDA guidance (https://www.fda.gov/media/121313/download). Participants can take approximately 5 minutes to drink the water. Participants will remain fasted for a minimum of 4 hours following each dose administration. Additional water is permitted ad libitum except for the period 1 hour before to 1 hour after administration of ALXN1840.

Table 5: Details of Study Intervention Administered

ARM Name	Treatments A, C, D, E, F	Treatment B
Study Intervention Name	ALXN1840	ALXN1840
Type	Drug	Drug
Dose Formulation	White, round, EC mini-tablet, diameter 3 mm	White, round, EC tablet, diameter 5 mm
Unit Dose Strength(s)	1.25 mg EC mini-tablet supplied as 4 × 1.25 mg EC mini-tablets within a size 0 capsule. Capsules will be opened to access the individual mini-tablets (details will be provided in the Study Manual).	15 mg
Dosage Level(s)	Treatment A: 12 × 1.25 mg EC mini-tablets (15 mg) Treatment C: 2 × 1.25 mg EC mini-tablets (2.5 mg) Treatment D: 4 × 1.25 mg EC mini-tablets (5 mg) Treatment E: 8 × 1.25 mg EC mini-tablets (10 mg) Treatment F: 24 × 1.25 mg EC mini-tablets (30 mg)	15 mg
Route of Administration	Oral	Oral
Use	Test	Reference
Packaging and Labeling	ALXN1840 will be provided in bottles. Each bottle will be labeled as required per country requirements.	ALXN1840 will be provided in treatment kits. Each kit will be labeled as required per country requirements.

Abbreviation: EC = enteric coated.

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.

2. Only participants randomized in the study may receive the study intervention and only authorized site staff may supply or administer the study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
    a. This responsibility includes the reporting of any product complaints to PPD within 1 business day. A product complaint is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, usability, safety, effectiveness, or performance of a product or clinical 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.
4. Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

- This is an open-label, 2-period study where, in order to minimize selection bias in treatment assignment, each participant will be randomized to one of 2 treatment sequences (Treatment A and B) in the Two-way Crossover Period. The randomization will be stratified by Baseline BMI. Two strata for Baseline BMI (< 25, 25 to < 32 kg/m^2) will be used.
- Eligible participants who meet all inclusion and no exclusion criteria included in the study will be assigned unique study participant numbers during randomization to one of 2 treatment sequences (Treatments A and B). Study participant numbers will not be reallocated once assigned.
- Participants will be re-randomized in the Dose-Proportionality Extension Period to one of 4 treatment sequences (Treatments C, D, E, and F). The re-randomized treatment assignment will be based on Baseline BMI as for the Two-way Crossover Period, with 2 strata for Baseline BMI (< 25, 25 to < 32) to be used. Block randomization will be used to equally randomly assign participants to each treatment.

6.4. Study Intervention Compliance

When participants are dosed at the site, they 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 recorded in the CRF (if the CRF is not the source document). The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

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

6.5. Concomitant Therapy

Any medication (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements), vaccine, or other specific categories of interest that the participant is receiving from 14 days prior to the first dose of study intervention 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.

6.5.1. Allowed Medicine and Therapy

- Paracetamol/acetaminophen at doses of a maximum 1000 mg per day is permitted for use as an exception with the approval of the Investigator.
- As per the ALXN1840 IB, in this study, Investigators should use caution in the co-administration of drugs known to be substrates of cytochromes 2C9 and 2B6 (CYP2C9 and CYP2B6). Common substrates of CYP2C9 include ibuprofen, which is permitted in this study. The Investigator must use ibuprofen with caution during the conduct of the study, and the ibuprofen dose must not exceed 1200 mg in any 24-hour period. Ibuprofen may only be used with approval of the Investigator.
- Concomitant procedures are not allowed unless medically indicated and/or permitted by Alexion or the Investigator or designee.
- Concomitant medications may be used during the study if deemed medically indicated by the Investigator. The Investigator or designee will notify Alexion of any AEs requiring administration of prescription medication(s) while on study.

6.5.2. Disallowed Medicine and Therapy

- Participants must abstain from taking prescription or nonprescription drugs (including vitamins and dietary or herbal supplements) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) before the start of study intervention until completion of the Follow-up Visit, unless, in the opinion of the Investigator and Alexion, the medication will not interfere with the study.
- Participants must abstain from taking prescription medications within 21 days or 5 half-lives (whichever is longer) of Day -1 or nonprescription drugs (including vitamins and dietary or herbal supplements) within 7 days or 5 half-lives (whichever is longer) before Day -1 and until completion of the Follow-up Visit.

6.6. Dose Modification

No dose modification is anticipated or planned. The highest single dose in this study will be 30 mg ALXN1840. In the completed Studies WTX101-101, WTX101-102, and WTX101-HV-106, single doses of up to 60 mg ALXN1840 were well tolerated in healthy male and female participants, with no maximum tolerated dose having been identified.

6.7. Intervention After the End of the Study

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) the study intervention. If the study intervention is definitively discontinued, the participant should remain in the study to be evaluated for safety follow-up. See the SoA (Table 1) 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 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 QTcF) after enrollment, the Investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

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

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

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

7.2. Participant Discontinuation/Withdrawal From the Study

- All efforts should be made to ensure participants are willing to comply with study participation prior to conducting the screening procedures. The study staff should notify Alexion and their site monitor of all study withdrawals as soon as possible. The reason for participant discontinuation must be recorded in the source documents and CRF.
- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- At the time of discontinuation from the study, participants will be seen and assessed by the Investigator or study physician and whenever possible, will undergo the procedures associated with the ET Visit. as shown in the SoA. See the SoA (Table 1) 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.
- If the participant is unreachable, then participant is lost to follow-up (not withdrawn, since withdrawn is a distinct event of removing informed consent)

Discontinuation of the study as a whole is handled as part of Section 10.1.8.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Table 1). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with Alexion immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1. Efficacy Assessments

No efficacy assessments will be obtained during this study.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Table 1).

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

PK collection should occur as close as possible to the scheduled time. Blood samples for assessing plasma PK/PD should be collected within ± 10% in minutes, or 30 minutes relative to the scheduled time, whichever is less.

All routine safety laboratory samples should be drawn following a minimum of 10 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 and weight will be measured and recorded at Screening only.
- A symptom-driven physical examination may be performed at other times, at the Principal Investigator's discretion.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

- Body temperature, heart rate, respiratory rate, and systolic and diastolic blood pressure (mmHg) will be assessed using consistent methods and equipment to allow comparability and reproducibility throughout the study.

- Blood pressure and pulse 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 pulse measurements should be preceded by at least 5 minutes of rest in supine position 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 and 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 Table 1 and Table 2) to obtain heart rate, PR, QRS, QT, and QTc intervals, and should be taken after the participant has been in supine position for a minimum of 5 minutes.
- Refer to Section 7.1 for QTc withdrawal criteria and any additional QTc readings that may be necessary. As with vital signs, if ECG interval measurements are abnormal, an additional 2 replicate measures will be performed with the mean of the 3 measured interval values used to confirm eligibility and recorded in the CRF.

8.2.4. Clinical Safety Laboratory Assessments

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

8.2.5. Suicidal Ideation and Behavior Risk Monitoring

Not applicable to this study.

8.2.6. Pregnancy

- Pregnancy data from female participants and female spouses/partners of male participants will be collected from the first dose of study intervention through 3 months postdose. 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 10.3.1) 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 10.3). 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 7.1).

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 nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

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

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification of an SAE by the Investigator to Alexion is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- Alexion has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. Alexion will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards/Independent Ethics Committees (IRBs/IECs), and Investigators.
- Suspected unexpected serious adverse reactions (SUSARs) must be reported according to local regulatory requirements and Alexion policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from Alexion will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Adverse Events of Special Interest

There are no AEs of special interest for this study.

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 Mo and PUF Mo as specified in the SoA (Table 1) via ICP-MS. Samples collected within ± 10% in minutes, or 30 minutes of the scheduled time, whichever is less, 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.
- Samples will be used to evaluate the PK of ALXN1840. Samples collected for analyses of plasma concentrations may also be used to evaluate safety aspects related to concerns arising during or after the study.
- Excess/additional samples may be stored for up to 5 years and used for PD and/or diagnostic biomarker development and research to understand the pathways associated with the mechanism of action of ALXN1840. These samples will not be used for genetic analyses (ie, RNA or DNA analyses).
- Genetic analyses will not be performed on these whole blood samples. Participant confidentiality will be maintained.

8.6. Pharmacodynamics

- Plasma total Cu, PUF Cu, and LBC are considered to be PD assessments. Samples for assessment of LBC will be retained and may be analyzed in the future. See Section 8.8 for assessment of plasma ceruloplasmin and ceruloplasmin-bound Cu.
- 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 Cu, and toxic Cu as measured by PUF Cu at the time points indicated in the SoA.

- 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).

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

- Plasma ceruloplasmin and ceruloplasmin-bound Cu samples will be retained and may be analyzed in the future.
- Blood samples will be collected as described in the SoA (Table 1) for plasma isolation as per the Laboratory Manual.
- 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).

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

The primary objective of this study is to assess the relative bioavailability of 12 × 1.25 mg EC tablets (Treatment A, test) versus a single 15 mg EC tablet (Treatment B, reference). This will be done using the Analysis of Variance (ANOVA) statistical model, model based least square geometric mean ratios of PK parameter and confidence intervals (90%) will be provided. There is no formal null hypothesis to be statistically tested.

9.2. Sample Size Determination

A sample size of 48 male or female participants (24 participants in each sequence) has been selected based on practicality and convention for this type of study. Considering potential for drop-out of the study (approximately 15%), a total of 48 participants will be enrolled to ensure a minimum of 40 participants complete the study.

9.3. Populations for Analyses

The population sets used for analysis sets are defined as follows:

Population	Description
Enrolled Set	All participants who agree to participate in the study following completion of the informed consent process and who satisfy the inclusion/exclusion criteria and are randomized.
Safety Set	All participants who receive at least 1 dose of ALXN1840
Pharmacokinetic Set	All participants who receive at least 1 dose of ALXN1840 and have evaluable PK data for total and/or PUF Mo (as surrogate measures of ALXN1840 PK) in plasma
Pharmacodynamic Set	All participants who receive at least 1 dose of ALXN1840 and have evaluable PD data in plasma

Abbreviations: ICF = informed consent form; Mo = molybdenum; PD = pharmacodynamics; PK = pharmacokinetics; PUF = plasma ultrafiltrate.

9.4. Statistical Analyses

In general, descriptive statistics for continuous variables will include number of non-missing values, arithmetic mean, SD, median, minimum, and maximum. Categorical variables will be summarized using percentages and frequency counts. Descriptive statistics and percentages and frequency counts will be summarized by treatment, and period, where appropriate.

All statistical analyses will be conducted using SAS® for Windows® Version 9.4 or higher.

A Statistical Analysis Plan (SAP) will be developed and finalized before data cutoff/database lock and will further describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data as appropriate. This section is a high-level summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. Efficacy Analyses

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

9.4.1.1. Analyses of Primary Endpoint

The primary analysis will be based on the PK Set.

The PK parameters for total and PUF Mo (C_{max}, AUC_t, and AUC_∞) will be evaluated using an ANOVA statistical model with dosing period, treatment, and sequence as the fixed effects, and participant as a random effect, using the natural logarithms of the data. Confidence intervals (CI, 90%) will be constructed for the least squares geometric mean ratio (GMR) for the ALXN1840 12 × 1.25 mg versus single 15 mg ALXN1840 dose for all 3 parameters using the natural log-transformed data. The GMRs and associated 90% confidence limits will be exponentiated back to the original scale.

The within-participant CV for the C_{max}, AUC_t, and AUC_∞ will be estimated using the mean squared error from the ANOVA. In addition, the geometric means and the associated 95% CIs of C_{max}, AUC_t, and AUC_∞ will be reported for each treatment.

Detailed PK analyses will be described in the SAP.

9.4.1.2. Analyses of Secondary Endpoints

All secondary analyses will be based on the PK Set.

Dose-proportionality will be assessed across all EC mini-tablet treatments (2.5 mg, 5 mg, 10 mg, 15 mg, 30 mg ALXN1840) graphically and by using a power model (Smith, 2000; Newlands, 2006; EMA, 2010). The following dose-normalized PK parameters will be assessed for dose proportionality: C_{max_n}, AUC_{t_n} and AUC_{∞_n}. The log (PK parameters for plasma total and PUF Mo) will be included as a response variable and log (dose) will be included as a fixed effect in the power model:

log(PK Parameter) = mu + beta*log(Dose)

where beta = 1 indicates perfect dose proportionality. Estimation of beta, along with its 90% CI, will be provided.

Additional approaches to test dose proportionality, such as an ANOVA model, will be explored (Calvo, 2005).

9.4.1.3. Analyses of Exploratory Endpoints

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

9.4.2. Safety Analyses

All safety analyses will be performed on the Safety Set.

Safety analyses will include an analysis of all AEs, ECGs, clinical laboratory data, physical examinations, and vital sign measurements using descriptive statistics. No inferential statistical analyses are planned on the safety parameters of this study. The incidence of AEs and SAEs will be summarized, by System Organ Class and Preferred Term for each period, treatment and

overall, by relationship to study intervention. Adverse events will also be summarized by period, 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, cell blood count with differential, and urinalysis) will be summarized by period (Two-way Crossover Period and Dose-Proportionality Extension Period) and 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.

The ECG parameters will be measured at the specified time points, including heart rate, PR, RR, QRS, QT, and corrected 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 period and treatment.

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

9.4.3. Pharmacokinetic/Pharmacodynamic Analysis

Pharmacokinetic analyses will be performed using the PK Set.

The following plasma PK parameters will be calculated as endpoints for total and PUF Mo (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 9.4 or higher (SAS Institute Inc., Cary, North Carolina), as applicable. Calculations of individual PK parameters will be based on measured total Mo and, when feasible, PUF Mo concentrations and the actual sampling times elapsed from the actual reference dosing time data recorded during the study.

- Time delay between the time of dosing and time of appearance of drug concentration in plasma (T_{lag}; for plasma total Mo with ALXN1840 administration)
- Maximum observed concentration in plasma (C_{max})
- Dose-normalized C_{max} (C_{max_n}); n = dose normalized
- Time to C_{max} (T_{max})
- Area under the plasma concentration (AUC) versus time curve from time 0 to the last quantifiable concentration (AUC_t)
- Dose-normalized AUC_t (AUC_{t_n})
- AUC versus time curve from time 0 to infinity (AUC_∞)
- Dose-normalized AUC_∞ (AUC_{∞_n})
- AUC extrapolated from time t to infinity as a percentage of total AUC_∞ ($\%AUC_{extrap}$)

- Apparent terminal-phase elimination rate constant (λ_z)
- Terminal elimination half-life ($t_{½}$)
- Apparent oral clearance (CL/F)
- Apparent volume of distribution (V_d/F)
- Relative bioavailability (F_{rel}) between test and reference treatments

Additional plasma PK parameters may be calculated if deemed appropriate.

Plasma concentrations of total and PUF Mo and time deviation data will be presented in a data listing by participant. Plasma concentration data will be summarized separately by time point for each treatment using the following descriptive statistics: number of participants, arithmetic mean, SD, CV, geometric mean, geometric CV, 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 and PUF Mo will be presented in data listings and summarized separately using the following descriptive statistics: number of participants, arithmetic mean, SD, arithmetic CV, geometric mean, geometric CV, median, minimum, and maximum.

Pharmacodynamic analyses will be performed using the PD Set.

Individual ALXN1840 PD, assessed as plasma total Cu and PUF Cu concentration versus 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 versus time data.

9.5. Interim Analyses

An interim analysis is planned after completion of the Two-way Crossover Period of the study to enable reporting of results that will inform the decision on safe and appropriate dosing with the 1.25 mg EC mini-tablets in the planned study in pediatric patients with WD who will be required to be treated with the starting dose of 2.5 mg ALXN1840.

9.6. Safety Review Committee

An ad-hoc Safety Review Committee must convene within 24 hours in the case of a treatment-emergent serious adverse event (TESAE) or the withdrawal of any subject due to an adverse reaction to determine whether any group toxicity rules apply and the impact on study continuation.

There is an option to have additional ad hoc Safety Review Committee meetings to discuss urgent issues should the need arise. The membership roster and requirements for documenting meeting discussions and outcome will be outlined in the Safety Review Committee charter. Further internal or external experts may be consulted by the Safety Review Committee as necessary.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable 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 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 Sub-Investigators will provide Alexion with sufficient, accurate financial information as requested to allow Alexion to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- It is the responsibility of the Investigator to obtain signed (written or electronic signature) informed consent from all study participants prior to performing 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 GCP guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study site.
- The medical record must include a statement that signed (written or electronic) informed consent was obtained before any screening procedures were performed with a participant, and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF(s).
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study, as applicable.
- 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. Original, signed (written or electronic) consent [or assent] forms must remain in each participant's study file and must be available for verification at any time.

10.1.4. Data Protection

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

10.1.5. Dissemination of Clinical Study Data

Study-related information and study results may be posted on publicly accessible clinical study databases (eg, the US website www.clinicaltrials.gov or the EU website 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 CRFs 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 5 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 EOS or ET Visit, all data have been collected and entered into an electronic data capture (EDC) system, all required documents and study supplies have been collected and reconciled, 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 ICH 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. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 6 will be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations. Investigators must document their review of each laboratory safety report and indicate whether out of range results are clinically significant or not clinically significant. All repeated laboratory test values must be recorded in the CRF.
- Women of childbearing potential should only be enrolled after a negative serum pregnancy test result at Screening. Additional urine pregnancy testing will be standard for the protocol unless serum testing is required by site policies, local regulation, or IRBs/IECs and should be performed per the time points specified in the SoA (Section 1.3). Screening pregnancy criteria are detailed in Section 5.1.

Table 6: Laboratory Assessments

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

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

[a] All events of ALT or AST ≥ 3 × ULN or bilirubin ≥ 1.5 × ULN (> 35% direct bilirubin) or INR > 1.5, must be reported as an AE.

[b] A sample for HbA1c is only required during the Screening Period, and not at every time point where samples for hematology, chemistry, urinalysis, and coagulation are required.

[c] Ceruloplasmin, ceruloplasmin-bound Cu, and LBC samples will be retained and may be used for diagnostic biomarker development.

[d] Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; Cu = copper; HbA1c = glycated hemoglobin; IEC = independent Ethics Committee; IgG/M = immunoglobulin G/M; IRB = Institutional Review Board; INR = international normalized ratio; LBC = labile bound copper; Mo = molybdenum; PUF = plasma ultrafiltrate; SAE = serious adverse event; ULN = upper limit of normal.

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

10.3.1. Definition of AE

AE Definition
• Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

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

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

10.3.2. Definition of SAE

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.

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

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 reactions (SUSARs) is defined as:

A serious event that is not listed in the IB and that the Investigator 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.
- 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.

Recording of AE and/or SAE

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories from National Cancer Institute CTCAE 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.
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

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

10.3.4. Reporting of SAEs

SAE Reporting to GDS via Paper Safety Reporting Form

- All SAEs will be recorded and reported to Alexion or designee immediately and within 24 hours awareness.
- SAEs will be reported using the Serious Adverse Event Report Form and submitted to Alexion Global Drug Safety (GDS). The Investigator must complete, sign, and date the Serious Adverse Event Report Form, verify the accuracy of the information recorded with the corresponding source documents, and send a copy via email or facsimile to the contact information provided below:
  - Email: PPD or Fax: PPD
- Additional follow-up information, if required or available, should be entered into the CRF and also 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/intervention for the SAE(s)
  - Outcome of the SAE(s)
  - Medical records and laboratory/diagnostic information
- All paper forms and follow-up information submitted to Alexion GDS **must** be accompanied by a cover page signed by the Investigator.
- Paper source documents and/or reports should be kept in the appropriate section of the study file.

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

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

Collection of pregnancy information:

- If a female participant or a male participant's female spouse/partner becomes pregnant during the conduct of this study, the Investigator must submit the "Pregnancy/Breastfeeding Reporting and Outcome Form" to Alexion GDS via fax or email:
  Email: PPD or Fax: PPD
  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. Appendix 5: Biomarkers

- Blood samples will be collected for biomarker analyses and the data will be used for research (eg, exploratory) related to ALXN1840 or WD and related diseases. The samples may also be used to develop tests/assays including diagnostic tests related to ALXN1840 and WD.
- The samples may be analyzed as part of a multistudy assessment of biomarkers in the response to ALXN1840 to understand study disease or related conditions.
- The results of biomarker analyses may be reported in the CSR or in a separate study summary.
- Alexion or designee will store the samples obtained for biomarker analyses in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on ALXN1840 continues but no longer than 5 years after all data have been collected for the study or other period as per local requirements.

10.6. Appendix 6: Abbreviations

A list of abbreviations and terms used in this study protocol is provided in Table 7.

Table 7: 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
ANOVA	Analysis of Variance
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
AUC_t	area under the plasma concentration versus time curve from time 0 to the last quantifiable concentration
AUC_∞	area under the plasma concentration versus time curve from zero to infinity
BMI	body mass index
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
CTFG	Clinical Trial Facilitation Group
CL/F	apparent oral clearance
C_{max}	maximum observed concentration
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CRU	clinical research unit
CTCAE	Common Terminology Criteria for Adverse Events
Cu	copper
CYP	cytochrome P450
CV	coefficient of variation
CYP2C9/2B6	cytochromes 2C9 and 2B6
EC	enteric-coated
ECG	electrocardiogram
EDC	electronic data capture
EMA	European Medicines Agency
EOS	End of Study
ET	Early Termination
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GDS	Global Drug Safety
GMR	geometric mean ratio
HbA1c	glycated hemoglobin

HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
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
Mo	molybdenum
NCC	non-ceruloplasmin-bound copper
$NCC_{corrected}$	NCC corrected for the amount of Cu bound to the TPC
PD	pharmacodynamic(s)
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
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal elimination half-life
T_{lag}	time delay between the time of dosing and time of appearance of Mo concentration
t_{max}	time to maximum concentration
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
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. Appendix 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	10 Jul 2020
Amendment 1	16 Sep 2020
Amendment 2	18 Dec 2020

Amendment 1 (16 Sep 2020)

Overall Rationale for the Amendment

This amendment has been prepared to address comments from the clinical research unit that will perform the study, so as to expand the population that can be enrolled, as well as to clarify procedures. Minor administrative edits were also made for clarification and consistency throughout the protocol. Details of the changes are presented in the table below.

Changes to the Protocol

Section # and Name	**Description of Change**	**Brief Rationale and/or Clarifications**
Section 1.1, Synopsis Section 4.1, Study Design Section 4.2, Scientific Rationale for Study Design Section 6.3, Measures to Minimize Bias: Randomization and Blinding Section 9.2, Sample Size Determination	Text relating to balance between males and females removed from the protocol	It is not necessary to balance for sex, as it is not expected that weight and sex will be confounding factors in a crossover study design and with stratification by BMI.
Section 1.3, Schedule of Activities, Table 1	Copper added to ceruloplasmin in the Schedule of Activities	Added to the sample collected for safety assessment
Section 1.3, Schedule of Activities, Table 1	Requirement for PK/PD samples removed from Day -1 assessments	PK/PD samples are already collected at Screening, so are not also required on Day -1
Section 5.1, Inclusion Criteria	Revision of limits on weight, BMI, and age for all participants: • ≥ 18 to 55 years • BMI: 18-32 kg/m^2 • Weight: 50-100 kg	To expand the potential population that can be enrolled in the study
Section 1.1, Synopsis Section 4.1, Study Design Section 6.3, Measures to Minimize Bias: Randomization and Blinding	Initial randomized treatment assignment will be based on Baseline BMI, in addition to at re-randomization. BMI adjusted to 32, as per the change in inclusion criterion. Sex will not be included as a factor in randomization or re-randomization.	Randomization and re-randomization will be based on the same factor (Baseline BMI). To remove sex as stratification factor as a limited number of female participants are expected to enroll in the study

Section 1.3, Schedule of Activities, Table 1 Section 8.2.2, Vital Signs Section 8.2.3, Electrocardiograms	Clarified that 5 minutes in the supine position is required for all vital sign measurements, including blood pressure and ECGs	To clarify the procedures
Section 6.1, Study Drug Administration	Text added stating that ALXN1840 will be administered with up to 240 mL of water following an overnight fast of at least 10 hours, and that participants will remain fasted for a minimum of 4 hours following each dose administration	To be in-line with FDA guidance for fasting pre- and post-dose (https://www.fda.gov/media/121313/download)
Section 8.2, Safety Assessments	Fasting time changed from 8 hours to 10 hours before laboratory assessments	To be in-line with FDA guidance for fasting as added to Section 6.1
Section 8.2.4, Clinical Safety Laboratory Assessments Section 10.2, Appendix 2: Clinical Laboratory Tests	Removal of text stating that all laboratory values from non-protocol specified laboratory assessments must also be recorded in the CRF. Addition of text that all repeated laboratory test values must be recorded in the CRF.	The previous text required collection of all laboratory test results outside of those specified in the protocol. Clinically significant laboratory test abnormalities will be reported as AEs. Clarified that all repeated laboratory test values must be recorded in the CRF.
All	Minor administrative edits	For clarification and consistency throughout the protocol

11. REFERENCES

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