A Phase 1, Randomized, 2-Period, 2-Way Cross-over Study to Assess the Single-Dose Pharmacokinetics of ALXN1840 Enteric-Coated Tablets at 2 Dose Strengths in Healthy Adult Subjects

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TITLE PAGE

Protocol Title:	A Phase 1, Randomized, Open-Label, 2-Way Crossover Study to Assess the Single-Dose Pharmacokinetics of ALXN1840 Enteric-Coated Tablets at 2 Dose Strengths in Healthy Adult Subjects
Protocol Number:	ALXN1840-HV-104
Compound Number:	ALXN1840
USAN/INN:	bis-choline tetrathiomolybdate
Amendment Number:	1
Short Title:	Pharmacokinetic Study of Oral ALXN1840 at 2 Dose Strengths in Healthy Adult Subjects
Sponsor Name	Alexion Pharmaceuticals, Inc. (Alexion)
Legal Registered Address:	121 Seaport Blvd. Boston, MA 02210 USA
Regulatory Agency Identifying Numbers:	IND 119006 EudraCT: 2019-000516-28

Approval Date:

Original Protocol	01 Mar 2019
Amendment 1	09 Apr 2019

Sponsor Signatory:

PPD

9-Apr-2019

Date

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INVESTIGATOR'S AGREEMENT

I have read the ALXN1840-HV-104 study protocol amendment 1 and agree to conduct the study in accordance with this protocol, all applicable government regulations, the principles of the ICH E6 Guidelines for Good Clinical Practice, and the principles of the World Medical Association Declaration of Helsinki. I also agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Printed Name of Investigator

Signature of Investigator

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Original Document	01 Mar 2019
Amendment 1	09 Apr 2019

Amendment 1 (09 Apr 2019)

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

Overall Rationale for the Amendment:

The protocol is being amended to align with changes that have been made by the UK Medicines and Healthcare products Regulatory Agency regarding adverse events.

Section # and Name	Description of Change	Brief rationale and/or clarifications
Substantial Revisions		
Section 6.6 Study Drug Stopping Rules	Change in study drug stopping rules in relation to adverse reactions	To align with the latest recommendations by the UK Medicines and Healthcare products Regulatory Agency regarding adverse reactions
Non-substantial Revisions		
Section 8.2.1 Physical Examination	Change to details of assessments of height, weight, and body mass index	To correct the text so that it aligns with the Schedule of Activities
Section 10.4 Recording and Follow-Up of AEs and/or SAEs	To remove the final bullet point, which states the following: • Any female subject who becomes pregnant while participating in the study may not be withdrawn from the study.	To correct a typographical error that was contradicting text in Section 2.3.2.1 that in the event of a pregnancy in a study subject, the subject will be discontinued from study drug.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 1, Randomized, Open-Label, 2-Way Crossover Study to Assess the Single-Dose Pharmacokinetics of ALXN1840 Enteric-Coated Tablets at 2 Dose Strengths in Healthy Adult Subjects.

Short Title: Pharmacokinetic Study of Oral ALXN1840 at 2 Dose Strengths in Healthy Adult Subjects.

Rationale:

The 5 mg ALXN1840 dose has been manufactured and selected to be tested in this study to support dosing in pediatric patients with Wilson disease (WD), in whom a lower starting dose than the starting dose for adult patients may be warranted.

The 15 mg enteric-coated (EC) tablet formulation is the current one being tested in the on-going Phase 3 Study WTX101-301. The 5 mg EC tablet formulation is new and has not been tested in humans. The per-period 15 mg ALXN1840 total dose selected for this study in healthy subjects is within the dose range demonstrated to be safe in healthy subjects and has demonstrated a favorable safety profile and treatment effects in patients with WD. Oral doses of 60 mg ALXN1840 in non-coated capsules or EC tablets (30 mg formulation), were tested in previous 3-period crossover bioavailability studies conducted in healthy male and female volunteers (Studies WTX101-101 and WTX101-102), and were considered to have a favorable safety profile and to be well tolerated. ALXN1840 doses of 15 to 120 mg/day (15 mg EC tablets or 30 mg capsules) have been tested in the Phase 2 Study WTX101-201 in patients with WD, with a favorable safety profile. In the on-going Phase 3 Study WTX101-301, patients are to start with a dose of 15 mg/day, followed by individualized dose titrations ranging from 15 mg/every other day and up to 60 mg/day. In summary, to date, 15 to 60 mg/day single or repeated daily doses have shown to have favorable safety profiles and to be well tolerated throughout the Phase 1 to Phase 3 clinical studies, in both healthy subjects and patients with WD.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the relative bioavailability of ALXN1840 administered orally as 3 × 5 mg EC tablets (test) versus 1 × 15 mg EC tablet (reference)	• PK parameters for plasma total Mo (C_{max}, AUC_t, and AUC_∞)
Secondary	
• To assess the overall safety and tolerability of ALXN1840	• Safety assessed by incidence of TEAEs and TESAEs, physical examination, vital signs measurements, clinical laboratory and 12-lead ECG results
Exploratory	
• Relationships between CL/F and body size — body weight (kg) and body mass index (BMI, kg/m²)	• CL/F, body weight, and body mass index
• To explore PD and biomarkers of 15 mg ALXN1840 among the following dosing regimens: either as a single 15 mg EC tablet (Treatment A) or 3 EC tablets of 5 mg (Treatment B)	• Absolute and percent changes of plasma copper levels (total Cu, Cp, CpC and NCC) • The NCC level will be corrected for the amount of Cu bound to the TPC ($NCC_{corrected}$)

Abbreviations: AUC_∞ = area under the plasma concentration versus time curve from zero 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 = clearance/bioavailability; C_{max} = maximum observed concentration; Cp = ceruloplasmin; CpC = ceruloplasmin-bound copper; Cu = copper; EC = enteric-coated; Mo = molybdenum; ECG = electrocardiogram; NCC = non-ceruloplasmin-bound copper; $NCC_{corrected}$ = NCC level corrected for the amount of Cu bound to the TPC; PD = pharmacodynamic(s); PK = pharmacokinetic(s); TEAE = treatment-emergent adverse events; TESAE = treatment-emergent serious adverse event; TPC = Cu-tetrathiomolybdate-albumin tripartite complex formed after ALXN1840 administration.

Overall Design:

This is a single-center, randomized, open-label, 2-way crossover study to assess the single-dose pharmacokinetics (PK) of ALXN1840 EC tablets at 2 dose strengths in healthy male and female adult subjects under fasting conditions. Pharmacokinetic parameters will be calculated based on the measurement of plasma total molybdenum (Mo) concentration. A total of 48 healthy, adult participants (20-28 male and 20-28 female) who complete the study screening assessments and meet all eligibility criteria will be enrolled to allow for a minimum of 40 subjects to complete the study (20-24 subjects in each sequence, 10-14 of each sex in each sequence).

The study has a Screening Period (Days -28 to -2), 2 Dosing Periods (Day -1 to Day 11 each), and an end-of-study (EOS) visit 14 days (+ 2 days) post final dose. After completing the Screening Period, enrolled subjects will be admitted to an inpatient facility (Clinical Research Unit [CRU]) on Day -1 for dosing on Day 1 in Dosing Period 1. Subjects will be readmitted to the CRU for Dosing Period 2 following a minimum of 14 days after the previous dose.

In each Dosing Period, subjects will receive 1 of the 2 treatments as outlined below:

Treatment A (reference)	1 × 15 mg ALXN1840 EC tablet
Treatment B (test)	3 × 5 mg ALXN1840 EC tablets

Abbreviation: EC = enteric-coated.

Subjects will return to the CRU 14 days (+2 days) after the final dose of study drug for the EOS visit with follow-up procedures, and to determine if any adverse event (AE) has occurred since the last study visit. If subjects withdraw from the study early, they will be seen and assessed by the Investigator, whenever possible, to undergo the procedures associated with the EOS visit. Subjects may be replaced at the discretion of the Sponsor.

The study will be conducted at a single site in the UK.

Number of Subjects:

A total of 48 subjects will be enrolled (20-28 male subjects and 20-28 female subjects) to ensure a minimum sample size of 40 subjects (20-24 subjects in each sequence, 10-14 of each sex in each sequence) complete the study.

Intervention Groups and Duration:

Each subject will receive both treatments in 1 of the 2 sequences as defined in the table below according to the study drug dosing regimen outlined above, where the single 15 mg EC tablet (Treatment A) is the "reference" dose and the 3 EC tablets of 5 mg (Treatment B) are the "test" dose.

Sequence Number	**Treatment Sequence**		**Male[a]**	**Female[a]**	**Total**
	Period 1	**Period 2**			
1	A	B	10-14	10-14	24
2	B	A	10-14	10-14	24
Total			**20-28**	**20-28**	**48**

[a] In an effort to achieve balance between males and females in each sequence, there will be no less than 20 and no more than 28 of either sex (ie, a maximum split in either direction of approximately 60%:40%).

The planned study duration is approximately 70 days; up to 27 days for screening, approximately 29 days for dosing and follow-up, and an interval of at least 14 days between the 2 Dosing Periods.

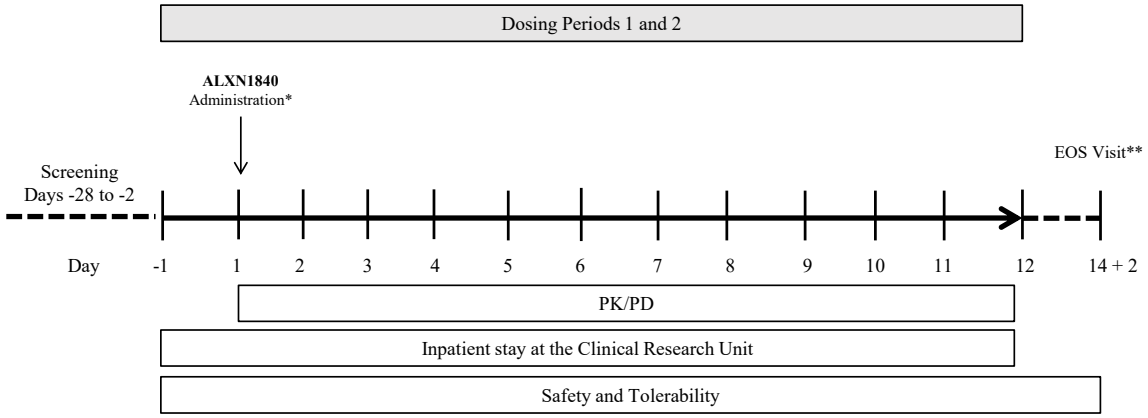
Data Monitoring Committee: There will not be a Data Monitoring Committee, but provision is included for an *ad hoc* Safety Review Committee, if needed.

Statistical Analyses:

The primary objective of this study is to assess the relative bioavailability of 3 × 5 mg EC tablets (test) versus 1 × 15 mg EC tablet (reference). Although there will be no formal bioequivalence test, the framework of 2 one-sided tests, with limits of 0.8 and 1.25, can be applied to assess the adequacy of the sample size. A post-hoc analysis of a previous bioavailability study (Study WTX101-102) found a within-subjects coefficient of variation (CV) of 0.34. For data from a two-period cross-over design, a total sample size of 40 subjects achieves 81% power at a 5% significance level when the true ratio of the means is 1, and the coefficient of variation is 0.34.

1.2. Schema

Figure 1: Study ALXN1840-HV-104 Schematic



* Subjects will leave the Clinical Research Unit on Day 11 of Dosing Period 1 and will be readmitted following a minimum of 14 days after the dose of study drug for Dosing Period 2.
** EOS visit to be performed 14 days (+2 days) after the final dose of study drug.
Abbreviations: EOS = end of study, PD = pharmacodynamics; PK = pharmacokinetics.

1.3. Schedule of Activities

Table 1: Schedule of Study Visits and Assessments – Screening Through End of Study

	Screening[a]	Study Days in Each Dosing Period[b]												EOS or ET[c]
Dosing Period 1: Days/Hours →	-28 to -2	-1[d]	1	2/24	3/48	4/72	5/96	6/120	7/144	8/168	9/192	10/216	11/240	14 + 2
Dosing Period 2: Days/Hours →			1	2/24	3/48	4/72	5/96	6/120	7/144	8/168	9/192	10/216	11/240	
Informed consent	x													
Inclusion/exclusion criteria[d]	x	x												
Medical history	x													
Randomization		x[e]												
Physical examination[f]	x	x												x
Height, weight, and BMI	x													x
12-Lead ECG[g]	x		x[h]	x			x							x
Vital signs (heart rate, BP, RR & T)[i]	x[g]		x[h]	x			x							x
Hematology, chemistry, urinalysis, and coagulation[h]	x		x[h]	x			x					x[j]		x
Serum Cp and Cu	x													
Serum pregnancy test (females only)[k]	x	x												x
FSH (postmenopausal females only)	x													
Alcohol breath test and urine drug screen	x	x												
HIV antibody/hepatitis B and C screen	x													
AE monitoring	⟷													
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Study drug administration[l]			x											
Plasma PK/PD biomarker samples[m]			x[h]	x	x	x	x	x	x	x	x	x	x	
Inpatient stay in the CRU		x	x	x	x	x	x	x	x	x	x	x	x	
Outpatient visits	x													x

[a] Within 28 days prior to Day -2 of the first dose of study drug in Dosing Period 1. Note that Screening only occurs once.

[b] After completion of Dosing Period 1, subjects 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.

[c] Subjects will return to the CRU 14 days (+2 days) following the final dose of study drug in Dosing Period 2 for an EOS evaluation. In the event of ET, the procedures listed at the EOS are performed prior to subject discharge.

[d] 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 patient is able to continue in the study.
[e] Randomization is to occur after the subject has met all inclusion and no exclusion criteria on Day -1 in Dosing Period 1
[f] 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.
[g] 12-lead ECG in triplicate will be taken 0.5 hours pre-dose, at 4 hours post-dose (before lunch) on Days 1, Day 2 and Day 5 (see Table 2), and at EOS for each Dosing Period. 12-lead ECG in triplicate will be conducted before PK/PD/biomarker blood sampling if these 2 events occur at the same time.
[h] See Table 2 for details
[i] At screening, supine and standing (orthostatic) blood pressures will be performed to exclude volunteers with orthostatic hypotension. Standing blood pressure will be measured after subjects have been standing for 1 minute.
[j] Samples for urinalysis and coagulation will not be obtained on Day 10.
[k] Serum pregnancy test is not required if the subject is confirmed to be post-menopausal.
[l] Study drug dosing will occur with the subject being in a fasted state.
[m] Blood samples for the measurement of plasma total Mo (PK) and total Cu, Cp, CpC, and NCC/$NCC_{corrected}$ (PD)

Abbreviations: AE = adverse event; BMI = body mass index; BP = blood pressure; Cp = ceruloplasmin; CpC = ceruloplasmin-bound copper; CRU = Clinical Research Unit; Cu = copper; EOS/ET = End of Study or Early Termination; FSH = follicle stimulating hormone; Mo = molybdenum; NCC = non-ceruloplasmin-bound copper; $NCC_{corrected}$ = NCC level corrected for the amount of Cu bound to the Cu-tetrathiomolybdate-albumin tripartite complex formed after ALXN1840 administration; PK = pharmacokinetics; RR = respiration rate; T = temperature.

Table 2: Schedule of Study Visits and Assessments – Continued

Study Day	Time (hour)	PK/PD/Biomarker Samples	Vital Signs	Hematology, Chemistry, Urinalysis, and Coagulation	12-lead ECG[a]
D1	-2				
	-1				
	-0.5	X	X	X	X
	0[b]				
	1	X	X		
	2	X			
	3	X			
	4	X	X	X	X[c]
	5	X			
	6	X			
	8	X	X		
	12	X	X		
D2	24	X	X	X	X
D3	48	X			
D4	72	X			
D5	96	X	X	X	X
D6	120	X			
D7	144	X			
D8	168	X			
D9	192	X			
D10	216	X		X[d]	
D11	240	X			

[a] 12-lead ECG in triplicate will be conducted before PK/PD/biomarker blood sampling if these 2 events occur at the same time.

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

[c] 12-lead ECG in triplicate will be performed 4 hours post-dose (before lunch).

[d] On Day 10, only chemistry, hematology, and non-fasting safety blood samples will be obtained. Samples for urinalysis and coagulation will not be obtained.

Abbreviations: D = day; PD = pharmacodynamic(s); PK = pharmacokinetic(s).

2. INTRODUCTION

2.1. Study Rationale

This study will assess the pharmacokinetics (PK) and safety of ALXN1840 EC tablets in healthy adult subjects at 2 dose strengths.

2.2. Background

ALXN1840 (bis-choline tetrathiomolybdate; formerly known as WTX101) is a novel, first-in-class, copper (Cu)-protein binding agent in development for the treatment of WD. ALXN1840 is targeted to address the following unmet medical needs:

- Rapid and sustained control of Cu and clinical symptoms of WD through the rapid formation of irreversible Cu-tetrathiomolybdate-protein complexes, leading to rapid Cu control without mobilizing free Cu that could cause tissue toxicity, including neurological deterioration that has been reported at the initiation of treatment with chelators. This hypothesis is supported by results from Study WTX101-201 in patients with WD (Weiss, 2017).
- Improved compliance over current chelator therapy through improved tolerability and the convenience of a simplified dosing regimen (once daily [QD]) compared to current therapeutic options (multiple daily dosing).

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

Two Phase 1 healthy subject studies (WTX101-101 and WTX101-102, N = 18 for each study) to assess the PK of ALXN1840 have been completed. Total plasma molybdenum (Mo) concentrations were used as a surrogate PK measure for tetrathiomolybdate.

Study WTX101-101 evaluated the relative exposure of 60 mg ALXN1840 (2 × 30 mg uncoated capsules [UCs]) without and with co-administration of a long-acting proton pump inhibitor (PPI) under fasted conditions, the latter also under fed conditions. Based on total plasma Mo, administration of the UC + PPI under fasted conditions resulted in a 30% increase in exposure compared to the UC alone. Administration of the UC + PPI fed resulted in a 22% decrease in exposure compared to the UC + PPI fasted. There was a decrease in the between-subject variability when the UC was administered with a PPI. The mean terminal elimination half-life ($t_{½}$) for total Mo was similar for all 3 treatments, with an overall mean of approximately 51 hours, or slightly over 2 days (Table 3).

Table 3: Total Molybdenum Pharmacokinetic Parameters From Study WTX101-101

Parameter[a]	Treatment		
	UC Fasted	UC + PPI Fasted	UC + PPI Fed
C_{max} (ng/mL)	331 ± 122 (18)	401 ± 78.3 (18)	385 ± 71.3 (18)
t_{max} (h)	4.48 (18) [1.08 – 10.0]	4.48 (18) [2.98 – 6.02]	5.99 (18) [3.48 – 8.02]
$AUC_{(0-t)}$ (h*ng/mL)	14,600 ± 7,023 (18)	18,537 ± 4,303 (18)	14,536 ± 3,663 (18)
AUC_{∞} (h*ng/mL)	16,435 ± 7,126 (17)	19,862 ± 4,665 (18)	15,603 ± 3,921 (18)
λ_z (1/h)	0.0137 ± 0.0035 (17)	0.0140 ± 0.0019 (18)	0.0142 ± 0.0031 (18)
$t_{½}$ (h)	53.1 ± 11.6 (17)	50.6 ± 7.46 (18)	50.7 ± 9.05 (18)
CL/F (L/h)	1.01 ± 0.54 (17)	0.72 ± 0.21 (18)	0.94 ± 0.38 (18)
V_z/F (L)	75.0 ± 38.9 (17)	52.1 ± 17.4 (18)	65.6 ± 17.1 (18)

[a] Arithmetic mean ± standard deviation (n) except for t_{max} for which the median (n) [range] is reported.
Abbreviations: AUC_{∞} = area under the plasma concentration versus time curve with the last concentration extrapolated based on the λ_z; $AUC_{(0-t)}$ = area under the plasma concentration versus time curve to the last measurable concentration; CL/F = Clearance/bioavailability; C_{max} = maximum observed concentration; λ_z = elimination rate constant; PPI = proton pump inhibitor; $t_{½}$ = terminal elimination half-life; t_{max} = time to maximum concentration; UC = uncoated capsule; V_z/F = apparent volume of distribution.

A total of 18 subjects were enrolled in Study WTX101-101, completed the study, and were included in the safety analysis. There were no deaths, serious adverse events (SAEs), or discontinuations due to adverse event (AEs) in the study. Overall, a total of 39 AEs were experienced by 12 (67%) subjects in this study. The percentages of subjects reporting AEs were similar following each of the 3 study treatments. Of the 39 AEs reported during the study, 38 AEs were mild (Grade 1) and 1 AE was moderate (Grade 2) in severity. One subject experienced 2 laboratory AEs of decreased hematocrit and decreased hemoglobin which were considered possibly related to study drug by the Investigator; however, both of these laboratory AEs were reported prior to dosing with ALXN1840 administration. Headache, contact dermatitis and sinus congestion were the most common AEs reported during the study and were reported by 3 to 6 (17% to 33%) subjects each. There was 1 AE considered by the Investigator to be likely related to study drug (headache) and 10 AEs considered to be possibly related to study drug; all other AEs were considered by the Investigator to be unlikely related or unrelated to study drug. There were no clinically important trends in the laboratory, vital signs, ECG, or physical examination assessments in the study.

Study WTX101-102 evaluated the relative exposure of ALXN1840 from an enteric-coated (EC) tablet under fed and fasting conditions compared to the current non-coated capsule (also referred to as UC) administered with a PPI (under fasting conditions) in order to confirm the in vivo performance characteristics, including the absorption profile, and food effect of the EC tablet in humans. There was a slight decrease in the plasma concentrations of total Mo after administration of the EC tablet fasted compared to the UC + PPI fasted. Similar trends were observed with respect to maximum observed concentration (C_{max}), area under the plasma concentration versus time curve (AUC) to the last measurable concentration ($AUC_{[0-t]}$), and AUC with the last concentration extrapolated based on the elimination rate constant (λz) ($AUC_{[inf]}$).

Nevertheless, examination of the individual subject data indicated that while a similar pattern was observed with some of the individual subjects, the majority of the subjects had a total Mo concentration-time profile that was comparable for the EC tablet and UC + PPI when both were administered under fasted conditions. However, administration of the EC tablet fed resulted in a 60% to 75% decrease in absorption which was consistent among the majority of subjects. The mean $t_{½}$ was essentially the same for all 3 treatments, with an overall mean of approximately 48 hours or 2 days (Table 4).

Table 4: Total Mo PK Parameters From Study WTX101-102

Parameter[a]	Treatment		
	EC Tablet Fasted	EC Tablet Fed	UC + PPI Fasted
T_{lag} (h)	2.00 (4)	3.00 (6)	---[b]
C_{max} (ng/mL)	376 ± 98.0 (18)	187 ± 118 (17)	442 ± 69.6 (18)
t_{max} (h)	4.54 (18) [3.00 – 9.53]	4.55 (17) [3.52 – 9.51]	4.50 (18) [2.99 – 10.0]
$AUC_{(o-t)}$ (h*ng/mL)	16,026 ± 5,635 (18)	5,740 ± 4,681 (17)	19,809 ± 3,509 (18)
AUC_{∞} (h*ng/mL)	17,258 ± 5,955 (18)	6,973 ± 5,065 (15)	21,047 ± 4,022 (17)
λ_z (1/h)	0.0149 ± 0.0023 (18)	0.0258 ± 0.0303 (15)	0.0145 ± 0.0014 (17)
$t_{½}$ (h)	51.0 ± 8.87 (18)	43.5 ± 20.9 (15)	48.2 ± 4.86 (17)
CL/F (L/h)	0.92 ± 0.51 (18)	6.34 ± 11.9 (15)	0.66 ± 0.13 (17)
Vz/F (L)	66.6 ± 34.0 (18)	175 ± 98.1 (15)	45.2 ± 8.31 (17)

[a] Arithmetic mean ± standard deviation (N) except for t_{max} for which the median (N) [Range] is reported.
[b] Parameter could not be estimated for any subject for this treatment.
Abbreviations: AUC_{∞} = area under the plasma concentration versus time curve with the last concentration extrapolated based on the λ_z; $AUC_{(0-t)}$ = area under the plasma concentration versus time curve to the last measurable concentration; CL/F = clearance/bioavailability; C_{max} = maximum observed concentration; EC = enteric-coated; λ_z = elimination rate constant; PK = pharmacokinetic(s); PPI = proton pump inhibitor; $t_{½}$ = terminal elimination half-life; T_{lag} = lag time; t_{max} = time to maximum concentration; UC = uncoated capsule; Vz/F = apparent volume of distribution.

A total of 18 subjects were enrolled, completed the study, and were included in the safety analysis. There were no deaths, SAEs, or discontinuation due to AEs in this study. Overall, a total of 21 AEs were reported by 7 (39%) subjects in this study. The percentages of subjects reporting AEs following ALXN1840 dosing were similar following each of the 3 study treatments. All AEs reported in the study were mild (Grade 1) in severity. Diarrhea, headache, and nasal congestion were the most frequently reported AEs in this study and were each reported by 2 (11%) subjects. There was 1 AE considered by the Investigator to be probably related to study drug (nausea) and 5 AEs considered to be possibly related to study drug (4 events of diarrhea and 1 event of nausea); all other AEs were considered to be unrelated to the study drugs. There were no clinically important trends in the laboratory, vital sign, ECG, or physical examination assessments in this study.

There were no apparent relationships between clearance/bioavailability (CL/F) and body size (weight, body mass index) in either Study WTX101-101 or Study WTX101-102, suggesting that a fixed dose, rather than a dose based on body size (ie, mg/kg or mg/m²) may be appropriate for ALXN1840.

ALXN1840 has been evaluated in 28 patients with WD in the Phase 2 Study WTX101-201. Final results from the main 24-week study showed that ALXN1840 monotherapy reduced mean serum non-ceruloplasmin-bound Cu by 72% at Week 24 compared with baseline. ALXN1840 treatment also resulted in significant improvements in neurological status and disability measured as a

change from baseline in Unified WD Rating Scale (UWDRS) Part III and Part II, respectively. In addition, liver status, as measured by the Modified Nazer Score and model for end-stage liver disease (MELD), was stabilized or improved in the majority of patients. Treatment with ALXN1840 was generally well-tolerated, with most reported AEs being mild (Grade 1) to moderate (Grade 2). Reversible liver function test elevations were observed in 39% of patients; these elevations were mild to moderate, asymptomatic, were associated with no notable increases in bilirubin (ie, no documented case of Hy's Law), and normalized with dose reduction or treatment interruption. No paradoxical neurological worsening was observed upon treatment initiation with ALXN1840 (Weiss, 2017). All subjects who completed the 24-week Dosing Period were enrolled in a 36-month Extension Phase. Preliminary available follow-up data at 48 weeks from the ongoing 36-month Extension Phase of the study were consistent with the 24-week Dosing Period results. No clear dose-proportionality was observed in Study WTX101-201. This result may have been due to the small sample size and relatively high inter-subject variability.

In a previous oncology study (PH1/097) with 18 patients with solid tumors, 90 mg to 210 mg of ALXN1840 co-administered with PPI showed a dose-related increase of exposure (Lowndes, 2008).

In total, tetrathiomolybdate has been evaluated in nearly 600 patients in studies of WD, oncology, macular degeneration, and primary biliary cirrhosis indications using either the ammonium or the bis-choline tetrathiomolybdate salt forms, and in 36 healthy volunteers in Phase 1 studies. ALXN1840 has been generally well-tolerated, and the most frequently reported drug-related AEs were changes in hematological parameters, fatigue, sulphur eructations, and other gastrointestinal (GI) symptoms. Aminotransferase elevations were much less common in subjects without WD compared with patients with WD; however, it should be noted that in the oncology program, which constitutes the majority of subjects without WD, causality of tetrathiomolybdate for these elevations was difficult to establish due to underlying disease.

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

2.3. Benefit/Risk Assessment

This is a healthy volunteer study and there is no direct benefit to study subjects. Identified and potential risks are described below.

More information about the known and expected benefits and risks and reasonably expected AEs with ALXN1840 may be found in the current edition of the IB.

2.3.1. Identified Risks

Many of the potential risks of ALXN1840 to patients with WD are not relevant to healthy volunteers; therefore, only those expected to be relevant risks for healthy subjects are discussed in this section.

In patients with WD, who received multiple daily doses of ALXN1840, the most commonly experienced potential drug effects were increased alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyltransferase (without increased bilirubin). Increases

occurred 4-10 weeks after daily dosing at 30 mg/day or higher. All were asymptomatic. Liver function tests normalized within 1-2 weeks of dose adjustments/treatment interruption.

Three patients with ALT increases of between 14.3 times and 29.3 times from baseline discontinued treatment. The second highest ALT (615 IU/L) concentration occurred in a patient who had initially received 120 mg/day of ALXN1840. The highest ALT (1341 IU/L) concentration occurred in a patient who had ALT elevations with previous penicillamine treatment. None of these 3 patients had a notable bilirubin increase, and all abnormal liver tests were reversible.

Other side effects observed with ALXN1840 with potential significance for the participating healthy subjects were thrombocytopenia, neutropenia, and anemia. In all cases, treated patients recovered after dose reduction.

All potential drug effects were reversible and only experienced after several weeks of daily dosing in patients with WD. The healthy volunteers in this study will receive 2 single doses of ALXN1840, a minimum of 14 days apart, which will also reduce the risk of adverse effects. The doses they will receive (as well as higher doses) have already been extensively tested in patients with WD.

Subjects will be closely monitored and remain in the CRU for a minimum of 10 days following each single dose administration. Safety blood samples will be taken at Screening and Day -1, Day 1 (4 hours post-dose), Day 2 (24 hours post-dose), Day 5 (96 hours post-dose), and Day 10 (216 hours post-dose), prior to discharge from the CRU, as well as at the EOS or Early Termination (ET) visit (if applicable).

2.3.2. Potential Risks

2.3.2.1. Pregnancy Exposure

No studies of ALXN1840 have been conducted in pregnant women. Pregnant or breastfeeding subjects will be excluded from the clinical study. To avoid pregnancy, appropriate precautions will be taken for subjects of childbearing potential as required in Section 6.8. In the event of a pregnancy in a study subject, the subject will be discontinued from study drug (Section 7) and followed up in accordance with Section 10.4.

3. OBJECTIVES AND ENDPOINTS

The study objectives and corresponding endpoints are presented in Table 5.

Table 5: Study ALXN1840-HV-104 Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the relative bioavailability of ALXN1840 administered orally as 3 × 5 mg EC tablets (test) versus 1 × 15 mg EC tablet (reference)	• PK parameters for plasma total Mo (C_{max}, AUC_t, and AUC_∞)
Secondary	
• To assess the overall safety and tolerability of ALXN1840	• Safety assessed by incidence of TEAEs and TESAEs, physical examination, vital signs measurements, clinical laboratory, and 12-lead ECG results
Exploratory	
• Relationships between CL/F and body size — body weight (kg) and body mass index (BMI, kg/m²)	• CL/F, body weight, and body mass index
• To explore PD and biomarkers of 15 mg ALXN1840 among the following dosing regimens: either as a single 15 mg EC tablet (Treatment A) or 3 EC tablets of 5 mg (Treatment B)	• Absolute and percent changes of plasma copper levels (total Cu, Cp, CpC and NCC) • The NCC level will be corrected for the amount of Cu bound to the TPC ($NCC_{corrected}$)

Abbreviations: AUC_∞ = area under the plasma concentration versus time curve from zero 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 = clearance/bioavailability; C_{max} = maximum observed concentration; Cp = ceruloplasmin; CpC = ceruloplasmin-bound copper; Cu = copper; EC = enteric-coated; Mo = molybdenum; NCC = non-ceruloplasmin-bound copper; $NCC_{corrected}$ = NCC level corrected for the amount of Cu bound to the TPC; PD = pharmacodynamic(s); PK = pharmacokinetic(s); TEAE = treatment-emergent adverse events; TESAE = treatment-emergent serious adverse event; TPC = Cu-tetrathiomolybdate-albumin tripartite complex formed after ALXN1840 administration.

4. STUDY DESIGN

4.1. Overall Design

This is a single-center, randomized, open-label, 2-way crossover study to assess the single-dose PK of ALXN1840 EC tablets at 2 dose strengths healthy male and female adult subjects under fasting conditions. Pharmacokinetic parameters will be calculated based on the measurement of plasma total Mo concentration. A total of 48 healthy, adult participants (20-28 males and 20-28 females) who complete the study screening assessments and meet all eligibility criteria will be enrolled to allow for a minimum of 40 subjects to complete the study (20-24 subjects in each sequence, 10-14 of each sex in each sequence).

The study has a Screening Period (Days -28 to -2), 2 Dosing Periods (Day -1 to Day 11 each), and an end-of-study (EOS) visit 14 days (+ 2 days post final dose). After completing the Screening Period, enrolled subjects will be admitted to an inpatient facility (Clinical Research Unit [CRU]) on Day -1 for dosing on Day 1 in Dosing Period 1. Subjects will be readmitted to the CRU for Dosing Period 2 following a minimum of 14 days after the previous dose.

Subjects will be randomized to 1 of the 2 treatment sequences, where the single 15 mg EC tablet (Treatment A) is the "reference" dose and the 3 EC tablets of 5 mg (Treatment B) are the "test" dose, as defined in Table 6.

Table 6: Study Drug Dosing Sequences

Sequence Number	Treatment Sequence		Male[a]	Female[a]	Total
	Period 1	Period 2			
1	A	B	10-14	10-14	24
2	B	A	10-14	10-14	24
Total			**20-28**	**20-28**	**48**

[a] In an effort to achieve balance between males and females in each sequence, there will be no less than 20 and no more than 28 of either sex (ie, a maximum split in either direction of approximately 60%:40%).

After completing the screening phase, enrolled subjects will be admitted to an inpatient facility (CRU) on Day -1 for dosing on Day 1. During Days 1 to 11 of each Dosing Period, subjects will remain at the CRU and have samples obtained for PK/pharmacodynamic (PD) biomarkers as well as safety evaluations performed according to the Schedule of Activities (Table 1 and Table 2). Subjects will be discharged 10 days after dosing within each Dosing Period (ie, on Day 11) following the 240-hour post-dose procedures, unless it is medically necessary to extend the confinement. Subjects will return to the CRU for Dosing Period 2 following a minimum of 14 days between the 2 Dosing Periods.

In each Dosing Period, subjects will receive 1 of the 2 treatments as outlined in Table 7.

Table 7: Study Drug Dosing

Treatment A (reference)	1 × 15 mg ALXN1840 EC tablet
Treatment B (test)	3 × 5 mg ALXN1840 EC tablets

Abbreviation: EC = enteric-coated.

Subjects will return to the CRU 14 days (+ 2 days) after the final dose of study drug for the EOS visit with follow-up procedures, and to determine if any AE has occurred since the last study visit. If subjects withdraw from the study early, they will be seen and assessed by the Investigator, whenever possible, to undergo the procedures associated with the EOS visit. Subjects may be replaced at the discretion of the Sponsor.

The planned study duration is approximately 70 days; up to 27 days for screening, approximately 29 days for dosing and follow-up, and an interval of at least 14 days between the 2 Dosing Periods.

The study will be conducted at a single site in the UK.

A Safety Review Committee may be used to evaluate the study data for subject safety and make recommendations on dose modification or termination of the study.

4.2. Scientific Rationale for Study Design

- This study is being conducted in healthy subjects and not patients with WD 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 typical Phase 1 clinical pharmacology studies for assessing the medication of interest and to minimize assignment bias.
- A 2-way crossover study design was adopted to control the variability within and between subjects.
- The interval between the 2 ALXN1840 Dosing Periods will be at least 14 days, based on the estimated mean half-life for ALXN1840 of approximately 2 days previously reported in the bioavailability Studies WTX101-101 and WTX101-102, where healthy subjects took oral dose at 60 mg. Therefore, the 14-day interval between Dosing Periods is considered sufficient to eliminate, on average, approximately more than 99.2% of the plasma total Mo before the next dose is administered. The 14-day interval after Period 2 dosing will also assure that the subjects will have virtually all the ALXN1840 eliminated at the EOS.

4.3. Justification for Dose

The 5 mg ALXN1840 dose has been manufactured and selected to be tested in this study to support dosing in pediatric patients with WD, in whom a lower starting dose may be warranted.

The 15 mg EC tablet formulation is the current formulation being tested in the on-going Phase 3 Study WTX101-301. The 5 mg EC tablet formulation is new and has not been tested in humans.

The per-period 15 mg ALXN1840 total dose selected for this study in healthy subjects is within the dose range demonstrated to be safe in healthy subjects and has demonstrated a favorable safety profile and treatment effects in patients with WD. Oral doses of 60 mg ALXN1840 in non-coated capsules or EC tablets (30 mg formulation), were tested in previous 3-period crossover bioavailability studies conducted in healthy male and female volunteers (Studies WTX101-101 and WTX101-102), and were considered to have a favorable safety profile and to be well tolerated. The 15 to 60 mg/day dose range has also been demonstrated to be efficacious with a favorable safety profile in treating patients with WD in the Phase 2 Study WTX101-201 (Weiss, 2017).

In summary, to date, 15 to 60 mg/day single or repeated daily doses have shown to have favorable safety profiles and to be well tolerated throughout the Phase 1 to Phase 3 clinical studies, in both healthy subjects and patients with WD.

4.4. End of Study Definition

A subject will be considered to have completed the study if the subject has completed all periods of the study including the EOS visit.

Measurement of the primary endpoint will be completed after the last visit of the last subject in the study. The end of the study is defined as the last visit for the last subject.

5. STUDY POPULATION

The study population will consist of adult healthy volunteers who meet study enrollment criteria. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Subjects will be eligible to be included in the study only if all of the following criteria apply:

Age/Sex

1. Male or female subject must be 18 to 45 years of age, inclusive, at the time of signing the informed consent.

Weight

2. Body weight ≤ 100 kg and body mass index within the range 18 – 25 kg/m^2, inclusive, at screening.

Pregnancy

3. Negative serum pregnancy test at screening and Day-1 for all women of childbearing potential.

Contraception

4. Female subjects of childbearing potential, if heterosexually active, and male subjects, if heterosexually active and with a female spouse or partner of childbearing potential or a pregnant or breastfeeding spouse or partner, must be willing to follow protocol-specified contraception guidance starting at least one menstrual cycle before first study drug administration and continuing for up to 3 months after the end of systemic exposure of the study drug (ie, 3 months after EOS visit) (described in Section 6.8).

Other Inclusion Criteria

5. Adequate venous access in the left or right arm to allow collection of a number of blood samples.
6. Willing and able to fast per the study requirements.
7. Satisfactory medical assessment with no clinically significant or relevant abnormalities as determined by medical history, physical examination, vital signs, 12-lead ECG, and clinical laboratory evaluation (hematology, biochemistry, coagulation, and urinalysis) that are reasonably likely to interfere with the subject's participation in or ability to complete the study, or to potentially confound interpretation of study results, as assessed by the Investigator.

Informed Consent

8. Willing and able to give written informed consent as described in Section 10.1.3, which includes compliance with the requirements listed in the informed consent form (ICF) and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions

1. Current or recurrent/chronic disease (eg, cardiovascular, hematological, neurological, endocrine, immunological, rheumatological, renal, hepatic or GI or other conditions) that or could affect clinical assessments or clinical laboratory evaluations.
2. Current or relevant history of physical or psychiatric illness that are not stable or may require a change in treatment, use of prohibited therapies during the study or make the subject unlikely to fully comply with the requirements of the study or complete the study, or any condition that presents undue risk from the study drug or study procedures.
3. Any other significant disease or disorder which, in the opinion of the Investigator, may put the subject at risk.
4. History of malignancy with the exception of a nonmelanoma skin cancer or carcinoma *in-situ* of the cervix that has been treated with no evidence of recurrence within 5 years.
5. Positive test for hepatitis B surface antigen (HBsAg) or HIV antibody at screening.
6. Acute or chronic hepatitis C virus infection (evidenced by detection of hepatitis C virus (HCV) antibody and confirmed by detection of HCV RNA.
7. 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

8. Use of prescription medications (excluding oral contraceptives) within 14 days prior to dosing on Day 1, except with prior approval of the Sponsor.
9. Use of nonprescription/ over-the-counter medications, including herbal remedies and supplements, within 7 days prior to dosing on Day 1.

Prior/Concurrent Clinical Study Experience

10. Participation (ie, last protocol-required study visit) in a clinical study within 90 days before initiation of dosing on Day 1.

Diagnostic Assessments

11. Supine blood pressure < 90/60 mmHg or > 140/90 mmHg at screening.
12. Serum ceruloplasmin (Cp) value outside of the normal range at screening.
13. Serum total Cu value outside of the normal range at screening.
14. Hemoglobin level below the lower limit of normal at screening.

15. Serum creatinine > upper limit of normal (ULN) of the reference range of the testing laboratory at screening or on Day -1.
16. Alanine aminotransferase, AST, or total bilirubin outside of normal reference range of the testing laboratory at screening.
17. Any clinically significant abnormal hematological parameters (per the Investigator's discretion).
18. Donated or lost 400 mL blood or more within the last 16 weeks preceding the first day of dosing.

Other Exclusion Criteria

19. Female subjects who are breastfeeding.
20. Prior exposure to ALXN1840.
21. Major surgery or hospitalization within 90 days prior to dosing on Day 1.
22. Use of tobacco in any form (e.g. smoking or chewing) or other nicotine-containing products in any form (e.g. gum, patch, electronic cigarettes) 6 months prior to the planned first day of dosing (Section 5.3.2).
23. History of illicit drug abuse, history of significant alcohol abuse within 1 year prior to the screening visit, or clinical evidence of substance and/or alcohol abuse within the 2 years before screening. Alcohol abuse is defined as regular weekly intake of more than 14 units (for both males and females), using the following NHS alcohol tracker http://www.nhs.uk/Tools/Pages/drinks-tracker.aspx.
24. Positive urine drug toxicology screen at screening or on Day -1.
25. Alcohol consumption within 48 hours prior to study drug administration or positive alcohol breath test at screening or on Day -1.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

- Subjects are required to abstain from ingesting food containing poppy seeds within 24 hours prior to admission.
- Subjects will receive standardized meals and snacks scheduled at the same time in each period of the study. No outside food or drink is permitted at the inpatient facility. All meals and snacks will be provided.
- Subjects will be administered the dose of ALXN1840 following an overnight fast of at least 10 hours. No food will be allowed for at least 4 hours post-dose. Water can be allowed as desired except for 1 hour before and after drug administration.

5.3.2. Caffeine, Alcohol, and Tobacco

Subjects will be required to abstain from:

- Ingesting caffeine- or xanthine-containing products (eg, coffee, tea, cola drinks, and chocolate) 24 hours before admission through discharge from the inpatient facility, and 24 hours before each study outpatient/follow-up visit.
- Ingesting alcohol 48 hours before admission through discharge from the inpatient facility, and 48 hours before each study outpatient/follow-up visit.
- Using tobacco in any form (e.g. smoking or chewing) or other nicotine-containing products in any form (e.g. gum, patch, electronic cigarettes) 6 months prior to the planned first day dosing through to the EOS visit.

5.3.3. Physical Activity

Subjects will be required to abstain from strenuous physical activity 48 hours prior to blood draws for clinical safety laboratory testing. Subjects should not start new physical training activities during the study until study completion (last visit).

5.4. Screen Failures and Replacements

Screen failures are defined as subjects who signed consent to take part in the study but were not randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT; Schulz, 2010) publishing requirements and to respond to queries from regulatory authorities.

Rescreening is not permitted where the cause is not deemed to be temporary. Subjects who initially failed due to temporary non-medically significant issues (eg, screening occurs outside the planned window) are eligible for rescreening one the cause has resolved.

Minimal information including ICF process and reason for screen failure will be source data reviewed. All subjects will be listed in the Screening progress report, and screen failure subjects will be reviewed by the clinical research associate

5.4.1. Criteria for Study Termination

The Investigator, competent authority, or Alexion may terminate the study for reasonable cause. Conditions that warrant termination of the study include, but are not limited to, the following:

- Discovery of an unexpected, serious, or unacceptable risk to subjects enrolled in the study.
- Decision on the part of Alexion to suspend or discontinue testing, evaluation, or development of the study drug.
- Failure of the Investigator to comply with the approved protocol, pertinent guidelines, and/or regulations.
- Submission of knowingly false information from the Investigator to Alexion and/or regulatory authorities.

6. STUDY DRUG

Study drug is defined as any investigational drug product(s), marketed product(s), or placebo, intended to be administered to a subject according to the protocol. ALXN1840 (bis choline tetrathiomolybdate), administered orally, is the only drug investigated in this study.

6.1. Study Drug Administered

The study drug composition and doses to be administered in this study are presented in Table 8.

Table 8: Study Drug Administered

Study Intervention Name:	ALXN1840 (formerly WTX101)
Dosage formulation:	EC tablets (containing either 15 mg ALXN1840 or 5 mg ALXN1840)
Unit dose strength(s)/Dosage level(s):	15 mg ALXN1840 EC tablet (Treatment A) 5 mg ALXN1840 EC tablet (Treatment B)
Route of Administration	Oral
Dosing instructions: *Additional instructions are provided in the pharmacy manual.*	Study drug will be administered as outlined in Table 6. All study medications will be taken with approximately 240 mL of water. Subjects will be instructed not to crush, split, or chew the study medication.
Packaging and Labeling *Additional instructions are provided in the pharmacy manual.*	ALXN1840 will be provided in bulk blisters with each tablet situated in one transparent thermoform cavity. Each blister will be labeled per country requirement.
Manufacturer	Catalent, Inc.

Abbreviation: EC = enteric-coated.
Source: ALXN1840 Investigator's Brochure

The blistered study drug will be supplied to the Investigator's site as bulk blistered inventory. The site's pharmacy will repackage the supplies into individual, labelled subject doses and perform Qualified Person certification of the repackaged product.

6.2. Packaging and labelling of IMPs

The labelling of the study drugs will be in compliance with Good Manufacturing Practice (GMP) specifications, as described in The Rules Governing Medicinal Products in the European Union, Volume 4, Annex 13, Investigational Medicinal Products, and any other or local applicable regulations.

Sample label(s) will be submitted to the UK health authorities according to the submission requirements.

6.3. Preparation/Handling/Storage/Accountability

- The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit and storage for all study drug received and any discrepancies will be reported and resolved prior to use of the study drug.

- Only subjects enrolled in the study may receive study drug and only authorized site staff may supply or administer study drug. All study drug 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.
- The Investigator, or qualified designee, is responsible for study drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Additional instructions are provided in the pharmacy manual.

6.4. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study where, in order to minimize selection bias in treatment assignment, subjects will be randomized to 2 treatment sequences.

Eligible subjects who meet all inclusion and no exclusion criteria will be assigned unique numbers for enrollment. Study subject numbers will not be reallocated once assigned.

In an effort to achieve balance between the number of males and females in the 2 sequences, the maximum split in either direction will be approximately 60%:40% (10-14 of each sex in each sequence).

6.5. Study Drug Compliance

Study drug will be administered to subjects in a controlled setting under the supervision of the Investigator, or designee, thereby ensuring compliance with study drug administration. Study center personnel will ensure that all subjects are adequately informed about the specific study drug dosing regimen required for compliance with the study protocol.

6.6. Study Drug Stopping Rules

6.6.1. Adverse Reaction Rules

An adverse reaction is any TEAE that is considered related to the study medication (for a full definition of related TEAEs, see Section 10.3.5).

Any TEAEs or TESAEs that are not considered related to study drug do not constitute adverse reactions or serious adverse reactions and, therefore, these rules do not apply.

6.6.1.1. General Adverse Reaction rules

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

Individual Adverse Reaction Rules

An individual subject will not receive the dose of ALXN1840 in the subsequent period, if either of the following occurs:

- Subject experiences any CTCAE Grade 3 (or higher) adverse reaction, or a serious adverse reaction, irrespective of severity/CTCAE grade.
- Subject experiences any CTCAE Grade 1 or 2 adverse reaction considered to be related to study drug that is considered a safety concern by the Safety Review Committee.

Group Adverse Reaction Rules

Dosing will be suspended for all subjects, or potentially only in an affected cohort, if either of the following occurs:

- One subject (among any of the 48 total subjects) experiences a non-serious, severe (CTCAE Grade 3) adverse reaction.
- One subject experiences a serious adverse reaction, irrespective of severity/CTCAE grade.

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

Special individual Adverse Reaction Rules

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

- Liver function test elevation
  - ALT or AST value > 3 × ULN together with bilirubin increase >2 × ULN.
  - ALT or AST value > 8 × ULN.
  - ALT or AST value > 3 × ULN, and symptomatic.
- Hematology
  - Hemoglobin reduction to an absolute value of 8g/dL (80g/L) or lower.
  - Platelet count reduction of > 50% from baseline or absolute value < 80.000/mm^3 (Day -1 blood samples).
- QT interval prolongation
  - A prolongation of the uncorrected QT interval of > 500ms (using consistent, technically valid triplicate ECG).

Special group AR rules

If 1 subject fulfils the special individual adverse reaction rules, and this could be reasonably attributed to study drug, a Safety Review Committee meeting will be arranged and, if necessary, dosing for all subjects will be temporarily suspended until the Safety Review Committee meets. At this meeting, a decision will be made regarding the continuation of dosing in the remaining subjects.

If it is then confirmed that 1 subject fulfils Hy's Law criteria, dosing will be suspended in all subjects and can only continue with a substantial amendment to the protocol that has been approved by the MHRA and ethics committee.

If 2 or more subjects fulfil any of the other special individual adverse reaction rules, dosing will be suspended in all subjects and can only continue if the Safety Review Committee decides that dosing can continue, and a substantial amendment is made to the protocol that is approved by the MHRA and ethics committee.

Details of the Safety Review Committee are provided in Section 8.4.

6.7. Concomitant Therapy

- Subjects must abstain from taking prescription drugs within 14 days prior to dosing on Day 1 and nonprescription drugs/ over-the-counter medications (including vitamins and dietary or herbal supplements) within 7 days prior to dosing on Day 1 until completion of the follow-up visit, unless, in the opinion of the Investigator and the Sponsor, the medication will not interfere with the study.
- As per the ALXN1840 IB, in this study, investigators should use caution in the co-administration of drugs known to be substrates of CYP2C9 and CYP2B6. Common substrates of CYP2C9 include ibuprofen, which is permitted in this study. Therefore, 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
- Topical skin products without significant systemic absorption are permitted for use during the study at the Investigator's discretion.
- Other concomitant medication may be considered on a case-by-case basis by the Investigator in consultation with the medical monitor if required.
- Concomitant procedures are not allowed unless medically indicated and/or permitted by the Sponsor or the Investigator or delegate.

6.8. Contraception Guidance

Female subjects who are documented as being of non-childbearing potential as defined in Section 10.4 are exempt from contraception requirements.

Female subjects of childbearing potential, if heterosexually active, must use highly effective contraception as defined below, starting at least one menstrual cycle before first study drug administration and continuing for up to 3 months after the end of systemic exposure of the study drug (i.e. 3 months after EOS visit).

Highly effective contraceptive methods for females are as follows:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation as follows:
  - Oral
  - Intravaginal

  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation as follows:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Male partner vasectomized (with documented evidence of azoospermia if possible)
- Abstinence (N.B. 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 treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject).

Male subjects, 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 drug (ie, 3 months after EOS visit). Barrier contraception is required even with documented medical assessment of surgical success of a vasectomy. Female spouses or partners of male subjects who are of childbearing potential must use highly effective contraception as defined above, starting at least 1 menstrual cycle before (the male subject's) first study drug administration and continuing until at least 3 months after the end of their male partner's systemic exposure to the study drug (ie, 3 months after EOS visit). Male subjects must not donate sperm and female subjects must not donate ova for at least 3 months after the end of systemic exposure of the study drug (ie, 3 months after EOS visit).

For male subjects 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.

6.9. Intervention after the End of the Study

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

7. DISCONTINUATION OF STUDY DRUG AND SUBJECT WITHDRAWAL

7.1. Discontinuation of Study Drug

Subjects who discontinue study drug, for any reason, should undergo all scheduled safety, PK and PD evaluations as specified in the Schedule of Activities (Table 1 and Table 2) in relation to the last dose they received.

If a subject withdraws consent and is unwilling to attend all scheduled procedures, then all attempts will be made to encourage them to attend for the EOS visit.

7.2. Subject Withdrawal From the Study

A subject 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.

If the subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

Data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed are specified in the Schedule of Activities (Table 1 and Table 2).

7.3. Lost to Follow Up

A subject 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 subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and leave a message on their primary contact number (if not answered), explaining the reason and need to attend visits. If not answered, the site will send an SMS to this number asking the volunteer to contact the site urgently.
- In parallel, the site will send an e-mail to the subject requesting the subject to attend the study visit. If no e-mail address is available, the site will send a written letter to the subject's primary address with the same information. These contact attempts must be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the Schedule of Activities (Table 1 and Table 2).

- Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor's medical monitor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the subject's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Activities.

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 presented in the Schedule of Activities (Table 1 and Table 2).

8.2.1. Physical Examination

A full physical examination will be performed at screening and at the beginning of each Dosing Period admission. A symptom-driven physical examination will be performed at the EOS visit and may be performed at other times, at the Investigator's discretion.

Each examination will include the following assessments: general appearance; skin; head, ears, eyes, nose, and throat; neck; lymph nodes; chest; heart; abdominal cavity; limbs; central nervous system; and musculoskeletal system.

Height and weight will also be measured and recorded at screening and the EOS visit. Body mass index will be calculated and recorded at screening and the EOS visit.

8.2.2. Vital Signs

Vital sign measurements will be taken after the subject has been resting in the supine position for at least 5 minutes and will include temperature (°C; tympanic), respiratory rate (RR), supine blood pressure, and heart rate. Orthostatic (standing) blood pressure will only be measured at

screening, after volunteers have been standing for 1 minute. The timing of vital sign measurements is described in the Schedule of Activities (Table 1 and Table 2). Out of range blood pressure or heart rate measurements will be repeated at the Investigator's discretion. Confirmed, clinically significant vital sign measurements will be recorded as TEAEs.

8.2.3. Electrocardiograms

8.2.3.1. Recording of 12-Lead ECGs

A triplicate 12-lead ECG will be obtained using a GE Marquette MAC1200® / MAC1200ST® recorder connected via a fixed network connection to the MUSE® Cardiology Information System (MUSE) after the subject has been resting for at least 10 minutes. 12-lead ECGs will be conducted before PK/PD/biomarker blood sampling if these 2 events occur at the same time. The timing of 12-lead ECGs is described in the Schedule of Activities (Table 1 and Table 2).

12-lead ECGs recorded during screening will be stored electronically on the MUSE information system. Only ECGs recorded electronically will be valid ECGs for any purpose other than safety assessment. ECG printouts may be filed in the subject's case report form (CRF) for medical safety reviews.

Each 12-lead ECG recorder will be set up to the required technical specifications and containing the information required to identify the records. Each ECG recording will be clearly identified (Subject ID, visit date, and the actual times of ECG recordings).

12-lead ECG recordings will be made after the subjects have been resting in a supine position for at least 10 minutes. The subjects will avoid postural changes during the ECG recordings and clinical staff will ensure that subjects are awake during the ECG recording.

At each time point, the 12-lead ECG will be recorded in triplicate, to reduce variance and improve the precision of measurement. The triplicates will be performed at approximately 1-minute intervals. Each ECG recording (trace) will last 10 seconds. Repeat ECGs will be performed until at least three 10-second ECG records per scheduled time-point meet the quality criteria set out in the Study Operations Manual and the applicable Standard Operating Procedure to enable reading and analyzing at least 5 complexes per derivation.

8.2.3.2. Safety Review of 12-Lead ECGs

All recorded 12-lead ECGs will be reviewed by the Investigator, or qualified designee, and the review findings will be documented in the CRF. If a subject shows an abnormal ECG, additional safety recordings (including the use of 5- or 12-lead Holter equipment) may be made and the abnormality be followed to resolution, if required.

8.2.4. Clinical Safety Laboratory Assessments

All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the Schedule of Activities (Table 1 and Table 2) and the laboratory manual. Clinical and laboratory assessments will be performed by a local laboratory to assess safety of ALXN1840. Laboratory assessments will include full liver safety tests, creatinine, and calculation of creatinine clearance.

- The Investigator must review the laboratory report, document this review, and record all clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study will 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 the Sponsor's medical monitor should be notified.
  - If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.
- The maximum amount of blood to be collected from each subject over the duration of the study, including any extra assessments that may be required, will not exceed 500 mL. Repeat or unscheduled samples may be obtained for safety and/or eligibility reasons or if there are any technical issues with the samples. Please refer to the laboratory manual for specific details regarding plasma sampling volumes.

8.2.5. Drug and Alcohol Screen

A urine sample for drug screen will be analyzed for the substances listed in Section 10.2. Timing of urine drug and alcohol breath tests is specified in the Schedule of Activities (Table 1 and Table 2).

8.2.6. Pregnancy Testing

Pregnancy testing will be performed in serum for all female subjects at the time points specified in the Schedule of Activities (Table 1 and Table 2).

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE and specific reporting requirements are located in Section 10.3. Adverse events will be reported to the Investigator or qualified designee by the subject (or, when appropriate, by a caregiver, surrogate, or the subject'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 drug or study procedures, or that caused the subject to discontinue the study drug (see Section 7).

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

All AEs and SAEs will be collected from signing of the informed consent form (ICF) until the EOS visit.

Medical occurrences that begin before the first dose of study drug and after obtaining informed consent will be recorded on the CRF and will be considered as medical history.

All SAEs will be recorded and reported to the Sponsor, or designee, within 24 hours, as indicated in Section 10.3. The Investigator will submit updated SAE data to the Sponsor within 24 hours of the data being available.

Investigators are not obligated to actively seek AEs or SAEs after the conclusion of study participation (i.e., after EOS visit).

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

8.3.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject 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 each subject at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 10.3). Further information on follow-up procedures is provided in Section 10.3.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study intervention under clinical investigation are met.
- The Sponsor 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. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Independent Ethics Committee (IEC), and Investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and the Sponsor's policy and forwarded to Investigators as necessary.
- An Investigator who receives a safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

- Incidence of all pregnancies in female subjects and if indicated female sexual partners of male subjects will be collected after the administration of study drug and for at least 3 months after the EOS visit thereafter.
- Complications of abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are AEs and may meet the criteria for SAEs (Section 10.3).
- If a pregnancy is reported, the Investigator should inform the Sponsor, or designee, within 24 hours of learning of the pregnancy. Specific pregnancy information to be collected is outlined in Section 10.3.6.

8.4. 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 (see Section 6.6).

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.

8.5. Treatment of Overdose

No cases of overdose have been reported during ALXN1840 clinical studies. Study drug will be administered and monitored by site personnel.

8.6. Pharmacokinetics

Whole blood samples will be collected for the measurement of plasma total Mo (PK) over time as specified in the Schedule of Activities (Table 1 and Table 2). Additional samples may be collected during the study if warranted and agreed upon between the Investigator and the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded. Other PK concentration measurements including, but not limited to, that of plasma ultrafiltrate (PUF) Mo may be conducted.

Additional samples may be collected during the study if warranted and agreed upon between the Investigator and Alexion. Details including further handling and processing instructions and sampling-time windows will be provided in the study laboratory manual.

8.7. Pharmacodynamics

After study drug administration, plasma samples will be collected for the measurement of plasma total Cu and non-ceruloplasmin-bound copper (NCC) over time as specified in the Schedule of Activities (Table 1 and Table 2). Calculations will also be performed for NCC and corrected NCC ($NCC_{corrected}$), the latter of which is non-Cp-bound and non-Mo-albumin-bound Cu.

Detailed calculation formulae will be provided in the statistical analysis plan (SAP). The actual date and time (24-hour clock time) of each sample will be recorded.

Additional samples may be collected during the study if warranted and agreed upon between the Investigator and the Sponsor. Details including further handling and processing instructions and sampling-time windows will be provided in the study laboratory manual.

8.8. Genetics

Genetics will not be evaluated in this study.

8.9. Biomarkers

After study drug administration, whole blood samples will be collected for the measurement of plasma Cp and ceruloplasmin-bound copper (CpC) as biomarkers as specified in the Schedule of Activities (Table 1 and Table 2). Analyses of other biomarker data including, but not limited to, those of PUF Cu may be conducted.

The actual date and time (24-hour clock time) of each sample will be recorded. Additional samples may be collected during the study if warranted and agreed upon between the Investigator and the Sponsor. Details including further handling and processing instructions and sampling-time windows will be provided in the study laboratory manual.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

Not applicable.

9.2. Sample Size Determination

The study sample size is not based on hypothesis testing with statistical considerations. A sample size of 40-48 subjects (20-24 subjects in each sequence; 10-14 male and female subjects in each sequence, with a maximum split in either direction of approximately 60%:40%) has been selected based on practicality and convention for this type of study. Considering potential for subject drop-out of the study, a total of 48 subjects will be enrolled with 20-28 male subjects and 20-28 female subjects.

The primary objective of this study is to assess the relative bioavailability of 3 × 5 mg EC tablets (Treatment B, test) versus 1 × 15 mg EC tablet (Treatment A, reference). Although there will be no formal bioequivalence test, the framework of 2 one-sided tests, with limits of 0.8 and 1.25, can be applied to assess the adequacy of the sample size. A post-hoc analysis of a previous bioavailability study (WTX101-102) found a within-subjects coefficient of variation (CV) of 0.34. For data from a two-period cross-over design, a total sample size of 40 subjects achieves 81% power at a 5% significance level when the true ratio of the means is 1, and the coefficient of variation is 0.34.

9.3. Populations for Analyses

The analysis sets are defined in Table 9.

Table 9: Study ALXN1840-HV-104 Analysis Sets

Population	Description
Enrolled	All subjects who sign the ICF
Safety Set	All subjects who receive at least 1 dose of study drug
Pharmacokinetic	All subjects who have sufficient plasma samples to enable the calculation of PK parameters
Pharmacodynamic	All subjects who have sufficient plasma samples which will enable the evaluation of the PD effects

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

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. Descriptive statistics for PK parameters will include number of observations, arithmetic mean, SD, arithmetic coefficient of variation (%CV), median, minimum, maximum, geometric mean and geometric %CV. Categorical variables will be summarized using percentages and frequency counts. Descriptive statistics and percentages and frequency counts will be summarized by sex, treatment, period, and sequence, where appropriate.

All statistical analyses will be conducted using SAS® for Windows® Version 9.3 or higher.

An SAP will be developed and finalized before data cutoff/database lock and will further describe the subject 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 analyses will be performed for this study.

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 (SOC) and Preferred Term for each treatment and overall, by relationship to study drug. Adverse events will also be summarized by treatment and overall by severity. Serious AEs and AEs resulting in withdrawal from the study will be listed. Subjects having multiple AEs within a category (eg, overall, SOC, Preferred Term) will be counted once in that category. For severity tables, a subject'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 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 subjects 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 each treatment.

All concomitant medications will be coded and summarized using the WHO Drug Dictionary.

9.4.3. Other Analyses

9.4.3.1. Pharmacokinetic Analyses

Individual ALXN1840 PK, assessed as plasma total Mo concentration-time data will be listed, plotted, and summarized with descriptive statistics, with mean PK data plotted. The following plasma total Mo PK parameters will be derived for individual subjects and summarized with descriptive statistics: C_{max} in plasma, time to maximum concentration (t_{max}) in plasma, area under the plasma concentration versus time curve from time 0 to the last quantifiable concentration (AUC_t), area under the plasma concentration versus time curve from time 0 (dosing) to infinity (AUC_∞), apparent terminal-phase elimination rate constant (λ_z), $t_{½}$, CL/F, apparent volume of distribution (V_d/F), and relative bioavailability (F_{rel}) between test and reference treatments.

Analyses of other PK data including, but not limited to those, of PUF Mo may be conducted. PK parameters will be calculated using Phoenix® WinNonlin®.

Detailed PK analyses will be described in the PK/PD data analysis plan (DAP), which will be finalized before database lock.

9.4.3.1.1. Bioavailability Analysis

The PK parameters for total Mo (C_{max}, AUC_t, and AUC_∞) will be evaluated using an Analysis of Variance (ANOVA) statistical model with Dosing Period, treatment, and sequence as the fixed effects, and subject as a random effect, using the natural logarithms of the data. Confidence intervals (90%) will be constructed for the least squares geometric mean ratios (GMR) for the 3 × 5 mg ALXN1840 versus 1 × 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-subject coefficient of variation 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% confidence intervals of C_{max}, AUC_t, and AUC_∞ will be reported for each treatment.

Detailed PK analyses will be described in the PK/PD DAP finalized before database lock.

9.4.3.1.2. Pharmacodynamic and Biomarker Analyses

Individual ALXN1840 PD and biomarkers, assessed as plasma total Cu (PD), NCC (PD), $NCC_{corrected}$ (PD), Cp (biomarker), and CpC (biomarker) concentration-time data will be listed and summarized with descriptive statistics and plotted. The same analyses will be conducted on the absolute and percent changes from baseline of these PD and biomarker concentration-time data. Analyses of other biomarker data including, but not limited to, those of PUF Cu may be conducted.

Detailed PD analyses will be described in the PK/PD DAP finalized before database lock.

9.5. Interim Analyses

No interim analyses are planned for this study.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

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

10.1.2. Financial Disclosure

Investigators and Sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor 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

- The Investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding the study.

- Subjects must be informed that their participation is voluntary. Subjects will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the subject. The Investigator must retain the original version of the signed ICF(s).

10.1.4. Data Protection

- Subjects will be assigned a unique identifier. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.
- The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate 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 the US National Institutes of Health website www.clinicaltrials.gov, the EU website www.clinicaltrialsregister.eu/, or other publically accessible websites as appropriate and in accordance with local regulations.

10.1.6. Data Quality Assurance

- All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor 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, IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor, 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 subjects 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. Study monitors will communicate with investigative sites on a regular basis regarding study protocol deviations. All protocol deviations will be appropriately documented by the Investigator or designee, and study monitors.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for a minimum of 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor. Unless otherwise specified, procedures, data collection, and evaluation will be conducted as per the study center's standard operating procedures.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. The Investigator or designee will prepare and maintain adequate and accurate source documents (medical records, ECG readings, AE and concomitant medication reporting, raw data collection forms) designed to record all observations and other pertinent data for each subject. Source documents are filed at the Investigator's site.
- Data entered in the CRF 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.

10.1.8. Study and Site Closure

The Sponsor, or designee, reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

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

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

- Failure of the Investigator to comply with the protocol, the requirements of the IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the Investigator
- Discontinuation of further study drug development

10.1.9. Publication Policy

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

10.2. Clinical Laboratory Tests

The tests detailed in Table 10 will be performed by the local laboratory.

- Protocol-specific requirements for inclusion or exclusion of subjects 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 ("CS") or not clinically significant ("NCS").

Table 10: Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	**Parameters**		
Hematology	Platelet count RBC count Hemoglobin Hematocrit	RBC indices: Mean corpuscular volume Mean corpuscular hemoglobin % Reticulocytes	WBC count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical chemistry	BUN Chloride Potassium Bicarbonate Sodium Glucose	AST ALT Alkaline phosphatase, Gamma glutamyltransferase HbA1C (Screening only) Urea	Total and direct bilirubin Total protein Albumin Creatinine Creatine phosphokinase
Coagulation	International normalized ratio, partial thromboplastin time, prothrombin time		
Routine urinalysis	Specific gravity, pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase Microscopic examination (if any leucocytes, more than a trace protein, nitrites, and blood [if not menstruating] are abnormal)		
Other screening tests	• 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]) • Cp and Cu concentrations in serum • HIV-1 and HIV-2 antibodies, HBsAg, anti-HBC IgG + IgM (if IgG positive), and anti-HCV with confirmation by HCV RNA • Serum hCG pregnancy test (as needed for women of childbearing potential) • FSH (postmenopausal females only)		

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; Cp = ceruloplasmin; Cu = copper; FSH = follicle stimulating hormone; HBsAg = hepatitis B surface antigen; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; RBC = red blood cells; WBC = white blood cells.

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

10.3.1. Adverse Event Definition

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

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

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition. • 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 (social and/or convenience admission to a hospital). • 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.

10.3.2. Adverse Reaction Definition

Adverse Reaction Definition
• An adverse reaction is any TEAE that is considered related to the study medication (for a full definition of related TEAEs, see Section 10.3.5)

10.3.3. Serious Adverse Event Definition

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

A serious adverse event 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 subject 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 were more severe.

3. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the subject 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 subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.4. Suspected Unexpected Serious Adverse Reactions

Suspected Unexpected Serious Adverse Reactions Definition

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the Investigator identifies as related to study drug or procedure. The US 21CFR312.32 and EU Clinical Trial Directive 2001/20/EC and the associated detailed guidance documents or national regulatory requirements in participating countries require the reporting of SUSARs. The Sponsor has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidance documents. Suspected unexpected serious adverse reactions will be reported to the national competent authority and IECs where applicable.

10.3.5. Recording and Follow-Up of AEs and/or SAEs

Adverse Event and Serious Adverse Event Recording

- When an AE or 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 or SAE information in the CRF.
- It is not acceptable for the Investigator to send photocopies of the subject's medical records to the Sponsor or designee 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 the Sponsor or designee. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Event Severity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories from CTCAE v5.0, published 27 Nov 2017. Each CTCAE term is a Lowest Level Term per MedDRA. Each Lowest Level Term will be coded to a MedDRA Preferred Term:

1. Grade 1: Mild (asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated)
2. Grade 2: Moderate (minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living [ADL])
3. Grade 3: Severe (severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL)
4. Grade 4: Life-threatening consequences; urgent intervention indicated
5. Grade 5: Death related to AE

Any change in the severity of an AE should be documented based on specific guidelines in the CRF Completion Guidelines.

Severity and seriousness must be differentiated: severity describes the intensity of an AE, while the term seriousness refers to an AE that has met specific criteria for an SAE as described above.

Causality Assessment

- An Investigator causality assessment (not related or related) must be provided for all AEs, both serious and nonserious based upon the Investigator's medical judgement and the observed symptoms associated with the event. This assessment must be recorded in the CRF and any additional forms as appropriate.
- Causality Assessment Descriptions
  - Not related: This relationship suggests that there is no causal association between the study drug and the reported event.
  - Related: This relationship suggests that there is causal association between the study drug and the reported event.

Follow-up of Adverse Events and Serious Adverse Events
• The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor or designee 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 subject dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor or designee with a copy of any postmortem findings including histopathology. • New or updated information will be recorded in the originally completed CRF. • The Investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of receipt of the updated information.

10.3.6. Reporting of Serious Adverse Events

Serious Adverse Event Reporting to the Sponsor or Designee via Paper Case Report Form
• All AEs must be assessed by the Investigator to determine if they meet criteria for an SAE. All SAEs must be reported to the Sponsor or designee immediately, or within 24 hours of the Investigator and/or study site staff becoming aware of the event, regardless of the presumed relationship to the study drug. • The Investigator must complete, sign, and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy via email or facsimile to the contact information provided below: – Email: PPD – Facsimile: PPD • Additional follow-up information, if required or available, should be entered into the CRF and sent to the Sponsor within 24 hours of the Investigator or study site staff becoming aware of this additional information via the reporting process outlined above. These reporting timelines need to be followed for all initial SAE cases and follow-up versions of the initial cases. • For all SAEs, the Investigator must provide the following: – Appropriate and requested follow-up information in the time frame detailed above – Causality of the serious event(s) – Outcome of the serious event(s) – Medical records and laboratory/diagnostic information • If applicable, additional information such as relevant medical records should be submitted to the Sponsor via the email address or facsimile number noted above. • All forms and follow-up information submitted to the Sponsor (eg, discharge summary) should be kept in the appropriate section of the study file.

10.4. Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

Women in the Following Categories are Not Considered Women of Childbearing Potential

1. Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy
    - Note: Documentation can come from the site personnel's review of the subject's medical records, medical examination, or medical history interview.
2. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range, as per local laboratory reference ranges, will be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
    - Female subjects on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Pregnancy Testing

- Women of childbearing potential should only be included after a negative serum pregnancy test. Additional pregnancy testing should be performed per the time points specified in the Schedule of Activities (Table 1 and Table 2).

Collection of Pregnancy Information

- Pregnancy data will be collected during this study for all subjects and a female spouse/partner of male subjects. Exposure during pregnancy (also referred to as exposure in utero) can be the result of either maternal exposure or transmission of drug product via semen following paternal exposure.
- If a female subject participating in this study or a male subject's female sexual partner of childbearing potential becomes or is found to be pregnant while being treated or exposed to study drug, the Investigator must submit the "Pregnancy Reporting and Outcome/Breast Feeding Form" to the Sponsor or designee via the same method as SAE reporting. (Section 10.3). When the outcome of the pregnancy becomes known,

the form should be updated and submitted to the Sponsor's Global Drug Safety (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 Reporting and Outcome Form/Breastfeeding" form) and any AEs experienced by the infant must be reported to the Sponsor's GDS or designee via facsimile or email (Section 10.3).
- A pregnancy in itself is not regarded as an AE unless there is a suspicion that the study drug 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). Elective abortions without complications should not be reported as AEs (Section 8.3.5).

10.5. Abbreviations

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

Table 11: List of Abbreviations and Definitions of Terms

Abbreviation	Definition
λ_z	apparent terminal-phase elimination rate constant
%CV	arithmetic coefficient of variation
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
CL/F	clearance/bioavailability
C_{max}	maximum observed concentration
CONSORT	Consolidated Standards of Reporting Trials
Cp	ceruloplasmin
CpC	ceruloplasmin-bound copper
CRF	case report form
CRU	clinical research unit
CTCAE	Common Terminology Criteria for Adverse Events
Cu	copper
CV	coefficient of variation
DAP	data analysis plan
EC	enteric-coated
EOS	End of Study
ET	Early Termination
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
GDS	Global Drug Safety
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	informed consent form
IEC	Independent Ethics Committee
MELD	model for end-stage liver disease

Mo	molybdenum
NCC	non-ceruloplasmin-bound copper
$NCC_{corrected}$	corrected NCC
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PPI	proton pump inhibitor
PUF	plasma ultrafiltrate
QT	interval between the start of the Q wave and the end of the T wave in an ECG
QTcF	QT interval corrected using the Fridericia's formula
RR	respiratory rate
SAE	serious adverse event
SAP	Statistical Analysis Plan
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
$t_{½}$	terminal elimination half-life
t_{max}	time to maximum concentration
TPC	Cu-tetrathiomolybdate-albumin tripartite complex formed after ALXN1840 administration
UC	uncoated capsules
ULN	upper limit of normal
UWDRS	Unified WD Rating Scale
V_d/F	apparent volume of distribution
WD	Wilson disease

11. REFERENCES

Lowndes SA, Adams A, Timms A, et al. Phase I study of copper-binding agent ATN-224 in patients with advanced solid tumors. Clin Cancer Res. 2008;14(22):7526-7534.

Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. Ann Intern Med. 2010;152(11):726-732.

Weiss KH, Askari FK, Czlonkowska A, et al. Bis-choline tetrathiomolybdate in patients with Wilson's disease: an open-label, multicentre, phase 2 study. Lancet Gastroenterol Hepatol. 2017;12:869-876.