A Phase 1, Randomized, 2-Period, 2-Sequence, Cross-over Study to Determine the Effect of ALXN1840 on the Metabolism of a CYP2B6 Substrate in Healthy Participants

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TITLE PAGE

Protocol Title: A Phase 1, Randomized, 2-Period, 2-Sequence, Cross-over Study to Determine the Effect of ALXN1840 on the Metabolism of a CYP2B6 Substrate in Healthy Participants

Protocol Number: ALXN1840-HV-103

Amendment Number: 1

Compound: ALXN1840 (bis choline tetrathiomolybdate)

Study Phase: 1

Short Title: Phase 1 Study of ALXN1840 on the Metabolism of a CYP2B6 Substrate in Healthy Participants

Sponsor Name: Alexion Pharmaceuticals, Inc.

Legal Registered Address:

121 Seaport Boulevard
Boston, MA 02210
USA

Regulatory Agency Identifier Number(s)

IND: 119,006

Approval Date:

Original Protocol	28 Apr 2020
Amendment 1	16 Mar 2021

Sponsor Signatory:

PPD

16-Mar-2021 | 15:34:50 EDT

PPD
Senior Director
Clinical Development Sciences

Date

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

INVESTIGATOR'S AGREEMENT

I have read this study protocol amendment 1 and agree to conduct the study in accordance with protocol amendment 1, 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 the original protocol and this protocol amendment.

PPD

Printed Name of Investigator

PPD

Signature of Investigator

17-MAR-2021

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Original Document	28 Apr 2020
Amendment 1	16 Mar 2021

Amendment 1 (16 Mar 2021)

Overall Rationale for the Amendment:

The protocol is being amended to increase the number of participants planned for randomization in the study from approximately 38 participants to approximately 52. A power outage due to extreme and unexpected inclement weather at the clinical research unit (CRU) during study conduct resulted in temperature excursion for many on-site pharmacokinetic (PK) samples. As a result, PK samples for 17 participants have been anticipated to be unviable pending further investigation and additional participants must be enrolled and randomized to ensure completion of at least 32 participants. This amendment will also incorporate all changes/clarifications previously approved in Protocol Administrative Change Letters 1 and 2, and minor updates to formatting and wording for clarity.

Section # and Name	Description of Change	Brief rationale and/or clarifications
Substantial Revision		
Synopsis Number of Participants Synopsis Intervention Groups and Duration (sequence table) Section 4.1 Overall Design (text and Table 3) Section 9.2 Sample Size Determination	Increased the number of participants enrolled and subsequently randomized in the study from approximately 38 to approximately 52, and changed "enrolled" to "randomized" when referring to the number of participants.	Additional participants must be enrolled and randomized to reach the necessary sample size of 32 completed participants because PK samples for 17 participants are anticipated unviable. For clarity, "randomized" is now used instead of "enrolled" when referring to the number of participants because the study's Statistical Analysis Plan defines the Enrolled Set as all participants who sign the ICF. Only randomized participants, not screen failures, should be included in the "approximately 52" and other participant numbers planned in this protocol amendment.
Minor Revisions/Clarifications per Administrative Change Letter 1 dated 28 Apr 2020		
Section 9.4.3.1 Pharmacokinetic and Pharmacodynamic Analyses	Note added after the PK sampling times to clarify that the 336 hours sample in Period 1 will be collected during the Period 2, Pre-dose (Day 1) Visit.	To clarify that there is no unique 336 hours sample collection in Period 1; it is the same as the sample to be collected during the Period 2, Pre-dose Visit.
Section 1.3 Schedule of Activities	Footnote "m" revised to say "12 mL" instead of "15 mL" will be collected for the serum sample retained for safety.	12 mL was determined sufficient for this sample.
Section 10.2 Appendix 2: Clinical Laboratory Tests	Footnote added to Table 7 (Protocol Required Safety Laboratory Assessment) for clarification.	To clarify that only HBsAg testing is necessary for exclusion of active HBV infection; anti-HBC laboratory collection is not required.
Minor Revisions/Clarifications per Administrative Change Letter 2 dated 09 Sep 2020		
Synopsis Intervention Groups and Duration (sequence table) Section 4.1 Overall Design Section 6.3 Measures to Minimize Bias: Randomization and Blinding	Removed the 60%:40% male/female ratio requirement for participant enrollment.	The CRU has had difficulty recruiting female subjects for the study, potentially due to COVID-19. The sponsor determined that removal of a specific sex ratio for participants would not affect the scientific validity of the study.

Section 8.5. Pharmacokinetics	Sample collection window statement changed from "larger" to "less" (ie, "Samples collected within ± 10% of the scheduled time, or 30 minutes whichever is less, will not be considered a protocol deviation.").	To ensure samples collected within the first 4 hours after dosing are collected within 10% of the scheduled collection time, which is less than 30 minutes.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A Phase 1, Randomized, 2-Period, 2-Sequence, Cross-over Study to Determine the Effect of ALXN1840 on the Metabolism of a CYP2B6 Substrate in Healthy Participants.

Short Title: Phase 1 Study of ALXN1840 on the Metabolism of a CYP2B6 Substrate in Healthy Participants.

Rationale:

ALXN1840 is considered to have potential for weak to moderate drug-drug interactions (DDI) due to inhibition of cytochrome P450 2B6 (CYP2B6) according to in vitro studies using human liver microsomes and simulations performed to assess the potential for DDI risks. This study has been designed to determine the effect of ALXN1840 enteric-coated (EC) tablets at a single dose of 60 mg (4 × 15 mg), on the metabolism of bupropion (bupropion hydrochloride [HCl], WELLBUTRIN SR), a sensitive CYP2B6 substrate, at a single dose of 150 mg. A single dose of 60 mg ALXN1840 as a perpetrator is considered appropriate due to lack of potential for time-dependent inhibition (TDI) under the maximum observed ALXN1840 concentration in plasma after repeated daily dosing at steady state. A single dose of 150 mg bupropion is considered appropriate due to its linear pharmacokinetics (PK) within the approved therapeutic dose range.

The 60 mg dose of ALXN1840 is the maximum allowed daily dose in the on-going Phase 3 Study WTX101-301 in patients with Wilson disease (WD). The 150 mg bupropion single dose has been selected based on the WELLBUTRIN SR United States Prescribing Information (USPI) (WELLBUTRIN SR) as it has limited safety concerns (such as seizure).

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To determine the effect of ALXN1840 on the PK of bupropion, a sensitive CYP2B6 substrate	• PK parameters of bupropion (maximum observed plasma concentration [C_{max}], area under the plasma concentration (AUC) versus time curve from time 0 to the last quantifiable concentration [AUC_t], and AUC versus time curve from time 0 to infinity [AUC_∞]) with and without the coadministration of ALXN1840
Secondary	
• To determine the effect of ALXN1840 on the PK of hydroxybupropion, the major active metabolite of bupropion • To determine the effect of ALXN1840 on the PK of plasma molybdenum (Mo) with the coadministration of bupropion • To determine the safety and tolerability of ALXN1840, with the coadministration of bupropion	• PK parameters of hydroxybupropion (C_{max}, AUC_t, and AUC_∞) with and without the coadministration of ALXN1840 • PK parameters for plasma total Mo (C_{max}, AUC_t, and AUC_∞) with the coadministration of bupropion • Safety assessed by incidence of treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs), physical examination, vital signs measurements, clinical laboratory and 12-lead electrocardiogram (ECG) results

Abbreviations: AUC_∞ = area under the plasma concentration versus time curve from time 0 to infinity; AUC_t = area under the plasma concentration versus time curve from time 0 to the last quantifiable concentration; C_{max} = maximum observed plasma concentration of the drug; CYP2B6 = Cytochrome P450 2B6; ECG = electrocardiogram; Mo = molybdenum; PK = pharmacokinetics; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event

Overall Design

This is a Phase 1, randomized, 2-period, 2-sequence, cross-over study designed to determine the effect of ALXN1840 on the metabolism of bupropion, a sensitive CYP2B6 substrate, in healthy male and female participants. The safety and tolerability of ALXN1840 will be determined along with ALXN1840 PK in plasma as measured via total Mo with the coadministration of bupropion.

Disclosure Statement: This is an open-label, 2-period, 2-sequence, cross-over study in healthy participants with randomization to 2 treatment sequences.

Number of Participants:

It is planned that approximately 52 participants will be enrolled and randomized at a single site.

Intervention Groups and Duration:

The study has a Screening Period (Day -28 to Day -2), two 11-day study periods (Day 1 to Day 11) with a minimum of 14 days between doses of bupropion, and an End of Study (EOS) Visit (Day 15 ± 2 days) after Period 2 dosing. Participants will report to the CRU on the day prior (Day -1) to both dosing periods.

In each study period, participants will receive one of the 2 treatments noted below:

- **Treatment A**: One 150 mg bupropion HCl salt tablet (WELLBUTRIN SR 150) with 240 mL water (fasting).
- **Treatment B**: One 150 mg bupropion HCl salt tablet (WELLBUTRIN SR 150) + 4 × 15 mg ALXN1840 EC tablets with 240 mL water (fasting).

Participants will receive each treatment as a single dose administration in the sequence as defined below.

Sequence number	**Treatment sequence**		**Total**
	Study Period 1	**Study Period 2**	
1	A	B	26
2	B	A	26
Total			**52**

Treatment A -One 150 mg bupropion HCl salt tablet (WELLBUTRIN SR 150) with 240 mL water (fasting)
Treatment B – One 150 mg bupropion HCl salt tablet (WELLBUTRIN SR 150) + 4 × 15 mg ALXN1840 enteric-coated tablets with 240 mL water (fasting)

The time between dosing bupropion alone or in combination with ALXN1840 in each treatment sequence will be a minimum of 14 days. Based on the estimated mean ALXN1840 half-life of approximately 2 days in healthy participants (under oral dose of 60 mg), a 14-day period between doses of bupropion is considered sufficient to eliminate, on average, approximately more than 99.2% of the plasma total Mo before the next dose of bupropion is administered. The mean elimination half-life (±SD) of bupropion after chronic dosing is 21 (± 9) hours (WELLBUTRIN SR). A 14-day period between doses of bupropion is sufficient to eliminate, on average, more than 99.2% of the plasma bupropion before the next dose of bupropion is administered.

Participants will return to the CRU on Day 15 (± 2 days) following Period 2 dosing for the EOS Visit with follow-up procedures, and to determine if any adverse events (AEs) have occurred since the last study visit. If participants withdraw from the study early, they will be seen and assessed by the Principal Investigator, and whenever possible, they are to undergo the procedures associated with the EOS Visit. Participants may be replaced at the discretion of Alexion.

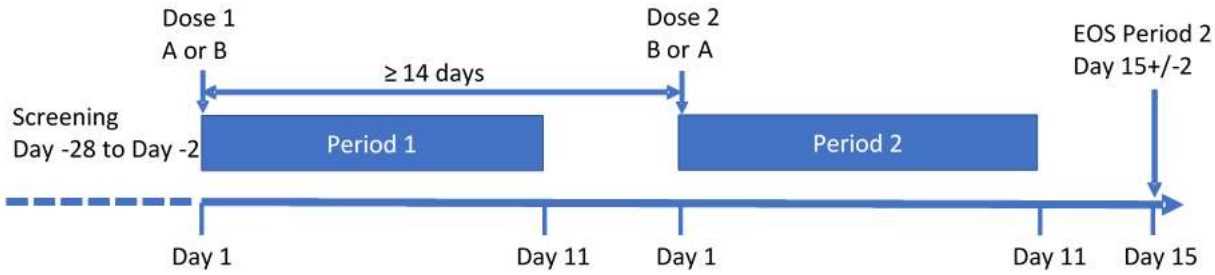
Participants may be asked or required to stay in the CRU between Periods 1 and 2, and/or before the EOS visit, for their own safety, and also to maintain the integrity of the conduct of the study.

Data Monitoring Committee:

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

1.2. Schema

Figure 1: Study ALXN1840-HV-103 Schematic



Participants will be admitted on Day -1 of each Period for Check in procedures. Eligible participants will be randomized on Day 1 immediately prior to dosing in Period 1.
Participants will receive treatment (A or B) based on randomization on Day 1 of each period.
Blood samples for PK analysis of total Mo (as a measure of ALXN1840) and bupropion will be collected in each period on Day 1 at pre-dose, 1, 2, 3, 4, 5, 6, 8, 12 and 24 hours (Day 2) and then at 24 hour intervals on Days 3, 4, 5, 6, 7, 8, 9, 10, and Day 11. The nominal 336-hour sample for Period 1will be collected pre-dose in Period 2.
Participants will be discharged on Day 11 of each period after completion of all procedures and review of all safety data. The end of study visit (EOS) will occur on Day 15 ± 2 of Period 2, with the collection of 336-hour PK sample for Period 2.
Participants may be asked or required to stay in the CRU between Periods 1 and 2, and/or before the EOS visit, for their own safety, and also to maintain the integrity of the conduct of the study.

1.3. Schedule of Activities

Table 1: Schedule of Activities

Study Procedures	S[a]	C-I[b]	Treatment Periods 1 and 2																				EOS or ET[c]
Days →	-28 to -2	-1	1										2	3	4	5	6	7	8	9	10	11	15 (±2)
Hours →			Pre-dose	0[d]	1	2	3	4	5	6	8	12	24	48	72	96	120	144	168	192	216	240	336[e]
Eligibility																							
Informed consent	x																						
Inclusion/exclusion criteria	x	x																					
Pregnancy test	x	x																					x
Urine alcohol test	x	x																					
Urine drug screen	x	x																					
HIV, Hepatitis B and C screen	x																						
Study Administrative																							
Medical history/demographics[f]	x																						
Physical examination[g]	x	x																					x
Weight	x	x																					
Height and BMI	x																						
Discussion/documentation of contraception method	x	x																					
Randomization				x[h]																			
Administration of Study Intervention[i]																							
Treatment A: bupropion or Treatment B: bupropion + ALXN1840				x																			
PK Blood Sample																							
Bupropion (Hydroxybupropion) and ALXN1840 PK			x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Pharmacogenetic sample																							
CYP2B6 genotyping		x																					

Table 1: Schedule of Activities (Continued)

Study Procedures	S[a]	C-I[b]	Treatment Periods 1 and 2																			EOS or ET[c]
Days →	-28 to -2	-1	1										2	3	4	5	6	7	8	9	10	11	15 (±2)
Hours →			Pre-dose	0[d]	1	2	3	4	5	6	8	12	24	48	72	96	120	144	168	192	216	240	336[e]
Laboratory Assessments																							
Chemistry[j], hematology, coagulation	x	x											x			x					x		x
Follicle stimulating hormone[k]	x																						
Urinalysis	x	x																					
Vitals signs measurements	x		x		x			x			x	x	x										x
12-Lead ECG[l]	x		x					x															
Retained sample (safety)[m]			x																				
AE monitoring and concomitant therapies review	←																						→

[a] Within 28 days prior to Day 1 of the first dose of study drug in Dosing Period 1. Note that Screening only occurs once.
[b] Participants will be admitted to the CRU at least 10 hours prior to study intervention.
[c] Participants are required to return to the CRU approximately Day 15 (± 2 days) following the final dose of study medication for an EOS evaluation. Participants may be asked or required to stay in the CRU between Periods 1 and 2, and/or before the EOS visit, for their own safety, and also to maintain the integrity of the conduct of the study. In the event of early termination/discontinuation (ET), the procedures listed at the EOS are performed prior to participant discharge.
[d] Hour 0 corresponds to the time of bupropion ± ALXN1840 administration. Unless stated otherwise, times listed are in relation to bupropion ± ALXN1840 dosing.
[e] The nominal 336-hour sample for Period 1 is to be collected pre-dose in Period 2.
[f] Parameters include age and sex. Race and ethnicity will be collected where permitted by local regulations.
[g] A full physical examination will be performed at Screening, Check-in for each period, and at the end of the study or upon ET. A symptom-driven physical examination may be performed at other times, at the PI's discretion.
[h] Randomization will occur before dosing.
[i] Each dose administration will be separated by at least 14 days between bupropion alone or in combination with ALXN1840 doses. There will be a minimum of 14 days between Day 1 of Period 1 and Day 1 of Period 2.
[j] Samples for chemistry will be obtained following a fast of at least 6 hours at Screening, and at Check-in. In case of dropouts, rechecks, and post dose chemistry, fasting is not required (Section 10.2).
[k] Only needed if claiming exemption from contraception requirement due to menopause.

[l] Triplicate 12-lead ECG will be taken at screening, pre-dose, and at 4 hours post-dose (before lunch) on Day 1. ECGs will be conducted before PK blood sampling if these 2 events are scheduled to occur at the same time.
[m] A single 12 mL sample will be retained for evaluation in the event of an unexpected safety finding; retained samples may be destroyed after completion of the clinical study report. The retained serum sample will only be collected pre-dose on Day 1 of Period 1.

Abbreviations: AE = adverse event; BMI = body mass index; C-I = Check-in; CRU = clinical research unit; ECG = electrocardiogram; EOS = End of Study; ET = Early Termination; FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; HR = heart rate; PI = Principal Investigator; PK = pharmacokinetics; S = Screening.

2. INTRODUCTION

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

2.1. Study Rationale

This study is being conducted to determine the effect of ALXN1840 at a single dose of 60 mg on the metabolism of bupropion, a sensitive cytochrome P450 2B6 (CYP2B6) substrate, at a single dose of 150 mg (WELLBUTRIN SR). ALXN1840 is considered to have the potential for weak to moderate drug-drug interactions (DDI) due to inhibition of CYP2B6, according to in vitro studies conducted using human liver microsomes and simulations performed to assess DDI risks (Study CYP0840-R2, Study 1907124 and Study AXP/1/B). This study has been designed and will be conducted in accordance with the current regulatory guidance issued by the US Food and Drug Administration (FDA) "Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions" (2020), European Medicines Agency (EMA) Committee for Medicinal Products for Human Use "Guideline on the Investigation of Drug Interaction" (2012), and the Japan Pharmaceuticals and Medical Devices Agency (PMDA) "Guideline on drug interaction for drug development" (2019).

Based on a mean ALXN1840 maximum observed plasma concentration (C_{max}) value of 3.92 µM with a single dose of 60 mg enteric-coated (EC) tablet under fasting conditions in healthy participants (Study WTX101-102), a steady state plasma total Mo C_{max} of 13.03 µM can be estimated, considering accumulation ratio of 3.33 with linear PK. In the Phase 2 Study WTX101-201, conducted in patients with WD, the observed highest plasma total molybdenum (Mo) concentration was 20.3 µM after repeated dosing at 60 mg; the dose was escalated to 120 mg at Week 4. Assuming all tetrathiomolybdate (the active ingredient in ALXN1840) in human plasma is free (a conservative approximation since 90% - 95% of the total Mo in plasma is bound to copper and albumin by forming tripartite complexes), there is no potential that ALXN1840 may induce cytochrome P450 (CYP) isoforms or inhibit p-glycoprotein, breast cancer resistance protein, or the organic anion and organic cation uptake transporters. However, as the estimated in vivo steady-state plasma levels of total Mo after dosing at 60 mg daily (13.03 µM) may exceed the drug concentration required to produce 50% of the maximal inhibition (IC_{50} value = 9.9 µM) of CYP2B6 in vitro, a moderate potential for inhibition of CYP2B6 was theoretically and conservatively anticipated (Study 030519b, Study 030709c, Study MC05063, and Study CYP0840-R2).

Subsequent in vitro studies in human liver microsomes (HLM) have shown a potential inhibitory effect (competitive and time-dependent) of ALXN1840 (and possibly its degradation products) on CYP2B6-mediated metabolism (Study CYP0840-R2 and Study 1907124). The IC_{50} value for the inhibitory effect on CYP2B6 was observed at 9.9 µM (4.3 µg/mL) with the estimated Ki values of 4.7 µM (2.0 µg/mL; Study CYP0840-R2, Study 1907124 and Study AXP/1/B). Furthermore, the Study 1907124 specifically examining the inactivation potential of ALXN1840 on CYP2B6 catalytic activity in vitro using HLM and the FDA recommended CYP2B6 probe substrate bupropion with the time-dependent probe inhibitor ticlopidine as active control (US Food and Drug Administration), demonstrated potential for time-dependent inhibition (TDI) at

ALXN1840 concentrations ≥ 100 µM. Because the maximum observed plasma total Mo concentration in the Phase 2 Study WTX101-201, conducted in patients with WD was 20.3 µM after repeated doing at 60 mg and then dose-escalated to 120 mg at Week 4, the observed in vitro TDI potential at ALXN1840 concentration of ≥ 100 µM is not anticipated in vivo even considering total Mo of 20.3 µM is 100% active and free ALXN1840. Assuming 10% of the total Mo is in the form of free and active ALXN1840, which is still conservative given that most of this 10% are likely ALXN1840 degradants such as molybdate, then the highest anticipated individual free and active ALXN1840 concentration is at 2.03 µM in patients with WD, when dosed at 120 mg daily at steady state. Overall, this, implies a negligible possibility for observing in vivo TDI with repeated daily doses of ALXN1840 at 60 mg or up to 120 mg in patients with WD.

Finally, a validated Simcyp® physiologically based pharmacokinetic model, developed using data from Study WTX101-HV-106, predicted a weak CYP2B6 inhibition potential for simulations of single dose ALXN1840 exposures at120 or 240 mg. The predicted geometric mean of the AUC ratio of bupropion was 1.08 for the highest simulated single dose of 240 mg ALXN1840 (Study AXP/1/B), indicating weak inhibitory potential in vivo (weak for AUC ratio of ≥ 1.25- to < 2-fold), per the 2020 FDA guidance on "Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions". For the highest simulated single dose of 240 mg ALXN1840, the maximum in vivo estimated free plasma concentration available to interact with CYP2B6 is estimated at 4.7 µM, after accounting for the formation of tetrathiomolybdate-Cu-albumin tripartite complexes (TPC), which is higher than the 2.03 µM noted above.

Overall, based on in vitro and in silico study results, the maximum total daily doses in clinical studies (currently 60 mg in Phase 3 Study WTX101-301, but previously up to 120 mg in Phase 2 Study WTX101-201) are not anticipated to reach steady-state ALXN1840 concentrations associated with TDI. According to the FDA guidance (US FDA "Clinical Drug Interaction Studies - Cytochrome P450 Enzyme - and Transporter-Mediated Drug Interactions" [2020]), a single dose study design using the highest anticipated clinically relevant dose will be appropriate and justified if there is no TDI. Therefore, single dose of ALXN1840 at 60 mg, which is the highest allowed dose in the on-going Phase 3 Study WTX101-301 conducted for treating patients with WD, is justified to be tested as a potential perpetrator for the CYP2B6 metabolism of a sensitive substrate bupropion.

CYP2B6 has been involved in the metabolism of 2% – 10% of clinically used drugs (Hedrich, 2016). Common substrates of CYP2B6 include, but are not limited to, artemisinin, bupropion, cyclophosphamide, efavirenz, ketamine, methadone, propofol, rifampicin, and sertraline. The potentially weak to moderate inhibitory effects of a single 60 mg ALXN1840 dose on a single dose 150 mg bupropion metabolism is anticipated to have a very limited safety concern (such as seizures), since a 2-fold increase in bupropion concentration is not anticipated (WELLBUTRIN SR).

Further details of the currently available drug metabolism, pharmacokinetics, and safety data are available in the Investigator's Brochure (IB) for ALXN1840.

2.2. Background

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

ALXN1840 rapidly forms irreversible TPC, which stabilize free and potentially toxic Cu leading to a reduction in the non-ceruloplasmin-bound Cu (NCC) concentrations or NCC corrected for TPC [$NCC_{corrected}$]) (Weiss, 2017).

Detailed descriptions of the chemistry, pharmacology, efficacy, and safety of ALXN1840 are provided in the IB for ALXN1840.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) forALXN1840 may be found in the IB and of bupropion in the prescribing information (WELLBUTRIN SR).

2.3.1. Risk Assessment

Details of the potential risks and mitigation strategy are provided in Table 2.

Table 2: Potential Risks and Mitigation Strategy

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
ALXN1840		
Dose-dependent elevations in transaminases (ALT and AST)	Generally mild to moderate in severity, asymptomatic and reversible with dose adjustments were reported, usually after 3 - 6 weeks of treatment in patients with WD	Regular monitoring of liver function tests
Anemia	Anemia has been observed in patients with WD, PBC and cancer, attributed to overtreatment and resultant Cu depletion	Monitoring complete blood count
Low white blood cell count (leukopenia, bone marrow toxicity)	Leukopenia and bone marrow toxicity (myelosuppression) have been observed in patients with WD and attributed to overtreatment and resultant Cu depletion	Monitoring complete blood count
Study Procedures		
Risks associated with the study design and procedures	Participants will undergo repeated blood draws to measure the PK of the study intervention and metabolism. Blood draws may result in ecchymosis, redness and	Blood draws are optimized for PK. A cannula may be placed to minimize needle sticks

	minor pain to the site. On rare occasion, infection or thrombophlebitis can occur	
Bupropion		
As per prescribing information	Bupropion prescribing information (WELLBUTRIN SR)	Participants will be monitored for adverse reactions and by regular laboratory assessments. Participants may be discontinued for significant drug related adverse events

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

2.3.2. Benefit Assessment

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

2.3.3. Overall Benefit: Risk Conclusion

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

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To determine the effect of ALXN1840 on the PK of bupropion, a sensitive CYP2B6 substrate	• PK parameters of bupropion (C_{max}, area under the plasma concentration (AUC) versus time curve from time 0 to the last quantifiable concentration [AUC_t], and AUC versus time curve from time 0 to infinity [AUC_∞]) with and without the coadministration of ALXN1840
Secondary	
• To determine the effect of ALXN1840 on the PK of hydroxybupropion, the major active metabolite of bupropion • To determine the effect of ALXN1840 on the PK of plasma Mo with the coadministration of bupropion • To determine the safety and tolerability of ALXN1840, with the coadministration of bupropion	• PK parameters of hydroxybupropion (C_{max}, AUC_t, and AUC_∞) with and without the coadministration of ALXN1840 • PK parameters for plasma total Mo (C_{max}, AUC_t, and AUC_∞) with the coadministration of bupropion • Safety assessed by incidence of treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs), physical examination, vital signs measurements, clinical laboratory and 12-lead electrocardiogram (ECG) results

Abbreviations: AUC_∞ = area under the plasma concentration versus time curve from time 0 to infinity; AUC_t = area under the plasma concentration versus time curve from time 0 to the last quantifiable concentration; C_{max} = maximum observed plasma concentration of the drug; CYP2B6 = cytochrome P450 2B6; ECG = electrocardiogram; PK = pharmacokinetics; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.

4. STUDY DESIGN

4.1. Overall Design

The study is being conducted as a randomized, 2-period, 2-sequence, cross-over study to determine the effect of a single dose of ALXN1840 (perpetrator) on the single dose bupropion (victim) kinetics in healthy male and female participants.

The study has a Screening period (Day -28 to Day -2), two 11-day study periods (Day 1 to Day 11) with a minimum of 14 days between doses of bupropion, and an End of Study (EOS) Visit (Day 15 ± 2 days) after Period 2 dosing. Participants will report to the clinical research unit (CRU) on the day prior (Day -1) to both dosing periods.

All participants will receive 1 treatment in each study period; treatment order will be defined based on randomization:

- **Treatment A**: One 150 mg bupropion HCl salt tablet (WELLBUTRIN SR 150) with 240 mL water (fasting).
- **Treatment B**: One 150 mg bupropion HCl salt tablet (WELLBUTRIN SR 150) + 4 × 15 mg ALXN1840 EC tablets with 240 mL water (fasting).

Based on randomization, participants will be administered either Treatment A or Treatment B in each period. A wash-out period of at least 14 days must separate dose administration in Period 1 and Period 2. Participants will remain institutionalized from the day prior to dosing until Day 11 following dose administration for each period.

The PK profile of ALXN1840 and bupropion will be determined by blood sampling following single dose administration over approximately 5 half-lives or more for both study interventions. Blood sampling for PK assessments will occur at pre-dose, 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216, 240, and 336 hours post-dose to ensure full assessment of exposure over time. The nominal 336-hour sample for Period 1 is pre-dose sample for Period 2. In addition to PK sampling, safety and tolerability will be assessed by monitoring AEs, vital signs, 12-lead electrocardiograms (ECGs), and laboratory parameters.

Following scheduled procedures on Day 11, participants will be discharged from the unit. If there are any participants with clinically significant abnormalities at the time of discharge, the Investigator should notify the Medical Monitor prior to discharge, and participants may be asked to remain institutionalized for further clinical monitoring.

Participants may be asked or required to stay in the CRU between Periods 1 and 2, and/or before the EOS visit, for their own safety, and also to maintain the integrity of the conduct of the study.

The End of Study (EOS) Visit will occur approximately 4 days after discharge from Period 2 after collection of the nominal 336-hour PK sample.

This study will include approximately 52 participants to complete at least 32 participants.

Participants will be randomized to one of two sequences as described in Table 3.

Table 3: Study Design

Sequence number	Treatment sequence		Total
	Study Period 1	Study Period 2	
1	A	B	26
2	B	A	26
Total			**52**

Treatment A - One 150 mg bupropion HCl salt tablet (WELLBUTRIN SR 150) with 240 mL water (fasting)
Treatment B – One 150 mg bupropion HCl salt tablet (WELLBUTRIN SR 150) + 4 × 15 mg ALXN1840 enteric-coated tablets with 240 mL water (fasting)

At the Investigator's discretion, additional participants may be screened to allow for a full enrollment of the study; therefore, it is possible that all eligible participants may not be included. Participants not included in the study will be discharged without dosing on Day 1.

4.2. Scientific Rationale for Study Design

This study is being conducted in healthy participants so that the assessments are not confounded by disease activity, comorbidities, or concomitant medications. The inclusion and exclusion criteria for this study are consistent with Phase 1 clinical pharmacology studies that assess the medication of interest and to minimize assignment bias.

A 2-way crossover study design was adopted to control the variability within and between participants. Given the desire to evaluate the impact of sequence of administration, the study is being conducted as a 2-sequence, 2-period cross-over study. Blood sampling for PK assessment will include measures for ALXN1840 and bupropion. Blood sampling timepoints support evaluation of time to reach maximum observed plasma concentration (T_{max}) and C_{max} and include a minimum of 5 half-lives between each study intervention.

The interval between dose administration in each period will be at least 14 days, based on the estimated mean half-life for ALXN1840 of approximately 2 days as previously reported in the bioavailability studies (Studies WTX101-101 and WTX101-102), where healthy participants took an oral dose at 60 mg. Therefore, a minimum of 14 days between dose administration is considered sufficient to eliminate, on average, approximately more than 99.2% of the plasma total Mo before a second dose of bupropion. The approximately 4-day interval after Period 2 dose administration will also ensure that the participants will have eliminated measurable concentrations of ALXN1840 at the EOS Visit regardless of the randomized dosing sequence. The mean elimination half-life (±SD) of bupropion after chronic dosing is 21 (± 9) hours, therefore a minimum of 14-day interval between single dose administrations is sufficient to eliminate greater than 99.2% of plasma bupropion.

4.3. Justification for Dose

ALXN1840

The maximum tolerated dose (MTD) of ALXN1840 is unknown. To date, the 60 mg single dose and repeated daily doses have shown a good safety profile and were well tolerated throughout the Phase 1 to Phase 3 clinical studies. The 60 mg dose is well within the dose range demonstrated to have a good safety profile in studies in healthy volunteers and patients with WD. The 60 mg dose is well within the dose range to have an acceptable safety profile in humans as

demonstrated in the completed bioavailability studies that were conducted in healthy male and female participants (Study WTX101-101 and Study WTX101-102) with a median (range) body weight of 80.8 kg (57.6 to 107.0 kg) as well as the completed Study WTX101-201, conducted in patients with WD.

Tetrathiomolybdate reacts with albumin-bound Cu in the liver or blood to form a stable tripartite complex which is excreted into the bile. Tetrathiomolybdate which does not bind to Cu and albumin, is not metabolized by the liver but undergoes hydrolysis to form molybdate anion, which is excreted in the urine. Therefore, findings from the human microsome study (Study CYP0840-R2) are considered an over-estimation of the effect to be observed in vivo. Given that in vitro inhibition was observed with the ALXN1840 parent drug and no apparent accumulation of free ALXN1840 as part of the plasma ultrafiltrate (PUF) Mo or non-TPC-bound Mo after ALXN1840 repeated dosing (preliminary results from Study WTX101-201), a single dose of ALXN1840 is considered to be sufficient to assess the inhibition potential of CYP2B6 using bupropion as the substrate. Single dose administration of the ALXN1840 tablet under fasted conditions resulted in a peak drug concentration of total Mo at approximately 4.54 hours, with a half-life of approximately 51 hours (Study WTX101-102).

Bupropion

Bupropion is extensively metabolized in humans. Following oral administration of 150 mg of 14C-bupropion in humans, 87% and 10% of the radioactive dose were recovered in the urine and feces, respectively. The fraction of the oral dose of bupropion excreted unchanged was only 0.5%, a finding consistent with the extensive metabolism of bupropion (WELLBUTRIN SR).

In humans, following oral administration of WELLBUTRIN SR tablet, peak plasma bupropion concentrations are usually achieved within 3 hours, followed by a biphasic decline. The terminal phase has a mean half-life of 14 hours, with a range of 8 to 24 hours. The mean elimination half-life (± SD) of bupropion after chronic dosing is 21 (± 9) hours, and steady-state plasma concentrations of bupropion are reached within 8 days. Plasma bupropion concentrations are dose-proportional following single doses of 100 to 250 mg.

Three metabolites have been shown to be active: hydroxybupropion, formed via hydroxylation of the tert-butyl group of bupropion, and the amino-alcohol isomers threohydrobupropion and erythrohydrobupropion, which are formed via reduction of the carbonyl group. In vitro findings suggest that cytochrome P450IIB6 (CYP2B6) is the principal isoenzyme involved in the formation of hydroxybupropion, while cytochrome P450 isoenzymes are not involved in the formation of threohydrobupropion. Oxidation of the bupropion side chain results in the formation of a glycine conjugate of meta-chlorobenzoic acid, which is then excreted as the major urinary metabolite. Because bupropion is extensively metabolized, there is the potential for drug-drug interactions, particularly with those agents that are metabolized by the cytochrome P450IIB6 (CYP2B6) isoenzyme. Following a single dose in humans, peak plasma concentrations of hydroxybupropion occur approximately 6 hours after administration of WELLBUTRIN SR tablets. Peak plasma concentrations of hydroxybupropion are approximately 10 times the peak level of the parent drug at steady state. The elimination half-life of hydroxybupropion is approximately 20 (± 5) hours, and its AUC at steady state is about 17 times that of bupropion. The times to peak concentrations for the erythrohydrobupropion and threohydrobupropion metabolites are similar to that of the hydroxybupropion metabolite. However, their elimination

half-lives are longer, 33 (± 10) hours and 37 (± 13) hours, respectively, and steady-state AUCs are 1.5 and 7 times that of bupropion, respectively.

Even though ALXN1840 is considered theoretically and conservatively to have potential for moderate inhibition of CYP2B6 in vitro. A dose of 150 mg is not expected to result in sufficiently high exposure to cause an increase in safety risk.

4.4. End of Study Definition

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

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

5. STUDY POPULATION

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

5.1. Inclusion Criteria

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

Age

1. Participants must be 18 to 50 years of age inclusive, at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Participants who are healthy as determined by medical evaluation including medical history, physical examination, vital signs, 12-lead ECG, and clinical laboratory evaluation (hematology, biochemistry, coagulation, and urinalysis) that are reasonably likely to interfere with the participant's participation in or ability to complete the study, or to potentially confound interpretation of study results, as assessed by the Investigator.
3. Adequate venous access in the left or right arm to allow collection of a number of blood samples.

Weight

4. Body weight ≥ 45 to ≤ 100 kg and body mass index (BMI) within the range of 18 to < 30 kg/m^2 at Screening.

Sex

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

    a. Male Participants:

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

(with documented evidence of azoospermia if possible) and agree to use a barrier method (male condom) for the stated time period, no additional contraceptive method is required by their female partner.

b. Female Participants:

- Female participants or female partners of male participants of childbearing potential (including breastfeeding females), if heterosexually active, must be willing to follow protocol-specified contraception guidance starting at least 1 menstrual cycle before first study intervention administration and continuing for at least 3 months after the end of systemic exposure of the study intervention (ie, 3 months after the EOS Visit). Female participants must not donate ova for at least 3 months after the EOS (ie. 3 months after the EOS Visit).
- Female participants who are documented as being of non-childbearing potential as defined in Section 10.4 are exempt from contraception requirements.
- Highly effective contraceptive methods for female participants and female partners of male participants are described in Section 10.4.
- Women of childbearing potential must have a negative highly sensitive serum pregnancy test at screening. Additional urine pregnancy testing will be standard for the protocol unless serum testing is required by site policies, local regulation, or IRB/IEC and should be performed per the time points specified in the SoA (Table 1:

Informed Consent

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

5.2. Exclusion Criteria

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

Medical Conditions

1. History or presence of/significant history of or current cardiovascular, respiratory, hepatic, renal, gastrointestinal, endocrinological, hematological, neurological disorder, seizure disorder or eating disorder (anorexia or bulimia). Participants with a history of gastric bypass, other surgical procedure, or medical condition that may significantly alter absorption of drugs.
2. Clinically significant multiple or severe drug allergies, food allergies, or allergies to study product or class of product or its derivatives.
3. Lymphoma, leukemia, or any malignancy within 5 years of Screening, except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years.
4. Breast cancer within the past 10 years.
5. Serum creatinine > upper limit of normal (ULN) of the reference range of the testing laboratory at Screening or on Check-in Period 1.

6. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin > ULN of the testing laboratory at Screening and Check-in. Participants with confirmed Gilbert's syndrome may be included with total bilirubin > ULN but below 3 × ULN if participant has a measured direct bilirubin < ULN.
7. Current or chronic history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).
8. QTc > 450 msec for male participants or > 470 msec for female participants
   NOTE A: The QTc is the interval between the start of the Q-wave and the end of the T-wave in an ECG (QT interval) corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), and/or another method. It is machine-read with Investigator review.
   NOTE B: The specific formula used to determine eligibility and discontinuation for an individual participant should be determined prior to initiation of the study; QTcF is preferred; however, QTcB may be used if QTcF cannot be measured.

Prior/Concomitant Therapy

9. Use or intended use of prescription medications (excluding oral contraceptives) within 14 days or 5 half-lives of the drug (whichever is longer) prior to dosing on Day 1, except with prior approval of Alexion. Participants may not have a medical condition that requires chronic medicinal therapy.
10. Use of nonprescription/ over-the-counter medications, including herbal remedies and supplements, within 7 days prior to dosing on Day 1 and/or intended use at any point over the duration of the study.

Prior/Concurrent Clinical Study Experience

11. Participation in a study resulting in loss of blood or donation of blood products in excess of 500 mL within 60 days prior to Day 1.
12. Exposure to more than 4 new investigational drugs within 12 months prior to dosing.
13. Current enrollment or past participation within the last 90 days before signing of consent in this or any other clinical study involving an investigational study intervention or any other type of medical research. For participants recently participating in clinical studies involving an investigational product with a prolonged half-life, participants may not participate in this study within 5-half-lives of the last dose administration.

Diagnostic assessments

14. Presence of hepatitis B surface antigen (HBsAg) at Screening or within 3 months prior to first dose of study intervention. Presence of HBsAg or positive hepatitis C antibody or ribonucleic acid (RNA) test result at screening or within 3 months prior to first dose of study intervention.
    - NOTE: Participants with positive hepatitis C antibody due to prior resolved disease can be enrolled if a confirmatory negative hepatitis C RNA test is obtained.
    - NOTE: The RNA test is optional and participants with negative hepatitis C antibody test are not required to also undergo hepatitis C RNA testing.

15. Positive pre-study alcohol or drugs of abuse screen.
16. Positive human immunodeficiency virus (HIV) antibody test.
17. Ongoing use of tobacco products or nicotine delivery systems.

Other Exclusions

18. Regular alcohol consumption within 6 months prior to the study defined as: an average weekly intake of > 14 units/week for males or > 7 units/week for females. One unit is equivalent to 8 g of alcohol: a half pint (~240 mL) of beer, one ~4 oz glass (125 mL) of wine or 1 (25 mL) measure of spirits.
19. Regular use of known drugs of abuse, based on the assessment of the investigator.
20. Prior exposure to ALXN1840 or other tetrathiomolybdate salt.
21. Sensitivity to any of the study interventions, or components thereof, or drug or other allergy that, in the opinion of the Investigator or Medical Monitor, contraindicates participation in the study.

5.3. Lifestyle Considerations

Participants must be able and willing to adhere to the following lifestyle restrictions.

Table 4: Healthy Participant Lifestyle Considerations

Items Participants Must Not Consume or Do	When Participants Must Stop	When Participants Can Restart
Tobacco in any form (eg, smoking or chewing) or other nicotine-containing products in any form (eg, gum, patch, electronic cigarettes or vaporized inhalation device)	From Screening	After the final study visit
Alcohol	48 hours before Check-in to the CRU (Day -1) and until discharge (Day 11), and 48 hours before the EOS Visit	Discharge from the clinical research unit and completion of EOS visit
Meals/snacks/water	Breakfast will be omitted on the Day of dosing (Day 1). With the exception of the day of dosing, water/fluids may be consumed ad libitum. On the day of dosing, participant must refrain from water intake from 1 hour before to one hour after with the exception of the 240 mL water provided for dose administration. On Day-1, Check-in for Period 1 and 2, the evening meal must be completed no later than 2100 hours. Participants will continue fasting for approximately 4 hours after dosing	Standard meals will be provided during institutionalization

Table 4: Healthy Participant Lifestyle Considerations (Continued)

Items Participants Must Not Consume or Do	When Participants Must Stop	When Participants Can Restart
Not consume any other substances known to be potent inhibitors or inducers of CYP450 enzymes. This includes food or drink products containing cranberry, pomegranate, star fruit, grapefruit, pomelos, exotic citrus fruits or Seville oranges (including marmalade and juices made from these fruits). Red wine should also not be consumed	Within 7 days before the planned first study intervention administration	After collection of the final PK sample for each study period
Caffeine-containing or xanthine-containing products (eg, tea, coffee, cola drinks, and chocolate).	During each dosing period, 24 hours before the planned first study intervention administration and each outpatient/ follow-up visit	After collection of the final PK sample for each study period
Strenuous physical activity	Starting 72 hours prior to each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during studies (eg, watching television, reading).	After study completion/last visit. Participants should not start new physical training activities during the study until study completion (last visit).
Any prescription medication. For details, see Section 5.2 Note: If participants have a medical need to take any medication or have any medications prescribed to them by a doctor, they should follow the medical advice but inform the Investigator as soon as possible afterwards. Participants should be informed not to stop taking any medication that has been prescribed by their doctor	14 days or 5 half-lives prior to dosing on Day 1	After the final study visit
Any nonprescription/over-the-counter medication, including herbal remedies and supplements. For details, see Section 5.2	Use of nonprescription/ over-the-counter medications, within 7 days prior to dosing on Day 1 and/or intended use at any point over the duration of the study. With Investigator approval, participants may take up to 1000 mg/day of acetaminophen	After the final study visit
Any herbal remedy or dietary supplement containing St John's Wort	2 weeks before the planned first study intervention administration	After study completion/last visit
Blood and plasma donation	Participation in a study resulting in loss of blood or donation of blood products in excess of 500 mL within 60 days prior to Day 1 (Section 5.2)	1 month after study completion/last visit

Items Participants Must Not Consume or Do	When Participants Must Stop	When Participants Can Restart
Participants must comply with the appropriate contraceptive requirements as stated in Section 10.4	Start times for contraceptives vary according to method used (see applicable contraceptive method in Section 10.4.)	See Section 10.4

Abbreviations: CYP450 = cytochrome P450; PK = pharmacokinetics.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details (eg, failed eligibility criteria), and any AEs, including any serious adverse events (SAEs) and any related concomitant medication, occurring during the screening period.

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

6. STUDY INTERVENTION

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

6.1. Study Intervention Administered

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

ALXN1840 and bupropion will be administered at the morning of Day 1.

Table 5: Details of Study Interventions Administered

ARM Name	Study Intervention	Comparator
Intervention Name	ALXN1840 (formerly WTX101)	Bupropion (Wellbutrin SR)
Type	Drug	Drug
Dose Formulation	Tablet	Tablet
Unit Dose Strength(s)	15 mg ALXN1840	150 mg
Dosage Level(s)	Single dose 60 mg administered as 4 × 15 mg ALXN1840 tablets	Administered as a single dose (1 × 150 mg tablet)
Route of Administration	Oral	Oral
Use	experimental/study intervention	comparator/reference
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by Alexion	Provided by the site
Packaging and Labeling	ALXN1840 will be provided in treatment kits that will each have a unique identification number and be packaged and labelled in accordance with all applicable regulatory requirements. At a minimum, the treatment kit label will provide the following information: study Sponsor identification, batch number, directions for use, required storage conditions, caution statements (including "New Drug-Limited by Federal Law to Investigational Use" language), study identification, and expiry date	Bupropion will be provided as per the prescribing information
Current/Former Name(s) or Alias(es)	Sponsor's name - Bis-choline tetrathiomolybdate USAN - Tiomolibdate choline	Wellbutrin SR

Abbreviations: IMP = investigational medicinal product; NIMP = noninvestigational medicinal product; USAN = United States adopted name

6.2. Preparation/Handling/Storage/Accountability

1. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer the study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored

(manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

2. The Investigator and/or delegated staff (ie, Pharmacist) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
    a. This responsibility includes the reporting of any product complaints to productcomplaints@alexion.com within 1 business day. A product complaint is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, usability, safety, effectiveness, or performance of a product or clinical study material and/or its packaging components after it is has been released for distribution to an end customer that affects the performance of such product.
3. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
    a. The ALXN1840 treatment kits should be stored at refrigerated conditions, 2°C to 8°C (36°F to 46°F).
    b. Bupropion should be stored according to the details in the package labeling.
4. Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

- This is an open-label, 2-period cross-over study where each participant will be randomized to 1 of 2 treatment sequences (AB or BA) to minimize selection bias in treatment assignment.
- Eligible participants who meet all inclusion and no exclusion criteria included in the study will be assigned unique study participant numbers for enrollment. Study participant numbers will not be reallocated once assigned.

6.4. Study Intervention Compliance

When participants are dosed at the site, participants will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of the dose will be recorded in the source documents and/or in the case report form (CRF). If the primary documentation is other than the electronic case report form (eCRF), all primary documentation should be filed on site as source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

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

6.5. Concomitant Therapy

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

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

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

6.5.1. Allowed Medicine and Therapy

- Paracetamol/acetaminophen at doses of a maximum 1,000 mg per day is permitted for use as an exception with the approval of the Investigator.
- As per the ALXN1840 IB, in this study, Investigators should use caution in the co-administration of drugs known to be substrates of CYP2B6. Common substrates of CYP2B6 include ibuprofen, which is permitted in this study. Therefore, the Investigator must use ibuprofen with caution during the conduct of the study. With the exception of the day of dosing in each period, ibuprofen may be used with the Investigator's approval; however, doses may not exceed 1,150 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.
- Concomitant medications are not allowed unless medically indicated and with agreement between Alexion and the Investigator.
- Concomitant procedures are not allowed unless medically indicated and/or permitted by Alexion or the Investigator.

6.5.2. Disallowed Medicine and Therapy

Participants must refrain from use or intended use of any prescription medications (excluding oral contraceptives) within 14 days or 5 half-lives of the drug (whichever is longer) prior to dosing on Day 1 and for the duration of the study (ie, until completion of the EOS visit).

Participants may not have a medical condition that requires chronic medicinal therapy. Use of nonprescription/over-the-counter medications, including herbal remedies and supplements, is not permitted within 7 days prior to dosing on Day 1 and for the duration of the study (ie, until completion of the EOS Visit).

6.6. Dose Modification

Not applicable. ALXN1840 and bupropion will be administered as single doses in the prescribed parts of the study.

6.7. Intervention After the End of the Study

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

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) the study intervention. If the study intervention is definitively discontinued, the participant should remain in the study to be evaluated for safety follow-up. See the SoA (Table 1) for data to be collected at the time of discontinuation of study intervention and follow-up.

Discontinuation of study intervention for abnormal liver function should be considered by the investigator if transaminase elevations (ie, AST or ALT) exceeds 3 × ULN or if the Investigator believes that it is in best interest of the participant.

If a clinically significant finding is identified (including, but not limited to QTcF ≥ 500 ms or QTcB ≥ 500 ms), the Investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. Review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

Participant should be considered for discontinuation from intervention if any of the following occur during the study:

- Serious hypersensitivity reaction;
- Severe uncontrolled infection;
- Use of disallowed medication;
- Pregnancy or planned pregnancy (see Section 10.4); or
- Alexion or the Investigator deems it is necessary for the participant.

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

7.2. Participant Discontinuation/Withdrawal From the Study

- All efforts should be made to ensure participants are willing to comply with study participation prior to conducting the screening procedures. The study staff should notify Alexion and their site monitor of all study withdrawals as soon as possible. The reason for participant discontinuation must be recorded in the source documents and CRF.
- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an Early Termination (ET) Visit should be conducted, as shown in the SoA (Table 1). See the SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

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

7.3. Lost to Follow-up

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

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

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

Discontinuation of specific site or of the study as a whole are handled as described in Section 10.1.8.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Table 1). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with Alexion immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screen failure, as applicable.
- Procedures conducted as part of the participant'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 SoA.
- Abnormal laboratory parameters may be repeated once during the Screening Period to ensure an accurate assessment of eligibility.
- Unscheduled blood samples may be taken at the discretion of the Investigator for assessment of safety issues.

8.1. Efficacy Assessments

No efficacy assessments will be obtained during this study.

8.2. Safety Assessments

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

For study Periods 1 and 2, when multiple procedures are scheduled to occur at the same time, the following order of events should be strictly adhered to whenever possible: Vital signs, ECG, blood sampling, study intervention administration, and meal.

Collection of samples for PK assessment should occur as close as possible to the scheduled time.

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. It will be performed at Screening, Check-in for each period, and at the EOS or upon ET. Height, BMI (at Screening only) and weight will also be measured and recorded as outlined in the SoA (Table 1).
- A symptom-driven physical examination may be performed at other times, at the study physician's discretion.

- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

- Oral temperature, pulse rate, respiratory rate, and systolic and diastolic blood pressure (mm Hg) will be assessed.
- Routine blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques should be used if repeat measurements are necessary due to abnormal results.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones). Ideally, the same arm for each participant should be used for measurements.

8.2.3. Vital signs will be measured in a semi-supine position after 5 minutes rest. Electrocardiograms

- Participants will be resting in the supine position for at least 15 minutes prior to and 5 minutes after each nominal time point for ECG extraction. Triplicate 12-lead ECG will be conducted as outlined in the SoA (see Table 1) to obtain heart rate, PR, QRS, QT, and QTc intervals. Heart rate and interval data will be recorded in the eCRF. QT corrected for heart rate using Fridericia's formula should be recorded as the QTc reading (unless unavailable and then QTcB may be recorded). Refer to Section 7 for QTc withdrawal criteria and any additional QTc readings that may be necessary.

8.2.4. Clinical Safety Laboratory Assessments

- See Section 10.2 for the list of clinical laboratory tests to be performed and the SoA (Table 1) for the timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. At the Investigator's discretion, all abnormal values may be repeated to confirm results. The laboratory reports must be filed with the source documents.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study after the last dose of the study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.
  - If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and Alexion notified.
  - All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA (Table 1).
  - All laboratory values from nonprotocol specified laboratory assessments also must be recorded in the CRF.

8.2.5. Suicidal Ideation and Behavior Risk Monitoring

For bupropion, as stated in the WELLBUTRIN SR USPI (WELLBUTRIN SR), there is "Increased risk of suicidal thinking and behavior in children, adolescents and young adults taking antidepressants. All patients should be monitored for worsening and emergence of suicidal thoughts and behaviors". This will be monitored throughout the study as listed in the SOA (Table 1) under "AE monitoring and concomitant therapies review".

8.2.6. Pregnancy

- Pregnancy data from female participants and female spouses/partners of male participants will be collected from the first dose of the study intervention through 90 days post the last dose and at the time points specified in the SoA. Any female participant who becomes pregnant while participating in the study will be discontinued from the study intervention. If a pregnancy is reported, the Investigator must immediately inform Alexion within 24 hours of awareness of the pregnancy and follow the procedures outlined in Section 10.4.
- For all Alexion products, both in development or post-approval, exposure during pregnancy must be recorded and the pregnancy followed until the outcome of the pregnancy is known (ie, spontaneous miscarriage, elective termination, normal birth, or congenital abnormality), even if the participant discontinues study intervention or withdraws from the study. The corresponding infant must be followed for 3 months postpartum.
- Pregnancy is not considered an AE (Section 10.4) unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication. However, complications of pregnancy and abnormal outcomes of pregnancy are AEs and may meet the criteria for a SAE (eg, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly) (Section 8.3). Elective abortions without complications should not be reported as AEs.

8.3. Adverse Events and Serious Adverse Events

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

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

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

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

8.3.1. Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

All AEs will be collected from the signing of the ICF until the EOS or ET Visit.

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

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

8.3.2. Method of Detecting AEs and SAEs

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

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

8.3.3. Follow-up of AEs and SAEs

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

8.3.4. Regulatory Reporting Requirements for SAEs

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

8.3.5. Adverse Events of Special Interest

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

8.3.6. Retained and Biobanked Sample

A single biobanked serum sample will be collected pre-dose to serve as a retained safety sample during the study. At the end of the study, pre-dose safety samples will be biobanked to support assay development and determination of normal Cu and Mo levels in healthy participants. Samples may be stored and used for up to 5 years following completion of the study.

8.4. Treatment of Overdose

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

Alexion does not recommend specific treatment for an overdose.

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

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

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

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

8.5. Pharmacokinetics

- Whole blood samples will be collected for the measurement of plasma concentrations of total Mo, bupropion and its metabolite hydroxybupropion as specified in the SoA (Table 1). Additional samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and Alexion. Collection of samples for PK evaluation should occur as close as possible to the scheduled time and actual time of collection should be documented on the eCRF. Samples collected within ± 10% of the scheduled time or 30 minutes, whichever is less, will not be considered a protocol deviation. In the event of a safety occurrence and after agreement between the Investigator and Medical Monitor, up to 3 additional PK sampling timepoints may be added.
- Instructions for the collection and handling of biological samples will be provided by Alexion. The actual date and time (24-hour clock time) of each sample will be recorded.

- Samples will be used to evaluate the effect of ALXN1840 on the PK of bupropion. Samples collected for analyses of plasma concentrations may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Excess/additional samples may be stored for up to 5 years and used for pharmacodynamic (PD) development and research to understand the pathways associated with the mechanism of action of ALXN1840; however, samples will not be used for genetic analyses (ie RNA or DNA analyses).

8.6. Pharmacodynamics

Plasma samples collected for PK may be used for analyzing the PD of ALXN1840 including, but not limited to plasma total Cu, ceruloplasmin (Cp), Cp-bound Cu (CpC), and potentially toxic Cu measured as labile-bound Cu (LBC) and PUF Cu and/or NCC/$NCC_{corrected}$.

8.7. Genetics

Blood samples for genetic testing of CYP2B6 polymorphism will be collected at clinical Check-in (Day -1). This study proposes to collect genetic polymorphism data to characterize potential impact of ALXN1840 on phenotypic CYP2B6 metabolism of bupropion and evaluate the potential effect of genetic polymorphism on the between-participant variability of bupropion PK. As this is an exploratory assessment, the study will not specifically select target participants with a certain proportion of CYP2B6 genotypes.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity

Not applicable.

8.10. Health Economics and Medical Resource Utilization

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

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The primary objective is to determine the effect of ALXN1840 on the PK of bupropion. There is no formal null hypothesis to be statistically tested and used to drive declaration of study success or failure.

To assure the study has enough participants, to estimate the inhibitory effect of ALXN1840 on the metabolism of bupropion with adequate precision, the sample size was determined using the conservative 90% confidence interval (CI) and 80% to 125% no-effect boundary approach described in the FDA Guidance "Clinical Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter Mediated Drug Interactions" (2020). This guidance notes the 80 to 125 % boundaries represent a very conservative standard for drugs that have wide safety "margins" and "the totality of evidence should be taken into consideration when determining the clinical impact of the DDI on the substrate drug". Therefore, if the estimated inhibition effect of ALXN1840 on bupropion PK lies outside this no-effect boundary, this should not be interpreted as a failed study.

9.2. Sample Size Determination

A default of no-effect boundary (80% to 125%) approach will be employed to assess whether there is an inhibition effect on the metabolism of bupropion in the presence of ALXN1840. For a 2 -period crossover study design, assuming the true ratio of the means (bupropion + ALXN1840 vs bupropion alone) on the PK parameters is 1 (C_{max}; area under the plasma concentration versus time curve from zero to infinity [AUC_{∞}]) and the bupropion intra-participant coefficient of variation (CV) is 0.30 (Dennison, 2018), a total sample size of 32 completed participants can achieve 90% power with two 1-sided tests, each with a type I error rate of 5% (two-sided type I error rate of 10%). The intra-participant CV is estimated using residual mean-square error (MSE) term in the ANOVA model. The CV is estimated as $100\% \times \sqrt{(\exp(MSE) - 1)}$ for the log-transformed PK parameters.

Assuming a 15% dropout rate, approximately 38 participants were planned to be enrolled and randomized in the original protocol. This protocol amendment is increasing the planned enrollment number because 17 of the 31 randomized participants (as of the date of this amendment) were anticipated to not have viable PK samples (pending further bioanalytical stability investigation) following a power outage at the CRU during study conduct. To reach the sample size of 32 completed participants necessary for sufficient study power as previously described, an additional 21 participants will be randomized to complete at least 18 of the 21 (assuming a similar 15% dropout rate for the additionally enrolled participants). Therefore, a total of approximately 52 participants will now be randomized in this study to still reach the aim of at least 32 completed participants.

9.3. Populations for Analyses

The following populations are defined (Table 6):

Table 6: Populations for Analyses

Population	Description
Enrolled Set	All participants who sign the ICF
Safety Set	All participants who receive at least 1 dose of study intervention
Pharmacokinetic/Pharmacodynamic (PK/PD) Analysis Set	All participants who have sufficient plasma samples to have evaluable PK data for bupropion and total Mo (as a measure of ALXN1840) in plasma

Abbreviation: ICF = informed consent form; Mo = molybdenum.

9.4. Statistical Analyses

Statistical methods described in this section will be further elaborated in a separate Statistical Analysis Plan (SAP). The SAP will be developed and approved before database lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing data.

Summary statistics will be computed and displayed by study group and by visit, where applicable. Descriptive statistics for continuous variables will include number of non-missing values, arithmetic mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using percentages and frequency counts.

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

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. Data will be summarized by study groups.

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

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

Electrocardiogram 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 World Health Organization (WHO) Drug Dictionary.

9.4.3. Other Analyses

9.4.3.1. Pharmacokinetic and Pharmacodynamic Analyses

Pharmacokinetic analyses will be performed using the PK/PD Analysis Set.

Blood samples for PK analysis of total Mo (as a measure of ALXN1840), bupropion and its metabolite, hydroxybupropion will be collected at the following time points: pre-dose and post-dose at 1, 2, 3, 4, 5, 6, 8, 12, 24, 48, 72, 96, 120, 144, 168, 192, 216, 240, and 336 hours in each period (Note: the 336 hours sample in Period 1 will be collected during the Period 2, Pre-dose [Day 1] Visit).

The following plasma PK parameters will be calculated as endpoints for total Mo, bupropion and hydroxybupropion using noncompartmental methods with Phoenix® WinNonlin® (Certara USA Inc., Princeton, New Jersey) Version 8.0 or higher or SAS Version 9.3 or higher (SAS Institute Inc., Cary, North Carolina), as applicable. Calculations will be based on the actual sampling times recorded during the study.

- Time delay between the time of dosing and time of appearance of drug concentration in plasma (T_{lag}; for plasma total Mo with ALXN1840 administration)
- Maximum observed concentration in plasma (C_{max})
- Time to C_{max} (T_{max})
- Area under the plasma concentration (AUC) versus time curve from time 0 to the last quantifiable concentration (AUC_t)
- AUC versus time curve from time 0 to infinity (AUC_∞)
- AUC extrapolated from time t to infinity as a percentage of total AUC_∞ ($\%AUC_{extrap}$)
- Apparent terminal-phase elimination rate constant (λ_z)
- Terminal elimination half-life ($t_{½}$)
- Apparent oral clearance (CL/F)
- Apparent volume of distribution (V_d/F)
- Metabolite to parent ratio based on AUC (MRAUC) and C_{max} (MRC_{max}) [estimated for bupropion and hydroxybupropion]

Additional plasma PK parameters may be calculated if deemed appropriate.

Plasma concentrations of total Mo, bupropion and hydroxybupropion and time deviation data will be presented in a data listing by participant. Plasma concentration data will be summarized

separately by analyte and time point for each treatment using the following descriptive statistics: number of participants, arithmetic mean, SD, coefficient of variation (CV), median, minimum, and maximum. Mean plasma concentration versus scheduled time profiles will be presented in figures on both linear and semilogarithmic scales. Individual plasma concentration versus actual time profiles will be presented similarly.

Pharmacokinetic parameters derived from plasma concentrations of total Mo, bupropion and hydroxybupropion will be presented in data listings and summarized separately using the following descriptive statistics: number of participants, arithmetic mean, SD, arithmetic CV, median, minimum, maximum, and 95% CI. Geometric mean and geometric CV will be presented for C_{max} and AUCs only.

The effect of ALXN1840 on the bupropion PK will be assessed using a linear mixed-effect model (SAS PROC MIXED) with treatment condition, sequence, and period as fixed effects and participant nested within sequence as a random effect. The model will be fitted to the natural-log-transformed PK parameters C_{max}, AUC_{∞} and AUC_t for estimation of effects and construction of CIs for the test treatment (Treatment B: 150 mg bupropion + 60 mg ALXN1840) compared with the reference treatment (Treatment A: 150 mg bupropion). The within-participant CV for the corresponding PK parameters will be estimated using the mean squared error from the statistical model. Confidence intervals (90%) will be constructed for the least-squares geometric mean ratio (GMR) estimates between the test and reference treatments for above PK parameters using the natural log-transformed data. The GMR estimates and the associated 90% confidence limits will be exponentiated back to the original scale. These analyses will be repeated to assess the effect of ALXN1840 on hydroxybupropion PK.

Analyses of other PK data including, but not limited to PUF Mo may be conducted.

Pharmacodynamic data of ALXN1840 including, but not limited to, plasma total Cu, Cp, CpC, and potentially toxic Cu measured as LBC and PUF Cu and/or assessed via $NCC/NCC_{corrected}$ may be analyzed and reported.

Details of the PK/PD analyses will be described in the PK/PD data analysis plan or included in the SAP, which will be finalized before database lock.

9.5. Interim Analyses

No interim analyses are planned for this study.

9.6. Data Monitoring Committee

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

9.7. Safety Review Committee

To ensure participant safety, ad hoc SRC meetings may be held to discuss urgent issues should the need arise. The ad hoc SRC must convene within 24 hours in the case of a TESAE or the withdrawal of any participant due to an adverse reaction.

The ad hoc SRC, consisting of the Investigator, Alexion Safety Physician and Alexion Medical Monitor will evaluate the study data, if needed, for participant safety and make recommendations on termination of the study.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

- It is the responsibility of the Investigator to obtain signed (written or electronic signature) informed consent from all study participants prior to any study-related procedures including screening assessments.
- The Investigator or his/her representative will explain the nature of the study (including but not limited to the objectives, potential benefits and risk, inconveniences, and the participant's rights and responsibilities) to the participant, defined according to local and country regulations where the study is taking place, and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants, or their legally authorized representative, will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, European Union (EU) General Data Protection Regulation (GDPR), ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was screened in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF(s).
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the signed (written or electronic) documentation (ie, a complete set of participant information sheets and fully executed signature pages) must be provided to the participant or the participant's legally authorized representative, as applicable. This document may require translation into the local language. Signed (written or electronic) consent forms must remain in each participant's study file and must be available for verification at any time.
- The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research. If sharing exploratory research results with the Investigator is not planned, the ICF should mention it. Participants or legally authorized representative will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

10.1.4. Data Protection

- Participants will be assigned a unique identifier by Alexion. Any participant records or datasets that are transferred to Alexion will contain the identifier only; participant

names or any information which would make the participant identifiable will not be transferred.

- The participant must be informed that his/her personal study-related data will be used by Alexion in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Alexion, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Dissemination of Clinical Study Data

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

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on a printed or electronic CRF unless transmitted to Alexion or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Alexion or its designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 2 years after the last marketing application approval, or if not approved, 2 years following the discontinuance of the test article for investigation, unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Alexion. No records may be transferred to another location or party without written notification to Alexion.

10.1.7. Source Documents

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

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

10.1.8. Study and Site Start and Closure

The study start date is the date on which the first participant signs the informed consent.

Alexion or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of Alexion. Study sites will be closed 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 Alexion or the Investigator may include but are not limited to:

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

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

10.1.9. Publication Policy

- Where possible, primary manuscripts reporting results of the primary efficacy endpoint or the final results will be submitted for publication within 12-18 months of the primary evaluation date or end of study, whichever is earlier.
- Investigators who participate as authors in manuscripts derived from Alexion-sponsored studies will agree to the prerequisites as outlined in the Alexion author engagement agreement prior to engaging in manuscript development.
- The Investigator agrees to submit proposals for new manuscripts (whether or not the proposed analyses are derived from protocol-specified endpoints) to Alexion for

review and consideration. All manuscripts or abstracts emanating from approved proposals are to be submitted to Alexion for review before submission to the journal/society. This allows Alexion to protect proprietary information and to provide comments.

  - The proprietary nature of some development work may preclude publication. In some cases, it may be necessary to delay a publication to allow Alexion to ensure protection of intellectual property.

- In general, primary publications, including congress and journal publications, containing the protocol-specified results of a study should occur prior to the publication of individual study site results or case reports. Alexion's policy prohibits duplicate publication, whereby the same results must not be published in multiple peer-reviewed journal manuscripts.

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

- Alexion will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, Alexion will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements and per the Alexion Publication Policy.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in Table 7 be performed by the local laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations. Investigators must document their review of each laboratory safety report and indicate whether out of range results are clinically significant ("CS") or not clinically significant ("NCS").
- Women of childbearing potential should only be enrolled after a negative serum pregnancy test result at screening. Additional urine pregnancy testing will be standard for the protocol unless serum testing is required by site policies, local regulation, or IRB/IEC and should be performed per the time points specified in the SoA (Table 1). Screening pregnancy criteria are detailed in Section 5.1.

Table 7: Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters		
Hematology	Platelet Count Red blood cell count Hemoglobin Hematocrit	RBC Indices: Mean corpuscular volume Mean corpuscular hemoglobin % Reticulocytes	WBC count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils
Clinical Chemistry	BUN Potassium Bicarbonate Sodium Glucose AST ALT Chloride	Alkaline phosphatase Direct bilirubin Total bilirubin Albumin Creatinine Creatine phosphokinase	
Coagulation	INR Partial thromboplastin time Prothrombin time		
Routine Urinalysis	Specific gravity pH Glucose Protein Blood Bilirubin Urobilinogen Nitrite Leukocyte esterase by dipstick Microscopic examination		

Table 7: Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Other Screening Tests	Urine alcohol and urine drug screen (to include at minimum: amphetamines, barbiturates, benzodiazepines, cocaine, opiates, phencyclidine, methamphetamine, 3,4-methylenedioxy-methamphetamine, methadone, and tetrahydrocannabinol [cannabinoids])
	Human immune deficiency virus (HIV)-1 and HIV-2 antibodies, HbsAg [a], anti-HBC IgG + IgM (if IgG positive), and anti- HCV with confirmation by HCV RNA
	Serum or urine hCG pregnancy test (as needed for women of childbearing potential)
	FSH (postmenopausal females only)

Note: All events of ALT ≥ 3 × upper limit of normal (ULN) and bilirubin ≥ 2 × ULN (> 35% direct bilirubin) or ALT ≥ 3 × ULN and international normalized ratio (INR) > 1.5, if INR measured which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

[a] Only HBsAg testing is necessary for exclusion of active HBV infection; anti-HBC laboratory collection is not required.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; FSH = follicle-stimulating hormone; HbsAg = hepatitis B surface antigen; HbA1C = hemoglobin A1C; HBC = hepatitis B core antigen; hCG = human chorionic gonadotropin; HCV = hepatitis C virus; HIV = human immunodeficiency virus; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cell; RNA = ribonucleic acid; WBC = white blood cell.

Investigators must document their review of each laboratory safety report.

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

10.3.1. Definition of AE

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

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

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

10.3.2. Definition of SAE

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

An SAE is defined as any untoward medical occurrence that, at any dose:
1. Results in death
2. Is life-threatening

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

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

3. Requires inpatient hospitalization or prolongation of existing hospitalization

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

4. Results in persistent disability/incapacity

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

5. Is a congenital anomaly/birth defect

6. Other situations:

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

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

Recording of AE and/or SAE

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

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories from National Cancer Institute CTCAE v5.0, published 27 Nov 2017:

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

Assessment of Causality

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

Follow-up of AEs and SAEs

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

10.3.4. Reporting of SAEs

SAE Reporting to Alexion GDS via Paper Safety Reporting Form

- All SAEs will be recorded and reported to Alexion or designee immediately and within 24 hours awareness.
- SAEs will be reported using the Safety Reporting Form and submitted to Alexion Global Drug Safety (GDS). The Investigator must complete, sign, and date the SAE pages, verify the accuracy of the information recorded on the SAE pages with the corresponding source documents, and send a copy via email or facsimile to the contact information provided below:
  - Email: clinicalsae@alexion.com or Fax: + 1.203.439.9347
- Additional follow-up information, if required or available, should be entered into the CRF and sent to Alexion GDS within 24 hours of the Investigator or study site staff becoming aware of this additional information via the reporting process outlined above.
- For all SAEs, the Investigator must provide the following:
  - Appropriate and requested follow-up information in the time frame detailed above
  - Causality of the SAE(s)
  - Treatment of/intervention for the SAE(s)
  - Outcome of the SAE(s)
  - Medical records and laboratory/diagnostic information
- All paper forms and follow-up information submitted to Alexion GDS **must** be accompanied by a cover page signed by the Investigator.
- Paper source documents and/or reports should be kept in the appropriate section of the study file.

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

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

- Collection of pregnancy information
  - If a female participant or a male participant's female spouse/partner becomes pregnant during the conduct of this study, the Investigator must submit the "Pregnancy/Breastfeeding Reporting and Outcome Form" to Alexion Global Drug Safety (GDS) via fax or email (see Section 10.3 [Appendix 3] for contact information). When the outcome of the pregnancy becomes known, the form should be updated and submitted to Alexion GDS. If additional follow up is required, the Investigator will be requested to provide the information.
  - Exposure of an infant to an Alexion product during breastfeeding must also be reported (via the "Pregnancy/Breastfeeding Reporting and Outcome Form") and any AEs experienced by the infant must be reported to Alexion GDS or designee via email or facsimile (see Section 10.3 for contact information).

10.5. Appendix 5: Abbreviations

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

Table 8: List of Abbreviations and Definitions of Terms

Abbreviation	Definition
λ_z	apparent terminal-phase elimination rate constant
AE	adverse event
ALT	alanine aminotransferase
ANOVA	Analysis of Variance
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
AUC_t	AUC from time 0 to the last quantifiable concentration
AUC_∞	AUC from zero to infinity
BMI	body mass index
BUN	blood urea nitrogen
CYP	cytochrome P450
CYP2B6	cytochrome P450 2B6
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CL/F	apparent oral clearance
C_{max}	maximum observed plasma 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
CTFG	Clinical Trial Facilitation Group
Cu	copper
CV	coefficient of variation
DDI	Drug-Drug Interactions
EC	enteric-coated
ECG	electrocardiogram
eCRF	electronic case report form
EMA	European Medicines Agency
EOS	End of Study
ET	Early Termination
EU	European Union
FDA	Food and Drug Administration

GCP	Good Clinical Practice
GDS	Global Drug Safety
GMR	geometric mean ratio
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HLM	human liver microsomes
IB	Investigator's Brochure
IC_{50} value	drug concentration required to produce 50% of the maximal inhibition
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
LAM	lactational amenorrhoea method
LBC	labile-bound copper
Mo	molybdenum
MSE	mean-square error
MTD	maximum tolerated dose
NCC	non-ceruloplasmin-bound copper
$NCC_{corrected}$	corrected NCC
NCS	not clinically significant
PBC	primary biliary cholangitis
PD	pharmacodynamics
PI	Principal Investigator
PK	pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
PUF	plasma ultrafiltrate
QT	interval between the start of the Q wave and the end of the T wave in an ECG
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	red blood cell
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SoA	Schedule of Activities
SOC	System Organ Class

SRC	Safety Review Committee
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	terminal elimination half-life
TDI	time-dependent inhibition
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
T_{max}	time to reach maximum observed plasma concentration
TPC	Tetrathiomolybdate-Cu-albumin tripartite complex formed after ALXN1840 administration
ULN	upper limit of normal
USPI	United States Package Insert
UWDRS	Unified Wilson Disease Rating Scale
V_d/F	apparent volume of distribution
WD	Wilson Disease
WHO	World Health Organization

10.6. Appendix 6: Protocol Amendment History

The protocol amendment summary of changes table for the current amendment is located directly before the Table of Contents.

DOCUMENT HISTORY			
Document	**Type of Amendment (Global or Country-specific)**	**Date**	**Summary of Key Changes in the Amendment**
Amendment 1	Not applicable	16 Mar 2021	Increased the number of participants randomized in the study from approximately 38 to approximately 52.
Original protocol	Not applicable	28 Apr 2020	Not applicable

11. REFERENCES

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