PROTOCOL TITLE PAGE

Protocol Title: A Phase 2, single-arm, pathologist-blinded study using liver biopsy specimens to assess copper concentration and histopathologic changes in patients with Wilson disease who are treated with ALXN1840 for 48 weeks followed by an extension treatment period with ALXN1840 for up to an additional 48 weeks

Protocol Number: ALXN1840-WD-205

Amendment Number: 5 (Global)

Compounds: ALXN1840 (bis-choline tetrathiomolybdate)

Study Phase: 2

Short Title: Copper concentration and histopathologic changes in liver biopsy in patients with Wilson disease who are treated with ALXN1840

Sponsor Name: Alexion Pharmaceuticals, Inc.

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Regulatory Agency Identifier Number(s)

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Approval Dates:

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Amendment 3 (Denmark)	**10 Aug 2020**
Amendment 4 (United Kingdom)	**23 April 2021**
Amendment 5 (Global)	**27 May 2022**

Alexion Signatory:

[redacted]

09-Jun-2022 | 08:53:28 EDT

Date

Medical Monitor Name and Contact Information can be found in the Study Contact List.
24-hour Emergency Contact: [redacted]

INVESTIGATOR'S AGREEMENT

I have read the Study ALXN1840-WD-205 protocol amendment 5 (Global) and agree to conduct the study in accordance with this protocol, all applicable government regulations, the principles of the ICH E6 Guidelines for Good Clinical Practice, and the principles of the World Medical Association Declaration of Helsinki. I also agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Amendment 5 (27 May 2022)

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union, the US Food and Drug Administration's (FDA) regulation at 21 CFR part 312.30(b), and any applicable local regulations.

Overall Rationale for the Amendment

This amendment has been prepared to add the requirement for Alexion approval prior to increasing the dose of ALXN1840, to add labile-bound copper (LBC) and directly measured non-ceruloplasmin-bound copper (dNCC) as exploratory endpoints, and to add an exploratory endpoint for the daily mean area under the effect-time curve (AUEC) for dNCC. Administrative Change Letters since approval of the previous protocol have also been incorporated. Changes are summarized in the table below.

Changes to the Protocol

Section # and Name	Description of Change	Brief Rationale and/or Clarifications
Section 1.1, Synopsis; Section 3, Objectives and Endpoints; Section 8.1.2, Non-Ceruloplasmin-Bound Copper	Added as exploratory endpoints: • absolute and percent change in directly measured non-ceruloplasmin-bound copper (dNCC) and labile-bound copper (LBC) from baseline to Week 48 • daily mean area under the effect-time curve (AUEC) of dNCC from 0 to 48 weeks	To align with other ALXN1840 Phase 2 and 3 studies.
Section 1.1, Synopsis, Drug Groups and Duration; Section 4.1 Overall Design; Section 4.3, Justification for Dose; Section 6.6 Dose Modification	Addition of text to clarify that Alexion approval is needed to increase the dose of ALXN1840 after an interruption or reduction.	To enhance Alexion oversight of dose escalations.
Section 1.2, Schema, Figure 1	Figure corrected to remove mention of treatment-naïve patients.	Treatment-naïve patients are not included in the study.
Section 1.3 Schedule of Activities, Table 1	Administer/dispense ALXN1840 added at Week 48 for patients continuing into the Extension Period (including footnote 'w' "only for patients continuing into the Extension Period").	Patients continuing into the Extension Period require dispensation of ALXN1840 at the Week 48 visit of the Treatment Period.
	Footnote 'o' added to Week 48 chemistry, coagulation, hematology panel, and urinalysis assessments	To align with current protocol procedure.

Section 1.3 Schedule of Activities, Table 1 and Table 2, Section 8.1.7, Imaging Techniques	FibroScan noted as preferred method of transient elastography instead of required method.	Other methods of transient elastography are permitted if FibroScan is not available.
Section 1.3 Schedule of Activities, Table 2	Footnote 'f' revised to "…..negative urine pregnancy test at each study visit."	To align with footnote 'm' in Table 1.
	12-lead ECG deleted at EOS visit	Not required.
	Extension Period Day 365 added to EOS visit	Correction of typographical error.
	Administer/dispense ALXN1840 deleted at Extension Period Day 337.	Extension Period Day 337 is the last visit in the Extension Period; treatment with ALXN1840 is complete.
Section 5.1, Inclusion Criteria	Inclusion criterion #1 for confirmation of diagnosis of Wilson disease changed to Leipzig score ≥ 4 (formerly > 4) and expanded to include historical test results.	A historical diagnosis of Wilson disease is sufficient. The original criteria for diagnosis of Wilson disease will be recorded in a case report form. It is not necessary to repeat the diagnostic evaluation of Wilson disease for this protocol.
Section 5.1, Inclusion Criteria; Section 8.3.5, Pregnancy; Section 10.4, Appendix 4, Pregnancy Information	Contraception guidance updated to include duration of use and type; duration of pregnancy follow-up revised.	To further define contraception and pregnancy follow-up requirements.
Section 5.2, Exclusion Criteria	Criterion #17 amended to exclude participation in another clinical study within 3 months (or 5 half-lives of the administered investigational medicinal product, whichever is longer) prior to study start.	More detailed language regarding exclusion of patients who participated in any interventional study prior to initiation of Study ALXN1840-WD-205.
Section 6.5, Concomitant Therapy	Standard of care treatment for Wilson disease added as prohibited medication during the Treatment and Extension Periods.	Standard of care treatment for Wilson disease and ALXN1840 should not be administered concomitantly.
Section 6.6, Dose Modification, Table 6	Addition of dose modification rules for increased triglycerides and total cholesterol.	To include guidance on dose modifications in the event of increased triglycerides or total cholesterol.
Section 8, Study Assessments and Procedures	Liver biopsy text revised to "Liver biopsy is the last pre-dose baseline procedure to be completed and must be completed within 14 days prior to the first dose of ALXN1840" (formerly "a minimum of 14 days").	To align with text in Section 8.6.

Section 8.6, Pharmacodynamics	Text updated to include all pharmacodynamic measures that will be evaluated.	For clarification and completeness.
10.1.1 Regulatory and Ethical Considerations	Modified text to remove specific reference to regional guidance and listed as examples only. Included the European Regulation No 536/2014 for clinical trials on medicinal products for human use as an example.	To include a more general statement as not all regional guidances previously included are applicable in every region.
Section 10.2 Appendix 2: Clinical Laboratory Tests, Table 8, Clinical Chemistry	Lipid profile (total cholesterol, LDL, HDL, and triglycerides added to the table of chemistry assessments.	Routine tests added for completeness.
Section 10.3, Appendix 3, Adverse Events, Reporting of Serious Adverse Events	Deleted instructions for reporting via paper case report form.	To align with current protocol procedure.
Section 10.5, Genetics	Retention of DNA sample changed from 10 years to 15 years.	To align with Alexion standard.
All sections	Minor editorial updates and corrections.	For clarification, and to ensure accuracy and consistency throughout the protocol.

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title:

A Phase 2, single-arm, pathologist-blinded study using liver biopsy specimens to assess copper concentration and histopathologic changes in patients with Wilson disease who are treated with ALXN1840 for 48 weeks followed by an extension treatment period with ALXN1840 for up to an additional 48 weeks

Short Title:

Copper concentration and histopathologic changes in liver biopsy in patients with Wilson disease who are treated with ALXN1840

Rationale:

This study is being conducted to assess the effect of ALXN1840 on changes in liver copper (Cu) concentration and liver histopathology in patients with Wilson disease (WD). Currently available standard of care (SoC) medications (ie, trientine, penicillamine, and zinc) control excess free Cu in the blood, but do not consistently reduce Cu overload in the liver. Conversely, tetrathiomolybdate (the active ingredient in ALXN1840) has been shown to reduce liver Cu stores in animal models (Suzuki, 1993; Suzuki, 1994; Suzuki, 1995; Ogra, 1995a; Ogra, 1995b; Ogra, 1996).

Accumulation of Cu in the liver leads to an increased risk of tissue and organ damage. Limited available data obtained from serial liver biopsies in patients with WD indicate that liver Cu concentration remains elevated, with no consistent reduction of liver Cu over time in patients treated with SoC beyond the first year (Medici, 2006; Scheinberg, 1987; Cope-Yokoyama, 2010; Gibbs, 1990). The impact of ineffective decoppering with SoC medications can be seen in patients with WD who discontinue treatment for WD, who are at risk for rapid progression to liver failure (Maselbas, 2010; Dziezyc, 2014). Unlike penicillamine or trientine, ALXN1840 can enter hepatocytes and compete with metallothionein to bind intracellular Cu (Suzuki, 1993). Copper bound to the tetrathiomolybdate complex is excreted into the bile, promoting net negative excretion of Cu from the liver (Ogra, 1995b). In the Long-Evans Cinnamon rat model of WD, treatment with tetrathiomolybdate leads to rapid reduction in liver Cu concentration (Suzuki, 1995).

The principal aim of this study is to evaluate the effect of ALXN1840 on reduction of liver Cu concentration at Week 48 of treatment compared with baseline in patients with WD who have been previously treated with SoC (ie, trientine, penicillamine, or zinc) for at least 1 year. Molybdenum concentration will also be assessed in the liver.

Objectives and Endpoints

Objectives	Endpoints
Treatment Period	
Primary	
To evaluate change in liver copper (Cu) concentration following treatment with ALXN1840 at Week 48 in patients with Wilson disease (WD)	Change from baseline to Week 48 in liver Cu concentration
Secondary	
To assess change in liver histopathology following treatment with ALXN1840	Change from baseline to Week 48 in steatosis, inflammation, and fibrosis
To evaluate the safety of ALXN1840 in patients with WD	Adverse events (AEs), vital signs, ECGs, clinical laboratory data, and physical examination data
To evaluate pharmacokinetics (PK) of ALXN1840	• ALXN1840 PK profiles in plasma at Week 6 (Day 43) and Week 36 (Day 253), of which ALXN1840 PK are measured as total molybdenum (Mo) and plasma ultrafiltrate (PUF) Mo • Pre-dose trough ALXN1840 concentrations in plasma at each study site visit • ALXN1840 concentrations in the liver biopsy specimen.
To evaluate the effects of ALXN1840 on clinical symptoms	Change from baseline in Clinical Global Impression-Improvement (CGI-I) Scale and the Clinical Global Impression-Severity (CGI-S) Scale
Exploratory	
To explore the effects of ALXN1840 on hepatic status	Change from baseline to Week 48 in: • Model for End Stage Liver Disease (MELD) score • Modified Nazer score
To assess changes in liver fibrosis and steatosis using non-invasive techniques	Liver stiffness by magnetic resonance (MR) elastography and transient elastography (Vibration-Controlled Transient Elastography/FibroScan), MR-proton density fat fraction (PDFF)
To explore changes in mitochondrial ultrastructure of the liver at Week 48	Change from baseline to Week 48 in mitochondrial ultrastructure by electron microscopy
To explore the change in Cu deposition in the eye at Week 48	Change from baseline to Week 48 in in Cu deposition in the eye by optical coherence tomography
To explore the change in pharmacodynamic (PD) and biomarkers with ALXN1840 treatment at Week 48	• Absolute and percent change in plasma total and PUF Cu and calculated non-ceruloplasmin-bound Cu (cNCC) concentrations, as well as directly measured NCC (dNCC), labile-bound Cu (LBC), ceruloplasmin (Cp) and Cp-bound Cu (CpC) from baseline to Week 48 • Daily mean area under the effect-time curve (AUEC) of dNCC from 0 to 48 weeks
To explore the effects of ALXN1840 on quality of life at Week 48	Change from baseline to Week 48 in quality of life measures of: • EuroQoL 5 Dimensions (EQ-5D) • Short form-36 (SF-36) • Chronic Liver Disease Questionnaire (CLDQ)
To assess treatment satisfaction of ALXN1840 at Week 48	Treatment Satisfaction Questionnaire for Medication-9 (TSQM-9)
To explore the effects of ALXN1840 on neurologic and psychiatric symptoms	Change from baseline to Week 48 in: • Brief Psychiatric Rating Scale-24 (BPRS-24) • Unified Wilson Disease Rating Scale (UWDRS)

Objectives	Endpoints
Extension Period	
All patients will continue to receive ALXN1840 in the 48-week Extension Period. All safety and efficacy parameters will be measured as detailed above at Week 48 in the Extension Period, except for liver biopsy, which will not be performed in the Extension Period.	

Overall Design:

This is a Phase 2, open-label, pathologist-blinded, multicenter study designed to evaluate the change in liver Cu concentration at Week 48 compared with baseline in adult patients with WD treated with ALXN1840 at doses up to 30 mg once a day (QD) who have been treated for at least 1 year with SoC (ie, penicillamine, trientine, or zinc). This study will include a Screening Period, Treatment Period, and an optional 48-week Extension Period.

In the Treatment Period, efficacy and safety will be assessed for ALXN1840 at Week 48 in patients with WD who are aged 18 years and older.

Patients who complete the Treatment Period will be offered the opportunity to participate in a 48-week Extension Period to evaluate the long-term safety and efficacy of ALXN1840. All patients will continue to receive ALXN1840 at doses up to 30 mg/day during the Extension Period. Note that there will be no liver biopsies during the Extension Period.

This study is pathologist-blinded for the assessments of liver histology samples.

Disclosure Statement: This is an open-label, single-arm study with outcome assessor-masking for the assessments of liver histology samples.

Number of Patients:

Approximately 28 patients will be enrolled into the study globally, such that approximately 24 evaluable patients complete the 48-week Treatment Period.

Drug Groups and Duration:

On Day 1 of the Treatment Period, patients will receive ALXN1840. Patients will be initiated at 15 mg once daily, then the dose will be increased to 30 mg once daily at Week 6.

In case of drug tolerability issues, the dose of ALXN1840 may be reduced or temporarily interrupted. Such dose changes must be discussed with the Alexion Medical Monitor and documented in the study record. Any subsequent dose increases must be approved by Alexion.

The planned study duration is approximately 100 weeks, including an up to 4-week Screening Period. A liver biopsy will be performed during the Screening Period within 14 days prior to the first dose of study drug, followed by a 48-week Treatment Period, which starts on the day of first dose of study drug, and an optional 48-week Extension Period.

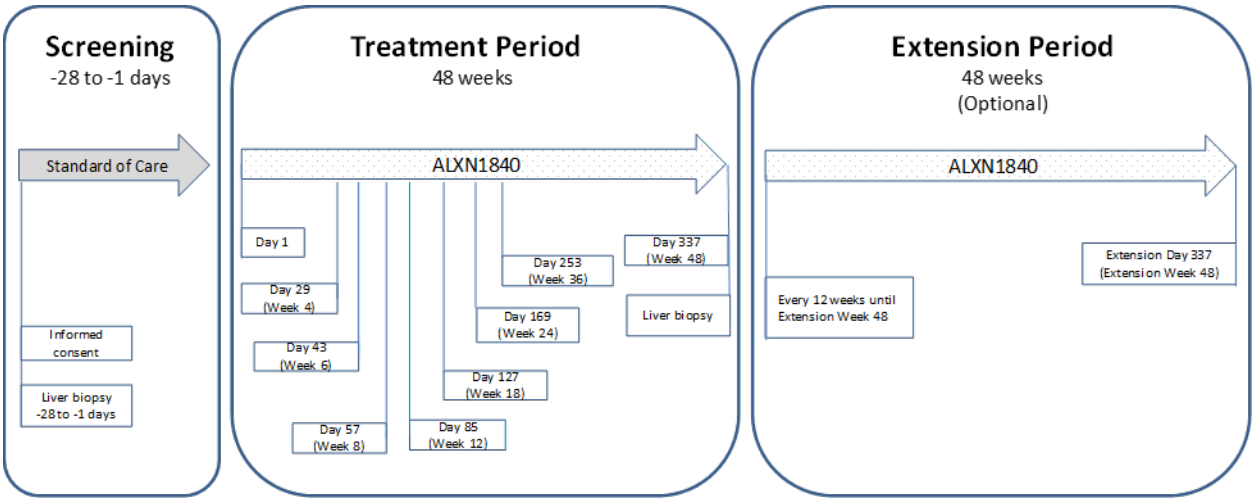
Data Monitoring Committee: An independent Data Monitoring Committee (DMC), comprising experts in relevant fields with no direct relationship to the study, will be appointed by Alexion. As detailed in a Charter (maintained separately from the study protocol), the DMC will review and monitor study data for safety, effectiveness, and study conduct, and make recommendations regarding study continuation, changes to the study population, and/or modification to study procedures.

Hepatic Adjudication Panel: A separate, independent Hepatic Adjudication Panel, both comprising experts in relevant fields, will be appointed by Alexion. The specific responsibilities for this Panel are described in a Charter (maintained separately from the study protocol).

1.2. Schema

A schematic view of the study design is provided in Figure 1.

Figure 1: Schema for Study ALXN1840-WD-205



1.3. Schedules of Activities

The Schedule of Activities (SoA) for the Screening and Treatment Periods is provided in Table 1. In the Screening Period, the liver biopsy should be performed after all other screening activities have been completed, including imaging, and the patient has met all inclusion and no exclusion criteria.

The Day 337 (Week 48) visit is the end of the Treatment Period and the beginning of the Extension Period (ie, the Week 48 visit and the Extension Period Day 1 visit will occur on the same day). All assessments for the Week 48 visit and the liver biopsy must be performed before the first dose of ALXN1840 on Day 1 of the Extension Period. Dosing of ALXN1840 on Extension Period Day 1 marks the beginning of the Extension Period. Patients who do not enter the Extension Period will discontinue dosing at Week 48 following the second liver biopsy and will have a final study visit for safety follow up at Day 365 (Week 52) of the Treatment Period.

The SoA for the Extension Period is provided in Table 2.

On study visit days where laboratory sampling is planned, patients will be asked to withhold any doses of ALXN1840 due to be taken prior to their visit, to allow laboratory samples to be taken pre-dose.

Laboratory specimen handling and processing instructions will be provided in the study laboratory manual. Blood samples should not be collected from a heparinized line.

Unscheduled visits that occur outside the protocol-specified visits are permitted at the discretion of the Investigator. Procedures, tests, and assessments conducted during unscheduled visits will be performed at the discretion of the Investigator.

Table 1: Schedule of Activities –Treatment Period

	Screening	Treatment Period													UNS[a]	Follow-Up[b]
Day	**-28 to -1**	**1**[c]	**8**[d]	**15**[d]	**29**[c]	**43**[c]	**57**[c]	**85**[c]	**127**[c]	**169**[c]	**211**[d]	**253**[c]	**295**[d]	**337**[c] / ET[e]		**365**
Week	**-4 to 0**		**1**	**2**	**4**	**6**	**8**	**12**	**18**	**24**	**30**	**36**	**42**	**48**		**52**
Window (days)			±3									±7	±3	±7		±7
Obtain informed consent (written or electronic)	X															
Review eligibility criteria	X[f]															
Medical history[g] and demographic parameters[h]	X															
WD medication history	X	X														
Physical examination	X													X		X
Abbreviated physical examination[i]		X			X	X	X	X	X	X		X				
Vital signs[j]	X	X			X	X	X	X	X	X		X		X		X
12-lead ECG	X					X								X		
FSH[k]	X															
HIV/hepatitis B and C testing	X															
DNA sample		X[l]														
Pregnancy test[m]	X	X			X		X	X	X	X		X		X		X
Chemistry, coagulation, hematology panel, and urinalysis[n]	X[o]	X			X	X	X	X	X	X		X		X[p]		X
Screening ultrasound (before liver biopsy)	X															
MRE, transient elastography (FibroScan preferred), MR-PDFF	X													X		
Optical coherence tomography	X													X		
Liver biopsy (see Section 5.3.2)	X													X		
Plasma PK/PD/biomarker samples[q]		X			X	X	X	X	X	X		X		X		
24-hour urine[r]		X			X			X		X		X		X		
UWDRS[s,t]		X												X		
CGI[s]		X[u]			X			X		X		X		X		
EQ-5D[s]		X								X				X		
TSQM-9[s]	X													X		

	Screening	Treatment Period													UNS[a]	Follow-Up[b]
Day	**-28 to -1**	**1**[c]	**8**[d]	**15**[d]	**29**[c]	**43**[c]	**57**[c]	**85**[c]	**127**[c]	**169**[c]	**211**[d]	**253**[c]	**295**[d]	**337**[c] / ET[e]		**365**
Week	**-4 to 0**		**1**	**2**	**4**	**6**	**8**	**12**	**18**	**24**	**30**	**36**	**42**	**48**		**52**
Window (days)			**±3**									**±7**	**±3**	**±7**		**±7**
SF-36[s]		X								X				X		
CLDQ[s]		X								X				X		
BPRS-24[s]		X								X				X		
AE, concomitant medication, and non-pharmacologic therapy/procedure[v]	←	———	———	———	———	———	———	———	———	———	———	———	———	———		→
Administer/dispense ALXN1840[w]		X			X	X	X	X	X	X		X		X[w]		

Note: Patients who complete the 48-week period of treatment will be offered the opportunity to participate in an up to 48-week Extension Period in which they will continue to receive ALXN1840.

[a] Unscheduled study visits may occur at any time during the study and may include any study procedures (including dispensing of ALXN1840) as deemed necessary by the Investigator. These visits may or may not be completed by a home healthcare nurse, where applicable, depending on the purpose of the unscheduled visit.

[b] Follow up visit procedures (Day 365) will be performed only for patients who do not enter the Extension Period and will be the EOS visit for these patients.

[c] Assessments on Day 1 and other study visit days where laboratory sampling is planned should be performed pre-dose.

[d] Weeks 1, 2, 30, and 42 (Days 8, 15, 211, and 295) assessments will be performed via a safety phone call. CGI-I and CGI-S, and UWDRS should be performed as soon as possible (as considered appropriate by the Investigator) if a neurological AE is reported. Investigators can perform additional study assessments or laboratory testing at their discretion.

[e] For patients continuing in the Extension Period, assessments at the Day 337 (Week 48) visit in the Treatment Period will be used as the Extension Period Day 1 assessments.

[f] Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened up to 2 times after agreement on required repeated assessments with the Alexion Medical Monitor.

[g] Demographic parameters include age and sex. Race and ethnicity will be collected only where allowable per local regulations.

[h] Wilson disease history will include details of any previous liver biopsies performed and treatment received.

[i] Abbreviated physical examination consists of a body system relevant examination based upon Investigator judgment and patient symptoms. At least 1 body system must be checked for an abbreviated examination.

[j] Vital signs include heart rate, blood pressure, respiration rate, temperature, height (Day 1 only; without shoes), and weight.

[k] Follicle-stimulating hormone will only be performed for post-menopausal females.

[l] The DNA sample is optional and can be collected at any time on or after Day 1; the sample will only be taken if the patient has provided informed consent (written or electronic) for this procedure.

[m] Serum and urine pregnancy tests will only be performed for females of childbearing potential. Female patients of childbearing potential must not be pregnant and not breastfeeding, and must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at each subsequent study visit. Positive urine pregnancy results must be confirmed by a serum pregnancy test.

[n] The MELD and modified Nazer scores will be calculated by a central laboratory.
[o] In addition to screening samples submitted to the central laboratory, additional samples for coagulation and hematology tests are to be performed at a local laboratory within 3 days before the liver biopsy, to assure the safety of the liver biopsy.
[p] Plasma samples will be obtained from the blood samples collected pre-dose on the day of all study visits. Patients should be instructed not to take their dose of ALXN1840 on the morning of scheduled study visits so that PK/PD/Biomarker samples are collected at pre-dose trough: total and PUF Mo (PK), total and PUF Cu, NCC (PD), Cp, and CpC (biomarker). At the Week 6 (Day 43) and Week 36 (Day 253) visits, serial blood samples will be collected for plasma PK/PD/Biomarker concentrations at the following time points: pre-dose at 0 hour, and at 2- and 4-hours post-dose.
[q] For the 24-hour urine sample, 500 mL will be considered the minimum acceptable sample size. Any amount < 500 mL will not be tested due to an insufficient sample collection. Urine collected will be used for 24-hour creatinine, Mo and Cu. Dispense container for 24-hour urine collection during the Screening Period, Day 1, and Day 57 (Week 8), Day 127 (Week 18), Day 169 (Week 24), and Day 253 (Week 36).
[r] The UWDRS is scheduled to be performed at Day 1 and Day 337 (Week 48) only but can also be performed as appropriate if a neurological adverse event is reported.
[s] Can be performed up to 7 days before Day 1, at the discretion of the Investigator.
[t] CGI-I is not performed at Day 1, only CGI-S.
[u] Adverse event, concomitant medication, and non-pharmacologic therapy/procedure are to be collected from signing of the ICF.
[v] Appropriately trained study staff will instruct patients on how to correctly dose themselves, including any changes to the dosing regimen. ALXN1840 will not be dispensed or administered at the Early Termination Visit.
[w] ALXN1840 dispensed/administered only for patients continuing into the Extension Period.

Abbreviations: AE = adverse event; BPRS = Brief Psychiatric Rating Scale-24; CGI = Clinical Global Impression; CGI-I = Clinical Global Impression-Improvement Scale; CGI-S = Clinical Global Impression-Severity Scale; CLDQ = Chronic Liver Disease Questionnaire; Cp = ceruloplasmin; Cp-C = ceruloplasmin-bound copper; Cu = copper; EOS = End of Study; EQ-5D = EuroQoL 5 Dimensions; ET = Early Termination; FSH = follicle-stimulating hormone; MELD = Model for End-Stage Liver Disease; Mo = molybdenum; MRE = magnetic resonance elastography; MR-PDFF = magnetic resonance-proton density fat fraction; NCC = non-ceruloplasmin bound copper; PD = pharmacodynamic; PK = pharmacokinetic; SF-36 = Short Form 36; SoC = standard of care; TSQM-9 = Treatment Satisfaction Questionnaire for Medication-9; UNS = unscheduled; UWDRS = Unified Wilson Disease Rating Scale; WD = Wilson Disease.

Table 2: Schedule of Activities – Extension Period

	Extension Period					UNS[a]	ET	EOS
Extension Period Day	**1[b,c]**	**85**	**169**	**253**	**337**			**365**
Window (days)	±7	**±7**						**±7**
Physical examination	X				X		X	X
Abbreviated physical examination[d]		X	X	X				
Vital signs[e]	X	X	X	X	X		X	X
12-lead ECG	X				X		X	
Pregnancy test[f]	X	X	X	X	X		X	X
Chemistry, coagulation, and hematology panel and urinalysis[g]	X	X	X	X	X		X	X
24-hour urine[h]	X		X		X			
MRE, transient elastography (FibroScan preferred), MR-PDFF	X				X			
Optical coherence tomography	X				X			
Plasma PK/PD/Biomarker samples[i]	X	X	X	X	X		X	
UWDRS[j]	X				X		X	
CGI	X		X		X		X	
EQ-5D	X		X		X		X	
TSQM-9	X				X		X	
SF-36	X		X		X		X	
CLDQ	X				X		X	
BPRS	X		X		X		X	
AE, concomitant medication, and non-pharmacologic therapy/procedure	←							→
Administer/dispense ALXN1840[k]	X	X	X	X				

Note: Patients who complete the 48-week Treatment Period will be offered the opportunity to participate in an Extension Period in which they will continue to receive ALXN1840. Patients may continue participation in the Extension Period and receive ALXN1840 until the product is registered and available to treat patients diagnosed with WD (in accordance with country specific regulations or for a maximum of 4 years, whichever comes first).

[a] Unscheduled study visits may occur at any time during the study and may include any study procedures (including dispensing of ALXN1840) as deemed necessary by the Investigator. These visits may or may not be completed by a home healthcare nurse, where applicable, depending on the purpose of the unscheduled visit.

[b] Assessments on Extension Period Day 1 and other study visit days where laboratory sampling is planned should be performed pre-dose.

[c] Assessments at the Day 337 (Week 48) visit of the Treatment Period will be used as the Extension Period Day 1 assessments.

[d] Abbreviated physical examination consists of a body system relevant examination based upon Investigator judgment and patient symptoms. At least 1 body system must be checked for an abbreviated examination.
[e] Vital signs include heart rate, blood pressure, respiration rate, temperature, height (Extension Period Day 1 only; without shoes), and weight.
[f] Serum and urine pregnancy tests will only be performed for females of childbearing potential. Female patients of childbearing potential must not be pregnant and not breastfeeding, and must have a negative urine pregnancy test at each study visit. Positive urine pregnancy results will be confirmed by a serum pregnancy test.
[g] The MELD and Nazer scores will be calculated by a central laboratory.
[h] For the 24-hour urine sample, 500 mL will be considered the minimum acceptable sample size. Any amount < 500 mL will not be tested due to an insufficient sample collection. The container for 24-hour urine collection should be dispensed at the study visit immediately prior to the next expected collection. Urine containers should be dispensed on Extension Period Day 1 and at the visit on Days 85 (Week 12). 24-hour urine collection should be submitted by the patient at Extension Period Days 1, 169 (Week 24), and 337 (Week 48).
[i] Plasma samples will be obtained from the blood samples collected pre-dose on the day of all study visits. Patients should be instructed not to take their dose of ALXN1840 on the morning of scheduled study visits so that PK/PD/Biomarker samples are collected at pre-dose trough: total and PUF Mo (PK), total and PUF Cu, NCC (PD), Cp, and CpC (biomarker).
[j] The UWDRS is scheduled to be performed at Extension Period Day 1 and Day 337 (Week 48) only but can also be performed as appropriate if a neurological adverse event is reported.
[k] ALXN1840 will not be dispensed or administered at the ET Visit.

Abbreviations: BPRS = Brief Psychiatric Rating Scale-24; CGI-I = Clinical Global Impression-Improvement Scale; CGI-S = Clinical Global Impression-Severity Scale; CLDQ = Chronic Liver Disease Questionnaire; EOS = End of Study; EQ-5D = EuroQoL 5 Dimensions; ET = Early Termination; ICF = informed consent form; MELD = Model for End-Stage Liver Disease; MRE = magnetic resonance elastography; MR-PDFF = magnetic resonance-proton density fat fraction; PD = pharmacodynamic; NCC = non-ceruloplasmin bound copper; PK = pharmacokinetic; SF-36 = Short Form 36; TSQM-9 = Treatment Satisfaction Questionnaire for Medication-9; UNS = unscheduled; UWDRS = Unified Wilson Disease Rating Scare; WD = Wilson Disease

2. INTRODUCTION

2.1. Study Rationale

This study is being conducted to evaluate the change in liver copper (Cu) concentration at Week 48 compared with baseline in adult patients with Wilson Disease (WD) treated with ALXN1840 at doses up to 30 mg/day.

Currently available standard of care (SoC) medications (ie, trientine, penicillamine, and zinc) control excess free Cu in the blood but have never been demonstrated prospectively to reduce Cu burden in the human liver. Conversely, tetrathiomolybdate (the active ingredient in ALXN1840), has been shown to reduce liver Cu stores in animal models (Suzuki, 1993; Suzuki, 1994; Suzuki, 1995; Ogra, 1995a; Ogra, 1995b; Ogra, 1996).

2.2. Background

2.2.1. Wilson Disease

Wilson Disease is an autosomal recessive disorder of impaired Cu transport. Mutations in the *ATP7B* gene result in deficient production of the Cu-transporter ATPase2, leading to impaired incorporation of Cu into ceruloplasmin (Cp), impaired biliary excretion of Cu, increased free and albumin-bound Cu, and Cu accumulation in liver, brain, and other tissues, with resulting organ damage and dysfunction (Pfeiffer, 2007). Ceruloplasmin is a serum ferroxidase, and in healthy humans, it contains greater than 95% of the Cu found in plasma (Hellman, 2002).

The prevalence of genetic markers associated with WD is approximately one per 30,000 population worldwide (Frydman, 1990; Reilly, 1993; Schilsky, 2002). Among people with an identified mutation, disease manifestation will be present in approximately 50%. The majority of patients are diagnosed before 30 years of age (Beinhardt, 2014). A recent nationwide, population-based epidemiological study based in France found the diagnosed prevalence of WD to be 1.5 per 100,000 population (Poujois, 2018).

Typical clinical presentation of WD is in adolescence to early adulthood. Genetic screening and genotype-phenotype correlation is complicated by a multitude (> 500) of associated *ATP7B* mutations; most individuals with WD are compound heterozygotes. Initial signs and symptoms of WD are predominantly hepatic (~40%), neurologic (~40%), or psychiatric (~20%), but patients often develop combined hepatic and neuropsychiatric disease. Untreated or inadequately treated patients have progressive morbidity, and mortality is usually secondary to liver cirrhosis. Liver transplantation is the only effective therapy for WD-associated acute liver failure; other causes of death associated with WD include hepatic malignancy and neurologic deterioration with severe inanition (Pfeiffer, 2007; Roberts, 2008).

The liver represents the primary Cu storage organ in humans. In healthy people, intracellular Cu homeostasis is tightly regulated. Copper is transported into cells by Cu transporter 1 (CTR1), and then transferred to Cu chaperones such as the Cu chaperones for antioxidant 1, cytochrome c oxidase, and superoxide dismutase. Copper accompanying the chaperone is delivered to a specific Cu-requiring enzyme. If excess amounts of Cu appear, the excess Cu is bound to metallothionein (MT) as monovalent Cu (Cu+) via Cu thiolate bridges by abundant cysteine

residues in MT, thus providing a stable storage mechanism limiting the potential for redox cycling (oxidative stress) and associated toxicity.

In patients with WD, Cu is not removed from the tissue compartments due to the deficient activity of ATPase2. This results in an accumulation of Cu, mainly in the liver where the protein is highly expressed in hepatocytes and then in the brain, but also in other organs. Within the capacity of MT biosynthesis, no apparent toxicity of Cu exists because MT tightly binds Cu. However, beyond the Cu buffering capacity of MT, free Cu ions appear and this excessive amount of free intracellular Cu triggers pro-oxidant properties, leading to an increased risk of tissue/organ damages with clinical manifestations as a result. It is assumed that the toxicity of Cu in WD is mediated by the free Cu that is not bound to MT due to the Cu overload (Ogra, 1996). Copper is then increased in the circulation and is available for uptake into other organs where it may cause damage, in particular, in the brain.

Treatment goals focus on compensating for impaired Cu metabolism, by reducing toxic free Cu, and maintaining normal Cu concentrations to improve organ function and patients' symptoms. The current treatments for WD are general chelator therapies D-penicillamine (Cuprimine, Depen) and trientine (eg, Cufence, Cuprior, Syprine), which non-specifically chelate Cu and promote urinary Cu excretion. In addition, zinc, which blocks dietary uptake of Cu, is used mainly for maintenance treatment. Zinc impairs the absorption of Cu by the induction of MT and Cu sequestration within the enterocytes of the gastrointestinal tract, which ultimately get sloughed and excreted in stool.

Disease control in patients with neurological symptoms at WD diagnosis is an area of particular concern. More than a third of patients presenting with neurological symptoms show no improvement after 4 years of treatment with chelators. In a recent study, approximately 50% of patients had residual neurological symptoms despite years of therapy on a Cu-modulating agent (Holscher, 2010). This failure to respond to chelation therapy with neurological presentation may reflect irreversible damage to the nervous system (Weiss, 2013). In addition, worsening of neurological symptoms on initiation of treatment has been reported in approximately 25% of patients initiated on penicillamine and trientine, and up to 50% of those patients never recover (Brewer, 1987; Brewer, 2006; Merle, 2007; Weiss, 2011; Kalita, 2014; Kalita, 2015). The mechanism behind this worsening is believed to be a mobilization of Cu from the liver leading to elevations in blood Cu associated with neurological progression (Brewer, 2009). This theory is supported by non-clinical data (Zhang, 2015; Chen, 2012).

Currently available drugs have high rates of treatment discontinuation due to adverse events (AEs) and treatment failure. They also need to be dosed 2 to 5 times per day and must be taken in the fasted state. Their AE profiles and complicated dosing regimens lead to poor treatment compliance and high rates of treatment failure, a major concern in a disease that requires life-long treatment such as WD (Maselbas, 2010; Dziezyc, 2014).

2.2.2. ALXN1840

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

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

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

ALXN1840 has been evaluated in 28 patients with WD in an open-label Phase 2 Study WTX101-201. Results from the main 24-week study showed that ALXN1840 monotherapy reduced mean serum non-ceruloplasmin-bound Cu (NCC) by 72% at Week 24 compared with baseline. ALXN1840 treatment also resulted in significant improvements in neurological status and disability measured as a change from baseline in Unified WD Rating Scale (UWDRS) Part III and Part II, respectively. In addition, liver status, as measured by the Modified Nazer Score and model for end-stage liver disease (MELD), was stabilized or improved in most patients. Treatment with ALXN1840 was generally well-tolerated, with most reported AEs being mild (Grade 1) to moderate (Grade 2). Reversible liver function test elevations were observed in 39% of patients; these elevations were mild to moderate, asymptomatic, were associated with no notable increases in bilirubin (ie, no documented case of Hy's Law), and normalized with dose reduction or treatment interruption. No paradoxical neurological worsening was observed upon treatment initiation with ALXN1840 (Weiss, 2017). All patients who completed the 24-week Initial Dosing Period were enrolled in a 36-month Extension Period to assess long-term efficacy and safety of ALXN1840.

Preliminary PK data at 48 weeks from the Extension Period of the study were consistent with the 24-week Dosing Period results. No clear dose-proportionality was observed in Study WTX101-201. This result may have been due to the small sample size and relatively high inter-patient variability.

In total, tetrathiomolybdate (bis-choline or ammonium salt of tetrathiomolybdate) has been evaluated in nearly 600 patients in studies of WD, oncology, macular degeneration, and primary biliary cirrhosis indications using either the ammonium or the bis-choline tetrathiomolybdate salt forms, and in 60 healthy volunteers in Phase 1 studies. ALXN1840 has been generally well--tolerated, and the most frequently reported drug-related AEs were changes in hematological parameters, fatigue, sulphur eructations, and other gastrointestinal symptoms. Aminotransferase elevations were much less common in oncology patients than in patients with WD treated with ALXN1840. The reason for this difference is not known, but it should be noted that oncology patients are unlikely to have excess liver Cu.

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

2.3. Benefit/Risk Assessment

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

2.3.1. Risk Assessment

Details of the potential risks and mitigation strategy are provided in Table 3. Further information on ALXN1840 is available in the IB.

Table 3: Potential Risks and Mitigation Strategy

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
ALXN1840		
Anemia	Anemia has been observed in patients with WD, attributed to overtreatment and resultant Cu depletion, see the IB	Monitoring complete blood count Dose modification (Section 6.6) or discontinuation (Section 7)
Dose-dependent elevations in transaminases (ALT and AST)	Generally mild to moderate in severity, asymptomatic and reversible with dose adjustments were reported, usually after 3-6 weeks of treatment. Results obtained from studies of ALXN1840 and ammonium tetrathiomolybdate in patients with WD; see the IB	Regular monitoring of liver function tests Dose modification (Section 6.6) or discontinuation (Section 7)
Low white blood cell count (leukopenia, bone marrow toxicity)	Leukopenia and bone marrow toxicity (myelosuppression) have been observed in patients with WD, attributed to overtreatment and resultant Cu depletion. Results obtained from studies of ALXN1840 and ammonium tetrathiomolybdate in patients with WD; see the IB	Dose modification (Section 6.6) or discontinuation (Section 7)
Study Procedures and Other		
Liver biopsy: bleeding, infection, liver laceration, pneumothorax, gallbladder injury	Overall rate of serious complications is approximately 1% and mortality at 0.2% Pain is most common complication with one quarter of patients experiencing right upper quadrant or shoulder pain, most common serious complication is bleeding with hemodynamic compromise occurring in 0.01% to 0.5% of cases and includes intraperitoneal hemorrhage, hematoma, and/or hemobilia. Additional complications include but are not limited to transient bacteremia, bile peritonitis, organ injury including pneumothorax (Reddy, 1997; Seeff, 2010; West, 2010; Boyum, 2016)	Abdominal ultrasound is required prior to biopsy to confirm adequate visualization of liver and adjacent structures (Section 5.1) Obese patients (BMI >30 kg/m^2) will be excluded from participating in the study (Section 5.1) Restrictions on antiplatelet and anticoagulant medications (Section 5.3.2) Patients must have a PT-INR < 1.5 (Section 5.2)

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Neurological worsening	Neurological worsening may occur due to disease progression or Cu mobilization	Dose modification (Section 6.6) or discontinuation (Section 7)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; Cu = copper; IB = Investigator's Brochure; PT-INR = prothrombin time-international normalized ratio; WD = Wilson disease.

2.3.2. Benefit Assessment

The main objective of effective WD treatment is to provide:

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

Potential benefits of study participation for patients include:

- Participation in a clinical study increases the patient's understanding of the pathophysiology and treatment of WD.
- Removal of total body Cu as a definitive treatment for WD.
- All patients will receive ALXN1840, ie, all patients will have access to a potentially more convenient and effective treatment for removing toxic free Cu from the blood and liver.
- Patients who participate in the study will contribute to improved care for other patients with WD in the future.

2.3.3. Overall Benefit: Risk Conclusion

Accounting for the measures taken to minimize risk to patients participating in this study, the potential risks identified in association with the administration of ALXN1840 and procedures performed in the study, including, but not limited to, liver biopsy are justified by the anticipated benefits that may be afforded to adult patients with WD.

3. OBJECTIVES AND ENDPOINTS

The study objectives and corresponding endpoints are presented in Table 4.

Table 4: Study ALXN1840-WD-205 Objectives and Endpoints

Objectives	Endpoints
Treatment Period	
Primary	
To evaluate change in liver copper (Cu) concentration following treatment with ALXN1840 at Week 48 in patients with Wilson disease (WD)	Change from baseline to Week 48 in liver Cu concentration
Secondary	
To assess change in liver histopathology following treatment with ALXN1840	Change from baseline to Week 48 in steatosis, inflammation, and fibrosis
To evaluate the safety of ALXN1840 in patients with WD	Adverse events (AEs), vital signs, ECGs, clinical laboratory data, and physical examination data
To evaluate pharmacokinetics (PK) of ALXN1840	• ALXN1840 PK profiles in plasma at Week 6 (Day 43) and Week 36 (Day 253), of which ALXN1840 PK are measured as total molybdenum (Mo) and plasma ultrafiltrate (PUF) Mo • Pre-dose trough ALXN1840 concentrations in plasma at each study site visit • ALXN1840 concentrations in the liver biopsy specimen.
To evaluate the effects of ALXN1840 on clinical symptoms	Change from baseline in Clinical Global Impression-Improvement (CGI-I) Scale and the Clinical Global Impression-Severity (CGI-S) Scale
Exploratory	
To explore the effects of ALXN1840 on hepatic status	Change from baseline to Week 48 in: • Model for End Stage Liver Disease (MELD) score • Modified Nazer score
To assess changes in liver fibrosis and steatosis using non-invasive techniques	Liver stiffness by magnetic resonance (MR) elastography and transient elastography (Vibration-Controlled Transient Elastography/FibroScan), MR-proton density fat fraction (PDFF)
To explore changes in mitochondrial ultrastructure of the liver at Week 48	Change from baseline to Week 48 in mitochondrial ultrastructure by electron microscopy
To explore the change in Cu deposition in the eye at Week 48	Change from baseline to Week 48 in in Cu deposition in the eye by optical coherence tomography
To explore the change in PD and biomarkers with ALXN1840 treatment at Week 48	• Absolute and percent change in plasma total and PUF Cu and calculated non-ceruloplasmin-bound Cu (cNCC) concentrations, as well as directly measured NCC (dNCC), labile-bound Cu (LBC), ceruloplasmin (Cp) and Cp-bound Cu (CpC) from baseline to Week 48 • Daily mean area under the effect-time curve (AUEC) of dNCC from 0 to 48 weeks
To explore the effects of ALXN1840 on quality of life at Week 48	Change from baseline to Week 48 in quality of life measures of: • EuroQoL 5 Dimensions (EQ-5D) • Short form-36 (SF-36) • Chronic Liver Disease Questionnaire (CLDQ)

Objectives	Endpoints
To assess treatment satisfaction of ALXN1840 at Week 48	Treatment Satisfaction Questionnaire for Medication-9 (TSQM-9)
To explore the effects of ALXN1840 on neurologic and psychiatric symptoms	Change from baseline to Week 48 in: • Brief Psychiatric Rating Scale-24 (BPRS-24) • Unified Wilson Disease Rating Scale (UWDRS)
Extension Period	
All patients will continue to receive ALXN1840 in the 48-week Extension Period. All safety and efficacy parameters will be measured as detailed above at Week 48 in the Extension Period, except for liver biopsy, which will not be performed in the Extension Period.	

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2, open-label multicenter study designed to evaluate the change in liver Cu concentration following 48 weeks of treatment with ALXN1840 at doses up to 30 mg/day in adult patients with WD who have previously been treated for at least 1 year with SoC (ie, trientine, penicillamine, or zinc).

On Day 1 of the Treatment Period, patients will receive ALXN1840. Patients will be initiated at 15 mg once daily, then the dose will be increased to 30 mg once daily at Week 6.

In case of drug tolerability issues, the dose of ALXN1840 may be reduced or temporarily interrupted. Such dose changes must be discussed with the Alexion Medical Monitor and documented in the study record. Any subsequent dose increases must be approved by Alexion.

The planned study duration is approximately up to 100 weeks, including a 4-week Screening Period. A liver biopsy will be performed during the Screening Period within 14 days prior to the first dose of study drug, followed by a 48-week Treatment Period, which starts on the day of first dose of study drug. Patients who complete the 48-week Treatment Period will be offered the opportunity to participate in a 48-week Extension Period to evaluate the long-term safety and efficacy of ALXN1840.

This study is pathologist-blinded for the assessments of liver histology samples.

If additional clinical evaluation outside of the visit schedule is deemed necessary by the Investigator, or if the patient meets dose modification criteria, then unscheduled visits can occur. Additionally, if there is clear neurological deterioration, as demonstrated by signs or symptoms of neurological worsening, then additional neurological assessments will be performed at the discretion of the Investigator.

An independent Data Monitoring Committee (DMC), comprising experts in relevant fields with no direct relationship to the study, will be appointed by Alexion to review and monitor study data for safety, effectiveness, and study conduct, and make recommendations regarding study continuation, changes to the study population, and/or modification to study procedures. Further details are provided in Section 9.5.

An independent Hepatic Adjudication Panel, comprising experts in relevant fields will be appointed by Alexion. Details of the Hepatic Adjudication Panel are provided in Section 9.6.

4.2. Scientific Rationale for Study Design

Currently available SoC medications (ie, trientine, penicillamine, and zinc) control excess free Cu in the blood, but do not consistently reduce Cu overload in the liver. Accumulation of Cu in the liver leads to an increased risk of tissue and organ damage. Limited available data obtained from serial liver biopsies in patients with WD indicate that liver Cu concentration remains elevated, with no consistent reduction of liver Cu over time in patients treated with SoC beyond the first year (Medici, 2006; Scheinberg, 1987; Cope-Yokoyama, 2010; Gibbs, 1990). The impact of ineffective decoppering with SoC medications can be seen in patients with WD who discontinue treatment for WD, who are at risk for rapid progression to liver failure (Maselbas, 2010; Dziezyc, 2014).

Preclinical data and results on thiomolybdates (bis-choline and ammonium tetrathiomolybdate) suggest that, unlike penicillamine or trientine, ALXN1840 may be able reduce liver Cu burden load in patients with WD. In vitro and preclinical data indicate that ALXN1840 may remove Cu from internal MT liver stores, promote mobilization of stable high affinity ALXN1840-Cu-albumin complexes, and enhance elimination of Cu. ALXN1840 may promote elimination of Cu through excretion of Mo:Cu complexes into bile, promoting net negative excretion of Cu from the liver. In the Long-Evans Cinnamon rat model of WD, treatment with tetrathiomolybdate leads to rapid reduction in the liver Cu concentration (Suzuki, 1993; Suzuki, 1994; Suzuki, 1995; Ogra, 1995a; Ogra, 1995b; Ogra, 1996).

While SoC treatment may promote elimination of Cu, no treatment has been demonstrated to result in a meaningful reduction of Cu in liver stores, which is thought to be key in reducing the risk of progression to liver failure.

The principal aim of this study is to confirm in humans that ALXN1840 reduces liver Cu concentration by studying the effect of 48 weeks of ALXN1840 treatment in patients with WD who have been previously treated with SoC (ie, trientine, penicillamine, or zinc).

To assess reduction in liver Cu concentration, liver biopsies will be taken prior to initiation of ALXN1840 and at Week 48 of treatment.

Liver biopsy for Cu concentration is considered the most effective means to show reduction in liver Cu; no other non-invasive surrogate marker is available to fully explore the impact of ALXN1840 on liver Cu stores. Although WD impacts patients of all ages, because it is a chronic disease, most treatment-experienced (ie, have received treatment for at least 1 year) patients are ≥ 18 years, therefore, including patients ≥ 18 years of age is representative of the population with WD.

To better understand the mechanism by which ALXN1840 results in reduction of liver Cu concentrations, the liver biopsy specimen will also be assessed for total Mo and concentrations will be correlated to blood total Cu and Mo concentrations.

In addition to evaluating liver Cu concentration, histology will be performed on the remaining liver tissue to assess the impact of ALXN1840 on liver inflammation and tissue injury, as well as progression in fibrosis.

Imaging (ie, magnetic resonance imaging [MRI] and transient elastography) will be performed to evaluate changes by non-invasive assessment of the liver. Optical coherence tomography will also be performed as a measure of Cu reduction with respect to Kayser-Fleischer rings.

4.3. Justification for Dose

For this study, the term “dose” refers to the following:

Dosing for ALXN1840 will be initiated at 15 mg once daily, then the dose will be increased to 30 mg once daily at Week 6.

A starting dose of 15-60 mg daily was shown to have an acceptable safety profile and was effective in reducing NCC in a Phase 2 study in patients with WD (Weiss, 2017). Elevation of hepatic transaminases and/or gamma glutamyl transferase occurred in 39% of patients in the Phase 2 study and were generally associated with higher doses of ALXN1840. Elevations of

liver enzymes were detected by routine laboratory monitoring and were managed by dose reduction or treatment interruption of ALXN1840. In this study, the starting dose will be 15 mg once daily for the first 6 weeks, then the dose will be titrated up to 30 mg once daily. Elevation of liver enzymes, if occurring, and management of other laboratory abnormalities or AEs, will be managed according to Table 6. Any change to dosing in response to laboratory results or AEs must be discussed with the Alexion Medical Monitor and documented in the study record. Subsequent dose increases must be approved by Alexion.

4.4. End of Study Definition

The end of the study is defined as the date of the last patient last visit of the 48-week Extension Period.

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

Patients are eligible to be included in the study only if all of the following criteria are met:

Age

1. Patients must be ≥ 18 years of age at the time of signing the informed consent.

Type of Patient and Disease Characteristics

2. Diagnosis of WD by Leipzig Criteria ≥ 4 documented by testing as outlined in the 2012 European Association for the Study of Liver (EASL) WD Clinical Practice Guidelines (Ferenci, 2003; EASL, 2012) or by historical test results for WD including some or all of the following:
   - Presence of Kayser Fleischer rings,
   - Neurological symptoms,
   - Serum ceruloplasmin below reference range,
   - Coombs-negative hemolytic anemia,
   - Elevated liver or urinary copper,
   - Presence of mutations in the *ATP7B* gene, or
   - Other, as considered appropriate, may be used instead to confirm the diagnosis of WD.
3. Continuous treatment for WD with penicillamine, trientine or zinc for at least 1 year in duration prior to screening
4. Adequate venous access to allow collection of required blood samples
5. Able to swallow intact ALXN1840 tablets
6. Body mass index < 30 kg/m2
7. Able to cooperate a percutaneous liver biopsy, including having the ability to lie flat and still throughout the procedure, and tolerate mild sedation, if required
8. Adequately visualized landmarks on screening ultrasound without evidence of significant ascites, hemangiomas, or other findings that would put the patient at unnecessarily high risk of complications

Sex

9. Male Patients:
   - Male patients are eligible to participate if they agree to the following during the drug period and for at least 90 days after the end of systemic exposure:
     - Refrain from donating sperm
     - PLUS either**:**
     - Be abstinent from heterosexual intercourse with a woman of childbearing potential (WOCBP) as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

- OR
- Must agree to use contraception/barrier as detailed below
  - Agree to use a male condom with spermicide
  - No contraception/barrier is required for men with a male sexual partner.
  - No contraception/barrier is required for men with a female sexual partner who is not of childbearing potential.

10. Female Patients:

- A female patient is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
  - Is not a WOCBP

    OR
  - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described in Section 10.4 starting at least one menstrual cycle before first study drug administration and continuing for at least 30 days after the end of systemic exposure of the study drug and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The Investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study drug.
  - A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours before the first dose of study drug (Table 1).
  - If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the patient must be excluded from participation if the serum pregnancy result is positive.
- Additional requirements for pregnancy testing during and after study drug are located in Section 10.4.
- The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Informed Consent

11. 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

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

1. Decompensated cirrhosis or MELD score >13

2. Modified Nazer score > 7 (Dhawan, 2005)
3. Clinically significant gastrointestinal bleed within past 3 months
4. Alanine aminotransferase > 2 × upper limit of normal (ULN)
5. History of bleeding abnormality or known coagulopathy, including platelet count < 100,000, and international normalized ratio for prothrombin time (PT-INR) ≥ 1.5; coagulopathy or bleeding risk due to medication is acceptable if medication can be safety discontinued for biopsy (see Section 5.3)
6. Patient unwilling to accept blood products, if required
7. Marked neurological disease requiring either nasogastric feeding tube or intensive inpatient medical care
8. Hemoglobin less than lower limit of the reference range for age and sex
9. Systemic disease or other illness, any disability acquired from trauma or another illness, or any deviation in laboratory values that are confirmed on re-examination to be clinically significant by the Investigator that would, in the opinion of the Investigator, compromise patient safety, interfere with evaluation of disability due to WD, or interfere with the collection or interpretation of study results
10. Patients in renal failure, defined as in end-stage renal disease on dialysis (chronic kidney disease [CKD] 5) or creatinine clearance < 30 mL/min (as calculated by the Modification of Diet in Renal Disease formula) (Levey, 2006).
11. Known sensitivity to ALXN1840, ALXN1840 excipients (anhydrous di-calcium phosphate, anhydrous sodium carbonate), or any of the ingredients contained in ALXN1840 or related compounds.
12. History or presence of/significant history of or current cardiovascular, respiratory, renal, gastrointestinal, endocrinological, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; constituting a risk when taking the study drug; or interfering with the interpretation of data
13. Lymphoma, leukemia, or any malignancy within the past 5 years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years
14. Current or chronic history of liver disease not associated with WD, or known hepatic or biliary abnormalities (with the exception of asymptomatic gallstones)
15. Use of nonprescription/ over-the-counter medications, including herbal remedies, nutritional supplements, or mineral supplements containing Cu, zinc, iron or Mo after dosing on Day 1 through the end of the study.
16. In the opinion of the Investigator, the patient and/or their legal guardian is likely to be non-compliant or uncooperative during the study

Prior/Concurrent Clinical Study Experience

17. Participation in any other interventional study during the study or for 3 months (or 5 half-lives of the administered investigational medicinal product, whichever is longer) prior to study start.

Diagnostic assessments

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

Other Exclusions

20. Regular alcohol consumption within 6 months prior to the study defined as > 14 units for males or > 7 units for females per week. One unit is equivalent to 8 g of alcohol: a half pint (approx. 240 mL) of beer, 1 glass (125 mL) of wine or 1 (25 mL) measure of spirits.
21. Abuse of illicit or prescribed drugs
22. Sensitivity to any drug or other allergy that, in the opinion of the Investigator or Alexion Medical Monitor, contraindicates participation in the study

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

Patients should follow their study doctor's advice regarding adherence to a low Cu diet.

ALXN1840 will be administered in the fasted state (1 hour before or 2 hours after meals) and will be taken with approximately 240mL of water.

5.3.2. Restrictions Relating to the Liver Biopsy

Prior to biopsy and following biopsy, the guidelines and restrictions apply (Rockey, 2009):

- Antiplatelet medications should be discontinued a minimum of 10 days before liver biopsy.
- Anticoagulant medications should be discontinued prior to liver biopsy. Warfarin should generally be discontinued at least 5 days prior to liver biopsy. Heparin and related products should be discontinued 12 to 24 hours prior to liver biopsy. Oral agents, including rivaroxaban, dabigatran, apixaban, and edoxaban, should be discontinued a minimum of 72 hours before liver biopsy (Douketis, 2019).
- Antiplatelet therapy may be restarted 72 hours after liver biopsy.
- Warfarin may be restarted 24 hours after liver biopsy.

5.4. Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently assigned to study drug. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients 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 serious adverse event (SAE) occurring during the Screening Period.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened up to 2 times after agreement on required repeated assessments with the Alexion Medical Monitor.

6. STUDY DRUG

Study drug is defined as any investigational drug intended to be administered to a study patient according to the study protocol, ie, ALXN1840.

6.1. Study Drugs Administered

Details of the study drug to be administered in this study are detailed in Table 5.

Table 5: Study Drugs Administered

Drug Name	ALXN1840
Type	Drug
Dose Formulation	White, round, delayed-release tablet
Unit Dose Strength(s)	15 mg
Dosage Level(s)	15 mg daily up to 30 mg daily
Route of Administration	Oral
Use	Experimental
IMP and NIMP	IMP
Sourcing	Provided centrally by Alexion
Packaging and Labeling	ALXN1840 will be provided in treatment kits that will each have a unique identification number and be packaged and labelled in accordance with all applicable regulatory requirements. At a minimum, the treatment kit label will provide the following information: 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.
Current/Former Name(s) or Alias(es)	bis-choline tetrathiomolybdate

Abbreviations: IMP = investigational medicinal product; NIMP = Noninvestigational medicinal product

6.2. Preparation/Handling/Storage/Accountability

- The ALXN1840 treatment kits must be stored at refrigerated conditions, 2°C to 8°C (36°F to 46°F).
- The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drug received and any discrepancies are reported and resolved before use of the study drug.
- Only patients enrolled in the study may receive study drug. Appropriately trained employees of the study site will instruct patients on how to correctly dose themselves with ALXN1840 at home.
- All study drug must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
- The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study drug accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

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

6.3. Measures to Minimize Bias: Randomization and Blinding

- There is no randomization and blinding of patients in this study, because it is a single-arm, open-label study.
- This study is only pathologist-blinded for the assessments of liver histology samples.
- Study drug will be dispensed at the study visits summarized in the SoAs (Table 1 and Table 2).

6.4. Study Drug Compliance

Compliance with ALXN1840 will be assessed by the study team at each study visit. Compliance will be assessed by direct questioning during the site visits and documented in the source documents and case report form (CRF) and checked against the medication returned by the patient. Any deviation from the prescribed dosing regimen including extra doses, missed doses and drug interruptions will be recorded in the electronic data capture (EDC) system.

Patients who take 80% or more of the prescribed doses of ALXN1840 in the first 48 weeks of the study will be considered to have shown acceptable compliance.

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

Once compliance with study drug has been calculated, patients will be dispensed new ALXN1840 to cover dosing requirements until the next in-clinic visit if required.

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

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements or other specific categories of interest) taken within 30 days prior to signing informed consent and throughout the duration of the study will be recorded in the source documents and on the appropriate CRF along with:

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

Medications specific for WD taken at any time prior to the study will also be recorded.

Patients may continue medications required to treat existing medical conditions as long as they are not anticipated to interfere with the conduct or outcome of the study. Patients should avoid starting or stopping medications and all potential medication changes should be reviewed by the Investigator to ensure changes are not expected to interfere with the outcome of the study.

The guidelines provided below are to be used by the Investigator, the study staff, and the patient to safeguard patient safety while maintaining data integrity.

Use of the following medications or contrast media is not prohibited; however, if used, this therapeutic change must be clearly documented as a concomitant medication. Please contact the Alexion Medical Monitor with questions. Refer to the current IB for potential inhibitory effect of ALXN1840 on the metabolism of certain drugs that are substrates of cytochrome P450 enzymes (eg, CYP2C9 and CYP2B6).

- Gadolinium- and iodine-containing contrast media are known to interfere with PK/PD tests on Mo. Gadolinium- and iodine-containing contrast media are requested not to be used within the 96 hours prior to Mo testing.
- Barium-containing contrast media are known to interfere with tests on Cu. Barium-containing contrast media are requested not to be used within the 96 hours prior to Cu testing.
- Acetaminophen/paracetamol must be limited to ≤ 1 g per day.

The following medications are prohibited during the study:

- Estrogens may interfere with biliary Cu excretion. Patients must not initiate estrogen therapy or estrogen-containing contraception on or after the Day 1 visit. Detailed guidance on allowed contraceptive methods and medication are provided in Section 10.4.
- Standard of care medications for WD (trientine, penicillamine, and zinc) must be discontinued prior to the start of the Treatment Period (Day 1) with ALXN1840 and should not be used throughout the duration of study treatment.
- Vitamin E has been used as an adjunctive therapy in WD treatment regimens. Patients must not initiate use of vitamin E during the study.
- Patients must not use vitamins and/or minerals containing Cu, zinc, iron, or Mo.

6.6. Dose Modification

Patients will be initiated on ALXN1840 at 15 mg once daily, then the dose will be increased to 30 mg once daily at Week 6 (Day 43).

The dose should be decreased or interrupted if any of the relevant Dose Modification Criteria are met (see Table 6). Deviation from the dose modification guidelines must be agreed with the Alexion Medical Monitor. Any subsequent dose increases must be approved by Alexion.

All patients will continue to be treated with ALXN1840 in the Extension Period at the same dose they received at the last study visit in the Treatment Period and ALXN1840 administration during the Extension Period will follow the same procedures as for the Treatment Period.

In case a dose modification is necessary for ALXN1840, it will be administered as per the details in Table 6.

Table 6: ALXN1840 Dose Modifications for Individual Patients

Test	Result	Conditions	Action with ALXN1840 Dosing	Changes in Safety Monitoring[a]	Re-Challenge[b]
ALT	> 5 × ↑ from baseline	ALT above reference range at baseline	Temporary interruption	Contact patient within 48 hours to arrange repeat testing Weekly repeat testing	At 15 mg QOD when ALT < 2 × ↑ from baseline.
	> 5 × ULN	ALT within reference range at baseline	Temporary interruption	Contact patient within 48 hours to arrange repeat testing Weekly repeat testing	At 15 mg QOD when ALT < 2 × ULN.
	> 2 × ↑ from baseline	ALT above reference range at baseline	Reduce dose to previous dose level if up-titration has occurred or reduce dose to 15 mg QOD if on 15 mg QD. No further dose ↑ until resolution of abnormality.	Weekly repeat testing	Not applicable.
	> 2 × ULN	ALT within reference range at baseline	Reduce dose to previous dose level if up-titration has occurred or reduce dose to 15 mg QOD if on 15 mg QD. No further dose ↑ until resolution of abnormality.	Weekly repeat testing	Not applicable.
Increased triglycerides	> 300 to 500 mg/dL or > 3.4 to 5.6 mmol/L	None	Reduce dose to previous dose level if up-titration has occurred or reduce dose to 15 mg QOD if on 15 mg QD. No further dose ↑ until resolution of abnormality.	Weekly repeat testing	Not applicable
	> 500 mg/dL or 5.6 mmol/L		Temporary interruption		At 15 mg QOD when triglyceride concentrations return to baseline
Increased total cholesterol	> 300 to 400 mg/dL or > 7.8 to 10.3 mmol/L	None	Reduce dose to previous dose level if up-titration has occurred or reduce dose to 15 mg QOD if on 15 mg QD. No further dose ↑ until resolution of abnormality.	Weekly repeat testing	Not applicable
	> 400 mg/dL or > 10.3 mmol/L		Temporary interruption		At 15 mg QOD when cholesterol concentrations return to baseline

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

Test	Result	Conditions	Action with ALXN1840 Dosing	Changes in Safety Monitoring[a]	Re-Challenge[b]
Bilirubin	> 2 × ULN	Accompanied by ALT > 3 × ULN, indicative of liver injury.	Temporary interruption	Weekly repeat testing	At 15 mg QOD or less frequent, when bilirubin is below ULN. Re-challenge under these conditions requires approval of the Alexion Medical Monitor.
UWDRS-III and clinical neurological assessment	Increase in UWDRS-III score from baseline as follows, AND is deemed clinically significant by the Investigator: Baseline UWDRS-III score < 20: ≥ 4-point increase OR Baseline UWDRS-III score ≥ 20: ≥ 6-point increase		Investigator and Alexion Medical Monitor will evaluate the need for dose modification (interruption, increase or decrease) based on Cu control parameters and relevant clinical data. Rationale for dosing decision must be documented in study record and re-evaluated at the next study visit.	Report neurologic adverse event of special interest and perform UWDRS Parts I, II and III. Re-evaluate neurologic status, including complete UWDRS examination, no later than next study visit, even if not planned per the SoA.	Discuss with the Alexion Medical Monitor.
Psychiatric assessment	Clinically significant signs of psychiatric worsening according to the BPRS		Investigator and Alexion Medical Monitor will evaluate the need for dose modification (interruption, increase or decrease) based on Cu control parameters and relevant clinical data. Rationale for dosing decision must be documented in study record and re-evaluated at the next study visit.	Re-evaluate psychiatric status no later than next study visit, even if not planned per the SoA.	Discuss with the Alexion Medical Monitor.

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

[b] A maximum of 3 re-challenges will be allowed. For re-challenges, patients who were on 15 mg QOD should be re-challenged at the 15 mg QOD dose. The Investigator, in consultation with the Medical Monitor, may change dose and dose frequency in patients who require re-challenge.

Abbreviations: ALT = alanine aminotransferase; BPRS = Brief Psychiatric Rating Scale-24; Cu = copper; QD = once daily; QOD = every other day; SoA = Schedule of Activities; ULN = upper limit of normal; UWDRS = Unified Wilson Disease Rating Scale.

6.7. Drug after the End of the Study

ALXN1840 will not be provided after the end of the 48-week Extension Period of the study.

7. DISCONTINUATION OF STUDY DRUG AND PATIENT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Drug

If it becomes necessary for a patient to permanently discontinue (definitive discontinuation) study drug, the patient must complete an Early Termination (ET) visit. See the SoAs (Table 1 and Table 2) for data to be collected at the time of discontinuation of study drug and follow-up, and for any further evaluations that need to be completed.

Discontinuation of study drug for abnormal liver chemistry tests should be considered by the Investigator when a patient meets one of the conditions outlined in the Dose Modification criteria (see Table 6) or if the Investigator believes that it is in best interest of the patient.

If a clinically significant finding is identified (including suicidality) after enrollment, the Investigator or qualified designee will determine if the patient can continue in the study and if any change in patient management is needed. Any new clinically relevant finding should be reported as an AE.

For clinically significant findings from baseline in QT interval corrected using Bazett's formula (QTcB) or Fridericia's formula (QTcF), review of the ECG printed at the time of collection must be documented.

For details relating to pregnancy, see Section 8.3.5 and Section 10.4.

See the SoAs (Table 1 and Table 2) for samples and data to be collected at the time of drug discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1. Temporary Discontinuation

Dose modification and reasons for interruption or discontinuation of dosing are detailed in Section 6.6 for ALXN1840.

7.1.2. Rechallenge

See Table 6 for details of rechallenge for ALXN1840.

7.2. Patient Discontinuation/Withdrawal from the Study

- A patient 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 ET visit should be conducted, as shown in the SoAs. See the SoAs for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed (Table 1 and Table 2).
- The patient will be permanently discontinued both from the study drug and from the study at that time.

- If the patient 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 patient 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.

Participation of a patient in this clinical study may be discontinued for any of the following reasons:

- The patient or/legal guardian withdraws consent or requests discontinuation from the study for any reason, is lost to follow-up or dies.
- Occurrence of any medical condition or circumstance that exposes the patient to substantial risk and/or does not allow the patient to adhere to the requirements of the protocol.
- Occurrence of a decompensated cirrhosis event which is not responsive to standard treatment.
  - A decompensation cirrhosis event is defined as acute esophageal or gastric variceal bleeding, development of new overt hepatic encephalopathy, or substantive *de novo* ascites formation.
- Any SAE, clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition which indicates to the Investigator that continued participation is not in the best interest of the patient.
- Patient becomes pregnant or is unwilling to comply with protocol requirements for highly effective contraception.
- Requirement to take prohibited concomitant medication or enroll in a clinical study of an experimental or unapproved/unlicensed therapy.
- Patient failure to comply with protocol requirements or study-related procedures.

7.3. Lost to Follow-up

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

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

- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoAs (Table 1 and Table 2). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with Alexion immediately upon occurrence or awareness to determine if the patient should receive study drug.
- Adherence to the study design requirements, including those specified in the SoAs, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Liver biopsy is the last pre-dose baseline procedure to be completed and must be completed within 14 days prior to the first dose of ALXN1840.
- Procedures conducted as part of the patient'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 (Table 1).
- Details of the maximum amount of blood to be collected from each patient over the duration of the study are provided in the laboratory manual and ICF.

8.1. Efficacy Assessments

The time points for all efficacy assessments are provided in the SoAs (Table 1 and Table 2).

8.1.1. Liver Biopsy Copper Content and Histologic Assessment

A percutaneous needle biopsy of the liver will be performed by a licensed trained expert as per standard of care and outlined in American Association for the Study of Liver Diseases (AASLD) guidelines (Rockey, 2009) at baseline and Week 48.

Cu content: one biopsy sample will be taken for the assessment of liver Cu concentration. Tissue samples will be dried, weighed, and stored in a Cu-free tube. Cu concentration will be determined at a central laboratory by inductively coupled plasma mass spectrometry and expressed as µg Cu/g dry weight.

The second biopsy sample will be used for histologic and electron microscopy assessment. If there is insufficient sample for all assessments, electron microscopy will be omitted.

Assessments of steatosis, inflammation, and fibrosis will include morphometric quantitation of hepatic fat, collagen, and alpha-smooth muscle actin (details of the analysis will be provided separately) (Jayakumar, 2019). Disease activity and fibrosis will be scored according to METAVIR criteria (METAVIR, 1994).

All biopsy specimens will be reviewed and scored by an independent expert hepatopathologist who is blinded to patient identity and biopsy order. Further details relating to the biopsies will be provided in a separate manual.

8.1.2. Non-Ceruloplasmin-Bound Copper

Because measures of NCC control in the blood are an exploratory assessment for efficacy of treatment with ALXN1840, plasma samples will be collected to measure the cNCC concentration, as well as dNCC, LBC, Cp, and CpC concentrations in the blood.

The LBC assay measures Cu in plasma that is not bound to either Cp or the tetrathiomolybdate-Cu-albumin tripartite complexes. The dNCC assay measures NCC in plasma. During treatment with ALXN1840, dNCC includes tetrathiomolybdate-Cu-albumin tripartite complexes.

8.1.3. Model for End-Stage Liver Disease

The MELD is a scoring system for assessing the severity of chronic liver disease in adults and adolescents aged 12 years and older. The MELD score (range 6-40, with higher values indicating more advanced disease) uses the patient's values for serum bilirubin, serum creatinine, and the PT-INR to predict survival. In patients with a MELD score > 11, the serum sodium value is also taken into account (UNOS, 2015).

The MELD score will be calculated by a central laboratory.

8.1.4. Modified Nazer Score

The modified Nazer Score is an assessment of liver status and consists of a composite of 5 laboratory parameters: aspartate aminotransferase, INR, bilirubin, albumin, and white blood cell count. The score has a total range of 0 to 20, and lower values indicate a healthier liver status (Dhawan, 2005).

The modified Nazer score will be calculated by a central laboratory.

8.1.5. Unified Wilson Disease Rating Scale (Parts I, II, and III)

The UWDRS is a clinical rating scale designed to evaluate the neurological manifestations of WD that generally can be divided into 3 movement disorder syndromes: dystonic, ataxic, and Parkinsonian syndrome. The UWDRS comprises 3 parts: UWDRS Part I (level of consciousness, item 1), UWDRS Part II (a patient-reported review of daily activity items [disability], items 2 to 11), and UWDRS Part III (a detailed neurological examination, items 12 to 34).

The UWDRS Part I and Part III will be assessed by a qualified neurologist, while UWDRS Part II may be reported to a member of the study team by the patient, family member, or caregiver (Czlonkowska, 2007; Leinweber, 2008).

8.1.6. Clinical Global Impression-Improvement Severity Scale and the Clinical Global Impression-Severity Improvement Scale

The Clinical Global Impression (CGI) rating scales are commonly used measures of symptom severity, treatment response, and the efficacy of treatments in treatment studies of adult and pediatric patients with mental disorders.

The CGI-Severity (CGI-S) scale is a 7-point scale that requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis. Considering total clinical experience, a patient is assessed

on severity of illness at the time of rating as: 1, normal, not at all ill; 2, borderline ill; 3, mildly ill; 4, moderately ill; 5, markedly ill; 6, severely ill; or 7, extremely ill.

The CGI-Improvement (CGI-I) scale is a 7-point scale that requires the clinician to assess how much the patient's illness has improved or worsened relative to a baseline state at the beginning of the intervention and rated as: 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; or 7, very much worse.

8.1.7. Imaging Techniques

Details of imaging techniques will be detailed in an Imaging Manual.

Magnetic Resonance Elastography and MR-PDFF

Baseline and follow-up MRI studies of the liver will be performed as detailed in the SoAs (Table 1 and Table 2) and read by a central radiologist with expertise in these methods. Hepatic steatosis will be quantified by magnetic resonance (MR)-proton density fat fraction (MR-PDFF). Hepatic stiffness will be quantitated by MR elastography (MRE) according to standard protocols.

Transient Elastography

Transient elastography (Fibroscan preferred) uses ultrasound and low-frequency elastic waves to quantify liver fibrosis. Vibration controlled transient elastography will be performed at visits as outlined in the SoAs (Table 1 and Table 2).

Optical Coherence Tomography

Optical coherence tomography uses light waves to map and measure the structures of the eye (Sridhar, 2017). Copper deposits in the anterior chamber of the eye will be photographed and quantitated at visits as outlined in the SoAs (Table 1 and Table 2).

Electron Microscopy

Electron microscopy enables examination of mitochondrial ultrastructure of the liver to determine whether hepatic mitochondrial function is affected negatively in WD (Einer, 2019).

The glutaraldehyde-fixed liver biopsy specimen will be processed by a qualified central laboratory to permit examination of subcellular ultrastructure using transmission electron microscopy and a descriptive assessment of electron microscopic images will be performed by an expert.

8.1.8. Quality of Life, Treatment Satisfaction, and Psychiatric Symptoms

8.1.8.1. EuroQoL 5 Dimensions

The EQ-5D consists of 2 different assessments – the EQ-5D-5L Descriptive System and the EQ Visual Analogue Scale (VAS). The descriptive system comprises measures of health-related quality of life state and consists of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels of severity: no problems, slight problems, moderate problems, severe problems, or extreme problems. The EQ VAS records the patient’s self-rated health on a vertical visual analogue scale. Together, this can be used as a quantitative measure of health outcome that reflects the patient’s own judgement.

8.1.8.2. Short Form Health Survey (SF-36)

The SF-36 is a 36-item survey that is used to assess the patient's view of their health. It consists of 8 scaled scores that are weighted sums of the questions in each section. The lower the score, the greater the disability:

- Vitality
- Physical functioning
- Bodily pain
- General health perceptions
- Physical role functioning
- Emotional role functioning
- Social role functioning
- Mental health

8.1.8.3. Chronic Liver Disease Questionnaire

The Chronic Liver Disease Questionnaire (CLDQ) is a 29-item instrument with 6 domains that measures longitudinal change over time in patients with chronic liver disease. Each domain is scored from 1 (worst possible function) to 7 (best possible function). The scores obtained correlate with the severity of liver disease (Younossi, 1999):

- Fatigue
- Activity
- Emotional function
- Abdominal symptoms
- Systemic symptoms
- Worry

8.1.8.4. Treatment Satisfaction Questionnaire for Medication

The Treatment Satisfaction Questionnaire for Medication-9 (TSQM-9) is used to assess the overall level of satisfaction or dissatisfaction with medication patients are taking. This composite scale is comprised of 3 items on the TSQM-9 survey:

- Overall, how confident are you that taking this medication is a good thing for you?
- How satisfied are you that good things about this medication outweigh the bad things?
- Taking all things into account, how satisfied or dissatisfied are you with this medication?

8.1.9. Brief Psychiatric Rating Scale-24

The Brief Psychiatric Rating Scale-24 (BPRS-24) is a 24-item instrument that allows the rater to measure psychopathology severity. The BPRS-24 assesses the following psychiatric symptoms:

- Somatic concern, Anxiety, Depression, Suicidality, Guilt, Hostility, Elated Mood, Grandiosity, Suspiciousness, Hallucinations, Unusual thought content, Bizarre behavior, Self-neglect, Disorientation, Conceptual disorganization, Blunted affect, Emotional withdrawal, Motor retardation, Tension, Uncooperativeness, Excitement, Distractibility, Motor hyperactivity, Mannerisms and posturing.

The presence and severity of psychiatric symptoms are rated on a Likert scale ranging from 1 (not present) to 7 (extremely severe).

The BPRS-24 can be performed by a qualified person (eg, neurologist, psychiatrist, psychologist, licensed mental health practitioner, social worker).

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoAs (Table 1 and Table 2).

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Note: A neurological examination will be conducted by a qualified neurologist for UWDRS Part III at the time points specified in the SoAs (see also Section 8.1.5).

8.2.2. Vital Signs

- Temperature, heart rate, respiratory rate, blood pressure, temperature, weight, and height (Day 1 only) will be assessed.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the patient in a quiet setting without distractions (eg, television, cell phones).
- Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, pulse, and respiratory rate.

8.2.3. Electrocardiograms

- Single 12-lead ECGs will be obtained, as outlined in the SoAs (Table 1 and Table 2) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 7 for QTc withdrawal criteria and any additional QTc readings that may be necessary. Note that QTcF is preferred, unless only QTcB is available.

- Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.
- The Investigator or designee will be responsible for reviewing the ECG to assess whether the ECG is within normal limits and determine the clinical significance of the results. These assessments will be indicated on the CRF.

8.2.4. Clinical Safety Laboratory Assessments

- See Section 10.2 for the list of clinical laboratory tests to be performed and to the SoAs for the timing and frequency (Table 1 and Table 2).
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 4 weeks after the last dose of study drug should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Alexion 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 SoAs (Table 1 and Table 2).
  - If laboratory values from non-protocol specified laboratory assessments performed at the institution’s local laboratory require a change in patient management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

8.2.5. Suicidal Ideation and Behavior Risk Monitoring

Patients with WD may occasionally develop suicidal ideation or behavior.

Patients being treated with ALXN1840 should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior, especially at the beginning and end of the course of drug, or at the time of dose changes, either increases or decreases. Consideration should be given to discontinuing the study medication in patients who experience signs of suicidal ideation or behavior, following a risk assessment.

Families and caregivers of patients being treated with ALXN1840 should be alerted about the need to monitor patients for the emergence of unusual changes in behavior, as well as the emergence of suicidal ideation and behavior and to report such symptoms immediately to the Investigator.

Baseline assessment of suicidal ideation and behavior/drug emergent suicidal ideation and behavior will be monitored during this study using the BPRS-24 at the time points specified in the SoAs (Table 1 and Table 2).

8.3. Adverse Events and Serious Adverse Events

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

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

Definitions and 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 informed consent until the follow-up visit at the time points specified in the SoAs (Table 1 and Table 2).

All SAEs will be recorded and reported to Alexion or designee within 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 patient has exited the study, and he/she considers the event to be reasonably related to the study drug, the Investigator must promptly notify Alexion Global Drug Safety (GDS).

8.3.2. Method of Detecting AEs and SAEs

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

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

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the patient 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 patients and the safety of a study drug 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 drug 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.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) 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. Pregnancy

- Pregnancy data will be collected during this study for all female patients and female spouses/partners of male patients. Exposure during pregnancy (also referred to as exposure in utero) can be the result of either maternal exposure or transmission of drug product via semen following paternal exposure. Female patients who become pregnant during the study must withdraw from the study.
- For all Alexion products in development, 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 patient discontinues study drug or withdraws from the study.
- If a female patient becomes pregnant from the first dose of study drug up to 30 days after the end of systemic exposure or a male patient's female partner becomes pregnant from the first dose of study drug up to 90 days after the end of systemic exposure, the Investigator must submit the "Pregnancy/Breastfeeding Reporting and Outcome Form" to Alexion GDS via email or fax (Section 10.4). 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 fax.
- Pregnancy in and of itself is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication. However, complications of pregnancy and abnormal outcomes of pregnancy are AEs

and may meet the criteria for an SAE (eg, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly). Elective abortions without complications should not be reported as AEs.

8.3.6. Adverse Events of Special Interest

No adverse events of special interest have been defined for this study.

8.4. Treatment of Overdose

For this study, any dose of ALXN1840 greater than the amount of study drug that exceeds the protocol required dose on a given dosing day or within a 24-hour time period will be considered an overdose. Alexion does not recommend specific treatment for an overdose of ALXN1840.

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, the Investigator should:

1. Contact the Alexion Medical Monitor immediately.
2. Closely monitor the patient for any AE/SAE and laboratory abnormalities.
3. Obtain a plasma sample for PK/PD analysis as soon as possible within 10 days from the date of the last dose of study drug if requested by the Alexion Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

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

8.5. Pharmacokinetics

- Blood samples will be collected for measurement of total and PUF Mo in plasma at the time points specified in the SoAs (Table 1 and Table 2).
- A maximum of 5 samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and Alexion. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.
- Instructions for the collection and handling of biological samples will be provided by Alexion. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples will be used to evaluate the PK of ALXN1840. Samples collected for analyses of total and PUF Mo may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

- Samples will be used for diagnostic biomarker development and research to understand the pathways associated with disease states and the mechanism of action of ALXN1840.

8.6. Pharmacodynamics

Blood samples will be collected for measurement of total and PUF Cu, cNCC, LBC, and dNCC in plasma at study visits indicated in the SoAs (Table 1 and Table 2).

A part of the liver tissue sample collected for biopsy within 14 days prior to Day 1 and again at Week 48 will be allocated for the measurement of total Mo and Cu concentrations in the liver tissue.

A maximum of 5 samples may be collected at additional time points during the study if warranted and agreed upon between the Investigator and Alexion. The timing of sampling may be altered during the course of the study based on newly available data (eg, to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

8.7. Genetics

A blood sample for DNA isolation will be collected from patients who have consented to participate in the genetic analysis component of the study. Participation is optional and requires specific informed consent for this procedure. Patients who do not wish to participate in the genetic research may still participate in the main study.

In the event of DNA extraction failure, a replacement genetic blood sample may be requested from the patient. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Section 10.5 for information regarding genetic research and details on processes for collection and shipment and destruction of these samples.

8.8. Biomarkers

Collection of samples for other biomarker research is also part of this study. The following samples for biomarker research are required and will be collected from all patients in this study as specified in the SoAs (Table 1 and Table 2):

- Blood samples will be collected to measure Cp and CpC
- Urine samples will be collected for analysis of urine creatinine, Cu and Mo

8.9. Immunogenicity Assessments

Not applicable.

8.10. Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

The hypothesis to be tested for the primary endpoint is:

H_0: $\mu_{ALXN1840} \geq 0$ vs H_1: $\mu_{ALXN1840} < 0$

where $\mu_{ALXN1840}$ is the mean change from baseline in liver Cu concentration (µg Cu/g dry liver) at Week 48.

9.2. Sample Size Determination

Cope-Yokoyama et al (Cope-Yokoyama, 2010) reviewed 6 previous liver biopsy studies on patients with WD before and after treatment with various SoC medications. From this review, data from 37 patients were available to calculate a weighted average of Cu concentration after treatment of 570 µg Cu/g dry liver. In addition, 13 individual patient data were available for both before and after treatment, with a standard deviation of paired difference of 319. It is expected that 48 weeks of treatment with ALXN1840 will reduce Cu concentration by 40%, from 570 to 342, for a reduction of 228. Using a t-test statistic, 24 patients in ALXN1840 will provide 92% power at a one-sided significance level of 0.025 to detect a reduction of 228, with a standard deviation of paired difference of 319, in Cu concentration.

Approximately 28 patients will be enrolled to accommodate a 15% dropout rate, such that approximately 24 evaluable patients complete the study.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined in Table 7.

Table 7: Populations for Analyses

Population	Description
Enrolled	All patients who sign the informed consent form
Safety Analysis Set in Treatment Period	All patients who receive at least 1 dose of treatment in the Treatment Period
Full Analysis Set in Treatment Period	All patients who receive at least 1 dose of treatment in the Treatment Period and have at least baseline liver Cu value
Per Protocol Set in Treatment Period	All patients who receive at least 1 dose of treatment in the Treatment Period and have both baseline and Week 48 liver Cu values. Patients with major protocol deviations that are likely to impact the primary efficacy endpoint analysis will be excluded from the Per Protocol Set. Major protocol deviations, and the Per Protocol Set, will be defined, documented, and agreed within Alexion prior to database lock.
Safety Analysis Set in Extension Period	All patients who receive at least 1 dose of ALXN1840 in the Extension Period
Full Analysis Set in Extension Period	All patients who receive at least 1 dose of ALXN1840 in the Extension Period and have at least baseline liver Cu value

Abbreviation: Cu = copper.

9.4. Statistical Analyses

All statistical analyses will be performed by Alexion or under the authority of Alexion. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP), which will be finalized prior to the data cut for the primary analysis at 48 weeks in the Treatment Period. Any deviations from the planned analysis as described in the SAP will be justified and recorded in the final study report. In general, descriptive statistics for continuous variables will include number of non-missing values, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using percentages and frequency counts.

All variables will be listed on a patient level. Baseline for all assessments will be defined as the last assessment yielding non-missing valid values taken prior to first dose of ALXN1840.

Data will be analyzed separately and sequentially for the Treatment Period and Extension Period.

All statistical analyses will be conducted using SAS® for Windows® Version 9.3 or higher (SAS Institute, Cary, North Carolina, USA).

9.4.1. Efficacy Analyses

9.4.1.1. Treatment Period

The primary objective of this study is to evaluate change in liver Cu concentration following treatment with ALXN1840 at 48 weeks in patients with WD. The primary analysis will be performed using the Full Analysis Set in the Treatment Period.

The change in liver Cu concentration will be evaluated using a paired samples t-test. For the primary analysis, a multiple imputation method will be used for missing data imputation.

Missing values for each patient will be imputed multiple times based on the estimated means from patients with similar baseline liver Cu concentration values. This approach will be used for all missing data at Week 48 due to any reason including, but not limited to, loss to follow-up and withdrawal of consent. The details of implementing this multiple imputation approach are as follows:

- Step 1: Missing values at Week 48 will be imputed 20 times via SAS PROC MI, using MCMC statement, including baseline and Week 48 liver Cu value; imputed values at Week 48 will be retained in the imputed datasets.
- Step 2: Apply paired samples t-test analysis for each of the 20 imputed datasets and save the mean and standard error at Week 48 from each of the 20 analyses.
- Step 3: Combine the 20 sets of analysis results via SAS PROC MIANALYZE. The combined treatment effect, confidence interval, and p-value will be estimated.

Sensitivity analyses will be performed to assess the robustness of the analysis result and will include:

- Use baseline value carried forward to impute missing Week 48 data
- Analyze primary endpoint using the Per Protocol Set, multiple imputation will be used to impute missing Week 48 data

Secondary and exploratory analyses will be performed using the Full Analysis Set in the Treatment Period.

For continuous endpoints that are measured multiple times between baseline and Week 48, data will be analyzed using mixed model repeated measures (MMRM) analysis. Fixed-effect terms will include visit and baseline value as covariates. An unstructured covariance will be used to model within-patient error.

For exploratory endpoints, data will be analyzed as observed, for endpoints that are only measured at baseline and Week 48, an analysis of covariance (ANCOVA) model will be used to analyze continuous endpoints, and a non-parametric ANCOVA model will be used to analyze ordinal outcomes. Baseline value will be included in the model.

9.4.1.2. Multiplicity Adjustment

No adjustments will be made for multiplicity of multiple endpoints.

9.4.2. Safety Analyses

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

Safety analyses will be performed using the Safety Analysis Set in the Treatment Period.

The verbatim terms as reported in the CRF by Investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 20.0 or higher and summarized by primary System Organ Class and Preferred Term.

Summary tables will include patient counts and percentages and will present separate tabulations for all AEs, SAEs, AEs leading to treatment discontinuation or withdrawal, and AEs leading to death.

Laboratory data will be summarized by laboratory parameter and by scheduled time point. Summary statistics will be applied for continuous laboratory parameters, and categorical laboratory parameters will be summarized by absolute and relative frequencies. Reference ranges will be used in the summary of laboratory data. Changes in laboratory parameters from the baseline over time will be summarized via summary statistics and shift tables to allow detection of clinically relevant changes.

Vital sign results will be evaluated by means of descriptive statistics and frequency tabulations. These tables will include shifts from baseline values to allow detection of clinically relevant changes. Abnormal vital sign results will be tabulated.

Physical examination results will be tabulated; abnormalities will be listed.

9.4.3. Other Analyses

The PK, PD, and biomarker analyses will be described in the SAP (or the PK/PD data analysis plan, as applicable), and finalized before database lock.

9.4.4. Interim Analyses

Regulatory submission(s) may be performed before all patients complete the Treatment Period. Interim analyses of safety and efficacy data may be performed to support theses submission(s). These analyses will be descriptive; they will not include formal hypothesis testing and will not be used to adapt the study. Consequently, no adjustments to control Type I error will be performed for the Treatment Period primary analysis.

Full details will be provided in interim and final SAPs.

9.4.5. Extension Period Analyses

Efficacy endpoints will be analyzed using descriptive summary statistics. Efficacy analyses will be performed using the Full Analysis Set in the Extension Period.

Safety analyses will include all AEs, ECGs, clinical laboratory data, physical examinations, and vital sign measurements using descriptive statistics. Safety analyses will be performed using the Safety Analysis Set in the Extension Period.

9.5. Data Monitoring Committee

An independent DMC, comprising experts in relevant fields with no direct relationship to the study, will be appointed by Alexion. As detailed in the DMC Charter (maintained separately from the study protocol), the DMC will review and monitor study data for safety, effectiveness, and study conduct, and make recommendations regarding study continuation, changes to the study population, and/or modification to study procedures. The activities of the DMC will be ongoing before, during, and after the Treatment Period, and through the end of the Extension Period. The specific responsibilities of the DMC are described in the DMC Charter.

Final decisions regarding the conduct of the study will be made by Alexion after consultation with the DMC. All appropriate regulatory authorities and ethics committees will be notified of significant actions taken as a result of DMC recommendations.

Each member of the DMC is required to sign an agreement, including confidentiality and financial disclosure statements, assuring no conflicts of interest as a condition for membership on the committee.

9.6. Hepatic Adjudication Panel

A separate independent Hepatic Adjudication Panel, comprising experts in hepatology and drug induced liver injury, will be appointed by Alexion. As detailed separately in the Hepatic Adjudication Panel charter (maintained separately from the study protocol), the Hepatic Adjudication Panel will review and monitor study data for abnormalities of liver tests and liver function that may impact safety, effectiveness, and study conduct, and make recommendations regarding study continuation, changes to the study population, and/or modification to study procedures. The specific responsibilities are described in the Hepatic Adjudication Panel charter.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, 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 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 patients.
- 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 the requirements of ICH guidelines and the IRB/IEC, all regional and national regulations as applicable (eg, CFR Title 21, Regulation [EU] No 536/2014 for clinical studies on medicinal products for human use, Directive 2001/20/EC), 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 patients prior to any study-related procedures including screening assessments.
- The Investigator or his/her representative will explain the nature of the study to the patient or his/her legally authorized representative and answer all questions regarding the study.
- Patients must be informed that their participation is voluntary. Patients or their legally authorized representative, defined according to local and country regulations where the study is taking place, will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that signed (written or electronic) informed consent was obtained before the patient was screened in the study and the date the consent was obtained. The authorized person obtaining the informed consent must also sign the ICF(s).
- Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the patient or the patient's legally authorized representative.

Patients who are rescreened are required to sign a new ICF (see Section 5.4).

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 patient the objectives of the exploratory research. Patients 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 patient's agreement to allow any remaining specimens to be used for exploratory research. Patients who decline to participate in this optional research will not provide this separate signature.

10.1.4. Data Protection

- Patients will be assigned a unique identifier by Alexion. Any patient records or datasets that are transferred to Alexion will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.
- The patient 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 patient who will be required to give consent for their data to be used as described in the informed consent.
- The patient 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 publically 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 patient data relating to the study will be recorded on a CRF unless transmitted to Alexion or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Alexion or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients 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 patient 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 patient.
- Data reported on the CRF or entered 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 patient is consented.

Alexion or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of 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 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 patients by the Investigator
- Discontinuation of further study drug 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 patient and should assure appropriate patient therapy and/or follow-up

10.1.9. Publication Policy

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

10.2. Appendix 2: Clinical Laboratory Tests

- Pregnancy testing should be conducted in accordance with the SoAs (Table 1 and Table 2).
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure plus an additional 30 days and correspond with the time frame for female patient contraception in Section 5.1.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the Investigator or required by local regulation, to establish the absence of pregnancy at any time during the patient's participation in the study.
- The tests detailed in Table 8 will be performed by a central laboratory, except for any ad hoc tests performed, eg, if an AE occurs.
- Protocol-specific requirements for inclusion or exclusion of patients 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.

Table 8: Protocol-Required Safety Laboratory Assessments

Clinical Chemistry	
Blood urea nitrogen (BUN)	Alanine aminotransferase
Potassium	Alkaline phosphatase
Creatinine	Urea
Creatine kinase	Magnesium
Sodium	Iron
Chloride	Zinc
Potassium	Total and direct bilirubin
Glucose	Total protein
Total carbon dioxide	Albumin
Aspartate aminotransferase	Calcium
Gamma glutamyltransferase	Phosphate
Total cholesterol	Triglycerides
LDL cholesterol	HDL cholesterol
Hematology	
Hematocrit	Red blood cell count (including nucleated red blood cells)
Platelets	Mean corpuscular volume
White blood cell count	Mean cell hemoglobin concentration
Mean cell hemoglobin	Lymphocytes
Neutrophils	Eosinophils
Monocytes	Prothrombin time
Basophils	International Normalized Ratio
Hemoglobin	Partial Thromboplastin Time

Urinalysis	
Bilirubin	Blood
Glucose	Ketones
Leukocytes	Microscopy
Nitrite	pH
Protein	Specific gravity
Urobilinogen	Red blood cells
Bacteria	White blood cells
Other Tests	
HIV, hepatitis B, and hepatitis C screen	Total Cu and total Mo
Ceruloplasmin	24-hour urine
Serum and urine pregnancy test[a]	24-hour urine creatinine, Cu and Mo
NCC	

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

Abbreviations: Cu = Copper; HDL = high density lipoprotein; IEC = Independent Ethics Committee; IRB = Institutional Review Board; LDL = low density lipoprotein; Mo = Molybdenum; NCC = non ceruloplasmin-bound Cu; PTH = parathyroid hormone.

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

Adverse Event Definition
• An AE is any untoward medical occurrence in a patient or clinical study patient, temporally associated with the use of study drug, whether or not considered related to the study drug. • 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 drug.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • Signs, symptoms, or the clinical sequelae, regardless of whether a suspected drug-drug interaction. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. • 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. • Pre-existing conditions that are detected after administration of study drug with an onset date prior to administration should be considered medical history.

Events <u>NOT</u> Meeting the AE Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • 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 investigational product are to be reported within 24 hours of Investigator/site awareness. Data on fetal outcome and breastfeeding will be collected for regulatory reporting and safety evaluation. • Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the patient's condition. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

Serious Adverse Event Definition

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

An SAE is defined as an AE that, at any dose:

1. Results in death

2. Is life-threatening

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

3. Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the patient 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 patient or may require medical or surgical drug 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.

Recording and Follow-Up of Adverse Event and/or Serious Adverse Event

Adverse Event and Serious Adverse Event Recording

- 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 or SAE information in the CRF.
- It is not acceptable for the Investigator to send photocopies of the patient'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 patient identifiers, with the exception of the patient 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 1 of the following categories from National Cancer Institute CTCAE v5.0, published 27 Nov 2017:

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

Adverse Event and Serious Adverse Event Recording

Increases in the severity of an AE should be documented to allow an assessment of the AE duration at each level of intensity to be evaluated. Adverse events characterized as intermittent require documentation of onset and duration of each episode, if the severity of the intermittent event changes.

Assessment of Causality

- The Investigator is obligated to assess the relationship between the study drug 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 (unrelated): There is no causal association with study drug
  - Related: There is causal (temporal) association to the study drug. Other conditions (concurrent illness, concurrent medication reaction, or progression/expression of disease state) do not appear to explain the event; the event corresponds with the known pharmaceutical profile; improvement on discontinuation; reappearance on rechallenge.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to Alexion or its designee. However, it is very important that the Investigator always makes an assessment of causality for every event before the initial transmission of the SAE data to Alexion or its designee.
- The Investigator may change his/her opinion of causality in light of follow-up information and send a 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 Adverse Events and Serious Adverse Events

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by 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 patient 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.

Reporting of Serious Adverse Events

Serious Adverse Event Reporting to Alexion or designee via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to Alexion GDS will be the RAVE Safety Gateway.
- If the electronic system is unavailable at the time that the Investigator or site becomes aware of an SAE, the site will use the paper Contingency Form for SAE reporting via email or fax. Email or facsimile transmission may be used in the event of electronic submission failure. Once the system becomes available again, the SAE report must be forwarded via the RAVE Safety Gateway.
- Email: [redacted] or Fax: [redacted] The site will enter the SAE data into the EDC system as soon as it becomes available.

Serious Adverse Event Reporting to Alexion or designee via an Electronic Data Collection Tool
• When further information becomes available, the EDC system should be updated with the new information and an updated SAE report should be submitted to Alexion GDS via the RAVE Safety Gateway. • After the study is completed at a given site, the EDC tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on the paper Contingency Form for SAE Reporting. • If applicable, additional information such as relevant medical records should be submitted to Alexion GDS via the email address or fax number noted above. • All paper forms and follow-up information submitted to Alexion outside of the RAVE Safety Gateway (eg, discharge summary) should be kept in the appropriate section of the study file and 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: Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

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

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy
    - For individuals with documented permanent infertility due to an alternate medical cause other than the above, (e.g., mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.
    - Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
    - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

Contraception Guidance:

Guidance for Female Patients

Female patients of non-childbearing potential are exempt from contraception requirements.

Female patients of child-bearing potential must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours before the first dose of study drug.

The Investigator is responsible for the review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

Female patients of child-bearing potential must use a highly effective method of contraception, including at least one of the following, starting at least one menstrual cycle before first study drug administration and continuing for at least 30 days after the end of systemic exposure of the study drug, including at least one of the following:

a. Intrauterine device (without Cu)

b. Progestogen-only hormonal contraception (either oral, injectable, or implantable) associated with inhibition of ovulation

c. Intrauterine progestogen releasing system

d. Bilateral tubal occlusion

e. Combined (estrogen and progestogen containing) hormonal contraception (either oral, intravaginal, or transdermal) associated with inhibition of ovulation. Estrogen-containing hormonal contraception is acceptable only if it has been used for at least 6 weeks immediately prior to the Day 1 visit. Estrogen-containing hormonal contraception may not be initiated during the study period.

f. Surgical sterilization of the male partner (medical assessment of azoospermia is required if vasectomy was performed within the prior 6 months)

Sexual abstinence for female patients

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse. In this study, abstinence is only acceptable if consistent with the patient's preferred and usual lifestyle. Abstinent female patients who wish to initiate a highly effective method of contraception during the study must refrain from heterosexual intercourse for at least 28 days.

Periodic abstinence (e.g. calendar, symptothermal, or post-ovulation methods) is not considered a highly effective method of contraception for female patients.

Other methods of contraception that are not considered highly effective for female patients

Barrier methods, such as male or female condoms, diaphragm, or cervical cap, used alone or in combination, are not acceptable.

Spermicides or spermicidal sponges, used alone or in combination with barrier methods, are not acceptable.

Withdrawal (coitus interruptus) is not acceptable.

Lactational amenorrhea is not acceptable.

Guidance for male patients with a partner who is a woman of childbearing potential

Male patients must use a condom and spermicide during heterosexual intercourse from the first dose of study intervention until at least 90 days after their final dose of study intervention.

Female partners of male patients who are of childbearing potential must use highly effective contraception as defined above, starting one menstrual cycle before (the male patient's) first study intervention administration and continuing until at least 90 days after the end of their male partner's systemic exposure to the study intervention.

Male patients must not donate sperm from the first dose of study intervention until at least 90 days after their final dose of study intervention.

Sexual abstinence for male patients

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse. In this study, abstinence is only acceptable if consistent with the patient's preferred and usual lifestyle. Abstinent male patients who become heterosexually active with a WOCBP must use a condom and spermicide during intercourse.

Periodic abstinence (e.g. calendar, symptothermal, or post-ovulation methods for a female partner) is not considered a highly effective method of contraception for male patients.

Collection of Pregnancy Information

Pregnancy data will be collected during this study for all female patients and female partners of male patients. Exposure during pregnancy (also referred to as exposure *in utero*) can be the result of either maternal exposure or transmission of drug product via semen following paternal exposure. If a female patient becomes pregnant from the first dose of study drug up to 30 days after the end of systemic exposure or a male patient's female partner becomes pregnant from the first dose of study drug up to 90 days after the end of systemic exposure, the Investigator must submit the "Pregnancy/Breastfeeding Reporting and Outcome Form" to Alexion GDS via email or facsimile. 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 or other study drug 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.

Pregnancy in itself is not regarded as an AE unless there is a suspicion that the study drug may have interfered with the effectiveness of a contraceptive medication. However, complications of pregnancy and abnormal outcomes of pregnancy are AEs and may meet the criteria for an SAE (eg, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly). Elective abortions without complications should not be reported as AEs.

Any female patient who becomes pregnant while participating in the study will be discontinued from study drug and withdrawn from the study.

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies to male participants who receive ALXN1840.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate "Pregnancy/Breastfeeding Reporting and Outcome Form" and submit it to Alexion within 24 hours of obtaining the consent. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to Alexion. Generally, the follow-up will be no longer than 3 months following the delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to Alexion within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to Alexion. Generally, follow-up will not be required for longer than 3 months beyond the delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such. Any post-study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to Alexion as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- Genetic variation may impact a patient's response to study drug, susceptibility to, and severity and progression of disease. Variable response to study drug may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting patients.
- DNA samples will be used for research related to ALXN1840 or WD and related diseases. They may also be used to develop tests/assays including diagnostic tests related to ALXN1840 and WD. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- DNA samples will be analyzed for variants in the coding and regulatory sequences of the *ATP7B* gene.
- Additional unspecified analyses may be conducted in the future if it is hypothesized that this may help resolve issues with the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to ALXN1840 or study drugs of this class to understand study disease or related conditions.
- The results of genetic analyses may be reported in the clinical study report or in a separate study summary.
- Alexion will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The DNA samples will be retained while research on ALXN1840 continues but no longer than 15 years or other period as per local requirements.

10.6. Appendix 6: Abbreviations

Abbreviation	Definition
AASLD	American Association for the Study of Liver Diseases
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate transaminase
AUEC	Area under the effect-time curve
BMI	Body mass index
BPRS	Brief Psychiatric Rating Scale-24;
CGI	Clinical Global Impression
CGI-I	Clinical Global Impression-Improvement Scale
CGI-S	Clinical Global Impression-Severity Scale
CIOMS	Council for International Organizations of Medical Sciences
CKD	Chronic kidney disease
CLDQ	Chronic liver disease questionnaire
cNCC	Calculated non-ceruloplasmin-bound Cu
CONSORT	Consolidated Standards of Reporting Trials
Cp	Ceruloplasmin
CpC	Ceruloplasmin bound Cu
CRF	Case report form
Cu	Copper
CYP	Cytochrome P450
DMC	Data Monitoring Committee
dNCC	Directly measure non-ceruloplasmin bound Cu
EASL	European Association for the Study of the Liver
EDC	Electronic data capture
EOS	End of Study
EQ-5D	EuroQoL 5 Dimensions
EQ VAS	EuroQol visual analog scale
ET	Early Termination
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GDS	Global Drug Safety
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ICF	Informed consent form
IEC	Institutional Ethics Committee
INR	International normalized ratio for prothrombin time

Abbreviation	Definition
IRB	Institutional Review Board
LLT	Lowest level term
LS	Least-squares
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End-Stage Liver Disease
MMRM	Mixed model repeated measures
Mo	Molybdenum
MR(E)	Magnetic resonance (elastography)
MRI	Magnetic resonance imaging
MT	Metallothionein
NCC	Non-ceruloplasmin-bound Cu
NIMP	Non-investigational medicinal product
PD	Pharmacodynamic(s)
PDFF	Proton density fat fraction
PK	Pharmacokinetic(s)
PT-INR	Prothrombin time-international normalized ratio
PUF	Plasma ultrafiltrate
QOD	Once every other day
QD	Once a day
SAE	Serious adverse event
SoA	Schedule of Activities
SoC	Standard of care
SUSAR	Suspected unexpected serious adverse reaction
TSQM-9	Treatment Satisfaction Questionnaire for Medication-9
ULN	Upper limit of normal
UNS	Unscheduled
UWDRS	Unified Wilson Disease Rating Scale
WD	Wilson disease
WOCBP	Woman of childbearing potential

10.7. Appendix 7: Protocol Amendment History

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

Original Protocol	20 Dec 2019
Amendment 1 (Austria)	07 May 2020
Amendment 2 (Germany)	03 Aug 2020
Amendment 3 (Denmark)	10 Aug 2020
Amendment 4 (United Kingdom)	23 April 2021

Amendment 1 (07 May 2020)

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

Overall Rationale for the Amendment

This amendment was prepared to add information on monthly pregnancy testing for female patients of childbearing potential who are enrolled in an interventional clinical study. This is a legal requirement in Austria, according to Article 30 of the Austrian Drug Law. This amendment applies only to Austria.

Changes to the Protocol

Section # and Name	Description of Change	Brief Rationale and/or Clarifications
Section 1.2 Schedule of Activities, Tables 1 and 2 Section 5.1, Inclusion Criteria Section 10.4 Appendix 4: Pregnancy Information	Addition of requirement for female subjects of childbearing potential to perform monthly pregnancy testing at their home throughout the study	It is a legal requirement in Austria to include monthly pregnancy tests in clinical studies
Figure 1	Figure corrected to remove mention of treatment-naïve patients	Treatment-naïve patients are not included in the study.
All sections	Minor editorial updates and corrections	For clarification, and to ensure accuracy and consistency throughout the protocol

Amendment 2 (03 Aug 2020)

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

Overall Rationale for the Amendment

This amendment was prepared to update exclusion criterion relating to clinical study experience and to add information on prohibited concomitant medication in response to a request by the Federal Institute for Drugs and Medical Devices in Germany (BfArM). Additional changes are included in the table below. This amendment only applies to Germany.

Changes to the Protocol

Section # and Name	Description of Change	Brief Rationale and/or Clarifications
Section 5.2, Exclusion Criteria	Prior clinical study experience limited to 3 months (or 5 half-lives of the administered investigational medicinal product, whichever is longer) prior to study start.	More detailed language regarding exclusion of patients who participated in any interventional study prior to initiation of Study ALXN1840-WD-205.
Section 6.5, Concomitant Therapy	Standard of care treatment for Wilson disease added as prohibited medication during the treatment period.	Standard of care treatment for Wilson disease and ALXN1840 should not be administered concomitantly.
Figure 1	Figure corrected to remove mention of treatment-naïve patients	Treatment-naïve patients are not included in the study.
All sections	Minor editorial updates and corrections	For clarification, and to ensure accuracy and consistency throughout the protocol

Amendment 3 (10 Aug 2020)

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

Overall Rationale for the Amendment

This amendment was prepared to add information on pregnancy testing for female patients of childbearing potential who are enrolled in an interventional clinical study in response to a request from the Danish Health Authority. Additional minor editorial updates were made for clarification and consistency. This amendment only applies to Denmark.

Changes to the Protocol

Section # and Name	Description of Change	Brief Rationale and/or Clarifications
Section 1.2, Schema, Figure 1	Figure corrected to remove mention of treatment-naïve patients	Treatment-naïve patients are not included in the study.
Section 1.1, Synopsis Section 1.3, Table 1, and Table 2 Section 4.1, Overall Design	Monthly pregnancy testing will be performed for 90 days after the last dose of ALXN1840.	Monthly pregnancy testing, according to the Clinical Trial Facilitation Group (CTFG) guideline on contraception in clinical trials, has been extended based on relevant exposure of ALXN1840.
Section 10.4, Appendix 4, Pregnancy Information	Contraception guidance updated to include duration of use and type.	To further define contraception requirements

All sections	Minor editorial updates and corrections	For clarification, and to ensure accuracy and consistency throughout the protocol

Amendment 4 (23 April 2021)

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

Overall Rationale for the Amendment

The main reason for preparation of this amendment was to add information regarding the coronavirus disease 2019 (COVID-19) vaccine risk assessment, as requested by the UK Medicines and Healthcare products Regulatory Agency (MHRA) in its updated guidance on managing clinical trials during the COVID-19 pandemic. This amendment only applies to the United Kingdom.

Changes to the Protocol

Section # and Name	Description of Change	Brief rationale and/or clarifications
Section 2.3.1.1, Coronavirus Disease 2019; Section 10.6 Appendix 6: COVID-19 Vaccine Risk Assessment	Text on the COVID-19 vaccine risk assessment performed with respect to ALXN1840 added.	To comply with the request by the MHRA for studies performed in the UK.
All sections	Minor editorial updates and corrections	For clarification, and to ensure accuracy and consistency throughout the protocol

Abbreviations: COVID-19 = coronavirus disease 2019; MHRA = Medicines and Healthcare products Regulatory Agency; UK =United Kingdom.

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