TITLE PAGE

Protocol Title:

A multicenter, randomized, controlled, open-label, rater-blinded study to evaluate efficacy, safety, pharmacokinetics, and pharmacodynamics of ALXN1840 versus standard of care in pediatric participants with Wilson disease

Protocol Number: ALXN1840-WD-302

Amendment Number: 3 (Global)

Compound: ALXN1840 (formerly known as ATN-224 and WTX101) or bis-choline tetrathiomolybdate (tiomolibdic acid, tiomolibdate choline)

Study Phase: 3

Short Title: Phase 3, open-label study of ALXN1840 versus standard of care in pediatric participants with Wilson disease

Sponsor Name: Alexion Pharmaceuticals, Inc.

Legal Registered Address:

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Regulatory Agency Identifier Number(s): IND 119006, EudraCT 2021-001015-82

Release Date:

Amendment 3 (Global)	08 Mar 2022
Amendment 2 (Germany)	08 Nov 2021
Amendment 1.1 (UK)	30 Sep 2021
Amendment 1 (UK)	07 Jul 2021
Original Protocol	15 Mar 2021

Sponsor Signatory:

[redacted]

09 Mar 2022

Date

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

INVESTIGATOR'S AGREEMENT

I have read the study protocol and agree to conduct the study in accordance with this protocol amendment 3 (Global), 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

Amendment 3 (Global) (08 Mar 2022)

This substantial amendment is considered to impact the scientific value of the study 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.

Rationale for the Amendment:

The main reason for this amendment is to reduce the maximum daily dose of ALXN1840 from 60 mg for adolescent participants and 30 mg for pediatric participants to 15 mg for all participants in this study. The decision to reduce the maximum daily dose was made based on results from the Primary Evaluation Period of the ongoing Phase 3 study WTX101-301.

In addition, changes that were made in the following country-specific protocol amendments and Administrative Change Letters have also been incorporated into this global amendment.

- Administrative Change Letter 1 (dated 09 Jun 2021): to change the guidance on blood volume and to make some minor clarifications and corrections.
- Protocol Amendment 1.1 (UK) (30 Sep 2021): the main change was to specify permitted gastrostomy devices in inclusion criterion #5, as requested by the UK Medicines and Healthcare products Regulatory Agency (MHRA).
- Administrative Change Letter 2 (dated 17 Sep 2021): the main change was to clarify when randomization would occur, so as to enable sites to perform randomization up to the start of Day 1 procedures, rather than just on Day -1.
- Administrative Change Letter 3 (dated 29 Oct 2021): to clarify that post-dose collection of PK/PD/biomarker samples is required for participants randomized to either ALXN1840 or SoC.
- Protocol Amendment 2 (Germany) (08 Nov 2021): changes were made in response to a request from the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM; German Federal Institute for Drugs and Medical Devices) to revise the time specification for reporting an SAE by the Investigator to Alexion to "immediately" instead of "within 24 hours" and to include text on the potential risk and mitigation strategies for pediatric participants. These changes are included in a new section for country-specific changes (Section 10.11).
- Administrative Change Letter 4 (dated 15 Dec 2021): to clarify the distribution of participants among strata, because the distribution (ie, the number of participants in each stratum) is a goal, and is not intended to be prescriptive.

Minor administrative changes were also made for consistency and clarity.

Changes from the original protocol are summarized in the table below.

Section # and Name	Description of Change	Brief rationale and/or clarifications
1.1 Synopsis 2.1 Study Rationale 4.3 Justification for Dose	Removal of term "standard" from "standard treatment" for WD from the protocol.	This change was made for consistency and to avoid confusion between 'standard treatment' and 'SoC'.
1.1 Synopsis 3 Objectives and Endpoints	**R**evisions to PK endpoints: • terminal elimination half-life; ($t_{1/2}$) removed • C_{trough} added Revision to text as follows: • Derived ~~population~~ **secondary** PK parameters such as revised to note that derived secondary PK parameters such as CL/F and Vd/F **(as appropriate)**	$t_{1/2}$ removed as not enough time points to calculate. Addition of C_{trough}, because there will be enough data to calculate this parameter. Revision of wording, because there may not be enough time points to calculate secondary PK parameters.
1.1 Synopsis 1.2 Schema, Figure 1 4.1 Overall Design	Addition of "a minimum of" to the number of participants in each stratum.	To clarify the distribution of participants among cohorts, because the distribution of the strata (ie, the number of participants) was an approximation and was not intended to be prescriptive. It was intended that a minimum of 6 participants should be included in each stratum (N = 24) and the remaining 24 participants can come from any of the strata in any combination.
1.1 Synopsis 1.3 Schedule of Activities, Table 1 4.1 Overall Design 4.2 Scientific Rationale for Study Design 8.6 Pharmacodynamics	Clarification in footnote l that PK, measured by plasma total molybdenum and PUF molybdenum, and PD, measured by plasma total copper and LBC, will be determined for all participants.	To clarify the post-dose collection of PK/PD/biomarker samples for participants randomized to either ALXN1840 or SoC.
1.1 Synopsis 2.3.1 Risk Assessment 4.1 Study Design 4.3 Justification for Dose 6.1 Study Interventions Administered, Table 5 6.1.1 Dose Modification for ALXN1840 6.6.1 Dose Modification for ALN1840, Table 5 8.4 Treatment of Overdose 10.8.1 Participants aged 12 to < 18 years	Removal of text relating to dose increases from 15 mg/day to a maximum of 60 mg/day. Text revised, as appropriate, to state that the maximum permitted daily dose is 15 mg.	It has been decided to limit the maximum dose to 15 mg/day, based on Primary Evaluation Period data from the ongoing Study WTX101-301.

Section # and Name	Description of Change	Brief rationale and/or clarifications
1.1 Synopsis	The following text on individualized doses for participants aged 3 to < 12 years has been removed. • Individualized doses ranging from 2.5 mg/day to 30 mg/day are allowed.	The preceding and subsequent text in the section adequately covers the range of dosing options.
1.2 Study Schema, Figure 1 1.3 Schedule of Activities, Table 1	Screening period changed from Day -28 to Day -2 to Day -28 to Day -1, with randomization to occur before Day 1 procedures begin.	To enable sites to perform randomization up to the start of Day 1 procedures, rather than just on Day -1.
1.3 Schedule of Activities, Table 1	Addition of text to note stating that participants who are randomized to ALXN1840 in Period 1 do not need to attend visits at Weeks 4, 6, 8, and 18 in Period 2.	Participants who are randomized to ALNX1840 in Period 1 will be attending visits every 12 weeks at the end of Period 1, so do not need to attend more regularly in Period 2.
	"ET" added to Week 24 in Period 2.	Added for clarity, because similar to Period 1, the ET visit would occur during Period 2 in the event of early termination.
	Aligned assessment of lipid panel with chemistry assessments.	To ensure that lipids are assessed at all time points that chemistry is assessed.
	Footnote k revised to state that transient elastography will be done when available. Footnote applied to the text "Transient elastography" and removed from the Screening and Day 1 timepoints.	To reflect that it may not be possible to perform transient elastography at all study sites.
	Text on alternative blood sampling schedule for infants deleted from footnote l.	To align with the change in guidance on blood sampling volumes (see below).
	Period 2 added to footnote l.	To clarify that plasma/serum samples will be collected predose in both Periods 1 and 2.
1.3 Schedule of Activities, Table 1 Section 8, Study Assessments and Procedures	Removal of text from the general footnote and footnote l stating that an alternative blood sampling schedule for infants will be given in the Study Operations Manual. Removal of the same text from Section 8, noting that it refers to "children and adolescents"	Guidelines on blood sampling are provided in Section 10.7. No separate guidelines for infants are required, because the minimum age for enrollment into the study is 3 years.
1.3 Schedule of Activities, Table 1 8.8 Biomarkers 10.2 Clinical Laboratory Tests, Table 10	Footnote l simplified to state that serum ceruloplasmin will be assessed separately to plasma ceruloplasmin (which will be assessed as part of the PK/PD/biomarker parameters).	To clarify that serum and plasma ceruloplasmin are analyzed separately.
1.3 Schedule of Activities, Table 1 10.2 Clinical Laboratory Tests	Text requiring pregnancy testing for 3 months after the EOS visit removed from footnote j and Section 10.2.	To align with Clinical Trials Facilitation Group (CTFG) guidance on contraception and pregnancy testing recommendations.
2.2 Background	Text on Study ALXN1840-HV-109 updated to state that relative bioavailability of the 1.25 mg enteric-coated mini-tablet	Updated because Study ALXN1840-HV-109 has been completed.

Section # and Name	Description of Change	Brief rationale and/or clarifications
	formulation of ALXN1840 compared with the 15 mg EC tablet was confirmed.	
2.3 Benefit/Risk Assessment	Text has been added stating that potential risk and mitigation strategies have been identified in line with the EU guidance "Ethical Considerations for Clinical Trials on Medicinal Products in Minors".	The change was made in response to a request from the BfArM (Germany) to assess and monitor the risk threshold by the Investigator, and to define it in the protocol.
2.3.1 Risk Assessment, Table 2	Potential risk, rationale for risk, and mitigation added regarding lipid elevations.	To include guidance for monitoring of lipids, based on observations of lipid elevations that have been observed in patients with WD.
4.2 Scientific Rationale for Study Design	Addition of text stating that SoC PD will be assessed in children and adolescents.	To clarify that SoC PD will be assessed in children and adolescents.
4.2 Scientific Rationale for Study Design 8.5 Pharmacokinetics 9.4.3 Pharmacokinetic, Pharmacodynamic, and Biomarker Analyses	Removal of "as surrogate measures of ALXN1840 PK" in text about analysis of samples.	Removed for clarity.
4.3 Justification for Dose	Table 4 deleted.	The table was deleted because the predicted dose range information in the table was modified due to the reduction in maximum dose. The information in the footnote was repurposed in the text to provide the necessary details.
5.1 Inclusion Criteria	Modification of the text in inclusion criterion #5, which now reads "Able to swallow intact ALXN1840 tablets or mini-tablets. Participants who require gastrostomy devices for feeding or medications may be enrolled if the inner diameter of the tube can accommodate an intact tablet or mini-tablet without obstruction."	This change was made in response to the request by the UK Medicines and Healthcare products Regulatory Agency (MHRA) to remove inclusion criteria that are not absolute and to predefine the attributes of the gastrostomy devices.
5.2 Exclusion Criteria	Removal of concomitant use of penicillamine, zinc, or trientine from exclusion criterion 10.	Concomitant use of medications is not an exclusion criterion, but is covered in Section 6.5.2 Disallowed Medicine and Therapy.
5.3.1 Meals and Dietary Restrictions	Addition of text stating that ALXN1840 mini-tablets may be administered with a small amount of apple sauce or yogurt.	Results from a food vehicle study found that mini-tablets are stable in apple sauce and yogurt, so these foods have been included as an option for administration of ALXN1840.
6.5.2 Disallowed Medicine and Therapy	Addition of text stating that vitamin E and estrogen should not be initiated during the study, but can be continued if already being taken.	To clarify that vitamin E and estrogen can continue to be taken during the study, if already being taken before the study start.
6.6.1 Dose Modification for ALXN1840, Tables 5 and 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 # and Name	Description of Change	Brief rationale and/or clarifications
8.2.3 Electrocardiograms	Removal of cross-reference to Section 7 for QTc withdrawal criteria and any additional QTc readings that may be necessary.	QTc withdrawal criteria are not required in this protocol.
8.3.5 Adverse Events of Special Interest	Text revised to state that all AESIs will be assessed by a panel of 3 independent neurologists.	To reflect that all AESIs will be assessed by a panel of 3 independent neurologists, not just SAEs of special interest.
8.6 Pharmacodynamics 8.8 Biomarkers	Addition of SoC to the text on analysis of PD.	To clarify that PD will be measured for SoC.
9.1.1 Primary Hypothesis 9.4 Statistical Analyses	Addition of PD to the types of evaluations in the study.	For completeness.
9.5 Interim Analyses	Text added to state when the primary and final analyses will take place. Text modified to state that interim analyses of data may be performed to support regulatory submission.	To clarify when the primary and final analyses will take place, and to note that interim analyses may be performed.
9.7 Neurological Event Adjudication Panel	Text revised to include AEs as well as SAEs.	To reflect that the Neuro Event Adjudication Panel will review and monitor study for all AEs, not just SAEs.
10.2 Clinical Laboratory Tests, Table 10	Removal of text in footnote relating to Hy's Law.	Text removed as not needed. If participants experience INR prolongation and they are admitted to hospital, the event will meet the definition and be recorded as an SAE.
	Removal of reference to glycated hemoglobin (HbA1c).	HbA1c is not assessed during the study.
10.3.2 Definition of SAE	Text added noting that SUSAR reporting will be in accordance with the Summary of Product Characteristics of the respective SoC products.	To clarify SUSAR reporting requirements for SoC as an implication of designating SoC as IMP.
10.4.2.1 Guidance for Female Participants	Addition of "associated with inhibition of ovulation" to the following text: • Combined (estrogen- and progestogen-containing) hormonal contraception - associated with inhibition of ovulation (either oral, intravaginal, or transdermal) for at least 6 weeks prior to first dose of study intervention.	For clarification and to align with CTFG guidance on contraception use in clinical studies.
10.7 Blood Sampling Volumes	Wording revised to state that the Investigator may, rather than should, apply an EMLA cream/plaster at the puncture site, and to add that use of an EMLA cream/plaster depends on clinical practice at the study site.	To reflect that EMLA cream/plaster use depends on clinical practice at the study site.
	Reference changed from the European Commission guidance to the US guidelines. From: • European Commission. European Commission Ethical Considerations for Clinical Trials on Medicinal Products Conducted	The guidance on blood sampling volumes has been changed from the European Commission guidance to the US National Institutes of Health guidelines, because the US guidelines allow Investigators to conduct all tests planned without

Section # and Name	Description of Change	Brief rationale and/or clarifications
	with the Paediatric Population: Recommendations of the ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to the good clinical practice in the conduct of clinical trials on medicinal products for human use. 2008 To: • POLICY- Guidelines for Limits of Blood Drawn for Research Purposes in the Clinical Center https://irb.research.chop.edu/sites/default/files/documents/g_nih_blooddraws.pdf" Text changed from: • Volume of blood samples: Per study participant, the study-related blood loss (including any losses in the collection procedure) should not exceed 3% of the total blood volume during a period of 4 weeks, and should not exceed 1% at any single time. The total volume of blood is estimated at 80 to 90 mL/kg body weight. 3% is 2.4 mL blood per kg body weight. To: Volume of blood samples: Per study participant, the study-related blood loss (including any losses in the collection procedure) should not exceed more than 5 mL/kg body weight (5% of total blood volume) in a single day and no more than 9.5 mL/kg (11% of total blood volume) over any 8-week period.	increasing the number of blood draw points.
10.11 Country-Specific Changes	Addition of a section detailing country-specific changes to the protocol. The changes included in this section apply to Germany only, and are as follows: • Changes to the time specification for reporting of SAEs • Addition of text on potential risk and mitigation strategies • Addition of text noting that measures have been taken to minimize the burden of participation and degree of distress for the pediatric and adolescent participants in the study.	To include changes requested by the BfArM in Germany that only apply to Germany.
All	Minor administrative changes.	For consistency and clarity.

Abbreviations: AESI = adverse event of special interest; BfArM = Bundesinstitut für Arzneimittel und Medizinprodukte (German Federal Institute for Drugs and Medical Devices); CL/F = apparent total body clearance; C_{trough} = trough (predose) concentration observed at the start of the dosing interval; EMLA = eutectic mixture of local anesthetics; EOS = end of study; ET = early termination; IMP = Investigational Medicinal Product; PD = pharmacodynamics; PK = pharmacokinetics: PUF = plasma ultrafiltrate; SAE = serious adverse event; SoC = Standard of Care; SUSAR = suspected unexpected serious adverse reaction; V_d/F = apparent volume of distribution;WD = Wilson disease.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title: A multicenter, randomized, controlled, open-label, rater-blinded study to evaluate efficacy, safety, pharmacokinetics, and pharmacodynamics of ALXN1840 versus standard of care in pediatric participants with Wilson disease

Short Title: Phase 3, open-label study of ALXN1840 versus standard of care in pediatric participants with Wilson disease

Rationale:

This study is being conducted to evaluate the efficacy, safety, pharmacokinetics (PK), and pharmacodynamics (PD) of ALXN1840 versus standard of care (SoC) in pediatric participants with Wilson disease (WD) who are 3 to < 18 years of age at the time of enrollment. Participants can be treatment-naïve or have previously received treatments approved for use in WD (penicillamine, trientine, zinc).

Wilson Disease is most commonly diagnosed in teenagers and young adults and rarely presents symptomatically before 5 years of age (Socha, 2018). In a European cohort of 1357 patients, the average age at diagnosis of WD was 19.8 years (± 10 years), and half of all patients were diagnosed before the age of 18 (Ferenci, 2019).

Treatments approved and used in adults with WD (penicillamine, trientine, zinc) are also approved for use in children and adolescents. However, significant unmet needs still exist with respect to efficacy, safety, tolerability, simplicity and frequency of dosing regimens, and especially with an appropriate compliance to therapy in young participants.

At the time of preparation of this protocol, ALXN1840 is being evaluated versus SoC in adolescent (12 years and above) and adult participants (18 years and above) with WD in an ongoing Phase 3, multicenter, randomized study (Study WTX101-301). Since data from adults cannot be fully extrapolated to the whole pediatric population, this study will evaluate the efficacy, safety, PK, and PD of ALXN1840, compared with SoC, administered for 48 weeks in participants with WD aged 3 to < 18 years. Efficacy data from this study will subsequently be assessed together with those from Study WTX101-301, using Bayesian extrapolation methods to determine the efficacy of ALXN1840 compared with SoC in pediatric participants.

Objectives and Endpoints

Objectives	Endpoints
Period 1: Up to Week 48	
Primary	
• To evaluate the efficacy of ALXN1840 administered for 48 weeks, compared to SoC, on copper control in participants with WD aged 3 to < 18 years of age at the time of enrollment	• Percentage change from baseline (Day 1) to 48 weeks in NCC in plasma. For ALXN1840-treated participants, the NCC in plasma will be corrected for the amount of copper bound to the ALXN1840 TPC ($NCC_{corrected}$)
Secondary	
• Evaluate the safety and tolerability of ALXN1840 administered for up to 48 weeks	• Incidence of adverse AEs/SAEs, AESIs, tolerability, clinical laboratory test data (including liver function tests), neurological and physical examination findings, 12-lead ECG data, and vital signs.

Objectives	Endpoints
• Evaluate PD and biomarkers of ALXN1840 vs SoC administered for 48 weeks	• AUEC for NCC • AUEC for plasma total copper • Biomarkers: observed, absolute and percentage changes of ceruloplasmin-bound copper and ceruloplasmin
• Evaluate the effects of ALXN1840 and SoC on the NCC responder rate	• NCC responder rate
• Evaluate the effects of ALXN1840 and SoC on participant reported disability status	• Change from baseline to Week 48 in the UWDRS Part II total score
• Evaluate the effects of ALXN1840 and SoC on rater-blinded neurological status	• Change from baseline in UWDRS Part III total score or individual items/subscales, as appropriate
• Evaluate PK of ALXN1840 administered for 48 weeks	Estimation of PK parameters and accumulation ratios • PK: C_{max}, t_{max}, C_{trough}, and AUC_{tau} on Day 1, Day 43 (Week 6), and Day 337 (Week 48) for plasma total molybdenum and plasma ultrafiltrate molybdenum concentrations, accumulation ratio of Day 43 to Day 1 and Day 337 to Day 1 based on C_{max}, C_{trough}, and AUC_{tau} • Derived secondary PK parameters such as CL/F and V_d/F (as appropriate)
• Evaluate the effects of ALXN1840 and SoC on global clinical symptoms as assessed by the Investigator	• CGI-I • Change from Baseline to Week 48 in CGI-S
• Evaluate the effects of ALXN1840 and SoC on hepatic status	• Change from Baseline to Week 48 in MELD score (ages 12 years and older) or PELD score (ages 3 to < 12 years) • Change from Baseline to Week 48 in Modified Nazer score
Exploratory	
• Evaluate the effects of ALXN1840 and SoC on hepatic fibrosis	• Change from Baseline to Week 48 in the FIB-4 Index and by transient elastography
• Evaluate the effects of ALXN1840 and SoC on psychiatric symptoms	• Change from Baseline to Week 48 in BPRS-24 and BPRS-C9
• Evaluate the effects of ALXN1840 and SoC on QoL/PROs	• Change from Baseline to Week 48 in QoL/PRO endpoint measures: – EQ-5D or EQ-5DY – PedsQL NOTE: These tests will be administered by parent/proxy for participants unable to complete independently.
• Evaluate participant satisfaction of treatment with ALXN1840 and SoC	• Change from Baseline to Week 48 in TSQM-9 NOTE: This questionnaire will be administered by parent/proxy for participants unable to complete independently.
• Evaluate the effects of ALXN1840 and SoC on 24-hour fecal copper and fecal molybdenum	• Change from Baseline to Week 6 in 24-hour fecal copper and fecal molybdenum
• Evaluate the effects of ALXN1840 and SoC on 24-hour urinary copper and urinary molybdenum	• Change from Baseline to Week 48 in 24-hour urinary copper and urinary molybdenum

Objectives	Endpoints
• Explore other directly measured pharmacodynamics (PD) and biomarkers of ALXN1840	• Daily mean AUEC of NCC, and plasma total copper from 0 to 24, and 24 to 48 weeks • Observed, absolute and percent changes of copper levels (total copper, PUF copper, LBC)
• Explore ALXN1840 effect on initial decoppering phase compared to SoC based on directly measured PK/PD and biomarkers	• Time to first confirmed increase in plasma NCC and total copper concentration • Time to minimum and maximum concentration of: – Plasma total copper – Plasma NCC – Plasma LBC – Ratio plasma NCC:total copper – Ratio plasma LBC:total copper – Plasma ceruloplasmin – Plasma CpC – Ratio plasma ceruloplasmin:total copper – Plasma CpC:total copper – 24-hour urinary molybdenum – Ratio urinary molybdenum:copper – Ratio 24-hour urinary molybdenum:dosed molybdenum
• Explore ALXN1840 effect on subsequent maintenance phase compared to SoC based on directly measured PK/PD and biomarkers	• Time for return to pre-dose baseline for the following PK/PD parameters: – Plasma total copper – Plasma NCC – Plasma LBC – Ratio plasma NCC: total copper – Ratio plasma LBC:total copper – Plasma ceruloplasmin concentration – Plasma CpC concentration – Ratio plasma ceruloplasmin:total copper – Ratio plasma CpC:total copper – 24-hour urinary molybdenum – Ratio urinary molybdenum:copper – Ratio urinary molybdenum:dosed molybdenum
Period 2: Weeks 48 to 72	
Exploratory	
• Safety and tolerability of ALXN1840 in the Extension Period	• AEs/SAEs, AESI, tolerability, clinical laboratory test data, physical examination findings, vital signs, and 12-lead ECG data
• Evaluate PD and biomarkers of ALXN1840	• AUEC for NCC • AUEC for plasma total copper • Observed, absolute and percent changes of copper levels (total copper, PUF copper, LBC) • Biomarkers: observed, absolute and percent changes of ceruloplasmin-bound copper and ceruloplasmin
• Evaluate the effects of ALXN1840 on hepatic status	• Change from Baseline in MELD/PELD score and modified Nazer score

Objectives	Endpoints
• Evaluate the effects of ALXN1840 on disability status	• Change from Baseline in UWDRS Part II
• Evaluate the effects of ALXN1840 on neurological status	• Change from Baseline in UWDRS Part III
• Evaluate the effects of ALXN1840 on hepatic fibrosis	• Change from Baseline in transient elastography and FIB-4 index
• Evaluate the effects of ALXN1840 on psychiatric symptoms	• Change from Baseline in BPRS-24 and BPRS-C9
• Evaluate the effects of ALXN1840 on global clinical symptoms as assessed by the Investigator	• Change from Baseline in CGI-I and CGI-S
• Evaluate the effects of ALXN1840 on QoL/PRO	• Change from Baseline to Week 72 in QoL/PRO endpoint measures: – EQ-5D or EQ-5DY – PedsQL NOTE: These tests will be administered by parent/proxy for participants unable to complete independently.
• Evaluate participant satisfaction of treatment with ALXN1840 and SoC	• Change from Baseline to Week 72 in TSQM-9 NOTE: This questionnaire will be administered by parent/proxy for participants unable to complete independently.

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AUCtau = area under the plasma concentration versus time curve from time 0 to the end of the dosing interval; AUEC = area under the effect versus time curve; BPRS-24 = Brief Psychiatric Rating Scale-24; BPRS-C9 = Brief Psychiatric Rating Scale for children; CGI-I = Clinical Global Impression-Improvement Scale; CGI-S = Clinical Global Impression-Severity Scale; CL/F = apparent total body clearance; C_{max} = maximum observed concentration; CpC = ceruloplasmin-bound copper; C_{trough} = trough (predose) concentration observed at the start of the dosing interval; ECG = electrocardiogram; EQ-5D(Y) = EuroQoL 5 Dimensions (Youth); FIB-4 = fibrosis-4; LBC = labile-bound copper; MELD = Model for End-stage Liver Disease; NCC = non-ceruloplasmin-bound copper; $NCC_{corrected}$ = corrected NCC; PD = pharmacodynamics; PELD = Pediatric End-stage Liver Disease; PedsQL = Pediatric Quality of Life Inventory; PK = pharmacokinetics; PRO = patient-reported outcome; PUF = plasma ultrafiltrate; QoL = quality of life; SAE = serious adverse event; SoC = standard of care; t_{max} = time to maximum concentration; TPC = tripartite complex; TSQM-9 = Treatment Satisfaction Questionnaire for Medication-9; UWDRS = Unified Wilson Disease Rating Scale; V_d/F = apparent volume of distribution; WD = Wilson Disease.

Overall Design

This is a randomized, controlled, open-label, rater-blinded study designed to evaluate the efficacy, safety, PK, and PD of ALXN1840 versus SoC in pediatric participants aged 3 to <18 years with a confirmed diagnosis of WD, who meet pre-specified laboratory parameters and do not have decompensated cirrhosis. PK measured by plasma total molybdenum and plasma ultrafiltrate (PUF) molybdenum, and PD measured by plasma total copper and labile-bound copper (LBC), will be determined for all participants.

The study includes 2 periods; the 48-week Primary Evaluation Period (Period 1) serves to evaluate the effect of ALXN1840 versus SoC on efficacy, safety, PK, and PD. Participants who complete the 48-week Period 1 will be offered the opportunity to participate in a 24-week Extension Period (Period 2), ie, up to 72 weeks in total, to further evaluate the safety and efficacy of ALXN1840.

Disclosure Statement: This is a randomized, controlled, open-label treatment study with 2 cohorts that is rater-blinded for the Unified Wilson Disease Rating Scale (UWDRS) assessment.

Number of Participants:

Approximately 48 participants will be randomized 1:1 to either ALXN1840 or SoC treatment with the goal of obtaining 40 evaluable participants at Week 48. Participants in Period 1 will be stratified by age group (3 to < 12 years, 12 to < 18 years) and into 1 of 2 cohorts:

- Cohort 1: Participants who have received SoC therapy (ie, chelation therapy with penicillamine or trientine, treatment with zinc, or a combination of both chelation and zinc therapy) for > 28 days prior to enrollment in the study
- Cohort 2: Participants who are treatment naïve or who have received SoC therapy for ≤ 28 days prior to enrollment in the study

The primary enrollment and randomization objective is to have at least 12 participants in each age group and to achieve balanced treatment assignments both overall and within each age group. A secondary goal is to have at least 3 participants assigned to each treatment within each cohort of each age group.

To achieve this goal, participants will be randomized to treatment within one of the following 4 age groups/cohort strata:

- Stratum 1: 3 to < 12 years old at randomization and Cohort 1 (prior SoC treatment > 28 days) (a minimum of 6 participants)
- Stratum 2: 3 to < 12 years old at randomization and Cohort 2 (prior SoC treatment ≤ 28 days) (a minimum of 6 participants)
- Stratum 3: 12 to < 18 years old at randomization and Cohort 1 (prior SoC treatment > 28 days) (a minimum of 6 participants)
- Stratum 4: 12 to < 18 years old at randomization and Cohort 2 (prior SoC treatment ≤ 28 days) (a minimum of 6 participants)

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

Intervention Groups and Duration:

Throughout Period 1, participants randomized to receive ALXN1840 will be administered ALXN1840 orally daily at the following doses:

- For participants aged 12 to < 18 years, ALXN1840 will be administered at a starting dose of 15 mg/day. Dose escalation is not permitted. Individualized doses ranging from 15 mg every other day to 15 mg/day are allowed. Doses of < 15 mg every other day may be considered, with approval of the Alexion Medical Monitor.

- For participants aged 3 to < 12 years, a lower starting dose of 2.5 mg/day will be administered for at least 4 weeks (based on scaling of the starting dose of 15 mg/day in the ongoing Study WTX101-301). Dose escalation is permitted but not required. The dose may be increased in increments of 2.5 mg daily with the permission of the Alexion Medical Monitor, depending on the participant's clinical status, $NCC_{corrected}$ concentrations, and safety laboratory results. Dose increases must occur at least 4 weeks apart and may only occur if no other dose modification (reduction or interruption) criteria apply. Participants who require doses of 15 mg daily may use the 15-mg tablet.

Individualized ALXN1840 dosing will be utilized throughout the study (Periods 1 and 2) based on the following parameters:

- Clinical criteria: dose-titration based on hepatic and neurological status
- $NCC_{corrected}$: dose-titration based on $NCC_{corrected}$ concentrations. The reference range for $NCC_{corrected}$ is 0.8 to 2.3 μM.
- Safety monitoring: dose modification criteria are based on regularly scheduled assessments for recognized hematological effects of copper lowering, hepatic testing, and neurological tests

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

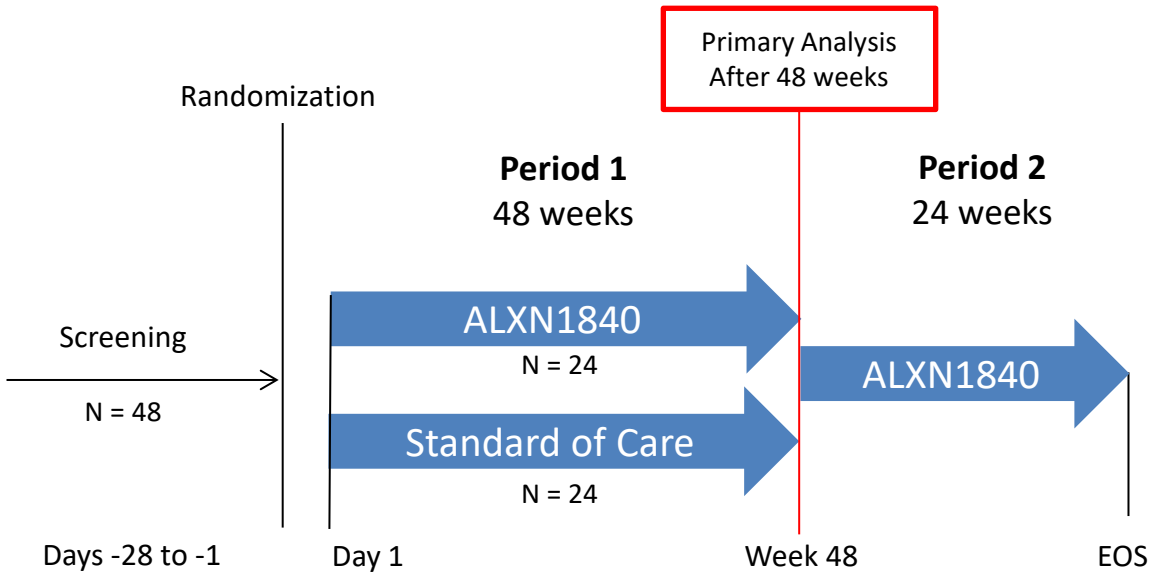
Participants randomized to receive SoC treatment will continue their current therapy or initiate SoC, ie, chelation therapy with penicillamine or trientine, zinc therapy, or a combination of both chelation and zinc therapy if they are not currently on SoC at the start of the study. The choice of SoC medication and dose will be individualized at the discretion of the Investigator.

Data Monitoring Committee: Yes

An independent Data and Safety Monitoring Board, a Neurological Event Adjudication Panel, and a Hepatic Adjudication Panel comprising experts in relevant fields with no direct relationship to the study will be implemented in this study.

1.2. Schema

Figure 1: Study Schematic



*At randomization, participants will be stratified by age group (3 to < 12 years and 12 to < 18 years) and into one of 2 cohorts (prior SoC treatment > 28 days or ≤ 28 days):

- Stratum 1: 3 to < 12 years old at randomization and Cohort 1 (prior SoC treatment > 28 days) (a minimum of 6 participants)
- Stratum 2: 3 to < 12 years old at randomization and Cohort 2 (prior SoC treatment ≤ 28 days) (a minimum of 6 participants)
- Stratum 3: 12 to < 18 years old at randomization and Cohort 1 (prior SoC treatment > 28 days) (a minimum of 6 participants)
- Stratum 4: 12 to < 18 years old at randomization and Cohort 2 (prior SoC treatment ≤ 28 days) (a minimum of 6 participants)

Abbreviations: EOS = End of study; SoC = standard of care.

1.3. Schedule of Activities

Table 1: Schedule of Activities

	Screening	Period 1													Period 2									UNS[a]	Follow-up/EOS[b]
Day	**-28 to -1**	**1[c]**	**8**	**15**	**29[c]**	**43[c]**	**57[c]**	**85[c]**	**127[c]**	**169[c]**	**211**	**253[c]**	**295**	**337[c]**	**1**	**8**	**15**	**29**	**43**	**57**	**85**	**127**	**169**		**197**
Week			**1[d]**	**2[d]**	**4**	**6**	**8**	**12**	**18**	**24**	**30[d]**	**36**	**42[d]**	**48/ET**		**1[d]**	**2[d]**	**4**	**6**	**8**	**12**	**18**	**24/ET**		**28**
Total Weeks			**1[d]**	**2[d]**	**4**	**6**	**8**	**12**	**18**	**24**	**30[d]**	**36**	**42[d]**	**48/ET**		**49[d]**	**50[d]**	**52**	**54**	**56**	**60**	**66**	**72/ET**		**76**
Window (days)			**±3**								**±7**	**±7**	**±3**	**±7**				**±3**				**±7**	**±7**		**±7**
Obtain informed consent/assent	X																								
Review eligibility criteria	X[e]																								
Randomization[f]	X																								
Medical history	X																								
WD medication history	X	X																							
Physical examination	X																								X
Abbreviated physical examination[g]		X			X	X	X	X	X	X		X		X	X			X	X	X	X	X	X		
Vital signs[h]	X	X			X	X	X	X	X	X		X		X	X			X	X	X	X	X	X		X
12-lead ECG	X	X			X					X				X				X					X		
HIV, hepatitis B & C screen	X																								
DNA sample		X[i]																							
Pregnancy test[j]	X	X			X	X	X	X	X	X		X		X	X			X	X	X	X	X	X		X
Urinalysis	X	X			X	X	X	X	X	X		X		X	X			X	X	X	X	X	X		X
Chemistry, coagulation, hematology, and lipid panel	X	X			X	X	X	X	X	X		X		X	X			X	X	X	X	X	X		X
Iron profile		X								X				X									X		
Transient elastography[k]	X	X								X				X	X								X		
Plasma/serum PK/PD/biomarkers samples[l]		X[l]			X	X[l]	X		X	X		X		X[l]	X			X	X	X	X	X	X		
24-hour urine[m]		X				X				X				X											

Table 1: Schedule of Activities

	Screening	Period 1													Period 2									UNS[a]	Follow-up/EOS[b]
Day	**-28 to -1**	**1[c]**	**8**	**15**	**29[c]**	**43[c]**	**57[c]**	**85[c]**	**127[c]**	**169[c]**	**211**	**253[c]**	**295**	**337[c]**	**1**	**8**	**15**	**29**	**43**	**57**	**85**	**127**	**169**		**197**
Week			**1[d]**	**2[d]**	**4**	**6**	**8**	**12**	**18**	**24**	**30[d]**	**36**	**42[d]**	**48/ET**		**1[d]**	**2[d]**	**4**	**6**	**8**	**12**	**18**	**24/ET**		**28**
Total Weeks			**1[d]**	**2[d]**	**4**	**6**	**8**	**12**	**18**	**24**	**30[d]**	**36**	**42[d]**	**48/ET**		**49[d]**	**50[d]**	**52**	**54**	**56**	**60**	**66**	**72/ET**		**76**
Window (days)			**±3**								**±7**	**±7**	**±3**	**±7**		**±3**						**±7**	**±7**		**±7**
24-hour feces[m]		X				X																			
UWDRS Parts I, II, and III[n]		X			X			X		X		X		X	X			X			X		X		
MELD/PELD and modified Nazer[o]	X	X			X			X		X		X		X	X			X			X		X		
Fibrosis-4[o]		X			X			X		X		X		X	X			X			X		X		
BPRS-24 and BPRS-C9[p]		X						X		X		X		X	X								X		
CGI-I[q] and CGI-S		X						X		X				X	X						X		X		
EQ-5D/EQ-5DY		X						X		X				X	X						X		X		
TSQM-9										X				X	X								X		
PedsQL		X						X		X				X	X						X		X		
AE and concomitant medication	◄	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	———	►	
Administer/dispense ALXN1840 or SoC[r]		X			X	X	X	X	X	X		X			X			X	X	X	X	X			

Notes: Participants randomized to SoC who complete Period 1 will be given ALXN1840 in Period 2. Participants randomized to ALXN1840 in Period 1 do not need to attend Period 2 visits at Weeks 4, 6, 8, and 18.

a. Unscheduled visits may occur at any time during the study and may include any study procedures (including dispensing of ALXN1840/SoC) as deemed necessary by the Investigator. These visits may or may not be completed by a home healthcare nurse depending on the purpose of the Unscheduled Visit.

b. Follow-up Visit procedures will be performed at Week 52 for participants who do not enter Period 2, ie, 4 weeks after the Week 48 visit.

c. Assessments on Day 1 and other study visit days where laboratory sampling is planned should be performed pre-dose. Assessments at the Week 48 (Day 337) visit in Period 1 should be used as the Period 2 Day 1 assessments.

d. Week 1, Week 2, Week 30, and Week 42 (Day 8, Day 15, Day 211, and Day 295) of Period 1, and Weeks 1 and 2 of Period 2 will be performed via a safety phone call. If a neurological AE is reported, the following assessments must be performed as soon as possible: UWDRS Parts II and III, CGI-I and CGI-S. Investigators can perform additional assessments or laboratory testing at their discretion.

e. 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 Medical Monitor.

f. Participants will be randomized before Day 1 procedures begin, after meeting all inclusion and none of the exclusion criteria. All procedures required at Screening must be completed prior to the Day 1 Visit.

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

[h.] Vital signs include heart rate, blood pressure, respiratory rate, temperature, height (without shoes), and weight.
[i.] 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 participant's parent/proxy has provided separate informed consent/assent.
[j.] Serum and urine pregnancy tests will only be performed for females of childbearing potential. Female participants of childbearing potential must not be pregnant and not breastfeeding and must have a negative serum pregnancy test at Screening. In addition to pregnancy tests detailed at the visits in the SoA, females of childbearing potential will be required to perform urine pregnancy tests at least every 4 weeks at their home or the study site throughout their time in the study. Positive urine pregnancy results will be confirmed by a serum pregnancy test.
[k.] Transient elastography will be done when available. If transient elastography results are available from within 28 days prior to Day 1, this procedure does not have to be repeated at the Day 1 Visit.
[l.] Plasma/serum samples will be obtained from the blood samples collected pre-dose on the day of all study visits in Period 1 and Period 2 for all participants. Participants should be instructed not to take their dose of ALXN1840 in the morning of scheduled study visits so that PK/PD/biomarker samples are collected at pre-dose trough: total and PUF molybdenum (PK), total and PUF copper, NCC, LBC (PD), ceruloplasmin (note that serum ceruloplasmin will be assessed separately to plasma ceruloplasmin, which will be assessed as part of the PK/PD/biomarker parameters), and CpC (biomarker). At the Day 1, Week 6 (Day 43), and Week 48 (Day 337) Visits, serial blood samples will be collected for plasma PK/PD/biomarker concentrations for all participants at the following time points: pre-dose at 0 hour, and at 2-, 4-, 8-, and 24-hours post-dose.
[m.] Urine collected will be used for 24-hour creatinine, molybdenum and copper. 24-hour urine will be collected at home and brought to the study site on Day 1, and Weeks 6, 24, and 48. 24-hour feces (optional) will be collected at home and brought to the study site on Day 1 and at Week 6. Containers for collection of urine and feces will be provided at the preceding study visit to collection.
[n.] The UWDRS Part I and III must be performed by a blinded neurologist who is unaware of the randomized treatment assignment.
[o.] To be calculated by the central laboratory.
[p.] The BPRS-24 (adolescents aged 12 to < 18 years) and BPRS-C9 (children aged 3 to < 12 years) can be performed by a qualified person who has completed the required training.
[q.] CGI-I is not performed at Day 1.
[r.] Appropriately trained study staff will administer the ALXN1840 on Day 1 and will instruct participants and their parent/proxy on how to correctly dose themselves on the days when they take drug at home. ALXN1840 will not be dispensed or administered at the Early Termination Visit. ALXN1840 will be monotherapy for WD. SoC medications may be taken through Day -1, then must be discontinued on Day 1 for participants randomized to ALXN1840.

Abbreviations: AE = adverse event; BPRS-24 = Brief Psychiatric Rating Scale-24; BPRS-C9 = Brief Psychiatric Rating Scale for children; CGI-I = Clinical Global Impression-Improvement; CGI-S = Clinical Global Impression-Severity; CpC = ceruloplasmin-bound copper; DNA = deoxyribonucleic acid; ECG = electrocardiogram; EQ-5D(Y) = EuroQoL 5 Dimensions (Youth); ET = Early Termination; FIB-4 = Fibrosis-4 Index; LBC = labile-bound copper; MELD = Model for End-stage Liver Disease; PD = pharmacodynamic; PELD = Pediatric Model for End-stage Liver Disease; PedsQL = Pediatric Quality of Life Inventory; PK = pharmacokinetic; PUF = plasma ultrafiltrate; SoC = standard of care; TSQM-9 = Treatment Satisfaction Questionnaire for Medication-9; UNS = unscheduled; UWDRS = Unified Wilson Disease Rating Scale; WD = Wilson disease.

2. INTRODUCTION

ALXN1840 (formerly known as ATN-224 or WTX101) or bis-choline tetrathiomolybdate (tiomolibdic acid, tiomolibdate choline) is a novel, copper-protein binding agent in development for the treatment of WD.

2.1. Study Rationale

This study is being conducted to evaluate the efficacy, safety, PK, and PD of ALXN1840, a novel copper-protein binding agent, versus SoC in pediatric participants with WD who are 3 to < 18 years of age. It is a part of the agreed Paediatric Investigational Plan for ALXN1840 (EMA Decision P/0234/2020).

Wilson Disease is most commonly diagnosed in teenagers and young adults, and rarely presents symptomatically before 5 years of age (Socha, 2018). Males and females are equally likely to be affected by WD. In a large European cohort of 1357 patients, the average age at diagnosis of WD was 19.8 years (± 10 years), and half of all patients were diagnosed before the age of 18 (Ferenci, 2019). The age of presentation of WD is generally over 5 years. Based on the literature and feedback from leading EU and US reference clinical institutions managing pediatric patients with WD, there are exceptionally few diagnosed cases of WD in children < 6 years of age. These exceptionally early newly diagnosed patients may include siblings or patients who may present symptoms as early as 3 years.

The same treatments approved and used in adults with WD (penicillamine, trientine, and zinc) are also approved for use in children and adolescents. However, significant unmet needs still exist with respect to efficacy, safety, simplicity and frequency of dosing regimens, and especially with an appropriate compliance to therapy in young participants. Currently available drugs have high rates of treatment discontinuation due to tolerability issues. They also need to be dosed 2 to 4 times per day. Their adverse event (AE) profiles and complicated dosing regimens lead to poor treatment compliance and, as a direct consequence, to high rates of treatment failure. This remains an area of major concern in the treatment of WD, which is a disease that requires life-long treatment (Maselbas, 2010; Dziezyc, 2014).

Unlike currently available treatments for WD, ALXN1840 is designed to provide an alternative copper-protein transport mechanism, rapidly form copper-protein complexes with very high specificity for copper to quickly remove excess copper in blood and promote biliary excretion of copper (the body's natural route of elimination) to reduce copper overload.

2.2. Background

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

Results from Studies WTX101-HV-106 and WTX101-201 support a proposed mechanism of action of ALXN1840 whereby copper is mobilized to the bloodstream and sequestered through the formation of stable tripartite complexes (TPCs).

In the Phase 2 proof of concept Study WTX101-201 in participants with WD, ALXN1840 demonstrated a sustained control of exchangeable copper as measured by $NCC_{corrected}$. Importantly, ALXN1840 treatment resulted in improvements in disability and neurologic symptoms as measured by the UWDRS, Parts II and III, and stabilization of liver function (Weiss, 2017). Treatment with ALXN1840 resulted in an acceptable safety and tolerability profile when initiated at 15 mg/day with Investigator-driven, individual participant titration of dose based on safety, $NCC_{corrected}$, and symptoms.

ALXN1840 is currently being evaluated in the Phase 3 multicenter, randomized Study WTX101-301 to assess the efficacy of ALXN1840 compared with SoC on plasma copper control as measured by $NCC_{corrected}$. Non-ceruloplasmin-bound copper in Study WTX101-301 can be measured via LBC or assessed via NCC/$NCC_{corrected}$ methods.

An enteric-coated 1.25 mg mini-tablet has been developed for participants who may find minitablets more acceptable than the 15 mg tablet, or require doses lower than 15 mg, such as those aged 3 to < 6 years. A Phase 1 Study ALXN1840-HV-109 has been conducted to compare the relative bioavailability and dose-proportionality for the 1.25 mg EC minitablet and the 15 mg EC tablet under fasting conditions in healthy participants.

The plasma total and PUF molybdenum concentration-time profiles as surrogate measures for ALXN1840 PK have shown that the ALXN1840 PK parameters were comparable between a single dose of ALXN1840 administered as 12 × 1.25 mg EC minitablets (15 mg total dose) and as 1 × 15 mg EC tablet without clinically relevant differences. Plasma total molybdenum PK parameters generally showed a dose-proportional increase from 2.5 mg to 30 mg for the ALXN1840 EC mini-tablet formulation. Plasma PUF molybdenum PK parameters showed a less than dose-proportional increase from 2.5 mg to 30 mg for the ALXN1840 EC mini-tablet formulation. ALXN1840 PK were apparently not affected by body weight or body mass index. There were no apparent differences in ALXN1840 PD parameters (plasma total and PUF copper concentrations) between 12 × 1.25 mg EC mini-tablets and the 15 mg reference EC tablet. There were modest, transient, and dose-dependent increases in plasma total copper concentration within 8 to 12 hours after dosing, but there were no apparent dose-dependent differences in PUF copper concentration.

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

2.3. Benefit/Risk Assessment

In line with the EU guidance "Ethical Considerations for Clinical Trials on Medicinal Products in Minors", potential risks and mitigation strategies have been identified that allow the investigators to assess and monitor risks associated with the study drug and participation in the study for each participant. Specific strategies aimed at assessment, monitoring, and mitigation of risks to the participants are detailed in Section 2.3.1 (Table 2 Potential Risks and Mitigation Strategy), Section 6.6 (Dose Modification), and Section 7 (Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal).

More detailed information about the known and expected benefits and risks and reasonably expected AEs of ALXN1840 can 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 2.

Table 2: 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 copper depletion, see the IB	Monitoring complete blood count Dose modification (Section 6.6) or discontinuation (Section 7) Reduced volume blood collection for participants < 12 years of age. See Section 10.7 for details of blood sampling volumes.
Elevation of lipids (Total Cholesterol and Triglyceride)	Lipid elevations were observed in patients with WD. These lipid elevations were generally mild to moderate in severity and occurred within 4-12 weeks after starting treatment with ALXN1840.	Regular monitoring of lipid concentrations. Dose modification (Section 6.6)
Elevation of 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	Maximum dose set as 15 mg/day. Regular monitoring of liver function tests Dose modification (Section 6.6) or discontinuation (Section 7)
Low white blood cell count (leukopenia, neutropenia)	Leukopenia and myelosuppression have been observed in patients with WD, potentially attributed to overtreatment and resultant copper 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		
Risks associated with the study design and procedures	Participants will undergo repeated blood draws to measure the PK and metabolism of the study intervention. Blood draws may result in ecchymosis, redness, and minor pain to the site. On rare occasion, infection or thrombophlebitis can occur.	Blood draws are optimized for PK. A cannula may be placed to minimize needle sticks during a single study visit, but shall not be left in place if the participant leaves the clinic. Details of the maximum number of attempts for sampling blood are provided in Section 10.7.
	Participants will be required to swallow tablets or mini-tablets that contain the study intervention. Participants should swallow the tablets or mini-tablets whole without crushing to maintain the enteric coating.	Training will be provided to ensure that participants swallow tablets or mini-tablets intact, without crushing. Mini-tablets have been developed for participants who are unable to swallow the 15 mg tablets. The mini-tablet should be removed from the capsule and swallowed individually, as needed.

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 copper depletion, see the IB	Monitoring complete blood count Dose modification (Section 6.6) or discontinuation (Section 7) Reduced volume blood collection for participants < 12 years of age. See Section 10.7 for details of blood sampling volumes.
Elevation of lipids (Total Cholesterol and Triglyceride)	Lipid elevations were observed in patients with WD. These lipid elevations were generally mild to moderate in severity and occurred within 4-12 weeks after starting treatment with ALXN1840.	Regular monitoring of lipid concentrations. Dose modification (Section 6.6)
Elevation of 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	Maximum dose set as 15 mg/day. Regular monitoring of liver function tests Dose modification (Section 6.6) or discontinuation (Section 7)
Neurological worsening	Neurological worsening may occur due to disease progression	Dose modification (Section 6.6) or discontinuation (Section 7)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; IB = Investigator's Brochure; PK = pharmacokinetic; WD = Wilson disease.

2.3.1.1. Coronavirus Disease 2019

The COVID-19 pandemic is active in many countries at the time of this original protocol. Given this unique circumstance, specific consideration has been given to the risks and benefits of the study as they relate to COVID-19, and the global and local changes that exist as a result of the pandemic. This assessment is described in Section 10.9.

2.3.2. Benefit Assessment

The main objective of effective WD treatment is to provide:

- Rapid and sustained control of copper and clinical symptoms of WD through the formation of irreversible copper-tetrathiomolybdate-protein complexes.
- Improved compliance over current SoC through improved tolerability and the convenience of a simplified dosing regimen (once daily) compared to current therapeutic options (multiple daily dosing).

Potential benefits of study participation for participants include:

- Participation in a clinical study increases the participant's understanding of the pathophysiology and treatment of WD.
- Removal of total body copper as a definitive treatment for WD.

- All participants will receive ALXN1840 in Period 2, ie, all participants will have access to a potentially more convenient and effective treatment for removing excess copper.
- Participants in the study will contribute to expanded knowledge that will potentially improve care for other people with WD in the future, particularly the pediatric population.

2.3.3. Overall Benefit: Risk Conclusion

Accounting for the measures taken to minimize risk to participants in this study, the potential risks identified in association with the administration of ALXN1840 are justified by the anticipated benefits that may be afforded to pediatric participants with WD.

3. OBJECTIVES AND ENDPOINTS

The study objectives and endpoints are presented in Table 3.

Table 3: Study ALXN1840-WD-302 Objectives and Endpoints

Objectives	Endpoints
Period 1: Up to Week 48	
Primary	
• To evaluate the efficacy of ALXN1840 administered for 48 weeks, compared to SoC, on copper control in participants with WD aged 3 to < 18 years of age at the time of enrollment	• Percentage change from baseline (Day 1) to 48 weeks in NCC in plasma. For ALXN1840-treated participants, the NCC in plasma will be corrected for the amount of copper bound to the ALXN1840 TPC ($NCC_{corrected}$)
Secondary	
• Evaluate the safety and tolerability of ALXN1840 administered for up to 48 weeks	• Incidence of AEs/SAEs, AESIs, tolerability, clinical laboratory test data (including liver function tests), neurological and physical examination findings, 12-lead ECG data, and vital signs.
• Evaluate PD and biomarkers of ALXN1840 vs SoC administered for 48 weeks	• AUEC for NCC • AUEC for plasma total copper • Biomarkers: observed, absolute and percentage changes of ceruloplasmin-bound copper and ceruloplasmin
• Evaluate the effects of ALXN1840 and SoC on the NCC responder rate	• NCC responder rate
• Evaluate the effects of ALXN1840 and SoC on participant reported disability status	• Change from baseline to Week 48 in the UWDRS Part II total score
• Evaluate the effects of ALXN1840 and SoC on rater-blinded neurological status	• Change from baseline in UWDRS Part III total score or individual items/subscales, as appropriate
• Evaluate PK of ALXN1840 administered for 48 weeks	Estimation of PK parameters and accumulation ratios • PK: C_{max}, t_{max}, C_{trough}, and AUC_{tau} on Day 1, Day 43 (Week 6), and Day 337 (Week 48) for plasma total molybdenum and plasma ultrafiltrate molybdenum concentrations, accumulation ratio of Day 43 to Day 1 and Day 337 to Day 1 based on C_{max}, C_{trough}, and AUC_{tau} • Derived secondary PK parameters such as apparent total body clearance (CL/F) and apparent volume of distribution (V_d/F) (as appropriate)
• Evaluate the effects of ALXN1840 and SoC on global clinical symptoms as assessed by the Investigator	• CGI-I • Change from Baseline to Week 48 in CGI-S
• Evaluate the effects of ALXN1840 and SoC on hepatic status	• Change from Baseline to Week 48 in MELD score (ages 12 years and older) or PELD score (ages 3 to < 12 years) • Change from Baseline to Week 48 in Modified Nazer score
Exploratory	

Table 3: Study ALXN1840-WD-302 Objectives and Endpoints

Objectives	Endpoints
• Evaluate the effects of ALXN1840 and SoC on hepatic fibrosis	• Change from Baseline to Week 48 in the FIB-4 Index and by transient elastography
• Evaluate the effects of ALXN1840 and SoC on psychiatric symptoms	• Change from Baseline to Week 48 in BPRS-24 and BPRS-C9
• Evaluate the effects of ALXN1840 and SoC on QoL/PROs	• Change from Baseline to Week 48 in QoL/PRO endpoint measures: – EQ-5D or EQ-5DY – PedsQL NOTE: These tests will be administered by parent/proxy for participants unable to complete independently.
• Evaluate participant satisfaction of treatment with ALXN1840 and SoC	• Change from Baseline to Week 48 in TSQM-9 NOTE: This questionnaire will be administered by parent/proxy for participants unable to complete independently.
• Evaluate the effects of ALXN1840 and SoC on 24-hour fecal copper and fecal Mo	• Change from Baseline to Week 6 in 24-hour fecal copper and fecal molybdenum
• Evaluate the effects of ALXN1840 and SoC on 24-hour urinary copper and urinary Mo	• Change from Baseline to Week 48 in 24-hour urinary copper and urinary molybdenum
• Explore other directly measured pharmacodynamics (PD) and biomarkers of ALXN1840	• Daily mean AUEC of NCC, and plasma total copper from 0 to 24, and 24 to 48 weeks • Observed, absolute and percent changes of copper levels (total copper, PUF copper, LBC)
• Explore ALXN1840 effect on initial decoppering phase compared to SoC based on directly measured PK/PD and biomarkers	• Time to first confirmed increase in plasma NCC and total copper concentration • Time to minimum and maximum concentration of: – Plasma total copper – Plasma NCC – Plasma LBC – Ratio plasma NCC:total copper – Ratio plasma LBC:total copper – Plasma ceruloplasmin – Plasma CpC – Ratio plasma ceruloplasmin:total copper – Plasma CpC:total copper – 24-hour urinary molybdenum – Ratio urinary molybdenum:copper – Ratio 24-hour urinary molybdenum:dosed molybdenum
• Explore ALXN1840 effect on subsequent maintenance phase compared to SoC based on directly measured PK/PD and biomarkers	• Time for return to pre-dose baseline for the following PK/PD parameters: – Plasma total copper – Plasma NCC – Plasma LBC – Ratio plasma NCC: total copper – Ratio plasma LBC:total copper – Plasma ceruloplasmin concentration – Plasma CpC concentration

Table 3: Study ALXN1840-WD-302 Objectives and Endpoints

Objectives	Endpoints
	– Ratio plasma ceruloplasmin:total copper – Ratio plasma CpC:total copper – 24-hour urinary molybdenum – Ratio urinary molybdenum:copper – Ratio urinary molybdenum:dosed molybdenum
Period 2: Weeks 48 to 72	
Exploratory	
• Safety and tolerability of ALXN1840 in the Extension Period	• AEs/SAEs, AESI, tolerability, clinical laboratory test data, physical examination findings, vital signs, and 12-lead ECG data
• Evaluate PD and biomarkers of ALXN1840	• AUEC for NCC • AUEC for plasma total copper • Observed, absolute and percent changes of copper levels (total copper, PUF copper, LBC) • Biomarkers: observed, absolute and percent changes of ceruloplasmin-bound copper and ceruloplasmin
• Evaluate the effects of ALXN1840 on hepatic status	• Change from Baseline in MELD/PELD score and modified Nazer score
• Evaluate the effects of ALXN1840 on disability status	• Change from Baseline in UWDRS Part II
• Evaluate the effects of ALXN1840 on neurological status	• Change from Baseline in UWDRS Part III
• Evaluate the effects of ALXN1840 on hepatic fibrosis	• Change from Baseline in transient elastography and FIB-4 index
• Evaluate the effects of ALXN1840 on psychiatric symptoms	• Change from Baseline in BPRS-24 and BPRS-C9
• Evaluate the effects of ALXN1840 on global clinical symptoms as assessed by the Investigator	• Change from Baseline in CGI-I and CGI-S
• Evaluate the effects of ALXN1840 on QoL/PRO	• Change from Baseline to Week 72 in QoL/PRO endpoint measures: – EQ-5D or EQ-5D-Y – PedsQL NOTE: These tests will be administered by parent/proxy for participants unable to complete independently.
• Evaluate participant satisfaction of treatment with ALXN1840 and SoC	• Change from Baseline to Week 72 in TSQM-9 NOTE: This questionnaire will be administered by parent/proxy for participants unable to complete independently.

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AUCtau = area under the plasma concentration versus time curve from time 0 to the end of the dosing interval; AUEC = area under the effect versus time curve; BPRS-24 = Brief Psychiatric Rating Scale-24; BPRS-C9 = Brief Psychiatric Rating Scale for children; CGI-I = Clinical Global Impression-Improvement Scale; CGI-S = Clinical Global Impression-Severity Scale; CL/F = apparent total body clearance; C_{max} = maximum observed concentration; CpC = ceruloplasmin-bound copper; C_{trough} = Trough (predose) concentration observed at the start of the dosing interval; ECG = electrocardiogram; EQ-5D(Y) = EuroQoL 5 Dimensions (Youth); FIB-4 = fibrosis-4; LBC = labile-bound copper; MELD = Model for End-stage Liver Disease; NCC = non-ceruloplasmin-bound copper;

$NCC_{corrected}$ = corrected NCC; PD = pharmacodynamics; PELD = Pediatric End-stage Liver Disease; PedsQL = Pediatric Quality of Life Inventory; PK = pharmacokinetics; PRO = patient-reported outcome; PUF = plasma ultrafiltrate; QoL = quality of life; SAE = serious adverse event; SoC = standard of care; t_{max} = time to maximum concentration; TPC = tripartite complex; TSQM-9 = Treatment Satisfaction Questionnaire for Medication-9; UWDRS = Unified Wilson Disease Rating Scale; V_d/F = apparent volume of distribution.

4. STUDY DESIGN

4.1. Overall Design

This is a multicenter, randomized, controlled, open-label, rater-blinded study designed to assess the efficacy, safety, PK, and PD of ALXN1840 versus SoC in pediatric participants aged 3 to <18 years with a confirmed diagnosis of WD, who meet pre-specified laboratory parameters and do not have decompensated cirrhosis. PK measured by plasma total molybdenum and plasma ultrafiltrate (PUF) molybdenum, and PD measured by plasma total copper and LBC will be determined for all participants.

The study includes 2 periods; the 48-week Period 1 serves to evaluate the effect of ALXN1840 versus SoC on efficacy, safety, and PD. Participants who complete the 48-week Period 1 will be offered the opportunity to participate in a 24-week, open-label Period 2, ie, up to 72 weeks in total, to evaluate the safety and efficacy of ALXN1840.

Approximately 48 participants will be randomized 1:1 to either ALXN1840 or SoC treatment with the goal of obtaining 40 evaluable participants at Week 48. Participants in the Primary Evaluation Period will be stratified by age group (3 to < 12 years, 12 to < 18 years) and into 1 of 2 cohorts:

- Cohort 1: Participants who have received SoC therapy (ie, chelation therapy with penicillamine or trientine, treatment with zinc, or a combination of both chelation and zinc therapy) for > 28 days prior to enrollment in the study.
- Cohort 2: Participants who are treatment naïve or who have received SoC therapy for ≤ 28 days prior to enrollment in the study.

The primary enrollment and randomization objective is to have at least 12 participants in each age group and to achieve balanced treatment assignments both overall and within each age group. A secondary goal is to have at least 3 participants assigned to each treatment within each cohort of each age group.

To achieve this goal, participants will be randomized to treatment within one of the following 4 age groups/cohort strata:

- Stratum 1: 3 to < 12 years old at randomization and Cohort 1 (prior SoC treatment > 28 days) (a minimum of 6 participants)
- Stratum 2: 3 to < 12 years old at randomization and Cohort 2 (prior SoC treatment ≤ 28 days) (a minimum of 6 participants)
- Stratum 3: 12 to < 18 years old at randomization and Cohort 1 (prior SoC treatment > 28 days) (a minimum of 6 participants)
- Stratum 4: 12 to < 18 years old at randomization and Cohort 2 (prior SoC treatment ≤ 28 days) (a minimum of 6 participants)

Throughout Period 1, participants randomized to receive ALXN1840 will be administered ALXN1840 orally daily at the following doses:

- Participants aged 12 to < 18 years will follow the same dosing paradigm as that in the ongoing Phase 3 Study WTX101-301 conducted in adults and adolescents.

ALXN1840 will be administered at a starting dose of 15 mg/day. Dose escalation is not permitted. Individualized doses ranging from 15 mg/day every other day to 15 mg/day are allowed. Doses of < 15 mg every other day may be considered, with approval of the Alexion Medical Monitor.

- For participants aged 3 to < 12 years, a lower starting dose of 2.5 mg/day will be administered for at least 4 weeks based on scaling of the starting dose of 15 mg/day in the ongoing Study WTX101-301. Dose escalation is permitted but not required. The dose may be increased in increments of 2.5 mg daily with the permission of the Alexion Medical Monitor, depending on the participant's clinical status, $NCC_{corrected}$ concentrations, and safety lab results. Dose increases must occur at least 4 weeks apart, and may only occur if no other dose modification (reduction or interruption) criteria apply. Participants who require doses of 15 mg daily may use the 15-mg adult tablet. The maximum dose for children under the age of 12 years is 15 mg/day.

Individualized ALXN1840 dosing will be utilized throughout the study based on the following parameters:

- Clinical criteria: dose-titration based on hepatic and neurological status
- $NCC_{corrected}$: dose-titration based on $NCC_{corrected}$ concentrations. The reference range for $NCC_{corrected}$ is 0.8 to 2.3 µM.
- Safety monitoring: dose modification criteria are based on regularly scheduled assessments for recognized hematological effects of copper lowering, hepatic testing, and neurological tests

Participants randomized to receive SoC treatment will continue their current therapy or initiate SoC, ie, chelation therapy with penicillamine or trientine, zinc therapy, or a combination of both chelation and zinc therapy if they are not currently on SoC at the start of the study.

4.2. Scientific Rationale for Study Design

The study is designed as a randomized, open-label, exploratory study. The dosing strategy is similar to that employed in the current Phase 3 Study WTX101-301, with adjustments to the doses for pediatric patients based on the population PK simulations (Section 4.3 and Section 10.8).

Following ALXN1840 administration, the active drug moiety, ie, the tetrathiomolybdate anion, rapidly binds copper to form TPCs, mostly in the liver and blood, and present as such in the systemic circulation. If TPCs are not rapidly formed, tetrathiomolybdate spontaneously undergoes serial hydrolysis to form molybdate, the most common form of nutrient molybdenum, and is excreted in the urine. The concentration of endogenous molybdenum in plasma is very low, therefore no background subtraction is required and plasma molybdenum can be attributed entirely to ALXN1840. Total molybdenum concentration cannot distinguish whether the molybdenum is protein-bound (mostly as TPC), free active drug as ALXN1840, intermediate hydrolysis products, or molybdate. To better characterize the amount of non-TPC bound drug and its unbound degradation products, plasma PUF molybdenum has also been measured, which represents the free parent drug (ALXN1840), short-lived intermediate hydrolysis products, and molybdate, which may have originated from the tetrathiomolybdate or from food intake as a

micronutrient. TTo better characterize the absorption, distribution, metabolism, and excretion of ALXN1840, the PK of both total molybdenum and PUF molybdenum will be characterized and described.

ALXN1840 PK and PD in children and adolescents with WD will be assessed in this study. SoC PD will be assessed in children and adolescents. ALXN1840 PK and PD parameters are expected to scale with the body weight per allometric rules since higher blood flow rates in children may have an impact on drug clearance. In addition, copper content within a participant's liver and, thus, liver volume may have an impact on the extent of drug binding in liver and clearance. Based on the ALXN1840 mechanism of action, it is anticipated that drug-copper binding and chemical degradation do not differ in the pediatric population compared with adults, after taking into account body weight and liver volume factors.

4.2.1. Participant Input in Design

WD patient/caregiver input into the study design was obtained and incorporated accordingly.

4.3. Justification for Dose

Results from Studies WTX101-101, WTX101-102, ALXN1840-HV-104, WTX101-HV-106, ALXN1840-HV-107, ALXN1840-HV-108, ALXN1840-HV-109, WTX101-201, and the ongoing Study WTX101-301 have shown that age, sex, or body weight are not significant covariates that may affect the PK of ALXN1840 in adults and adolescents.

In the ongoing Phase 3 Study WTX101-301, participants were initially administered ALXN1840 at a dose of 15 mg/day. Incremental dose increases are permitted, but not required, up to a maximum of 60 mg/day. In the completed 48-week Primary Evaluation Period of Study WTX101-301, the overall mean daily dose of ALXN1840 was 15.6 mg with a minimum daily dose of 12.6 mg and a maximum daily dose of 19.8 mg. Results from the Primary Evaluation Period showed approximately 3-fold greater copper mobilization from tissue to blood during treatment with ALXN1840 compared with SoC, as measured by daily mean dNCC $AUEC_{0\text{-}48\ weeks}$ (μmol/L).

Although 15 to 60 mg/day single or repeated daily doses have been shown to have acceptable safety profiles and to be generally well tolerated throughout the Phase 1 to Phase 3 clinical studies in both healthy adults and adult participants with WD, approximately 15% of the participants in Study WTX101-301 experienced ≥ Grade 2 ALT elevations during treatment with ALXN1840. In summary, the maximum daily dose permitted in Study ALXN1840-WD-302 has been set as 15 mg/day.

Selection of the starting and maximum doses for ALXN1840-WD-302 in the pediatric population aged 3 to < 12 years is based on a combination of standard body weight-based allometric principles and on the approach to account for potential changes in liver copper content in pediatric participants driven by age-based changes in liver volume.

Participants receiving the 1.25 mg mini-tablets who require a dose of 15 mg may be switched to the 15 mg tablet formulation. Participants may down-titrate to15 mg every other day, or a lower or less frequent dose, as appropriate.

To support the dose selection, a population PK model for ALXN1840 was developed based on data from healthy volunteers and patients with WD. Single dose PK data from 18 healthy

volunteers (Study WTX101-102) and 27 patients (Study WTX101-201) were utilized for model building for the adult dosing. Simulations for pediatrics were based on typical parameter estimates without including variability components. For each simulation, the starting dose and concentration ranges were derived from the typical participants within the investigated age cohort at the extremes of the bodyweight range.

Based on the modelling results, additional pediatric PK/PD studies were deemed unnecessary as endorsed in the agreed pediatric investigational plan (PIP) with the EMA Decision P/0234/2020. The general approach of dose selection for pediatric investigation used here is consistent with the EMA guidance (ICH E11(R1), 2017).

Starting and maximal doses were selected using a conservative approach that involved consideration of lower end of the range, derived from the scaling methods, and further adjustment downward to a lower dose to ensure safety in the pediatric population aged 3 to <12 years. This cautious approach to starting and maximal dose selection (ie, adjustment downward to the lower end of the projected dose range) for participants aged 3 to < 12 years is supported by the fact that ALXN1840 has greater binding affinity to copper compared with other treatments.

ALXN1840 PK and PD processes are expected to scale with the body weight per allometric rules since higher blood flow rates in children may have an impact on drug clearance. In addition, copper content within a participant's liver and, thus, liver volume, may have an impact on extent of drug binding in liver and clearance. Based on the ALXN1840 mechanism of action, it is expected that drug-copper binding and chemical degradation do not differ in the pediatric population compared with adults, after taking into account body weight and liver volume factors.

The results of the population PK simulation are provided in Section 10.8.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed both Period 1 and Period 2 of the study including the last scheduled procedure shown in the Schedule of Activities (SoA) for Period 2.

The end of the study is defined as the date the last participant completes the last visit shown in the SoA of Period 2.

5. STUDY POPULATION

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

5.1. Inclusion Criteria

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

Age

1. Participants must be aged 3 to <18 years at time of signing the informed consent/assent.

Type of Participants and Disease Characteristics

2. Established diagnosis of WD by Leipzig-Score ≥ 4 documented by testing as outlined in the 2012 European Association for the Study of Liver WD Clinical Practice Guidelines (Ferenci, 2003; EASL, 2012). Note: Historical test results for WD, including some or all of the following: presence of KF rings, neurologic symptoms, serum ceruloplasmin below the 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 Wilson disease.
3. Participant's parent/proxy must be willing and able to give written informed consent and the participant must be willing to give written informed assent (if applicable as determined by the central or local Institutional Review Board [IRB]/Institutional [or Independent] Ethics Committee [IEC]). If allowable per local regulations, a participant's Legally Acceptable Representative (LAR) may provide informed consent if a participant is unable to do so.
4. Adequate venous access to allow collection of required blood samples.
5. Able to swallow intact ALXN1840 tablets or mini-tablets. Participants who require gastrostomy devices for feeding or medications may be enrolled if the inner diameter of the tube can accommodate an intact tablet or mini-tablet without obstruction.
6. Willing to avoid intake of foods and drinks with high contents of copper throughout the study duration

Sex

7. Female participants of childbearing potential and male participants must follow protocol-specified- contraception guidance as described in Section 10.4.

Informed Consent

8. Capable of giving signed informed consent or assent as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the informed consent or assent form and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions

1. Decompensated hepatic cirrhosis.
2. MELD score > 13 (ages 12 to <18) or PELD score > 13 (ages 3 to < 12).
3. Modified Nazer score > 7 (Dhawan, 2005).
4. Clinically significant gastrointestinal (GI) bleed within past 3 months
5. Alanine aminotransferase (ALT) > 2 × upper limit of normal (ULN) for participants treated for > 28 days with WD therapy (Cohort 1).
6. ALT > 5 × ULN for treatment naïve participants or participants who have been treated for ≤ 28 days (Cohort 2)
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. History of seizure activity within 6 months prior to informed consent/assent.

Prior/Concomitant Therapy

10. Previous use of ALXN1840 or ammonium tetrathiomolybdate.

Prior/Concurrent Clinical Study Experience

11. The use of an investigational drug within 30 days before initiation of the first dose of study intervention.

Diagnostic assessments

12. Participants in renal failure, defined as in end-stage renal disease on dialysis (chronic kidney disease stage 5 [CKD 5]) or estimated glomerular filtration rate < 30 mL/min/1.73m^2.
13. Active infection with hepatitis B virus (positive hepatitis B surface antigen) or C virus (participants with positive hepatitis C antibody result would require confirmation of active disease with a positive hepatitis C polymerase chain reaction test), or seropositivity for HIV.
14. Any disability acquired from trauma or another illness that, in the opinion of the Investigator, could interfere with evaluation of disability due to WD.
15. Systemic disease or other 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 participant safety or interfere with the collection or interpretation of study results.

Other Exclusions

16. Pregnant (or females who are planning to become pregnant) or breastfeeding females.

17. Known sensitivity to ALXN1840, ALXN1840 excipients (anhydrous di-calcium phosphate, anhydrous sodium carbonate), or any of the ingredients contained in ALXN1840 or related compounds.
18. 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 14 g of alcohol: a half pint (approx. 240 mL) of beer, 1 glass (125 mL) of wine or 1 (25 mL) measure of spirits.
19. Abuse of illicit or prescribed drugs.
20. In the opinion of the Investigator, the participant and/or their parent/proxy is likely to be non-compliant or uncooperative during the study.

5.3. Lifestyle Considerations

5.3.1. Meals and Dietary Restrictions

- Participants should follow their study doctor's advice regarding adherence to a low copper diet.
- ALXN1840 will be administered in the fasted state (1 hour before or 2 hours after meals) and will be taken with up to approximately 240 mL of water. ALXN1840 mini-tablets may also be administered with a small amount (approximately 5 mL or 5 g) of apple sauce or yogurt and swallowed immediately (no substitutions are permitted). Further details are provided in the Pharmacy Manual.

5.4. Screen Failures

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

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

6. STUDY INTERVENTION

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

6.1. Study Interventions Administered

Participants randomized to receive SoC treatment will continue their current therapy or initiate chelation therapy with penicillamine or trientine, zinc, or a combination of both chelation and zinc therapy if they are not currently on SoC at the start of the study.

Standard of care treatment should be stored according to the details in the package labeling.

Details of ALXN1840 administered in the study are provided in Table 4.

Table 4: Study Intervention Dosage and Mode of Administration

Drug Name	ALXN1840 (formerly WTX101)
Type	Drug
Dose formulation	• 15 mg white to off-white round enteric coated tablet • 2.5mg capsule containing 2 × 1.25 mg round white to off-white enteric coated mini-tablets
Unit dose strength(s)	• 15 mg enteric coated tablet containing choline tetrathiomolybdate • 1.25 mg enteric coated mini-tablet containing choline tetrathiomolybdate
Dosage level(s)	• Participants aged 12 to < 18 years: 15 mg/day • Participants aged 3 to < 12 years: starting dose of 2.5 mg/day, with increase in increments of 2.5 mg up to 15 mg/day. Dose escalation requires the agreement of the Alexion Medical Monitor.
Route of administration	Oral
Use	Experimental/study intervention
IMP or NIMP	IMP
Sourcing	Provided by Alexion
Packaging and labeling	ALXN1840 will be provided in treatment kits that will each have a unique identification number and be packaged and labelled in accordance with all applicable regulatory requirements. At a minimum, the treatment kit label will provide the following information: Alexion study identification, batch number, directions for use, required storage conditions, caution statements (including "New Drug-Limited by Federal Law to Investigational Use" language), study identification, and expiry date.
Current/former name(s) or alias(es)	bis-choline tetrathiomolybdate/tiomolibdic acid/WTX101

Abbreviations: IMP = investigational medicinal product; NIMP = noninvestigational medicinal product.

6.1.1. Study Intervention(s) Packaging and Labeling

At a minimum, ALXN1840 will be labeled with:

- The protocol number
- Lot number/expiry date
- Alexion name and address
- Instructions for use and storage

ALXN1840 will be labeled according to the country's regulatory requirements.

6.2. Preparation/Handling/Storage/Accountability

1. The Investigator, or designee, must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
    a. The ALXN1840 treatment kits should be stored at refrigerated conditions, 2°C to 8°C (36°F to 46°F).
2. Only participants enrolled in the study may receive the study intervention and only authorized site staff may supply study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
    a. This responsibility includes the reporting of any product complaints to productcomplaints@alexion.com within 1 business day. A product complaint is defined as any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, usability, safety, effectiveness, or performance of a product or clinical study material and/or its packaging components after it is has been released for distribution to an end customer that affects the performance of such product.
4. Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

6.3. Measures to Minimize Bias: Randomization and Blinding

Participants will be randomized after meeting all inclusion and none of the exclusion criteria.

Participants will be randomized, stratified by cohort, via an interactive voice/web response system in a 1:1 ratio to treatment with ALXN1840 or continued treatment with SoC in Cohort 1, or as continued or initial therapy in Cohort 2.

This study is rater-blinded for the UWDRS assessment only. The rater will be blinded and will have no knowledge of the participant's treatment assignment and no access to systems that could result in potential unblinding of treatment assignment. Both raters and participants will be instructed to avoid lines of inquiry, questions, and responses that could potentially lead to their unblinding. The rater assessments will be strictly limited to administration of the protocol specified instruments and assessments.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the case

report form (CRF). The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. Study site personnel will examine each participant's mouth to ensure that the study intervention was ingested.

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

When participants self-administer study intervention(s) at home (assisted or supervised by their parent or caregiver, as appropriate), compliance with the study intervention will be assessed at each visit by counting returned tablets during the site visits, and will be documented in the source documents and CRF. Deviation(s) from the prescribed dosage regimen should be recorded in the CRF.

Records of the doses dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for planned and unplanned intervention delays and/or dose reductions will also be recorded in the CRF.

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

6.5. Prior and Concomitant Therapy

Any medication (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements), or vaccine, or other specific categories of interest) that the participant is receiving within 30 days prior to enrollment or receives during the study must be recorded along with:

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

Medications specific for copper control in WD taken at any time prior to the study (ie, all penicillamine, trientine or zinc ever taken for WD) will be recorded in a specific CRF for Prior WD Treatment.

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

6.5.1. Allowed Medicine and Therapy

Investigators should use caution in the coadministration of drugs known to be substrates of cytochromes 2C9 and 2B6 (CYP2C9 and CYP2B6).

6.5.2. Disallowed Medicine and Therapy

Concomitant use of penicillamine, trientine or zinc is prohibited for participants who are treated with ALXN1840 during the randomized Primary Evaluation Period (Period 1) or Open-label Extension Period (Period 2). Standard of care medications may only be taken by participants randomized to SoC during Period 1.

Use of nonprescription/ over-the-counter medications, including herbal remedies, nutritional supplements, or mineral supplements containing copper, zinc, iron, or molybdenum after dosing on Day 1 through the end of the study is also disallowed.

Vitamin E and estrogen should not be initiated during the study but can be continued if already being taken.

6.6. Dose Modification

Alexion should be notified within 24 hours of any laboratory, vital sign, electrocardiogram (ECG) abnormality, or AE that is considered of clinical concern by the Investigator. Investigators must notify Alexion immediately of study intervention discontinuation. The decision to discontinue study intervention should not be delayed for causality assessment.

6.6.1. Dose Modification for ALXN1840

The ALXN1840 dose should be lowered or interrupted if any of the relevant dose modification criteria are met. Deviation from the dose modification guidelines must be agreed with the Alexion Medical Monitor.

Adolescent Participants

Adolescent participants (12 to <18 years) who are randomized to ALXN1840 in Period 1 will be initiated on ALXN1840 at 15 mg/day. Specific criteria for dose reduction or temporary interruption of dosing of ALXN1840 are detailed in Table 5. Repeat testing of laboratory parameters which prompt dose modification criteria should follow the instructions in Table 5. Laboratory testing should be performed through the Central Laboratory if possible. Results from non-scheduled safety laboratory assessments performed at a local laboratory must be recorded in the CRF.

Table 5: ALXN1840 Dose Modifications for Individual Adolescent Participants

Test	Result	Conditions	Action with ALXN1840 Dosing	Changes in Safety Monitoring[a]	Rechallenge[b,c]
ALT	> 5 × ↑ from Baseline	ALT above reference range at Baseline	Temporary interruption	Contact participant within 48 hours to arrange repeat testing (weekly repeat testing)	At 15 mg QOD when ALT < 2 × ↑ from Baseline.
	> 5 × ULN	ALT within reference range at Baseline	Temporary interruption	Contact participant within 48 hours to arrange repeat testing (weekly repeat testing)	At 15 mg QOD when ALT < 2 × ULN.
	> 2 × ↑ from Baseline	ALT above reference range at Baseline	Reduce dose - to 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 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 15 mg QOD if on 15 mg QD.	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 15 mg QOD if on 15 mg QD.	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
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 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]	Rechallenge[b,c]
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 15 mg QOD if on 15 mg QD. No further dose ↑ until resolution of abnormality.	Weekly repeat testing	Not applicable.
Neutrophils	$< 1.0 \times 10^3/\mu L$	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 15 mg QOD if on 15 mg QD. No further dose ↑ until resolution of abnormality.	Weekly repeat testing	Not applicable.
Bilirubin	> 2 × ULN	Accompanied by ALT > 3 × ULN, indicative of liver injury	Temporary interruption	Weekly repeat testing	At 15 mg QOD or less frequent, when bilirubin is below ULN. Rechallenge under these conditions requires approval of the Alexion Medical Monitor.
Neurological assessment	Evidence of neurologic worsening by AEs or by neurologic physical exam assessment.		Investigator and Alexion Medical Monitor will evaluate the need for dose modification (interruption, increase or decrease) based on copper control parameters and relevant clinical data. Rationale for dosing decision must be documented in study record and reevaluated at the next study visit.	All neurologic worsening should be documented as AEs and followed up until study completion or resolution of symptoms.	Discuss with the Alexion Medical Monitor.

Test	Result	Conditions	Action with ALXN1840 Dosing	Changes in Safety Monitoring[a]	Rechallenge[b,c]
Psychiatric assessment	Evidence of clinically significant acute psychiatric worsening which may include, but is not limited to, suicidality, acute depression, or psychosis.		Investigator and Alexion Medical Monitor will evaluate the need for dose modification (interruption, increase or decrease) based on copper control parameters and relevant clinical data. Rationale for dosing decision must be documented in study record and reevaluated at the next study visit.	Worsening psychiatric symptoms will be documented as AEs in the eCRF and will be followed until completion of the study or resolution of symptoms.	Discuss with the Alexion Medical Monitor.

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

[b] For rechallenges, participants who were on ALXN1840 15 mg QOD should be rechallenged at the 15 mg QOD dose.

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

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

Pediatric Participants

Pediatric participants (age 3 to < 12 years) will be initiated on ALXN1840 at 2.5 mg/day. Following the first 4 weeks, the dose may be increased, in increments of 2.5 mg at least 4 weeks apart to a maximum of 15 mg/day with the agreement of the Alexion Medical Monitor. Incremental dose increase is permitted but not required. Specific criteria for dose reduction, temporary interruption of dosing, or restriction of dose increases of ALXN1840 are detailed in Table 6. Repeat testing of laboratory parameters that prompt dose modification criteria should follow the instructions in Table 6. Laboratory testing should be performed through the Central Laboratory if possible. Results from non-scheduled safety laboratory assessments performed by a local laboratory must be recorded in the CRF.

Table 6: ALXN1840 Dose Modifications for Individual Pediatric Participants

Test	Result	Conditions	Action with ALXN1840 Dosing	Changes in Safety Monitoring[a]	Rechallenge[b,c]
ALT	> 5 × ↑ from Baseline	ALT above reference range at Baseline	Temporary interruption	Contact participant within 48 hours to arrange repeat testing (weekly repeat testing)	At 1.25 mg QD when ALT < 2 × ↑ from Baseline.
	> 5 × ULN	ALT within reference range at Baseline	Temporary interruption	Contact participant within 48 hours to arrange repeat testing (weekly repeat testing)	At 1.25 mg QD 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 1.25 mg QD if on 2.5 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 1.25 mg QD if on 2.5 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 1.25 mg QD if on 2.5 mg QD. No further dose increase until resolution of abnormality.	Weekly repeat testing	Not applicable
	>500 mg/dL or 5.6 mmol/L		Temporary interruption		At 1.25 mg QD 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 1.25 mg QD if on 2.5 mg QD.	Weekly repeat testing	Not applicable
	>400 mg/dL or >10.3 mmol/L		Temporary interruption		At 1.25 mg QOD when cholesterol concentrations return to baseline

Test	Result	Conditions	Action with ALXN1840 Dosing	Changes in Safety Monitoring[a]	Rechallenge[b,c]
Hemoglobin	< 8 g/dL in the absence of bleeding	None	Temporary interruption	Weekly repeat testing	At 1.25 mg QD 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 1.25 mg QD if on 2.5 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 1.25 mg QD 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 1.25 mg QD if on 2.5 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 1.25 mg QD 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 1.25 mg QD if on 2.5 mg QD. No further dose ↑ until resolution of abnormality.	Weekly repeat testing	Not applicable.
Bilirubin	> 2 × ULN	Accompanied by ALT > 3 × ULN, indicative of liver injury	Temporary interruption	Weekly repeat testing	At 1.25 mg QD or less frequent, when bilirubin is below ULN. Rechallenge under these conditions requires approval of the Alexion Medical Monitor.

Test	Result	Conditions	Action with ALXN1840 Dosing	Changes in Safety Monitoring[a]	Rechallenge[b,c]
Neurological assessment	Evidence of neurologic worsening by AEs or by neurologic physical exam assessment.		Investigator and Alexion Medical Monitor will evaluate the need for dose modification (interruption, increase or decrease) based on copper control parameters and relevant clinical data. Rationale for dosing decision must be documented in study record and re-evaluated at the next study visit.	All neurologic worsening should be documented as AEs and followed up until study completion or resolution of symptoms.	Discuss with the Alexion Medical Monitor.
Psychiatric assessment	Evidence of clinically significant acute psychiatric worsening which may include, but is not limited to, suicidality, acute depression, or psychosis.		Investigator and Alexion Medical Monitor will evaluate the need for dose modification (interruption, increase or decrease) based on copper control parameters and relevant clinical data. Rationale for dosing decision must be documented in study record and re-evaluated at the next study visit.	Worsening psychiatric symptoms will be documented as AEs in the eCRF and will be followed until completion of the study or resolution of symptoms.	Discuss with the Alexion Medical Monitor.

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

[b] For rechallenges, participants who were on ALXN1840 2.5 mg QD should be rechallenged at the 1.25 mg QD dose.

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

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

6.6.2. Dose Modification for Standard of Care

To the extent possible, without compromising the safety of individual participants, the type of SoC medication should not be changed throughout the 48-week Period 1, unless required as part of the treatment (eg, if a participant initiates SoC at the start of the study).

Similarly, to the extent possible, without compromising the safety of individual participants, the dosing of the SoC medication should remain consistent throughout Period 1, unless required as part of the treatment (eg, titration of SoC initiated at the start of the study).

If the SoC dose, frequency, or specific drug agent (ie, penicillamine, trientine or zinc) needs to be changed for efficacy or safety reasons, the specific change and rationale for it must be documented. The rationale for a change from one agent to another (eg, a change from penicillamine or trientine to zinc due to intolerance or AE) must also be documented. Deviation from the dose modification guidelines must be agreed with the Alexion Medical Monitor.

Specific criteria for dose modification of SoC if neurologic or psychiatric worsening occurs are detailed in Table 7.

Table 7: Standard of Care Dose Modifications for Individual Participants

Test	Result and Conditions	Action With SoC Dosing	Changes in Safety Monitoring[a]	Re-Challenge[a]
UWDRS Part III and clinical neurological assessment	Increase in UWDRS Part III score from Baseline as follows AND is deemed clinically significant by the Investigator: Baseline UWDRS Part III score <20: ≥ 4-point increase OR Baseline UWDRS Part III score ≥20: ≥6-point increase	Investigator and Medical Monitor will evaluate the need for dose modification (interruption, increase or decrease) based on copper control parameters and relevant clinical data. Rationale for dosing decision must be documented in study record and re-evaluated at the next study visit.	Report neurologic adverse event of special interest and perform complete UWDRS examination. Re-evaluate neurologic status, including complete UWDRS examination, no later than next study visit, even if not planned per the SoA.	Discuss with the Medical Monitor.
Psychiatric assessment	Clinically significant signs of psychiatric worsening	Investigator and Medical Monitor will evaluate the need for dose modification (interruption, increase or decrease) based on copper control parameters and relevant clinical data. Rationale for dosing decision must be documented in study record and re-evaluated at the next study visit.	Re-evaluate psychiatric status no later than next study visit, even if not planned per the SoA.	Discuss with the Medical Monitor.

[a.] The Investigator, in consultation with the Medical Monitor, may change dose and dose frequency in participants who require re-challenge.

Abbreviations: SoA = Schedule of Activities; UWDRS = Unified Wilson Disease Rating Scale.

6.7. Intervention After the End of the Study

Following completion of Period 2 of the study, participants will either:

- Transition to therapy that was discontinued before enrollment, or
- Participants who have successfully completed all study assessments and were not withdrawn prematurely may be eligible for post-study access if deemed in the best interest of the patient by the treating physician. Participants will receive study drug for up to 2 years or until 1) the study drug is registered or approved and available by prescription or 2) the study drug can be provided via Alexion post-study/early access programs as allowed by local laws and regulations, whichever occurs first. Only the investigational drug will be available for post-study/early access.

All participants should return to the site for the EOS Visit on Day 197 of Period 2 (+/- 7 days).

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) the study intervention. If the study intervention is definitively discontinued, the participant should have an Early Termination Visit and return within 4 weeks to be evaluated for safety follow-up. See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

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

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

See the SoA (Section 1.3) for samples and data to be collected at the time of study intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.2. Participant Discontinuation/Withdrawal from the Study

- All efforts should be made to ensure participants are willing to comply with study participation prior to conducting the Screening procedures.
- The study staff should notify Alexion and their site monitor of all study withdrawals as soon as possible. The reason for participant discontinuation must be recorded in the source documents and CRF.
- A participant must be withdrawn from this study if they receive an experimental or unapproved/unlicensed therapy.
- A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.
- At the time of discontinuing from the study, if possible, an Early Termination Visit should be conducted, as shown in the SoA. See the SoA (Section 1.3) for data to be

collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

  - The participant will be permanently discontinued both from the study intervention and from the study at that time.

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

7.3. Lost to Follow-up

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

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

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

Discontinuation of specific sites or of the study as a whole are handled as part of Section 10.1.8.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Medical Monitor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All Screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1. Efficacy Assessments

Planned time points for all efficacy assessments are provided in the SoA (Section 1.3).

8.1.1. Assessment of Copper

Because measures of non-ceruloplasmin-bound copper control in the blood are the primary assessment for efficacy of treatment with ALXN1840, plasma samples will be collected to measure total copper, ceruloplasmin, ceruloplasmin-bound copper (CpC), NCC, and LBC in the blood. In ALXN1840-treated patients, an additional calculation will be performed that corrects the NCC level for the amount of copper bound to the ALXN1840 tripartite complex ($NCC_{corrected}$).

The AUEC for plasma total copper concentration over time aims to quantify the dynamic tissue mobilization and decoppering effect of ALXN1840. This assessment is also applicable to SoC treatments. AUEC will be calculated for direct NCC and plasma total copper.

Ongoing bioanalytical method development of new techniques to measure directly the TPC copper may allow additional analyses of copper control to be performed. As the method to indirectly estimate NCC concentration results in approximately 20% of samples from healthy participants yielding physiologically impossible negative values for NCC, the direct NCC and LBC assays have been developed. The LBC method measures exchangeable plasma copper that is not bound to either ceruloplasmin or the ALXN1840 TPC.

8.1.2. Model for End-stage Liver Disease and Pediatric End-stage Liver Disease scores

The Model for End-stage Liver Disease (MELD) is a scoring system for assessing the severity of chronic liver disease in adults and adolescents aged 12 years and above. The MELD score (range 6-40, with higher values indicating more advanced disease) uses the participant's values for serum bilirubin, serum creatinine, and the international normalized ratio (INR) for prothrombin time to predict survival. In participants with a MELD score > 11, the serum sodium is also taken into account (UNOS, 2015).

The Pediatric End-stage Liver Disease (PELD) score is used to estimate 90-day survival in the absence of liver transplantation (McDiarmid, 2002; Chang, 2018). The components of the PELD score are total bilirubin, INR, albumin, age, and growth failure. The PELD cutoff of > 13 was chosen to exclude participants with advanced liver failure, comparable to a MELD score > 13 or a modified Nazer score > 7 (Dhawan, 2005).

The MELD and PELD scores will be calculated by a Central Laboratory.

8.1.3. 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 participant-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 neurologist who is blinded to the treatment randomization, while UWDRS Part II may be reported to a non-blinded member of the study team by the participant, family member, or caregiver (Czlonkowska, 2007; Leinweber, 2008). The UWDRS has not been formally evaluated in children. However, the components of Part I (level of consciousness), Part II (participant or caregiver-reported disability) and Part III (neurologic examination findings) are not fundamentally different between adults and children. Participants aged 12 years and older are expected to be able to comply with UWDRS assessments without modification. The UWDRS assessments should be conducted to the greatest extent feasible in children < 12 years.

8.1.4. Clinical Global Impression-Severity Scale and the Clinical Global Impression 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 participants with mental disorders.

Clinical Global Impression-Severity Scale

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

Clinical Global Impression-Improvement Scale

The Clinical Global Impression-Improvement scale (CGI-I) is a 7-point scale that requires the clinician to assess how much the participant'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.

8.1.5. Fibrosis-4 Index and Transient Elastography

The FIB-4 Index is a formula used to predict liver fibrosis based on standard biochemical values (ALT, AST, and platelet count) and age. The FIB-4 Index will be calculated by a Central Laboratory.

Transient elastography is a non-invasive imaging method that evaluates the degree of liver fibrosis or fatty deposits in the liver, by determining the speed of sound waves through the liver utilizing a sonogram.

8.1.6. Modified Nazer Score

The modified Nazer score is an assessment of liver status and consists of a composite of 5 laboratory parameters: AST, 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.

8.1.7. Brief Psychiatric Rating Scale-24

The Brief Psychiatric Rating Scale-24 (BPRS-24) is a 24-item instrument for adolescents aged 12 to < 18 years and the that allows the rater to measure psychopathology severity. 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, etc) who has completed the training required to administer the instrument.

The BPRS-C9 is a 9-item instrument for children aged 3 to < 12 years. The presence and severity of symptoms are rated on a scale ranging from 1 (not present) to 6 (extremely severe). As with the BPRS-24, the BPRS-C9 can be performed by a qualified person who has been appropriately trained.

8.1.8. EuroQoL 5 Dimensions

The EuroQoL 5 Dimensions (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 participant's self-rated health on a vertical VAS. Together, this can be used as a quantitative measure of health outcome that reflects the participant's own judgement.

Note that although the EQ-5D is designed for use in participants aged 16 years and older, the EQ-5D can also be used in participants aged 12 to 15 years and is appropriate given these participants will be followed for several years in the study (Van Reenen, 2014).

8.1.8.1. EQ-5D Youth

The child-friendly EQ-5D version (EQ-5D-Y) was introduced as a more comprehensible instrument suitable for children and adolescents. The wording was changed to be more suitable for children and adolescents, the most severe label for the mobility dimension was changed from

"confined to bed" to "a lot of problems walking about" to increase the applicability and sensitivity of the mobility dimension, and the instructions for the EQ VAS task were simplified, making the task easier to complete and to score (https://euroqol.org/eq-5d-instruments/eq-5d-y-about/).

8.1.9. 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 participants 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?

The TSQM-9 is expected to be completed by adolescent participants and by the parent or caregiver for younger participants.

8.1.10. Pediatric Quality of Life Inventory

The Pediatric Quality of Life Inventory (PedsQL™) Measurement Model is a modular approach to measuring health-related quality of life in healthy children and adolescents and those with acute and chronic health conditions.

The 23-item PedsQL™ Generic Core Scales were designed to measure the core dimensions of health as delineated by the World Health Organization (WHO), as well as role (school) functioning. The 4 Multidimensional Scales and 3 Summary Scores are:

Scales

- Physical Functioning (8 items)
- Emotional Functioning (5 items)
- Social Functioning (5 items)
- School Functioning (5 items)

Summary Scores

- Total Scale Score (23 items)
- Physical Health Summary Score (8 items)
- Psychosocial Health Summary Score (15 items)

8.1.11. Urinary and Fecal Copper Excretion

24-hour urinary copper excretion will be assessed at Baseline, Week 6, Week 24, and Week 48 in all participants.

24-hour fecal copper excretion will be assessed at Baseline and Week 6 in all participants. This assessment is optional.

Containers for collection of urine and feces will be provided at the preceding study visit. The purpose of these assessments is to assess the change from Baseline in urinary and fecal copper excretion in participants with WD who are treated with ALXN1840 or SoC.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

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

Pharmacokinetic collection should occur as close as possible to the scheduled time.

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, GI, and neurological systems.
- An abbreviated physical examination consists of a body system relevant examination based upon Investigator judgment and participant symptoms. At least 1 body system must be checked for an abbreviated examination.
- A symptom-driven physical examination may be performed at other times, at the Principal Investigator's discretion.

8.2.2. Vital Signs

- Body temperature, heart rate, respiratory rate, and systolic and diastolic blood pressure (mm Hg) will be assessed. Height and weight will also be measured and recorded.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones). Ideally, the same arm for each participant should be used for measurements.
- Vital signs will be measured in a supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and heart rate. Vital signs will consist of a single pulse and blood pressure measurement. If vital signs are abnormal as defined by inclusion/exclusion criteria, 2 additional vital signs measurements will be made. The average of the 3 vital signs measurements will be recorded in the CRF and used to determine participant eligibility. The average of the blood pressure readings will be recorded in the CRF.

8.2.3. Electrocardiograms

- Triplicate 12-lead ECGs will be conducted as outlined in the SoA (see Section 1.3) to obtain heart rate, PR, QRS, QT, and QTc intervals. As with vital signs, if ECG interval measurements are abnormal, an additional triplicate will be performed and recorded in the CRF.

8.2.4. Clinical Safety Laboratory Assessments

- See Section 10.2 for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant 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 participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or after the last dose of study intervention should be repeated until the values return to normal or Baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.
  - If such values do not return to normal/Baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and Alexion notified.
  - All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the laboratory manual and the SoA.
  - If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant 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

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

Participants being treated with study intervention 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 intervention, or at the time of dose changes, either increases or decreases. Consideration should be given to discontinuing the study intervention in participants who experience signs of suicidal ideation or behavior, following a risk assessment.

Families and caregivers of participants being treated with study intervention should be alerted about the need to monitor participants 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 study Investigator.

Baseline assessment of suicidal ideation and behavior/intervention emergent suicidal ideation and behavior will be monitored during the study using the BPRS-24 and BPRS-C9 (Section 8.1.7).

8.2.6. Pregnancy

- Pregnancy data from female participants and female spouses/partners of male participants will be collected from first dose of study intervention up to 3 months after the last dose of study intervention. Any female participant who becomes pregnant while participating in the study will be discontinued from the study intervention and withdrawn from the study. If a pregnancy is reported, the Investigator must immediately inform Alexion within 24 hours of awareness of the pregnancy and follow the procedures outlined in Section 10.4.
- For all Alexion products, both in development or post-approval, exposure during pregnancy must be recorded and the pregnancy followed until the outcome of the pregnancy is known (ie, spontaneous miscarriage, elective termination, normal birth or congenital abnormality), even if the participant discontinues the study intervention or withdraws from the study. The corresponding infant must be followed for 3 months postpartum.
- Pregnancy is not considered as an AE (Section 10.4.3) unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication. However, complications of pregnancy and abnormal outcomes of pregnancy are AEs and may meet the criteria for an SAE (eg, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly) (Section 8.3). Elective abortions without complications should not be reported as AEs.

8.3. Adverse Events and Serious Adverse Events

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

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

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

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

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

All AEs and SAEs will be collected from the signing of the ICF until the EOS Visit.

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

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

See Section 10.11 for instructions specific to Germany.

8.3.2. Method of Detecting AEs and SAEs

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

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

8.3.3. Follow-up of AEs and SAEs

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

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification of an SAE by the Investigator to Alexion is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- Alexion has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. Alexion will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ IECs, and Investigators.
- Alexion is required to submit individual suspected unexpected serious adverse reaction (SUSAR) reports (defined in Section 10.3.2) in the format of MedWatch 3500 or Council for International Organizations of Medical Sciences (CIOMS) I Form to health authorities and Investigators as required. Forms submitted to Investigators will be blinded to treatment assignment. In limited circumstances, the blind may be broken in the case of urgent safety issues that could compromise participant safety.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from Alexion will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Adverse Events of Special Interest

Any new neurological symptom or clinically significant worsening of an ongoing neurological symptom after initiation of study intervention (ALXN1840 or SoC) will be designated an adverse event of special interest (AESI), whether serious or non-serious. All AESIs should be recorded in the eCRF and AESIs meeting the criteria for an SAE should be reported per Section 8.3.4.

If a participant has an AESI, in addition to assessments deemed clinically relevant by the Investigator, the following assessments should be performed to the extent possible to help assess the AE and participant status: UWDRS Part III, and the CGI-I and CGI-S. The Investigator or Sub Investigator can perform additional assessments or laboratory testing at their discretion.

All adverse events of special interest (serious or nonserious) will be assessed by a panel of 3 independent neurologists not participating in the study. The panel will assess the probability that clinically significant worsening or a new clinically significant neurological symptom is related to disease progression or caused by the study intervention (ALXN1840 or SoC). They will be blinded to the treatment given to the participant. All available relevant participant information will be provided to this panel to aid in their assessment. The assessment of AESIs by the panel will be independent of and in addition to the usual assessments of the AE, including assessments of severity (intensity) and causality, by both the Investigator and Alexion.

8.4. Treatment of Overdose

For participants receiving ALXN1840, an overdose is defined as any daily dose exceeding 15 mg for adolescents aged 12 to < 18 years and in children < 12 years of age.

For participants receiving SoC, an overdose is defined as any daily dose exceeding the maximum daily dose listed on the local label in that country.

Alexion does not recommend specific treatment for an overdose.

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

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

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

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

8.5. Pharmacokinetics

- Whole blood samples will be collected for analyzing plasma concentrations of total molybdenum and PUF molybdenum as specified in the SoA (Section 1.3).

- 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.
- Excess/additional samples may be stored for up to 5 years and used for PD and/or diagnostic biomarker development and research to understand the pathways associated with the mechanism of action of ALXN1840. These samples will not be used for genetic analyses (ie, RNA or DNA analyses).
- Genetic analyses will not be performed on the whole blood samples collected for PK/PD analysis.

8.6. Pharmacodynamics

- Whole blood will be collected for measurement of plasma total and PUF copper, NCC, and LBC as specified in the SoA (Section 1.3).
- 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.
- Plasma samples will be used to evaluate ALXN1840 or SoC PD via the measurement of total copper and copper measured as NCC and PUF copper, and/or LBC, or assessed via NCC/$NCC_{corrected}$ methods. Samples collected for PD measurements of ALXN1840 and SoC may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.
- Excess/additional samples may be stored for up to 5 years and used for PD and/or diagnostic biomarker development and research to understand the pathways associated with the mechanism of action of ALXN1840 (see also Section 10.6). These samples will not be used for genetic analyses (ie, RNA or DNA analyses).

8.7. Genetics

A blood sample for DNA isolation will be collected from participants who have consented to participate in the genetic analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

Details on processes for collection and shipment and destruction of these samples can be found in the laboratory manual. Details of the use, analysis, and storage of the DNA samples collected are provided in Section 10.5.

8.8. Biomarkers

ALXN1840 biomarkers such as ceruloplasmin and CpC will be measured in plasma/serum samples. Note that serum ceruloplasmin will be analyzed separately to plasma ceruloplasmin.

Please see Section 8.6 for details of ALXN1840 or SoC PD measurements such as plasma total copper and PUF copper and/or LBC, or assessed via NCC/$NCC_{corrected}$ methods.

Further details of biomarker analyses are provided in Section 10.6.

8.9. Immunogenicity Assessments

Not applicable.

8.10. Health Economics Data and/or Medical Resource Utilization

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

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

9.1.1. Primary Hypothesis

This study is not statistically powered to be a stand-alone hypothesis testing study with respect to efficacy. Efficacy data from this study will subsequently be combined with those of the ongoing Phase 3 Study WTX101-301, which includes participants ≥12 years of age, using Bayesian extrapolation methods to assess the efficacy of ALXN1840 and SoC in pediatric participants with WD.

Accordingly, the evaluations of PK, PD, safety, and efficacy of ALXN1840 and SoC will be summarized descriptively using frequentist statistical methods. A separate analysis and report will present the results of the Bayesian extrapolations, which use adult/adolescent participants in Study WTX101-301 and pediatric participants in Study ALXN1840-WD-302 to perform statistical testing of the efficacy of ALXN1840 compared with SoC in pediatric participants.

9.2. Sample Size Determination

This study will enroll 48 pediatric participants (1:1 ratio to ALXN1840 or SoC) with the goal of obtaining 40 evaluable participants at Week 48.

The proposed sample size for this study was assessed for its adequacy for the extrapolation Study ALXN1840-WD-303 via simulation using the proposed Bayesian hierarchical model. To explore the performance of the design, 3 distinct states of efficacy were considered in each of the populations with respect to the mean 48 week change in NCC/$NCC_{corrected}$:

1. ALXN1840 is superior to SoC by 15%
2. ALXN1840 is equivalent to SoC; and
3. ALXN1840 is inferior to SoC by 15%.

Given the 2 populations (adult population: adults in Study WTX101-301, and pediatric population: pediatrics in Study ALXN1840-WD-302 plus adolescents from Study WTX101-301), there are 9 possible combinations representing potential underlying scenarios. For each of these scenarios, 5,000 studies were simulated and the proportion of studies that claim non-inferiority in the pediatric participant population was estimated. Statistical power is captured in scenarios in which ALXN1840 is either superior or equivalent to SoC in the pediatric participant population. Type I error is captured in scenarios in which ALXN1840 is inferior to SoC in the pediatric participant population. Table 8 shows the simulation results assuming a standard deviation of 30% (absolute) on the 48-week change in NCC/$NCC_{corrected}$.

The proposed primary analysis for the pediatric extrapolation Study ALXN1840-WD-303 has 70% to 99% power for scenarios in which ALXN1840 is either equivalent or superior to SoC in both populations and has Type I error <13% when ALXN1840 is inferior to SoC in the pediatric population. These calculations assume 165 adult participants and 15 adolescents from Study WTX101-301(2:1 ratio to ALXN1840 or SoC) have evaluable 48-week data, and 40 evaluable pediatric participants (1:1 ratio to ALXN1840 or SoC) have evaluable 48-week data from Study ALXN1840-WD-302. The data simulations were done using FACTS v6.3.

To accommodate a 15% dropout rate, a total of 48 pediatric participants will be enrolled.

Table 8: Simulated Power for Pediatric Extrapolation Study ALXN1840-WD-303 Primary Analysis

Adult Population	Pediatric Population		
	Superior	**Equivalent**	**Inferior**
Superior	99.2%	69.9%	9.8%
Equivalent	99.0%	73.6%	12.7%
Inferior	83.1%	23.8%	1.0%

9.3. Populations for Analyses

The population sets used as analysis sets are defined in the following:

Population	Description
Screened	All participants who sign the ICF.
Enrolled	All participants who agree to participate in the study following completion of the informed consent process and who satisfy the inclusion/exclusion criteria and are randomized.
Safety Analysis Set	All participants who receive at least 1 dose of ALXN1840 or SoC treatment.
Full Analysis Set	All participants who receive at least 1 dose of ALXN1840 or SoC treatment.
Per Protocol Set	All participants who receive at least 1 dose of ALXN1840 or SoC treatment and have both baseline and Week 48 NCC/$NCC_{corrected}$ concentrations. Participants with major protocol deviations that are likely to impact the primary 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.
Extension Analysis Set	This dataset includes all participants who enter Period 2 and receive at least 1 dose of ALXN1840 in the Period 2
Pharmacokinetic/Pharmacodynamic Analysis Set	All participants who have sufficient plasma samples to enable the calculation of PK parameters and provide PK/PD profiles.

Abbreviations: ICF = informed consent form; PD = pharmacodynamic; PK = pharmacokinetic; SoC = standard of care.

9.4. Statistical Analyses

The evaluations of PK, PD, safety, and efficacy of ALXN1840 and SoC in this study will be summarized descriptively using summary statistics.

A separate analysis and report will present the results of the Bayesian extrapolations and statistical testing of the efficacy of ALXN1840 compared with SoC in pediatrics (Study ALXN1840-WD-303). The analyses at Weeks 48 and 72 will be performed and reported sequentially and separately.

The evaluation of safety and efficacy of ALXN1840 from 48 to 72 weeks will be summarized by the treatment groups assigned in Period 1 using descriptive statistics. For participants who are randomized to ALXN1840 in Period 1, change/percent change from Period 1 baseline and change/percent change from Period 2 baseline will both be summarized. For participants who were randomized to SoC in Period 1, only change/percent change from Period 2 baseline will be summarized.

Missing data will not be imputed.

Statistical methods described in this section will be further elaborated in a separate Statistical Analysis Plan (SAP). Summary statistics will be computed and displayed by treatment group and by visit, where applicable. Descriptive statistics for continuous variables will minimally include the number of participants, mean, standard deviation (SD), minimum, median, and maximum. For categorical variables, frequencies and percentages will be presented. Graphical displays will be provided as appropriate.

Analyses will be performed using the SAS® software Version 9.4 or higher.

9.4.1. Efficacy Analyses

9.4.1.1. Analyses of Primary Efficacy Endpoint

The primary endpoint, the percentage change from Baseline to 48 weeks in NCC/$NCC_{corrected}$ concentrations, will be analyzed by treatment group within each cohort and by treatment group overall using descriptive summary statistics. Analyses will be based on the Per Protocol Set and Full Analysis Set.

Subgroup analysis may be performed (eg, age group) if sample sizes permit.

9.4.1.2. Analyses of Secondary Efficacy Endpoints

Analyses of secondary efficacy endpoints will be based on the Full Analysis Set. All secondary efficacy endpoints will be summarized by treatment groups within each cohort and by treatment group overall using descriptive statistics.

Subgroup analysis may be performed (eg, age group) if sample sizes permit.

9.4.1.3. Multiplicity Adjustment

No statistical testing, not applicable.

9.4.1.4. Analyses of Exploratory Endpoints

All exploratory endpoints will be summarized by treatment groups within each cohort and by treatment group overall using descriptive statistics using the Full Analysis Set.

9.4.2. Safety Analyses

All safety analyses will be performed on the Safety Set.

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

Treatment-emergent adverse events (TEAEs) are defined as those AEs with onset after the first dose of randomized treatment or existing events that worsened in severity after the first dose of randomized treatment. Events reported with a partial onset date (eg, month and year are reported, but the day is missing) will be considered to be treatment-emergent if it cannot be confirmed that the event onset was prior to the first dose of study drug based on the available date entries.

Additionally, for patients randomized to SoC in Period 1 who switch to ALXN1840 in Period 2, any AEs that initiate after the switch or existing events that worsen in severity will be attributed to ALXN1840.

No inferential statistical analyses are planned for the safety parameters of this study.

An overall summary of TEAEs will be presented by treatment, including frequency of participants experiencing the event (n) and relative frequency (n/N*100, where N is the number of patients in the Safety Set for each treatment group). The summary will include categories indicating how many events are TEAEs, treatment-emergent SAEs, and treatment-emergent non-SAEs. Within TEAEs, the following subcategories will also be summarized:

- Severity of TEAEs (Grade 1 through Grade 5)
- Related TEAEs (not related, related)
- TEAEs leading to withdrawal of study drug
- TEAEs leading to death

The incidence of AEs and SAEs will be summarized by System Organ Class and Preferred Term for each treatment and overall, and by relationship to study intervention. Adverse events will also be summarized by treatment and overall by severity. Serious AEs and AEs resulting in withdrawal from the study will be listed. Participants having multiple AEs within a category (eg, overall, System Organ Class, Preferred Term) will be counted once in that category. For severity tables, a participant's most severe event within a category will be counted.

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

Electrocardiogram parameters will be measured at the specified time points as per the SoA (Section 1.3), including heart rate, PR, RR, QRS, QT, and QT intervals corrected for heart rate using Fridericia's formula (QTcF intervals). The average of the triplicate ECG readings at the time points collected will be calculated, and changes from Baseline values will be assessed by each treatment.

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

9.4.3. Pharmacokinetic, Pharmacodynamic, and Biomarker Analyses

For PK, PD, and biomarker endpoints, analyses will be performed using the PK/PD Analysis Set.

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

- Maximum observed concentration (C_{max})
- Time to maximum concentration (T_{max})
- Trough (predose) concentration observed at the start of the dosing interval (C_{trough})
- Area under the plasma concentration versus time curve (AUC) over the dosing interval (AUC_{tau})

Additional plasma PK parameters may be calculated if deemed appropriate. Population PK analysis may be formed with pooled data from other clinical studies if deemed appropriate. Population PK parameters such as, but may not be limited to, apparent total body clearance (CL/F) and apparent volume of distribution (V_d/F) will be estimated for addition modeling and simulation purposes.

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

Pharmacokinetic parameters derived from plasma concentrations of total molybdenum and PUF molybdenum (if measured) will be presented in data listings and summarized separately using the following descriptive statistics: number of participants, arithmetic mean, GM, SD, arithmetic CV, GMCV, median, minimum, and maximum.

For PD (total and PUF (if measured) copper, NCC, LBC and NCC/$NCC_{corrected}$) and biomarker endpoints (ceruloplasmin, CpC), concentration versus time data will be listed and summarized with descriptive statistics and plotted. The same analyses will be conducted on the absolute and percent changes from Baseline of these concentration versus time data.

The following plasma PD parameters, as data permits, will be calculated for total copper, NCC, and LBC using noncompartmental methods with Phoenix® WinNonlin® Version 8.0 or higher or SAS Version 9.4 or higher, as applicable.

- Maximum observed effect after dosing (CE_{max})
- Time after dosing at which the maximum effect was observed (TE_{max})
- Area under the effect versus time curve (AUEC) from the start of dose administration to the last observed quantifiable concentration ($AUEC_t$)

Pharmacodynamic parameters derived from plasma concentrations of total copper, NCC, and LBC will be presented and summarized by analyte and day similar to PK parameters.

Additional PK/PD correlation plots and analysis may be performed.

9.5. Interim Analyses

The primary analysis will be performed after 48 weeks and the final analysis after completion of Period 2. Interim analyses of data may be performed to support regulatory submissions. These analyses will be descriptive only; they will not include formal hypothesis testing and will not be used to adapt the study. Full details will be provided in the SAP.

Interim efficacy data will also be used in an efficacy extrapolation to develop evidence for ALXN1840 efficacy on copper control for pediatric participants (ages 3 to < 18 years) using adult/adolescent participant data from Studies WTX101-301 and ALXN1840-WD-302. Full details of the extrapolation exercise will be provided in a separate analysis and report.

9.6. 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. The specific responsibilities of the DMC will be described in the DMC Charter.

9.7. Neurological Event Adjudication Panel

A separate independent Neuro Event Adjudication Panel, comprising independent experts in relevant fields will be appointed by Alexion. As detailed in the Neuro Event Adjudication Panel Charter (maintained separately from the study protocol), the Neuro Event Adjudication Panel will review and monitor study data for neurological AEs/SAEs 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 Neuro Event Adjudication Panel Charter.

9.8. 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. 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 substantial amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
  - If any of these documents require regulatory/health authority approval per local regulations, Alexion will also obtain such approval before the study is initiated.
- Any substantial amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- For studies to be approved by the Medicines and Healthcare products Regulatory Agency: The Investigator will notify the IRB/IEC of deviations from the study protocol or GCP as defined by UK legislation as a serious breach or as required by IRB/IEC procedures.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, Directive 2001/20/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and 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 and assent, where applicable from all study participants and/or his/her legally authorized representative, defined according to local and country regulations where the study is taking place, prior to any study-related procedures including Screening assessments.
- The Investigator or his/her representative will explain the nature of the study (including but not limited to the objectives, potential benefits and risks, inconveniences, and the participant's rights and responsibilities) to the participant or his/her legally authorized representative, defined according to local and country regulations where the study is taking place, and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent or assent or a certified translation if applicable, that meets the requirements of 21 CFR 50, local regulations, EU General Data Protection Regulation (GDPR), ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study site.
- The participant's medical record must include a statement that signed (written or electronic) informed consent or assent was obtained before the participant was screened in the study and the date the written consent was obtained. The authorized person obtaining the informed consent or assent must also sign the informed consent or assent form(s).
- Participants must be reconsented or reassented to the most current version of the informed consent or assent form(s) during their participation in the study.
- A copy of the signed (written or electronic) informed consent or assent documentation (ie, a complete set of participant information sheets and fully executed signature pages) must be provided to the participant or the participant's legally authorized representative, as applicable. This document may require translation into the local language. Signed (written or electronic) consent [or assent] forms must remain in each participant's study file and must be available for verification at any time.
- A participant who is rescreened is not required to sign another ICF unless an updated ICF is available.

10.1.4. Data Protection

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

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

- Participants must be informed that their personal study related data will be used in accordance with applicable data protection law, and participants must also be informed of any individuals rights they may have with regard to their personal data. Participants will be informed about how their personal study related data will be disclosed, and will be required to agree to the information contained in the informed consent and provide consent to the processing of their personal data, if required by applicable data protection law.
- Participants must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by Alexion, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- Alexion as a data controller has implemented privacy and security controls designed to help protect participant personal data; including information security controls, firewalls, incident detection, and secure transfer measures.
- In the event of any accidental or unlawful destruction, loss, alteration, unauthorized disclosure of, or access to, personal data ("breach"), the controller has implemented procedures and measures to promptly address and mitigate any risk to the data participant. In the event of a breach, the controller will notify the appropriate regulatory authorities and/or the data participant in accordance with applicable data protection law.

10.1.5. Dissemination of Clinical Study Data

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

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic case report forms (CRFs) unless transmitted to Alexion or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Alexion or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and

verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

  - Remote source data verification may be employed where permitted by local regulations.
  - The scope of the source data verification will be described in detail in the Clinical Monitoring Plan.

- 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 study intervention, unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Alexion. No records may be transferred to another location or party without written notification to Alexion.

10.1.7. Source Documents

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

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

Per ICH E6 (R2) guidelines and good documentation practice requirements, source documents and study records in all media (eg, paper, electronic) must be Attributable, Legible, Contemporaneous, Original, Accurate, and Complete.

10.1.8. Study and Site Start and Closure

The study start date is the date on which the first participant is consented or assented.

Alexion reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of Alexion. Study sites will be closed after the study is completed or following the decision to close or terminate the study. A study site is considered closed when all participants have completed the End of Study or Early Termination Visit, all data have been collected and entered into an electronic data capture (EDC) system, all required documents and study supplies have been collected, and a study-site closure visit has been performed.

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

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

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

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

10.1.9. Publication Policy

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

10.1.10. Good Clinical Practice Compliance

Alexion and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, ICH GCP Guideline E6 R2, EU Directive 2001/20/EC, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of Alexion and/or the company organizing/managing the research on behalf of Alexion to inspect study data, participants' medical records, and CRFs in accordance with current GCP and respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

Alexion ensures that local regulatory authority requirements are met before the start of the study. Alexion (or designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of study intervention for shipment to the site.

10.2. Clinical Laboratory Tests

- The tests detailed in Table 9 will be performed by the Central Laboratory.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- Pregnancy testing: Women of childbearing potential can only be enrolled after a negative serum pregnancy test result at Screening. Additional urine pregnancy testing will be standard for the protocol unless serum testing is required by site policies, local regulation, or IRB/IEC and should be performed per the time points specified in the SoA (Section 1.3). In addition to pregnancy tests detailed at the visits in the SoA, females of childbearing potential will be required to perform urine pregnancy tests at least every 4 weeks at their home or the study site throughout their time in the study. Screening pregnancy criteria are detailed in Section 5.1.

Table 9: Protocol-Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Hematology	• Platelet count • RBC count • Hemoglobin • Hematocrit • RBC indices (MCV, MCH, % reticulocytes) • White blood cell count with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
Clinical chemistry[a]	• ALT • Alkaline phosphatase • AST • Blood urea nitrogen • Calcium • Ceruloplasmin (note that serum and plasma ceruloplasmin are assessed separately) • Cholesterol • Creatinine • Gamma glutamyltransferase • Glucose • Potassium • Sodium • Total and direct bilirubin • Total protein • Lipid profile
Iron profile	• Iron profile (plasma iron, ferritin, transferrin saturation)
Routine urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick • Microscopic examination (if blood or protein is abnormal)
Coagulation	• Prothrombin time • Partial thromboplastin time • International normalized ratio
Other Screening tests	• Highly sensitive serum or urine human chorionic gonadotropin pregnancy test at Screening and urine at subsequent study visits, with confirmation by serum test if the urine test is positive (as needed for women of childbearing potential) • HIV antibody screen • Hepatitis B surface antigen • Hepatitis C virus antibody (positive antibody screen should be confirmed by RNA test)

a Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 6.6.

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; HIV= human immunodeficiency virus; INR = international normalized ratio; MCH = mean corpuscular hemoglobin; MCV = mean corpuscular volume; RBC = red blood cell; SAE = serious adverse event; ULN = upper limit of normal.

Investigators must document their review of each laboratory safety report.

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

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment (ICH E2A). • Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

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

Events Not Meeting the AE Definition
• Medical or surgical procedure (eg, endoscopy, appendectomy): The condition that leads to the procedure is the AE. Situations in which an untoward medical occurrence did not occur (eg, hospitalization for elective surgery if planned before the signing the ICF, admissions for social reasons or for convenience). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen. • A medication error (including intentional misuse, abuse, and overdose of the product) or use other than what is defined in the protocol is not considered an AE unless there is an untoward medical occurrence as a result of a medication error. • Cases of pregnancy that occur during maternal or paternal exposure to study intervention are to be reported within 24 hours of Investigator/site awareness. Data on fetal outcome and breastfeeding will be collected for regulatory reporting and safety evaluation. • Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, 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.

10.3.2. Definition of SAE

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

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

1. Results in death

2. Is life-threatening

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

3. Requires inpatient hospitalization or prolongation of existing hospitalization

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

4. Results in persistent disability/incapacity

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

5. Is a congenital anomaly/birth defect

6. Other situations:

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

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

An event that is assessed as serious by the Investigator and/or Alexion that is not listed in the appropriate Reference Safety Information (IB) and has been assessed that there is at least a reasonable possibility that the event is related to the investigational medicinal product by the Investigator and/or Alexion.
Alexion has procedures that will be followed for the recording, medical assessment, and expedited reporting of SUSARs that are consistent with global regulations, legislation, and guidance documents.
For the purposes of this study, SoC SUSAR reporting will be in accordance with Section 4.8 of the Summary of Product Characteristics (SmPC) of the respective SoC products.

Suspected unexpected serious adverse reactions will undergo expedited reporting to the national regulatory authorities, IRBs/IECs, and Investigators following local regulatory reporting requirements where applicable.

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

Recording of AE and/or SAE

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRF.

Recording of AE and/or SAE

- It is not acceptable for the Investigator to send photocopies of the participant's medical records to Alexion in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Alexion GDS. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Alexion.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

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

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

An event is defined as "serious" when it meets at least one of the predefined outcomes as described in the definition of an SAE, not when it is rated as severe.

Assessment of Causality

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

Follow-up of AEs and SAEs
• The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Alexion to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide Alexion with a copy of any postmortem findings including histopathology. • New or updated information will be recorded in the originally completed CRF. • The Investigator will submit any updated SAE data to Alexion within 24 hours of receipt of the information. See Section 10.11 for instructions specific to Germany.

10.3.4. Reporting of SAEs

SAE Reporting to Alexion
• All SAEs will be recorded and reported to Alexion or designee immediately and within 24 hours of awareness. See Section 10.11 for instructions specific to Germany. • The primary mechanism for reporting an SAE to Alexion will be the electronic data collection tool. • 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 fax or email. Facsimile transmission or email may be used in the event of electronic submission failure. – Email: clinicalsae@alexion.com or Fax: + 1.203.439.9347 • The site will enter the SAE data into the EDC system as soon as it becomes available. • When further information becomes available, the EDC should be updated within 24 hours with the new information and an updated SAE report should be submitted to Alexion. • After the study is completed at a given site, the electronic data collection tool will be taken offline 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 a paper Contingency Form for SAE Reporting. • If applicable, additional information such as relevant medical records should be submitted to Alexion 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) MUST be accompanied by a cover page signed by the Investigator. • Paper source documents and/or reports should be kept in the appropriate section of the study file.

10.4. Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Definitions

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 (eg, 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 one of the following:
    - Documented hysterectomy
    - Documented bilateral tubal ligation or bilateral salpingectomy
    - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, 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. Permanent sterilization at least 6 weeks prior to the Day 1 Visit.

10.4.2. Contraception Guidance

Contraceptive use by male or female participants should be consistent with local regulations regarding the methods of contraception utilized for those participating in clinical studies. If teratogenic effects are suspected to be transferred to a fetus/embryo from a female spouse/partner of a male participant, pregnancy follow-up information will be obtained for the partner who becomes pregnant (refer to Section 10.4.3.1). In these cases, follow-up will be conducted on the pregnant partner in the same manner as a female participant who becomes pregnant during the study.

10.4.2.1. Guidance for Female Participants

Female participants of childbearing potential must have a negative pregnancy test (urine or serum) as required by local regulations within 24 hours before the first dose of study intervention. In addition to pregnancy tests detailed at the visits in the SoA (Section 1.3), females of childbearing potential will be required to perform urine pregnancy tests at least every 4 weeks at their home or the study site throughout their time in the study.

- 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.

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.

A highly effective method of contraception, including at least 1 of the following must be used until at least 3 months after the final dose of study intervention.

1. Intrauterine device (without copper) in place for at least 6 weeks prior to first dose of study intervention.
2. Progestogen-only hormonal contraception associated with inhibition of ovulation (either oral, injectable, or implantable) for at least 6 weeks prior to first dose of study intervention.
3. Intrauterine progestogen releasing system for at least 6 weeks prior to first dose of study intervention.
4. Bilateral tubal occlusion for at least 6 weeks prior to first dose of study intervention.
5. Combined (estrogen- and progestogen-containing) hormonal contraception - associated with inhibition of ovulation (either oral, intravaginal, or transdermal) for at least 6 weeks prior to first dose of study intervention. Estrogen-containing hormonal contraception is acceptable only if it has been used for at least 6 weeks immediately prior to the first dose. Estrogen-containing hormonal contraception may not be initiated during the study period.
6. Surgical sterilization of the male partner (medical assessment of azoospermia is required if vasectomy was performed within 6 months prior to first dose of study intervention). Male partner is still required to use condom during sexual intercourse.
7. Sexual abstinence for female participants:
    a. 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 participant's preferred and usual lifestyle. Abstinent female participants must refrain from heterosexual intercourse for at least 3 months after the final dose of study intervention.

Female participants must not donate ova from the first dose of study intervention until at least 3 months after their final dose of study intervention.

The following methods of contraception are considered unacceptable in this study:

- Periodic abstinence (calendar, symptothermal or post ovulation methods
- Withdrawal (coitus interruptus)
- Spermicides only
- Lactational amenorrhea method
- Female condom and male condom should not be used together
- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide

- Cap, diaphragm, or sponge with spermicide
- A combination of male condom with cap, diaphragm, or sponge with spermicide (double barrier methods)

10.4.2.2. Guidance for Male Participants

Male participants must use a condom during heterosexual intercourse from the first dose of study intervention until at least 3 months after their final dose of study intervention.

Female partners of male participants who are of childbearing potential must use highly effective contraception as defined above, starting at least 6 weeks before (the male participant's) first study intervention administration and continuing until at least 3 months after the end of their male partner's systemic exposure to the study intervention.

Male participants must not donate sperm from the first dose of study intervention until at least 3 months after their final dose of study intervention.

10.4.2.2.1. Sexual Abstinence for Male Participants

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 participant's preferred and usual lifestyle. Abstinent male participants who become heterosexually active must use a condom during intercourse.

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

10.4.3. Collection of Pregnancy Information

Pregnancy data will be collected during this study for female participants and female spouses/partners of male participants from the first dose of study intervention until 3 months after the final dose of study intervention is administered. Any female participant who becomes pregnant during the study must be discontinued from the study intervention and withdrawn from the study.

Exposure during pregnancy (also referred to as exposure in utero) can be the result of either maternal exposure or transmission of study intervention via semen following paternal exposure. If a female participant or a male participant's female spouse/partner becomes pregnant during the conduct of this study, the Investigator must submit the "Pregnancy/Breastfeeding Reporting and Outcome Form" to Alexion GDS via facsimile or email within 24 hours of awareness of the pregnancy. 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 study intervention 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 via email or facsimile.

Pregnancy is not regarded as an AE unless there is a suspicion that the study intervention may have interfered with the effectiveness of a contraceptive medication. However, complications of pregnancy and abnormal outcomes of pregnancy are AEs and may meet the criteria for an SAE

(eg, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly). Elective abortions without complications should not be reported as AEs.

10.4.3.1. 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 only to male participants who receive study intervention.
- 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 GDS within 24 hours of learning of the partner's pregnancy. 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 GDS. Generally, the follow-up will be for up to 3 months following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

10.4.3.2. 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 GDS within 24 hours of learning of a participant's pregnancy.
- For all Alexion products, both in development or postapproval, exposure during pregnancy must be recorded and the pregnancy followed, until the outcome of the pregnancy is known (ie, spontaneous miscarriage, elective termination, normal birth, or congenital abnormality), even if the participant discontinues the study intervention or withdraws from the study. The 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 estimated 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 poststudy pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to Alexion. 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.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention and be withdrawn from the study.

10.5. Genetics

Use/Analysis of Deoxyribonucleic Acid

- Genetic variation in the *ATP7B* gene may impact a patient's response to study intervention, susceptibility to, and severity and progression of disease. 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 WD. They may also be used to develop tests/assays including diagnostic tests related to ALXN1840 and WD.
- DNA samples will be analyzed for variants in the coding and regulatory sequences of the *ATP7B* gene and other genes, if considered related to WD. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data, such as identifying gene mutations that may affect the metabolism of ALXN1840.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to ALXN1840 or study interventions of this class to understand study disease or related conditions.
- The results of genetic analyses may be reported in the clinical study report (CSR) or in a separate study summary.
- Alexion or designee will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on ALXN1840 continues but no longer than 10 years or other period as per local requirements.

10.6. Biomarkers

- Blood samples will be collected for biomarker analyses and the data will be used for research (eg, exploratory) related to ALXN1840 or WD and related diseases. The samples may also be used to develop tests/assays including diagnostic tests related to ALXN1840 and WD.
- The samples may be analyzed as part of a multistudy assessment of biomarkers in the response to ALXN1840 to understand study disease or related conditions.
- Biomarker samples will not be used for genetic testing.
- The results of biomarker analyses may be reported in the CSR or in a separate study summary.
- Alexion or designee will store the samples obtained for biomarker analyses in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on ALXN1840 continues but no longer than 5 years after all data has been collected for the study or other period as per local requirements.

10.7. Blood Sampling Volumes

The following procedures for blood collection should be adhered to:

1. Number of attempts: The number of attempts for sampling blood is limited to 3 times per day. This means that after 3 punctures for collection of blood have been performed and no or insufficient blood could be collected, no other puncture will be done on the same day.
2. Volume of blood samples: Per study participant, the study-related blood loss (including any losses in the collection procedure) should not exceed more than 5 mL/kg body weight (5% of total blood volume) in a day and no more than 9.5 mL/kg (11%) of total blood volume) over any 8-week period. If an Investigator decides to deviate from these limits, the deviation must be fully documented, and the investigator should provide justification for the deviation. If the required blood volume cannot be obtained, due to the above-mentioned safety limits, priority will be given to safety-relevant investigations.
3. Eutectic mixture of local anesthetics (EMLA) cream/plaster: To minimize the possible pain and discomfort due to collection of blood, the Investigator may apply an EMLA cream/plaster at the puncture site, depending on clinical practice at the study site.

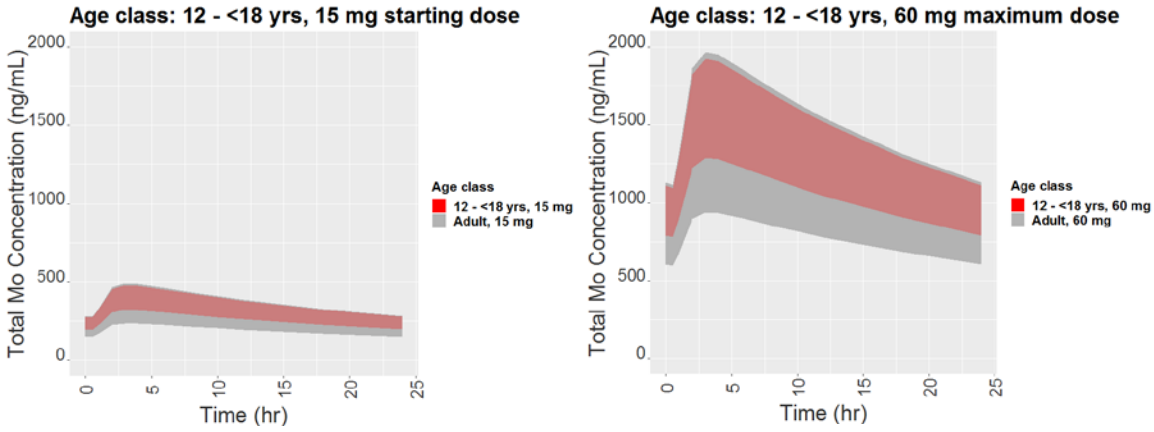
Reference: POLICY – Guidelines for Limits of Blood Drawn for Research Purposes in the Clinical Center. Available at:
https://irb.research.chop.edu/sites/default/files/documents/g_nih_blooddraws.pdf

10.8. Population PK Simulations and Dose Selection in Pediatric Participants with Wilson Disease

10.8.1. Participants aged 12 to < 18 years

The simulation showed that projected PK exposure range for participants aged 12 to < 18 years (Figure 2) are expected to be overlapping with the exposure range for adults at the proposed dose of 15 mg in Studies WTX101-301 and ALXN1840-WD-302.

Figure 2: Projected Pharmacokinetic Exposure Range for Participants Aged 12 to < 18 Years



Simulations are based on a 2-compartmental population-PK model for pediatric participants based on allometric scaling of adult population-PK model currently under development using Day 1 PK data from Study WTX101-201 in participants with WD and relevant PK data from Study WTX101-102 in healthy volunteers. Simulations results will be updated once final data are available from the Study WTX101-201.
Abbreviations: hr = hour; Mo = molybdenum; PK = pharmacokinetic; WD = Wilson Disease; yrs = years.
Source: Population PK modelling simulations (data on file)

The 15 mg EC tablet formulation is the current formulation being used for administration of the dose and subsequent individualized dose modifications in the ongoing Phase 3 Study WTX101-301, which includes participants aged 12 years and older, as per Protocol Amendment 1. The 15/day single or repeated daily doses has been shown to have favorable safety profiles and to be well tolerated throughout the Phase 1 to Phase 3 clinical studies in both healthy adults and adult participants with WD.

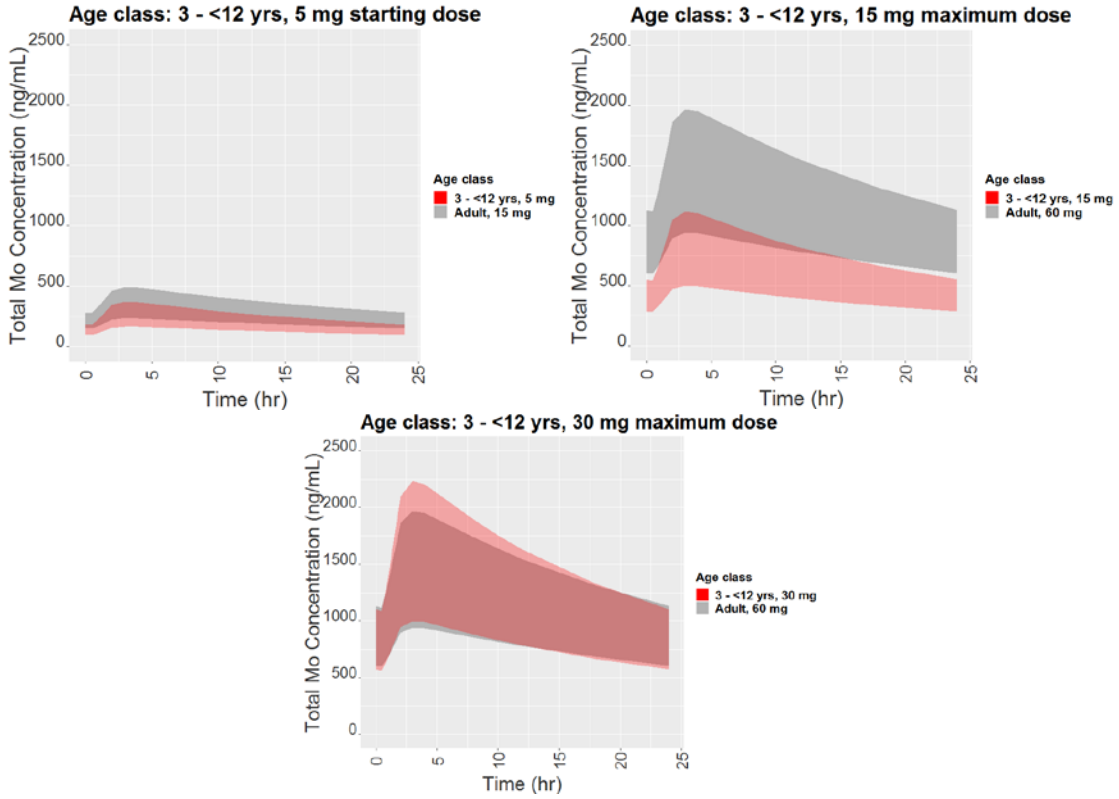
Of note, the current ongoing Phase 3 Study WTX101-301 has enrolled 17 pediatric participants, including a participant weighing 39.5 kg who was dosed at the starting dose of 15 mg ALXN1840 once daily, and has shown an acceptable safety profile. To date, the TEAEs observed in the adolescent participants are similar to those reported in the overall study.

10.8.2. Participants aged 3 to < 12 years

The projected PK exposures at the starting dose of 5 mg every other day are lower than those in adults administering a starting dose of 15 mg, a more conservative dosing approach in the youngest age group of 3 to < 12 years. The projected exposures at the original maximum dose (ie, 30 mg once daily) allowed for participants aged 3 to < 12 years in Study ALXN1840-WD-

302 are similar to those administering the highest dose (ie, 60 mg once daily) allowed in the ongoing Phase 3 Study WTX101-301 in adults and adolescents (Figure 3).

Figure 3: Projected Pharmacokinetic Exposure Range for Patients Aged 3 to < 12 Years



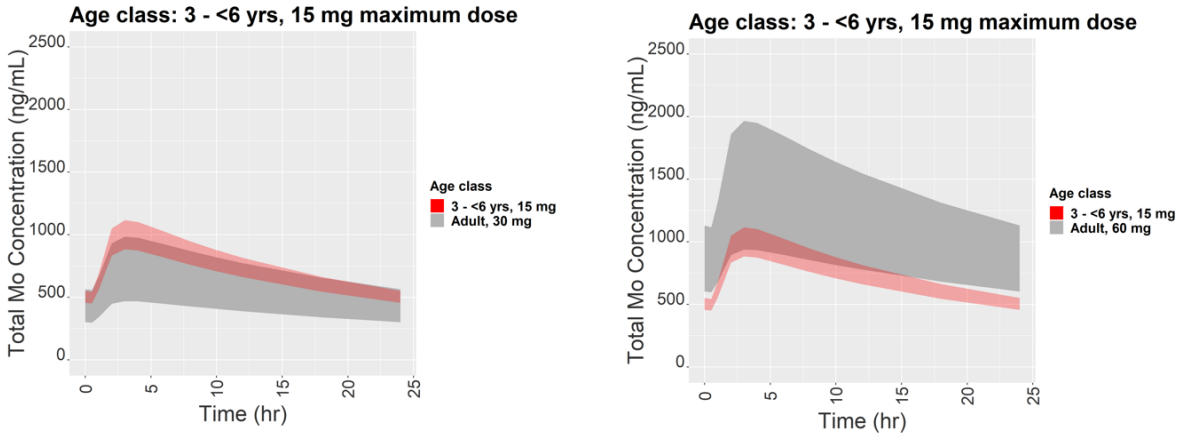
Simulations are based on a 2-compartmental population-PK model for pediatric participants based on allometric scaling of adult population-PK model currently under development using Day 1 PK data from Study WTX101-201 in patients with WD and relevant PK data from Study WTX101-102 in healthy volunteers. Simulations results will be updated once final data are available from Study WTX101-201.
Abbreviations: hr = hour; Mo = molybdenum; PK = pharmacokinetic; WD = Wilson Disease; yrs = years; QD = once daily; QOD = every other day.

Source: Population PK modelling simulations (data on file)

Looking specifically at participants aged 3 to < 6 years, the modeling results showed that a 5 mg dose has comparable exposure as 15 mg administered to adult participants, and that a 15 mg dose has a higher exposure than 30 mg but a lower exposure than 60 mg administered to adult participants (Figure 4). Hence, the predicted dose range for participants aged 3 to < 6 years is 5 mg to 15 mg, which is anticipated to provide comparable safety and efficacy outcomes to those in adolescent and adult participants over 12 years of age with a dose range of 15 mg to 60 mg allowed in the ongoing Phase 3 Study WTX101-301.

A more conservative starting dose at 2.5 mg will be used for the pediatric study ALXN1840-WD-302 for participants aged 3 to < 12 years.

Figure 4: Projected Pharmacokinetic Exposure Range for Participants Aged 3 to < 6 Years



Source: Population PK modelling simulations (data on file)

10.9. COVID Safety Measures

The COVID-19 pandemic has the potential to restrict access to ALXN1840 and SoC treatment and safety monitoring visits for study participants. During this pandemic period, Alexion has set up mitigation measures providing additional options whereby study procedures, laboratory assessments, safety monitoring and study drug dispensation may be conducted (Table 10). These include visits at the participant's home, by an investigator or home healthcare provider, in-person, by telephone or by video conference, at another study site located near the participant's home, or an alternative center located near the participant's home. These visits are conducted under the orders of the study site Investigator by trained qualified staff and in accordance with all national, state, and local laws or regulations.

Participants with WD may be at risk of complications if treatment is missed or delayed. Alexion has not identified a safety signal with ALXN1840 that would prevent its use during a viral infection and does not recommend suspending treatment in participants receiving ALXN1840 or SoC. The risk to benefit assessment favors continuity of treatment for WD, when possible.

Informed consents forms will permit release of medical records for participants transferring to another study site and to enable remote data verification where permitted.

The future of this pandemic is uncertain. These specific measures in the conduct of the study are intended to be temporary. Alexion intends to revert back to the original measures described in the protocol after the end of the pandemic period. Alexion will be making every effort to maintain participant safety in the setting of COVID-19 transmission while continuing treatment for WD. Any questions concerning the mitigation measures in place should be discussed with the Alexion Medical Monitor.

Table 10: COVID-19 Clinical Study Mitigation Measures (Optional and Temporary) for Study ALXN1840-WD-302

Study Impact	Clinical Study Temporary Measures				Justification for COVID-19 Mitigation
	Site Staff via Home Visit/Phone/Video	Alternative staff at home	Alternative study/local site	Courier	
Abbreviated physical examination	PI/Sub-I				Due to COVID-19 pandemic restrictions, participant study visits may need to be completed remotely at the participant's home, by site staff. This alternative temporary measure will limit impact of the pandemic on the parameter assessment.
Vital signs (Weight, temp, BP and HR)	PI/Sub-I/SC/Other certified staff	Home Healthcare Provider	Primary Care Physician/ Other		Due to COVID-19 pandemic restrictions, participant study visits may need to be completed remotely at the participant's home, by site staff or home healthcare provider, at another study site located near the participant's home, or an alternative center located near the participant's home. This alternative temporary measure will limit impact of the pandemic on the parameter assessment.
12-lead ECG	PI/Sub-I/SC/Other certified staff	Home Healthcare Provider	Primary Care Physician/ Other		Due to COVID-19 pandemic restrictions, participant study visits may need to be completed remotely at another study site located near the participant's home, or an alternative center located near the participant's home. This alternative measure will limit impact of the pandemic on the parameter assessment.
DNA sample	In-clinic after restriction is lifted				NA
Pregnancy test[a]	PI/Sub-I/SC/Other certified staff	Home Healthcare Provider	Primary Care Physician/ Other	Courier may be used for shipment of lab kits from site to participant	Due to COVID-19 pandemic restrictions, participant study visits may need to be completed remotely at the participant's home, by site staff or home healthcare provider, at another study site located near the participant's home, or an alternative center located near the patient's home. Site staff and home healthcare providers will be trained on the study laboratory manual to ensure proper collection, processing, shipping of samples. If local labs are used for collection of safety samples, results and reference ranges will be collected. This alternative temporary measure will limit impact of the pandemic on the parameter assessment.
Urinalysis	PI/Sub-I/SC/Other certified staff	Home Healthcare Provider	Primary Care Physician/ Other	Courier may be used for shipment of lab kits from site to participant	Due to COVID-19 pandemic restrictions, participant study visits may need to be completed remotely at the participant's home, by site staff or home healthcare provider, at another study site located near the patient's home, or an alternative center located near the participant's home. Site staff and home healthcare providers will be trained on the study laboratory manual to ensure proper collection, processing, shipping of samples. If local labs are used for collection of safety samples, results and reference ranges will be collected. This alternative temporary measure will limit impact of the pandemic on the parameter assessment.

Table 10: COVID-19 Clinical Study Mitigation Measures (Optional and Temporary) for Study ALXN1840-WD-302

Study Impact	Clinical Study Temporary Measures				Justification for COVID-19 Mitigation
	Site Staff via Home Visit/Phone/Video	Alternative staff at home	Alternative study/local site	Courier	
Chemistry, coagulation, hematology panel[a]	PI/Sub-I/SC/Other certified staff	Home Healthcare Provider	Primary Care Physician/ Other	Courier may be used for shipment of lab kits from site to participant	Due to COVID-19 pandemic restrictions, participant study visits may need to be completed remotely at the participant's home, by site staff or home healthcare provider, at another study site located near the participant's home, or an alternative center located near the patient's home. Site staff and home healthcare providers will be trained on the study laboratory manual to ensure proper collection, processing, shipping of samples. If local labs are used for collection of safety samples, results and reference ranges will be collected. This alternative temporary measure will limit impact of the pandemic on the parameter assessment.
AEs[a]	PI/Sub-I	Home healthcare provider to query patient about changes from last visit. Contact Investigator if any changes.			Due to COVID-19 pandemic restrictions, participant study visits may need to be completed remotely at the participant's home, by site staff or home healthcare provider. This alternative temporary measure will limit impact of the pandemic on the parameter assessment.
Concomitant Medications[a]	PI/Sub-I	Home healthcare provider to query patient about changes from last visit. Contact Investigator if any changes.			Due to COVID-19 pandemic restrictions, participant study visits may need to be completed remotely at the participant's home, by site staff or home healthcare provider. This alternative temporary measure will limit impact of the pandemic on the parameter assessment.
MELD, PELD, and modified Nazer	NA				NA
Fibrosis-4	NA				NA
Transient elastography	In-Clinic after restriction is lifted				NA
Plasma/serum PK/PD/Biomarkers and Biobank samples	PI/Sub-I/SC/Other certified staff	Home Healthcare Provider	Primary Care Physician/ Other	Courier may be used for shipment of lab kits from site to participant	Due to COVID-19 pandemic restrictions, participant study visits may need to be completed remotely at the participant's home, by site staff or home healthcare provider, at another study site located near the participant's home, or an alternative center located near the patient's home. This alternative temporary measure will limit impact of the pandemic on the parameter assessment.

Table 10: COVID-19 Clinical Study Mitigation Measures (Optional and Temporary) for Study ALXN1840-WD-302

Study Impact	Clinical Study Temporary Measures				Justification for COVID-19 Mitigation
	Site Staff via Home Visit/Phone/Video	Alternative staff at home	Alternative study/local site	Courier	
24-hour urine and feces Cu and Mo	PI/Sub-I/SC/Other certified staff	Home Healthcare Provider		Courier may be used for shipment of lab kits from site to participant	Due to COVID-19 pandemic restrictions, participant study visits may need to be completed remotely at the participant's home by site staff or home healthcare provider. This alternative temporary measure will limit impact of the pandemic on the parameter assessment.
Investigational Product (IP)	PI/Sub-I/SC/Other certified staff	Home healthcare provider may transport IP from site to patient		Courier may be used for shipment of IP from site to participant	Due to COVID-19 pandemic restrictions, participant study visits may need to be completed remotely at the participant's home, by site staff or home healthcare provider, at another study site located near the participant's home, or an alternative center located near the participant's home. IP may be transported by site staff, home healthcare provider, or shipped to patient via courier in a refrigerated (ALXN1840, trientine) or ambient (zinc, penicillamine) container. This alternative temporary measure will limit impact of the pandemic on the IP supply to the patient.
UWDRS II	Site staff Phone/Video				Due to COVID-19 pandemic restrictions, participant study visits may need to be completed remotely at the participant's home by site staff. This alternative temporary measure will limit impact of the pandemic on the parameter assessment. .
UWDRS I & III	Video by Neurologist if feasible				Due to COVID-19 pandemic restrictions, participant study visits may need to be completed remotely at the participant's home by site staff. This alternative temporary measure will limit impact of the pandemic on the parameter assessment.
BPRS-24 and BPRS-C9	Site staff Phone/Video				Due to COVID-19 pandemic restrictions, participant study visits may need to be completed remotely at the patient's home by site staff. This alternative temporary measure will limit impact of the pandemic on the parameter assessment.
CGI-S, CGI-I	Site staff Phone/Video				Due to COVID-19 pandemic restrictions, participant study visits may need to be completed remotely at the participant's home by site staff. This alternative temporary measure will limit impact of the pandemic on the parameter assessment.
EQ-5D/ EQ-5DY	Participant to complete	Home healthcare provider may provide completed questionnaire to site		Courier may be used for shipment of questionnaires from site to participant	Due to COVID-19 pandemic restrictions, participant study visits may need to be completed remotely at the participant's home, by site staff or home healthcare provider. This alternative temporary measure will limit impact of the pandemic on the parameter assessment.

Table 10: COVID-19 Clinical Study Mitigation Measures (Optional and Temporary) for Study ALXN1840-WD-302

Study Impact	Clinical Study Temporary Measures				Justification for COVID-19 Mitigation
	Site Staff via Home Visit/Phone/Video	Alternative staff at home	Alternative study/local site	Courier	
TSQM-9	Participant to complete	Home healthcare provider may provide completed questionnaire to site		Courier may be used for shipment of questionnaires from site to participant	Due to COVID-19 pandemic restrictions, participant study visits may need to be completed remotely at the participant's home, by site staff or home healthcare provider. This alternative temporary measure will limit impact of the pandemic on the parameter assessment.
Re-consent	Site staff Phone/Video	Home healthcare provider may provide signed consent to site			Due to COVID-19 pandemic restrictions, participant study visits may need to be completed remotely at the participant's home, by site staff or home healthcare provider. This alternative temporary measure will limit impact of the pandemic on the re-consent of participants if needed.

a. Critical for safety monitoring

10.10. Abbreviations

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
AUCtau	area under the plasma concentration versus time curve from time 0 to the end of the dosing interval
AUEC	area under the effect versus time curve
$AUEC_t$	area under the effect versus time curve from the start of dose administration to the last observed quantifiable concentration
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (German Federal Institute for Drugs and Medical Devices)
BPRS-24	Brief Psychiatric Rating Scale-24
BPRS-C9	Brief Psychiatric Rating Scale for children;
CE_{max}	maximum observed effect after dosing
CFR	Code of Federal Regulations
CGI	Clinical Global Impression
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity
CIOMS	Council for International Organizations of Medical Sciences
CKD	chronic kidney disease
CL/F	apparent total body clearance
C_{max}	maximum observed concentration
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CpC	ceruloplasmin-bound copper
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trials Facilitation Group
CV	coefficient of variation
CYP	cytochrome P450
CYP2C9/2B6	cytochromes 2C9 and 2B6
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
ECG	electrocardiogram
EDC	electronic data capture
EMLA	eutectic mixture of local anesthetics

EOS	End of Study
EQ-5D	EuroQoL 5 Dimensions
EQ-5DY	EuroQoL 5 Dimensions Youth
ET	Early Termination
FIB-4	fibrosis 4
FSH	follicle stimulating hormone
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GDS	Global Drug Safety
GI	gastrointestinal
GM	geometric mean
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HRT	hormonal replacement therapy
IB	Investigator's Brochure
ICH	International Council for Harmonisation
ICF	informed consent form
IEC	Independent Ethics Committee
IMP	investigational medicinal product
INR	international normalized ratio
IRB	Institutional Review Board
IUD	intrauterine device
LBC	labile-bound copper
MELD	Model for End-stage Liver Disease
MHRA	Medicines and Healthcare products regulatory Agency
Mo	molybdenum
NCC	non-ceruloplasmin-bound copper
$NCC_{corrected}$	non-ceruloplasmin-bound copper concentration corrected for the amount of copper bound to the TPC
NIMP	noninvestigational medicinal product
PD	pharmacodynamic
PedsQL	Pediatric Quality of Life Inventory
PELD	Pediatric End-stage Liver Disease
PK	pharmacokinetic(s)
PRO	patient-reported outcome
PUF	plasma ultrafiltrate
QD	once daily
QOD	every other day
QoL	quality of life
QTcF	QT interval corrected for heart rate using Fridericia's formula
RNA	ribonucleic acid

SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SoA	Schedule of Activities
SoC	standard of care
SUSAR	suspected unexpected serious adverse reaction
TE_{max}	time after dosing at which the maximum effect was observed
t_{max}	time to maximum concentration
TPC	(tetrathiomolybdate-copper-albumin) tripartite complex
TSQM-9	Treatment Satisfaction Questionnaire for Medication-9
ULN	upper limit of normal
UWDRS	Unified Wilson Disease Rating Scale
VAS	Visual Analogue Scale
V_d/F	apparent volume of distribution
WD	Wilson disease
WHO	World Health Organization
WOCBP	woman of childbearing potential

10.11. Country-Specific Changes

The following changes only apply to Germany, and have been incorporated from Protocol Amendment 2 (08 Nov 2021), which was prepared in response to a request from the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM; German Federal Institute for Drugs and Medical Devices) to revise the time specification for reporting an SAE by the Investigator to Alexion to "immediately" from "within 24 hours" and "should not exceed 24 hours", and to include text on the potential risk and mitigation strategies for pediatric participants.

- Section 8.3.1 Time Period and Frequency for Collecting AE and SAE Information
  - For Germany, all SAEs will be recorded and reported to Alexion or the designee immediately, and the Investigator will submit any updated SAE data to Alexion immediately after they become available.
- Section 10.3.3 Recording and Follow-up of AE and/or SAE

In Germany, the Investigator will submit any updated SAE data to Alexion immediately after receipt of the information.

- Section 10.3.4 Reporting of SAEs
  - For Germany, all SAEs will be recorded and reported to Alexion or designee immediately after awareness.

In addition, Section 2.3.4 Burden of Participation and Degree of Distress was added to Protocol Amendment 2 in response to a request by the BfArM to assess and monitor the burden of participation in this clinical study by the investigator, and to define it in the protocol.

- Section 2.3.4 Burden of Participation and Degree of Distress
  - The burden of participation in this study has been minimized to significantly reduce the degree of distress typically associated with participating in a clinical study for children and adolescents. No additional assessments, tests, visits, or procedures other than those described in the SoA (Table 1) should be performed, unless warranted for the evaluation and management of safety events, or for follow up of the participants. The Investigator will monitor the degree of distress and may contact the Medical Monitor to mitigate potential increase in the degree of distress.

10.12. Protocol Amendment History

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

DOCUMENT HISTORY			
Document	**Type of Amendment (Global or Country-specific)**	**Date**	**Summary of Key Changes in the Amendment**
Amendment 3	Global	08 Mar 2022	See Summary of Changes table
Amendment 2	Germany	08 Nov 2021	See below
Amendment 1.1	UK	30 Sep 2021	See below
Amendment 1	UK	07 Jul 2021	See below
Original protocol	Global	15 Mar 2021	Not applicable

Amendment 2 (Germany) (08 Nov 2021)

This amendment was considered to be substantial and applied only to Germany.

Rationale for the Amendment:

The reason for this amendment was in response to a request from the Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM; German Federal Institute for Drugs and Medical Devices) to revise the time specification for reporting an SAE by the Investigator to Alexion to "immediately" from "within 24 hours" and "should not exceed 24 hours", and to include text on the potential risk and mitigation strategies for pediatric participants.

The changes are described below. Note that these changes are included in Section 10.11 (Country-Specific Changes) of this current protocol amendment 3.

Section # and Name	**Description of Change**	**Brief rationale and/or clarifications**
Section 8.3.1 Time Period and Frequency for Collecting AE and SAE Information Section 10.3.3 Recording and Follow-up of AE and/or SAE Section 10.3.4 Reporting of SAEs	The time specification for reporting an SAE by the Investigator to Alexion was revised to state immediately, instead of within 24 hours. The same change was applied to reporting of follow-up information.	The change was made in response to a request from the BfArM, because in Germany, the Investigator has to inform the Sponsor of an SAE immediately.
2.3 Benefit/Risk Assessment	Text has been added stating that potential risk and mitigation strategies have been identified in line with the EU guidance "Ethical Considerations for Clinical Trials on Medicinal Products in Minors"	The change was made in response to a request from the BfArM to assess and monitor the risk threshold by the Investigator, and to define it in the protocol.
2.3.4 Burden of Participation and Degree of Distress	Section added to note that measures have been taken to minimize the burden of participation and degree of distress for the pediatric and adolescent participants in this study, and that the Investigator will monitor the degree of distress.	The change was made in response to a request from the BfArM to assess and monitor the burden of participation in this clinical study by the investigator, and to define it in the protocol.

Abbreviations: BfArM = Bundesinstitut für Arzneimittel und Medizinprodukte (German Federal Institute for Drugs and Medical Devices); SAE = serious adverse event

Amendment 1.1, UK (30 Sep 2021)

This amendment was considered to be substantial and applied only to the UK.

Overall Rationale for the Amendment:

The main reason for this amendment was to specify gastrostomy devices in inclusion criterion #5, as requested by the UK Medicines and Healthcare products Regulatory Agency (MHRA).

Additional changes were also made for consistency and clarity.

Changes from protocol amendment 1 are detailed in the table below.

Section # and Name	Description of Change	Brief rationale and/or clarifications
1.1 Synopsis	Removal of term "standard" from "standard treatment" from the protocol	This change was made for consistency and to avoid confusion between 'standard treatment' and 'standard of care'
Addition of IMP wording for standards of care including SUSAR reporting 5.1 Inclusion Criteria	Modification of the text in inclusion criterion #5, which now reads • Able to swallow intact ALXN1840 tablets or mini-tablets. Participants who require gastrostomy devices for feeding or medications may be enrolled if the inner diameter of the tube can accommodate an intact tablet or mini-tablet without obstruction.	This change was made in response to the request by MHRA to remove inclusion criteria that are not absolute and to predefine the attributes of the gastrostomy devices.
10.3.2 Definition of SAE	Text added noting that SUSAR will be in accordance with the Summary of Product Characteristics of the respective SoC products	To clarify SUSAR reporting requirements for SoC.

Abbreviations: SoC = Standard of Care; SUSAR = suspected unexpected serious adverse reaction

Amendment 1, UK (07 Jul 2021)

This amendment was considered to be substantial and applied only to the UK.

Overall Rationale for the Amendment:

The main reason for this amendment was to include language relating to 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.

Additional changes were also made to incorporate changes made in Administrative Change Letter 1, dated 09 Jun 2021, which were to change the guidance on blood volume and to make some minor clarifications and corrections. Minor administrative changes were also made for clarity.

Note that COVID-19 specific text was not included in this protocol amendment 3 (Global) because it was specific to the UK, but other updates incorporated with Amendment 1 have been included in this amendment.

Changes from the original protocol are detailed in the table below.

Section # and Name	Description of Change	Brief rationale and/or clarifications
1.2 Study Schema, Figure 1 1.3 Schedule of Activities, Table 1	Screening period changed from Day -28 to Day -2 to Day -28 to Day -1, with randomization to occur before Day 1 procedures begin.	To enable sites to perform randomization up to the start of Day 1 procedures, rather than just on Day -1.
1.3 Schedule of Activities, Table 1	"ET" added to Week 24 in Period 2	Added for clarity, because similar to Period 1, the ET visit would occur during Period 2 in the event of early termination.
	Footnote k revised to state that transient elastography will be done when available.	To reflect that it may not be possible to perform transient elastography at all study sites.
	Text on alternative blood sampling schedule for infants deleted from footnote l.	To align with the change in guidance on blood sampling volumes (see below).
	Period 2 added to footnote l.	To clarify that plasma/serum samples will be collected predose in both Periods 1 and 2.
1.3 Schedule of Activities, Table 1 Section 8, Study Assessments and Procedures	Text in the footnote stating that an alternative blood sampling schedule for infants will be given in the Study Operations Manual.	Guidelines on blood sampling are provided in Section 10.7. No separate guidelines for infants are required, because the minimum age for enrollment into the study is 3 years.
1.3 Schedule of Activities, Table 1 8.8 Biomarkers 10.2 Clinical Laboratory Tests, Table 10	Footnote l simplified to state that serum ceruloplasmin will be assessed separately to plasma ceruloplasmin (which will be assessed as part of the PK/PD/biomarker parameters).	To clarify that serum and plasma ceruloplasmin are analyzed separately.
1.3 Schedule of Activities, Table 1 10.2 Clinical Laboratory Tests	Text requiring pregnancy testing for 3 months after the EOS visit removed from footnote j and Section 10.2.	To align with CTFG guidance on contraception and pregnancy testing recommendations, and to be consistent with the Phase 3 study WTX101-301.
6.5.2 Disallowed Medicine and Therapy	Addition of text stating that vitamin E and estrogen should not be initiated during the study, but can be continued if already being taken.	To clarify that vitamin E and estrogen can be taken during the study, if already being taken before the study start.
8.2.3 Electrocardiograms	Removal of cross-reference to Section 7 for QTc withdrawal criteria and any additional QTc readings that may be necessary.	QTc withdrawal criteria are not required in this protocol.
10.2 Clinical Laboratory Tests, Table 10	Removal of text in footnote relating to Hy's Law.	Text removed as not needed. If participants experience INR prolongation and they are admitted to hospital, the event will meet the definition and be recorded as an SAE.
10.7 Blood Sampling Volumes	Wording revised to state that the Investigator may, rather than should, apply an EMLA cream/plaster at the puncture site, and to add that use of an EMLA cream/plaster depends on clinical practice at the study site.	To reflect that EMLA cream/plaster use depends on clinical practice at the study site.
	Reference changed from the European Commission guidance to the US guidelines.	The guidance on blood sampling volumes has been changed from

Section # and Name	Description of Change	Brief rationale and/or clarifications
	From: • European Commission. European Commission Ethical Considerations for Clinical Trials on Medicinal Products Conducted with the Paediatric Population: Recommendations of the ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to the good clinical practice in the conduct of clinical trials on medicinal products for human use. 2008 To: • POLICY- Guidelines for Limits of Blood Drawn for Research Purposes in the Clinical Center https://irb.research.chop.edu/sites/default/files/documents/g_nih_blooddraws.pdf" **Text changed from:** • Volume of blood samples: Per study participant, the study-related blood loss (including any losses in the collection procedure) should not exceed 3% of the total blood volume during a period of 4 weeks, and should not exceed 1% at any single time. The total volume of blood is estimated at 80 to 90 mL/kg body weight. To: • Volume of blood samples: Per study participant, the study-related blood loss (including any losses in the collection procedure) should not exceed more than 5 mL/kg body weight (5% of total blood volume) in a single day and no more than 9.5 mL/kg (11% of total blood volume) over any 8-week period.	the European Commission guidance to the US National Institutes of Health guidelines, because the US guidelines allow Investigators to conduct all tests planned without increasing the number of blood draw points.
10.10 COVID-19 Vaccine Risk Assessment	Text on the COVID-19 vaccine risk assessment performed with respect to ALXN1840 added.	A vaccine risk assessment has been requested by the UK MHRA for studies performed in the UK.
All	Minor administrative changes.	For clarity.

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