TITLE PAGE

Protocol Title:

A PHASE 3, RANDOMIZED, RATER-BLINDED, MULTI-CENTER STUDY TO EVALUATE THE EFFICACY AND SAFETY OF ALXN1840 ADMINISTERED FOR 48 WEEKS VERSUS STANDARD OF CARE IN PATIENTS WITH WILSON DISEASE AGED 12 YEARS AND OLDER WITH AN EXTENSION PERIOD OF UP TO 60 MONTHS

Protocol Number: WTX101-301

Amendment Number: 3 (Global)

Compound Number: ALXN1840 (formerly WTX101)

Short Title:

Multicenter Study of Efficacy and Safety of ALXN1840 versus Standard of Care in Patients with Wilson Disease Aged 12 Years and Older

Sponsor Name:
Alexion Pharmaceuticals, Inc.

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Regulatory Agency Identifying Number(s):

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Original Protocol	07 Nov 2017
Amendment 1	17 Jan 2019
Amendment 1.1 (Japan)	25 Mar 2019
Amendment 1.2 (Netherlands)	22 May 2019
Amendment 1.3 (Germany)	17 May 2019
Amendment 1.4 (Sweden)	21 May 2019
Amendment 1.5 (Germany)	10 Jul 2019
Amendment 1.6 (Austria)	30 Apr 2020
Amendment 2 (Global)	25 Mar 2021
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Amendment 3 (Global)	27 Apr 2022

Sponsor Signatory:

[redacted]

02-May-2022 | 15:19:06 EDT

[redacted]

Date

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

INVESTIGATOR'S AGREEMENT

I have read the Study WTX101-301 protocol amendment 3 and agree to conduct the study in accordance with this protocol, all applicable government regulations, the principles of the ICH E6 Guidelines for GCP, and the principles of the World Medical Association Declaration of Helsinki. I also agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Amendment 3 (Global), 27 Apr 2022

This amendment is considered to substantially impact the conduct 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.

Overall Rationale for the Amendment:

The main reason for this amendment is to add the requirement for Alexion approval prior to increasing the dose of ALXN1840. Administrative Letters since approval of the previous amendment have also been incorporated. Changes from protocol amendment 2 are summarized in the table below.

Section # and Name	Description of Change	Brief Rationale and/or clarifications
Section 1.2, Schedule of Activities, Table 1	• Collection of Wilson disease medication history deleted on Day 1.	• Wilson disease medication history collected at Screening so not needed at Day 1 as well.
	• Administer/dispense ALXN1840 added at Week 48 only for patients continuing in the extension period.	• To align with current operating procedures of this study.
Section 1.2, Schedule of Activities, Table 2	• Plasma/serum PK/PD, Biomarkers, and Biobank samples added at Extension Period Week 264 and Early Termination	• To align with current operating procedures of this study.
	• Non-verbal Stroop test added (Administrative Letter 10.1).	• The non-verbal Stroop test was included in the original protocol and inadvertently deleted in Amendment 2.
Section 1.2, Schedule of Activities, Table 3	• Footnote added to Day 1 24-hour urine, transient elastography, and BPRS: assessments will be done only for patients from Study WTX101-201. • CGI, EQ-5D, and TSQM-9 added to Extension Period Weeks 168 and 192.	To align with current operating procedures of this study.
Section 4.3.1, ALXN1840; Section 6.2.3.2 Dose Modification ALXN1840	Addition of text to clarify that Alexion approval is needed to increase the dose of ALXN1840.	To enhance Alexion oversight of dose escalations.
Section 5.1 Inclusion criteria	Inclusion criterion 1 for diagnosis of Wilson disease was expanded to include historical diagnosis (Administrative Letter 9)	To further clarify the process for confirming the score for patients who were diagnosed prior to the establishment of the 2012 European Association for the Study of Liver Wilson Disease Clinical Practice Guidelines.
Section 6.2.3.2, Dose Modifications, Table 4	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
10.1.1 Regulatory and Ethical Considerations	Modified text to remove specific reference to regional guidance and listed as examples only. Included the European Regulation No 536/2014 for clinical trials on medicinal products for human use as an example.	To include a more general statement as not all regional guidances previously included are applicable.
Section 10.2.1, Clinical Laboratory Tests; Chemistry, Table 12	HDL cholesterol added	To align with current operating procedures of this study.
All sections	Minor editorial updates and corrections	For clarification, and to ensure accuracy and consistency throughout the protocol.

Abbreviations: BPRS = Brief Psychiatric Rating Scale; CGI = Clinical Global Impression; EQ-5D = European Quality of Life Five Dimension; HDL = high density lipoprotein; PK = pharmacokinetics; PD = pharmacodynamics; TSQM-9 = Treatment Satisfaction Questionnaire for Medication.

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1.1. Synopsis

Protocol Title: A Phase 3, Randomized, Rater-Blinded, Multi-Center Study to Evaluate the Efficacy and Safety of ALXN1840 Administered for 48 Weeks versus Standard of Care in Patients with Wilson Disease Aged 12 Years and Older, with an Extension Period of up to 60 Months

Short Title: Multicenter Study of Efficacy and Safety of ALXN1840 versus Standard of Care in Patients with Wilson Disease Aged 12 Years and Older

Rationale:

This study is being conducted to assess the efficacy and safety of ALXN1840 (formerly WTX101), a novel, first-in-class, copper-protein binding agent versus standard of care (SoC) in patients with Wilson Disease (WD) who are 12 years of age or older (18 years and older in Germany). Unlike current treatments for WD, ALXN1840 is designed to provide an alternative copper-protein transport mechanism, and rapidly form copper-protein complexes with very high specificity for copper to quickly treat the underlying disease by mobilizing excess tissue copper and promoting biliary excretion of copper (the body's natural route of elimination) to reduce copper overload.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To evaluate the efficacy of ALXN1840 administered for 48 weeks, compared to standard of care (SoC), on copper control in WD patients aged 12 years and older	• Daily mean area under the effect-time curve (AUEC) of directly measured non-ceruloplasmin-bound copper (dNCC) from 0 to 48 weeks
Secondary	
• Establish the safety and tolerability of individualized dosing of ALXN1840	Incidence of • Adverse events/serious adverse events (AE/SAEs) • Clinical laboratory test data • Neurological and physical examination findings • 12-lead electrocardiogram (ECG) data • Vital signs
• Evaluate the effects of ALXN1840 on disability status	• Change from baseline in the Unified Wilson Disease Rating Scale (UWDRS) Part II total score
• Evaluate the effects of ALXN1840 on neurological status	• Change from baseline in UWDRS Part III total score and individual item/subscales (arising from a chair, gait, handwriting, and speech)
• Evaluate the global effects of ALXN1840 on global clinical symptoms	• Clinical Global Impression-Improvement Scale (CGI-I) • Change from baseline in Clinical Global Impression-Severity Scale (CGI-S)

• Evaluate the effects of ALXN1840 on hepatic status	• Change from baseline in Model for End-Stage Liver Disease (MELD) score
• Evaluate the efficacy of ALXN1840 administered for 48 weeks, compared to SoC, on copper control in WD patients aged 12 years and older	• Absolute change from baseline (Day 1) to 48 weeks in calculated NCC (cNCC) in plasma. • Percentage change from baseline in cNCC in plasma. For ALXN1840-treated patients, the cNCC in plasma will be corrected for the amount of copper bound to the ALXN1840 tripartite complex (TPC) ($cNCC_{corrected}$)
• Evaluate the effects of ALXN1840 on the cNCC responder rate	• cNCC responder rate at 48 weeks
Exploratory	
• Explore the effects of ALXN1840 on the individual patient's 3 most troublesome symptoms related to WD	• Individualized assessment of each patient's 3 most troublesome symptoms
• Explore the effects of ALXN1840 on hepatic fibrosis	• Change from baseline in the Fibrosis-4 (FIB 4) Index and by transient elastography
• Explore the effects of ALXN1840 on hepatic status	• Change from baseline in Modified Nazer Score
• Explore the effects of ALXN1840 on psychiatric symptoms	• Change from baseline in Brief Psychiatric Rating Scale-24 (BPRS-24)
• Explore the effects of ALXN1840 on the following Quality of Life (QoL)/Patient Reported Outcomes (PRO)	Change from baseline in QoL/PRO endpoint measures: • EuroQoL 5 Dimensions (EQ-5D) • Treatment Satisfaction Questionnaire for Medication-9 (TSQM-9)
• Explore the change in the timed 25F Walk Test	• Change from baseline in timed 25F Walk Test
• Explore the change in the 9-hole Peg Test (9-HPT)	• Change from baseline in 9-HPT
• Explore the change in the non-verbal Stroop Interference Test	• Change from baseline in non-verbal Stroop Interference Test
• Explore the change in the Digit Span Test.	• Change from baseline in Digit Span Test
• Explore other directly measured pharmacodynamics (PD) and biomarkers of ALXN1840	• Plasma total copper, plasma ultrafiltrate (PUF)-copper, dNCC, labile bound copper (LBC), ceruloplasmin (Cp), and ceruloplasmin-bound copper (CpC) concentration-time profiles in plasma • Daily mean AUEC of plasma dNCC (from 0 to 24 and 24 to 48 weeks) • Daily mean AUEC of LBC from 0 to 48 weeks • Daily mean AUEC of plasma total copper from 0 to 48 weeks • Absolute and percentage change from baseline (Day 1) to 48 weeks in dNCC • Absolute and percentage change from baseline (Day 1) to 48 weeks in LBC
• Explore ALXN1840 effect on initial decoppering phase compared to SoC based on	• Time to first confirmed increase in plasma dNCC and total copper concentration

directly measured pharmacokinetic (PK)/PD and biomarkers	• Time to minimum and maximum concentration of: – Plasma total copper – Plasma dNCC – Plasma LBC – Ratio plasma dNCC:total copper – Ratio plasma LBC:total copper – Urinary molybdenum – Ratio urinary molybdenum:copper – Ratio urinary molybdenum:dosed molybdenum – Plasma Cp – Plasma CpC – Ratio plasma Cp:total copper – Ratio plasma CpC:total copper – Ratio plasma CpC:Cp
• 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 measures: – Plasma total copper – Plasma dNCC – Plasma LBC – Ratio plasma dNCC: total copper – Ratio plasma LBC:total copper – Urinary molybdenum – Ratio urinary molybdenum:copper – Ratio urinary molybdenum:dosed molybdenum – Plasma Cp concentration – Plasma CpC concentration – Ratio plasma Cp:total copper – Ratio plasma CpC:total copper – Ratio plasma CpC:Cp
• Explore PK of ALXN1840	• Total molybdenum and PUF-molybdenum concentration-time profiles in plasma
• Evaluate the effects of ALXN1840 on the LBC responder rate	• LBC responder rate at 48 weeks
• Explore the change in 24-hour urinary copper and urinary molybdenum	• Change from baseline to 48 weeks in 24-hour urinary copper and urinary molybdenum
Extension Period	
• Long term safety and efficacy	• AEs, AESI, SAEs, laboratory tests (chemistry, hematology, coagulation, and urinalysis with microscopy), pregnancy testing in females of childbearing potential, physical examinations, vital signs, and ECGs. • CGI-I and the change from baseline in CGI-S • Change from baseline in MELD score • Change from baseline in UWDRS Part II total score • Change from baseline in UWDRS Part III total score and individual item/subscales

	(arising from a chair, gait, handwriting, and speech) • NCC/$NCC_{corrected}$ responder rate • LBC responder rate • Concentration-time profiles of the directly measured PK/PD and biomarkers

Abbreviations: 25F = 25-foot; 9-HPT = 9-hole peg test; AE = adverse event; AESI = adverse event of special interest; AUEC = area under the effect-time curve; BPRS-24 = Brief Psychiatric Rating Scale-24; CGI-I = Clinical Global Impression-Improvement Scale; CGI-S = Clinical Global Impression-Severity Scale; Cp = ceruloplasmin; CpC = ceruloplasmin-bound copper; ECG = electrocardiogram; EQ-5D(Y) = EuroQoL 5 Dimensions (Youth); FIB-4 = Fibrosis-4; LBC = labile bound copper; MELD = Model for End-stage Liver Disease; (d)(c)NCC = (directly measured) (calculated) non-ceruloplasmin-bound copper; $cNCC_{corrected}$ = calculated corrected NCC; PD = pharmacodynamics; PK = pharmacokinetics; PRO = Patient Reported Outcomes; PUF = plasma ultrafiltrate; QoL = quality of life; SAE = serious adverse event; SoC = standard of care; TPC = tripartite complex; TSQM-9 = Treatment Satisfaction Questionnaire for Medication-9; UWDRS = Unified Wilson Disease Rating Scale

Overall Design:

This is a randomized, rater-blinded, multi-center study assessing the efficacy and safety of ALXN1840 versus SoC. In the Primary Evaluation Period, efficacy and safety will be assessed for an individualized ALXN1840 dosing regimen compared with SoC administered for 48 weeks in patients with WD who are aged 12 years and older (18 years and older in Germany). Approximately 180 patients will be enrolled globally.

Patients meeting all inclusion and no exclusion criteria will be enrolled into the study and studied as outpatients. Eligible patients with WD will be enrolled into 1 of 2 cohorts.

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

All enrolled patients will be randomized by cohort in a 2:1 ratio to treatment with ALXN1840 or SoC (either as continued therapy in Cohort 1 or as continued or initial therapy in Cohort 2). Treatments will be assigned randomly, stratified by cohort.

Patients who are randomized to receive ALXN1840 will be required to withhold treatment with SoC for ≥ 48 hours immediately prior to first study assessment on Day 1. Patients who are randomized to ALXN1840 will receive ALXN1840 as delayed-release tablets for oral administration at doses ranging from 15 mg every other day (QOD) to 60 mg once daily (QD). Efficacy and safety assessments will be performed at scheduled visits, while adverse events (AEs) and concomitant medications will be monitored continuously throughout the study. Patients randomized to SoC will initiate treatment or continue treatment on their current regimen where possible, without compromising the safety of individual patients.

The Primary Evaluation Period will consist of an up to 28-day Screening Period, a 1-day Enrollment Visit, a 48-week Treatment Period, and a Follow-up Visit 4 weeks after the last dose for patients who do not elect to continue in the Extension Period.

Patients in Study WTX101-301 who have completed the 48-week Treatment Period and patients who completed participation in Study WTX101-201 will be offered the opportunity to participate in an up to 60-month Extension Period to evaluate the long-term safety and efficacy of ALXN1840.

An independent Data Monitoring Committee (DMC), a Hepatic Adjudication Panel, and a Neurological Adverse Event (Neuro AE) Panel comprising experts in relevant fields with no direct relationship to the study, will be appointed by the sponsor. As detailed in their respective Charters (maintained separately from the study protocol), these committees will review and monitor study data for safety, effectiveness, and study conduct, and make recommendations regarding study continuation, changes to the study population, and/or modification to study procedures.

Number of Patients:

Approximately 180 patients will be enrolled and randomized by cohort in a 2:1 ratio to treatment with ALXN1840 or SoC to obtain data from approximately 150 evaluable patients (100 ALXN1840, 50 SoC) for the primary analysis (Section 9.2.7).

Statistical Analysis:

The primary endpoint is the daily mean AUEC of directly measured plasma non-ceruloplasmin copper (dNCC) from 0 to 48 weeks. The AUEC for plasma dNCC concentration will be calculated using the trapezoidal rule, and then divided by number of days to yield a mean AUEC of plasma dNCC from baseline to Week 48.

The primary efficacy analysis will be conducted on the available Week 48 data from the Primary Evaluation Period for all patients. A clinical study report (CSR) will be produced based on efficacy, safety, pharmacokinetic (PK), and pharmacodynamic (PD) data collected through the end of the 48-week Primary Evaluation Period. A final CSR to summarize long-term efficacy, safety, PK, and PD parameters will be produced at the end of the Extension Period.

Mean AUEC of plasma dNCC concentration from baseline to 48 weeks will be compared between ALXN1840 and SoC using an analysis of covariance (ANCOVA) statistical model; treatment arm, baseline plasma dNCC concentration, and cohort, will be included in the model. Tests will be performed at a significance level of 0.05 (2-sided).

Model-based estimates of the difference between randomized treatments (ALXN1840 – SoC) in $AUEC_{0\text{-}48W}$, along with a 2-sided 95% confidence interval (CI) and p-value, will be provided. If the lower 2-sided 95% CI exceeds 0 µM, superiority will be concluded.

The secondary efficacy endpoints and the methods for analyzing them will be defined in the Statistical Analysis Plan (SAP).

1.2. Schedule of Activities

The Schedule of Activities (SoA) for Screening and the Primary Evaluation Period is provided in Table 1. The Week 48 visit is the end of the Primary Evaluation Period and the beginning of the Extension Period (ie, the Week 48 visit and the Extension Day 1 visit occur on the same day). All assessments for the Week 48 visit will be performed prior to dosing of ALXN1840. Dosing of ALXN1840 on Extension Day 1 marks the beginning of the Extension Period. Patients who do not enter the Extension Period will discontinue dosing at Week 48 and will have a final study

visit for safety follow up at Week 52. The SoA for the Extension Period for patients who received SoC during the Primary Evaluation Period is provided in Table 2. The SoA for the Extension Period for patients who received ALXN1840 during the Primary Evaluation Period and for patients who completed Study WTX101-201 is provided in Table 3.

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

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

Unscheduled visits that occur outside the protocol-specified visits are permitted at the discretion of the Investigator. Procedures, tests, and assessments conducted during unscheduled visits will be performed at the discretion of the Investigator (Section 8.7).

Table 1: Schedule of Activities in the Primary Evaluation Period

Day	Screening[a]	Treatment Period													UNS[b]	Follow-up[c]
	-28	1[d]	8	15	29[d]	43[d]	57[d]	85[d]	127[d]	169[d]	211	253[d]	295	337[d]		365
Week			1[e]	2[e]	4	6	8	12	18	24	30[e]	36	42[e]	48/ET[f]		52
Window (days)			±3									±7	±3	±7		±7
Obtain informed consent/assent	X															
Review eligibility criteria	X[g]															
Randomization[h]	X															
Medical history	X															
WD medication history	X															
Physical examination	X															X
Abbreviated physical examination[i]		X			X	X	X	X	X	X		X		X		
Vital signs[j]	X	X			X	X	X	X	X	X		X		X		X
12-lead ECG	X	X			X			X		X				X		X
FSH[k]	X															
HIV/hepatitis B & C screen	X															
DNA sample		X[l]														
Pregnancy test[m]	X	X			X	X	X	X	X	X		X		X		X
Urinalysis	X	X			X	X	X	X	X	X		X		X		X
Chemistry, coagulation, hematology panel	X	X			X	X	X	X	X	X		X		X		X
MELD and modified Nazer[n]	X	X			X	X	X	X	X	X		X		X		X
Fibrosis-4[n]		X			X	X	X	X	X	X		X		X		X
Transient elastography		X[o]												X		

Day	**Screening[a]**	**Treatment Period**													**UNS[b]**	**Follow-up[c]**
	-28	**1[d]**	**8**	**15**	**29[d]**	**43[d]**	**57[d]**	**85[d]**	**127[d]**	**169[d]**	**211**	**253[d]**	**295**	**337[d]**		**365**
Week			**1[e]**	**2[e]**	**4**	**6**	**8**	**12**	**18**	**24**	**30[e]**	**36**	**42[e]**	**48/ET[f]**		**52**
Window (days)			**±3**									**±7**	**±3**	**±7**		**±7**
Plasma/serum PK/PD/Biomarkers and Biobank samples[p]	X	X			X	X	X	X	X	X		X		X		
24-hour urine[q]		X			X			X		X		X		X		
UWDRS Parts I, II, and III[r,s]		X			X			X		X		X		X		
BPRS-24[s,t]		X								X				X		
CGI[u]		X			X			X		X		X		X		
EQ-5D		X			X			X		X		X		X		
TSQM-9					X			X		X		X		X		
3 most troublesome symptoms[s, v]		X						X		X				X		
Timed 25F Walk Test[s]		X						X		X				X		
9-hole Peg Test[s]		X						X		X				X		
Non-verbal Stroop Interference Test[s]		X						X		X				X		
Digit Span Test[s]		X						X		X				X		
Adverse event and concomitant medication	←	→														
Administer/dispense ALXN1840 or SoC[w]		X			X	X	X	X	X	X		X		X[x]		

Note: Patients who complete the 48-week period of randomized treatment in Study WTX101-301 will be offered the opportunity to participate in an up to 60-month open-label Extension Period in which they will receive ALXN1840.

a. Patients randomized to receive ALXN1840 will withhold treatment with SoC for ≥ 48 hours prior to first study assessment on Day 1.
b. Unscheduled study 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. Refer to Section 8.7.
c. Follow-up visit procedures (Week 52) will be performed only for patients who do not enter the Extension Period. The Week 52 visit will be the End of Study visit for these patients.
d. Assessments on Day 1 and other study visit days where laboratory sampling is planned should be performed pre-dose.

e. Week 1, Week 2, Week 30, and Week 42 (Day 8, Day 15, Day 211, and Day 295) will be performed via a safety phone call. If a neurological adverse event 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.
f. Assessments at the Week 48 visit in the Primary Evaluation Period may be used as the Extension Period Day 1 assessments.
g. 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.
h. Patients will be randomized after meeting all inclusion and none of the exclusion criteria. Randomization may be required on or before Day-2 to allow for SoC to be withheld for ≥ 48-hours for patients randomized to receive ALXN1840 as noted in footnote a. All procedures required at Screening must be completed prior to the Day 1 visit.
i. Abbreviated physical examination consists of a body system relevant examination based upon Investigator judgment and patient symptoms. At least 1 body system must be checked for an abbreviated exam.
j. Vital signs include height (Day 1 only; without shoes), heart rate, blood pressure, respiration rate, temperature, and weight.
k. Follicle-stimulating hormone will only be performed for post-menopausal females.
l. The DNA sample is optional and can be collected at any time on or after Day 1; the sample will only be taken if the patient has provided separate informed consent.
m. Serum and urine pregnancy tests will only be performed for females of childbearing potential. Female patients of childbearing potential must not be pregnant nor breastfeeding and must have a negative serum pregnancy test at Screening. Positive urine pregnancy results will be confirmed by a serum pregnancy test. In addition to pregnancy tests detailed at the visits in the Schedule of Activities, females of childbearing potential in Austria only 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.
n. To be calculated by the Central Laboratory.
o. 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.
p. Plasma or serum samples will be obtained from the blood samples collected pre-dose on the day of visit. See Section 8.5.
q. For the 24-hour urine sample, 500 mL will be considered the minimum acceptable sample size. Any amount < 500 mL will not be tested due to an insufficient sample collection. Urine collected will be used for 24-hour creatinine, molybdenum, and copper. The container for 24-hour urine collection during should be dispensed at the study visit immediately prior to the next expected collection. Urine containers should be dispensed at the Screening Period, Day 1, and Weeks 8, 18, 24, and 36.
r. The UWDRS Part I and III must be performed by a blinded neurologist.
s. With the exception of Day 1, assessment can be completed within 2 days of the study visit day.
t. The BPRS-24 can be performed by a qualified person who has completed the required training.
u. CGI-I is not performed at Day 1.
v. In addition to collection via a paper questionnaire, the patient's 3 most troublesome symptoms may also be recorded by the site staff via video for patients who provide separate informed consent.
w. Appropriately trained study staff will administer the ALXN1840 on Day 1 and will instruct patients 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.
x. ALXN1840 dispensed/administered only for patients continuing into the Extension Period.

Abbreviations: BPRS-24 = Brief Psychiatric Rating Scale-24; CGI = Clinical Global Impression; CGI-I = Clinical Global Impression-Improvement Scale; CGI-S = Clinical Global Impression-Severity Scale; EOS = End of Study; EQ-5D = EuroQoL 5 Dimensions; ET = Early Termination; FSH = follicle-stimulating hormone; MELD = Model for End-Stage Liver Disease; PD = pharmacodynamic; PK = pharmacokinetic; SoC = standard of care; TSQM-9 = Treatment Satisfaction Questionnaire for Medication-9; UNS = unscheduled; UWDRS = Unified Wilson Disease Rating Scale; WD = Wilson Disease.

Table 2: Schedule of Activities in the Extension Period for Patients Who Received Standard of Care in the Primary Evaluation Period

Extension Study Day	Extension Treatment Period																								UNS[a]	ET	EOS
	1[b,c]	8	15	29	43	57	85	127	169	211	253	295	337	421	505	589	673	841	1009	1177	1345	1513	1681	1849			1877
Extension Study Week		1[c]	2[c]	4	6	8	12	18	24	30[c]	36	42[c]	48[e]	60	72	84	96	120	144	168	192	216	240	264			268
Window (days)				±3		±7	±3						±7														
Physical examination	X			X	X	X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X		X	X
Vital signs[d]	X			X	X	X	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	X
Pregnancy test[f]	X			X	X	X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X		X	X
Chemistry, coagulation, hematology panel, and urinalysis	X			X	X	X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X		X	X
24-hour urine[g]	X			X			X		X		X		X		X		X	X	X	X	X	X	X	X			
MELD and modified Nazer[h]	X			X	X	X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X		X	X
Fibrosis-4[h]	X			X	X	X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X		X	X
Transient elastography	X												X				X		X		X			X		X	X
Plasma/serum PK/PD/ Biomarkers and Biobank samples[i]	X			X	X	X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X		X	
UWDRS Parts I, II, and III[j,k]	X			X			X		X		X		X	X	X	X	X	X	X	X	X	X	X	X		X	
BPRS-24[k,l]									X				X		X		X	X	X	X	X	X	X	X		X	
CGI	X			X			X		X		X		X		X		X	X	X	X	X						
EQ-5D	X			X			X		X		X		X		X		X	X	X	X	X						
TSQM-9	X			X			X		X		X		X		X		X	X	X	X	X						
3 most troublesome symptoms[k,m]	X						X		X				X														
Timed 25F Walk Test[k]	X						X		X				X														

Extension Study Day	Extension Treatment Period																								UNS[a]	ET	EOS
	1[b,c]	8	15	29	43	57	85	127	169	211	253	295	337	421	505	589	673	841	1009	1177	1345	1513	1681	1849			1877
Extension Study Week		1[c]	2[c]	4	6	8	12	18	24	30[c]	36	42[c]	48[e]	60	72	84	96	120	144	168	192	216	240	264			268
Window (days)				±3		±7	±3						±7														
9-hole Peg Test[k]	X						X		X				X														
Non-verbal Stroop Test[k]	X						X		X				X														
Digit Span Test[k]	X						X		X				X														
Adverse event and concomitant medication[n]	←																							→			
Administer/ dispense ALXN1840[o]	X			X	X	X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X			

Note: All patients who complete the 48-week period of randomized treatment in Study WTX101-301 will be offered the opportunity to participate in an up to 60-month open-label Extension Period in which they will receive ALXN1840.

a. Unscheduled study visits may occur at any time during the protocol and may include any study procedures (including dispensing of ALXN1840) as deemed necessary by the Investigator. These visits may or may not be completed by a home healthcare nurse depending on the purpose of the unscheduled visit. Refer to Section 8.7.
b. Assessments on Day 1 and other study visit days where laboratory sampling is planned should be performed pre-dose.
c. The Week 1, Week 2, Week 30, and Week 42 Visits will be performed via safety phone calls. During these phone visits, adverse events and concomitant medications will be assessed and recorded. If a neurological adverse event is reported, the following assessments must be performed as soon as possible: UWDRS Parts II and III, the CGI-I and CGI-S. Investigators can perform additional assessments or laboratory testing at their discretion.
d. Vital signs include height (Day 1 only; without shoes), heart rate, blood pressure, respiration rate, temperature, and weight.
e. Assessments at the Week 48 Visit will also be used as the Extension Period Day 1 assessments.
f. Serum and urine pregnancy tests will only be performed for females of childbearing potential. Female patients of childbearing potential must not be pregnant nor breastfeeding and must have a negative serum pregnancy test at Screening. Positive urine pregnancy results will be confirmed by a serum pregnancy test. In addition to pregnancy tests detailed at the visits in the Schedule of Activities, females of childbearing potential in Austria only 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.
g. For the 24-hour urine sample, 500 mL will be considered the minimum acceptable sample size. Any amount < 500 mL will not be tested due to an insufficient sample collection. The container for 24-hour urine collection should be dispensed at the study visit immediately prior to the next expected collection. Urine containers should be dispensed on Extension Study Day 1 and Weeks 8, 18, 24, 36, 60, 84, 96, 120, 144, 168, 192, 216, and 240.
h. To be calculated by the Central Laboratory.
i. Plasma or serum samples will be obtained from the blood samples collected pre-dose on the day of visit. See Section 8.5.
j. The UWDRS Part I and III must be performed by a blinded neurologist.
k. With the exception of Day 1, assessment can be completed within 2 days of the study visit day.
l. The BPRS-24 can be performed by a qualified person who has completed the required training.
m. In addition to collection via a paper questionnaire, the patient's 3 most troublesome symptoms may also be recorded by the site staff via video for patients who provide separate informed consent. Note: this information is not required to be collected via video in the Extension Period of the study and also for patients who switch from SoC to ALXN1840 during the first year of the Extension Period.
n. Adverse events and concomitant medications will be assessed and recorded via phone calls at Extension Study Safety Phone Visits (Weeks 1, 2, 30, and 42).
o. Appropriately trained employees of the study site will administer the ALXN1840 on Day 1 and will instruct patients 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.

Abbreviations: CGI = Clinical Global Impression; CGI-I = Clinical Global Impression-Improvement Scale; CGI-S = Clinical Global Impression-Severity Scale; ECG = electrocardiogram; EOS = End of Study; EQ-5D = EuroQoL 5 Dimensions; ET = Early Termination; MELD = Model for End-Stage Liver Disease; PD = pharmacodynamic; PK = pharmacokinetic; SoC = standard of care; TSQM-9 = Treatment Satisfaction Questionnaire for Medication-9; UNS = unscheduled; UWDRS = Unified Wilson Disease Rating Scale; WD = Wilson Disease

Table 3: Schedule of Activities in the Extension Period for Patients Who Received ALXN1840 in Study WTX101-301 Primary Evaluation Period or Completed the Main Period of Study WTX101-201

	Extension Treatment Period														UNS[a]	ET	EOS
Extension Study Day	**1[b,d]**	**85**	**169**	**253**	**337**	**505**	**673**	**841**	**1009**	**1177**	**1345**	**1513**	**1681**	**1849**			**1877**
Extension Study Week		**12**	**24**	**36**	**48**	**72**	**96**	**120**	**144**	**168**	**192**	**216**	**240**	**264**			**268**
Extension Study Day (including Primary Evaluation Period)		**421**	**505**	**589**	**673**	**841**	**1009**	**1177**	**1345**	**1513**	**1681**	**1849**	**2017**	**2185**			**2213**
Extension Study Week (including Primary Evaluation Period)		**60**	**72**	**84**	**96**	**120**	**144**	**168**	**192**	**216**	**240**	**264**	**288**	**312**			**316**
Window (days)		**±7**															
Informed consent[c]	X																
Inclusion/exclusion criteria	X																
Physical examination	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Vital signs[e]	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
12-lead ECG	X[d]				X		X		X		X		X	X		X	X
Pregnancy test[f]	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Chemistry, coagulation, and hematology panel and urinalysis	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
24-hour urine[g,h]	X[d,i]		X		X	X	X	X	X	X	X	X	X	X			
MELD and modified Nazer[j]	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Fibrosis-4[j]	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Transient elastography	X[d,i]				X		X		X		X		X			X	X
Plasma/serum PK/PD/ Biomarkers and Biobank samples[k]	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
UWDRS Parts I, II, and III[l,m]	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
BPRS[n]	X[d,i]		X		X	X	X	X	X	X	X	X	X	X		X	
CGI	X[d]		X		X	X	X	X	X	X	X					X	

EQ-5D	X[d]		X		X	X	X	X	X	X	X					X	
TSQM-9	X[d]		X		X	X	X	X	X	X	X					X	
Adverse event and concomitant medication	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X
Administer/dispense ALXN1840[o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X			

Note: Patients who complete either the main study period of Study WTX101-201 or the 48-week period of randomized treatment in Study WTX101-301 will be offered the opportunity to participate in an up to 60-month open-label Extension Period in which they will receive ALXN1840. If a patient from Study WTX101-201 qualifies for the Extension Period and chooses to participate, they must sign an additional ICF for the Extension Period. Note that visits at Weeks 12 (Week 60 overall) and 36 (Week 84 overall) of the Extension Period are not required for patients who previously completed the main period of Study WTX101-201.

a. Unscheduled study visits may occur at any time during the study and may include any study procedures (including dispensing of ALXN1840) as deemed necessary by the Investigator. These visits may or may not be completed by a home healthcare nurse depending on the purpose of the unscheduled visit. Refer to Section 8.7.
b. Assessments on Day 1 and other study visit days where laboratory sampling is planned should be performed pre-dose.
c. Only patients who rollover from Study WTX101-201 will consent to participate in Study WTX101-301 at the start of the Extension Period.
d. Assessments at the Week 48 Visit will also be used as the Extension Period Day 1 assessments.
e. Vital signs include height (Day 1 only; without shoes), heart rate, blood pressure, respiration rate, temperature, and weight.
f. Serum and urine pregnancy tests will only be performed for females of childbearing potential. Female patients of childbearing potential must not be pregnant nor breastfeeding and must have a negative serum pregnancy test at Screening. Positive urine pregnancy results will be confirmed by a serum pregnancy test. In addition to pregnancy tests detailed at the visits in the Schedule of Activities, females of childbearing potential in Austria only 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.
g. For the 24-hour urine sample, 500 mL will be considered the minimum acceptable sample size. Any amount < 500 mL will not be tested due to an insufficient sample collection.
h. The container for 24-hour urine collection should be dispensed at the study visit immediately prior to the next expected collection. Urine containers should be dispensed on Extension Weeks 60, 84, 96, 120, 144, 168, 192, 216, 240, 264, and 288.
i. Only for patients from Study WTX101-201.
j. To be calculated by the Central Laboratory.
k. Plasma or serum samples will be obtained from the blood samples collected pre-dose on the day of visit. See Section 8.5.
l. The UWDRS Part I and III must be performed by a blinded neurologist.
m. With the exception of Day 1, assessment can be completed within 2 days of the study visit day.
n. The BPRS-24 can be performed by a qualified person who has completed the required training.
o. ALXN1840 will not be dispensed or administered at the Early Termination Visit.

Abbreviations: BPRS-24 = Brief Psychiatric Rating Scale-24; CGI-I = Clinical Global Impression-Improvement Scale; CGI-S = Clinical Global Impression-Severity Scale; EOS = End of Study; EQ-5D = EuroQoL 5 Dimensions; ET = Early Termination; ICF = informed consent form; MELD = Model for End-Stage Liver Disease; PD = pharmacodynamic; PK = pharmacokinetic; TSQM-9 = Treatment Satisfaction Questionnaire for Medication-9; UNS = unscheduled; UWDRS = Unified Wilson Disease Rating Scale; WD = Wilson disease

2. INTRODUCTION

2.1. Study Rationale

This study is being conducted to assess the efficacy and safety of ALXN1840, a novel, first-in-class, copper -protein binding agent versus standard of care (SoC) in patients with Wilson Disease (WD) who are 12 years of age or older (18 years and older in Germany). Currently available drugs have high rates of treatment discontinuation due to tolerability and efficacy issues. They also need to be dosed 2 to 4 times per day and must be taken in the fasted state. Their AE profiles and complicated dosing regimens lead to poor treatment compliance and high rates of treatment failure, a major concern in 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, and rapidly form copper-protein complexes with very high specificity for copper to quickly treat the underlying disease by mobilizing excess tissue copper and promoting biliary excretion of copper (the body's natural route of elimination) to reduce copper overload.

2.2. Background

2.2.1. Wilson Disease

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

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

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

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

In patients with WD, copper is not removed from the tissue compartments due to the deficient activity of ATPase2 due to its absence or reduced function. This results in an accumulation of copper, mainly in the liver where the protein is highly expressed in hepatocytes and then in the brain, but also in other organs. Within the capacity of MT biosynthesis, no apparent toxicity of copper exists because MT tightly binds copper. However, beyond the copper buffering capacity of MT, free copper ions appear and this excessive amount of free intracellular copper triggers pro-oxidant properties, leading to an increased risk of tissue/organ damages with clinical manifestations as a result. Historically, it has been assumed that the hepatic toxicity of copper in WD is mediated by copper that is not bound to ceruloplasmin or MT (Ogra, 1996). Increased non-ceruloplasmin-bound copper (NCC) from the liver then enters the circulation in a form that is mostly bound to albumin and is available for uptake into other organs where it may cause damage. Therefore, the plasma calculated NCC (cNCC) concentration may serve as an important biomarker for tissue copper overload. However, achieving a normalized plasma cNCC concentration does not necessarily reflect normalized tissue copper levels, particularly in organs with relatively slow copper exchange, such as the brain (Pfeiffenberger, 2019).

The optimal treatment goal of an effective therapy for WD should be to remove excessive copper from the tissues. The current treatments for WD are general chelator therapies D-penicillamine (Cuprimine, Depen) and trientine (Syprine), which non-specifically chelate copper and promote urinary copper excretion. In addition, zinc, which blocks dietary uptake of copper, is used mainly for maintenance treatment. Zinc impairs the absorption of copper by the induction of MT in the enterocytes of the gastrointestinal (GI) tract. As tissue copper concentrations are not readily sampled, the adequacy of therapeutic copper control is currently monitored through periodic assessment of the 24-hour urinary copper excretion (Roberts, 2008; EASL 2012). The daily urinary copper excretion rate and plasma NCC concentration are both highly variable and neither is ideal for monitoring therapeutic copper control (Pfeiffenberger 2019).

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

in the central nervous system is an evolutionary and long-term process. Excessive copper in the body as a whole (not just from the liver) may gradually accumulate in the central nervous system over time, which is also reflected in the time it typically takes to show efficacy after WD treatment such as ALXN1840 (approximately 2 years).

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

2.2.2. ALXN1840

ALXN1840 (bis-choline tetrathiomolybdate) is a novel, first-in-class, copper-protein binding agent in development for treatment of WD. ALXN1840 targets the following medical needs:

- Rapid and sustained control of copper and clinical symptoms, with a low risk of neurological worsening – through the rapid formation of irreversible copper tetrathiomolybdate-protein complexes leading to a rapid copper mobilization and elimination that could protect patients with WD from tissue toxicity including neurological deterioration. 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).
- A therapeutic option that is efficacious and well tolerated, and suitable for all naïve and pre-treated patients, including those with neurological symptoms who are at greatest risk of neurological deterioration during the initial phases of chelation therapy.
- Improved compliance over long-term treatment through an improved tolerability and the convenience of a simplified dosing regimen (once daily [QD]) compared to current therapeutic options (multiple daily dosing in the fasted state).

ALXN1840 (bis-choline tetrathiomolybdate) has been chosen for clinical development in WD due to its improved stability properties compared with ammonium tetrathiomolybdate, which has been studied in WD and other indications. Good Laboratory Practice studies conducted in Sprague-Dawley rats and Beagle dogs have shown that the salt cation (ammonium or bis-choline) does not impact the pharmacokinetic (PK) or pharmacodynamic (PD) effects of tetrathiomolybdate, and ammonium tetrathiomolybdate as well as bis-choline tetrathiomolybdate non-clinical and clinical data to date support the efficacy and safety of ALXN1840.

ALXN1840 has been evaluated in patients with WD in the Phase 2 Study WTX101-201, which enrolled 28 patients with WD. Final results from the main 24-week study showed that ALXN1840 monotherapy reduced mean serum $cNCC_{corrected}$ by 72% at Week 24 compared with baseline. The reduction in $cNCC_{corrected}$ was sustained through Week 72 or longer. Initial increases in total plasma copper, exchangeable copper, and labile bound copper (LBC, mostly bound to albumin) were observed, followed by a gradual decline to baseline or even lower. These results suggest that ALXN1840 mobilizes copper from tissues to blood, forming copper-albumin-tetrathiomolybdate complexes that are ultimately eliminated from the body,

thereby meeting the treatment goal of a therapy for WD that removes excessive copper from tissues such as the liver.

ALXN1840 treatment also resulted in significant improvements in neurological status and disability measured as a change from baseline in Unified WD Rating Scale (UWDRS) Part III and Part II, respectively. In addition, liver status, as measured by the Modified Nazer Score, was stabilized or improved in the majority of patients. Treatment with ALXN1840 was generally well-tolerated, with most reported AEs being mild (Grade 1) to moderate (Grade 2). Reversible liver function test elevations were observed in 39% of patients; these elevations were generally mild to moderate, asymptomatic, and normalized with dose adjustments. No paradoxical neurological worsening was observed upon treatment initiation with ALXN1840 (Weiss, 2017). All patients who completed the 24-week Study Period were enrolled in a 36-month Extension Period. Preliminary available follow-up data at 48 weeks from the ongoing 36-month Extension Period of the study were consistent with the 24-week Study Period results.

The clinical study experience with tetrathiomolybdate in WD also consists of 120 patients with WD treated with ammonium tetrathiomolybdate. The information presented is based on peer-reviewed literature (eg, non-Wilson Therapeutics AB sponsored studies) (Brewer, 2003; Brewer, 2006; Brewer, 2009). Additionally, ALXN1840 (bis-choline tetrathiomolybdate) has been administered to 5 patients with WD in a named patient program in Canada and Sweden.

In addition to the WD studies performed, there has been extensive clinical study experience with both ammonium tetrathiomolybdate and ALXN1840 in patients with other conditions, which contributes to the knowledge of the safety of tetrathiomolybdate in humans.

In total, tetrathiomolybdate has been evaluated in more than 800 patients in studies of WD, oncology, macular degeneration, and primary biliary cirrhosis indications using either the ammonium or the bis-choline tetrathiomolybdate salt forms, in 36 healthy volunteers in Phase 1 studies, where bis-choline salt of tetrathiomolybdate was tested in uncoated capsules or enteric-coated tablets. ALXN1840 has been generally well-tolerated, and the most frequently reported drug-related AEs in WD were increases in hepatic transaminases. Aminotransferase elevations were much less common in patients without WD compared with patients with WD; however, it should be noted that in the oncology program, which constitutes the majority of patients without WD, causality of tetrathiomolybdate for these elevations was difficult to establish due to underlying disease.

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

2.3. Benefit/Risk Assessment

More information about the known and expected benefits and risks and reasonably expected AEs with ALXN1840 may be found in the current edition of the Investigator's Brochure. Detailed information about the known and expected benefits and risks and reasonably expected AEs of treatments administered as SoC may be found in the relevant product labels.

2.3.1. Potential Benefits

The main objective of effective WD treatment is to provide rapid copper control, ie, mobilization and elimination of copper. The current goal of treatment for WD is to establish and maintain

negative or neutral whole-body copper balance (Roberts, 2008; EASL, 2012). As such, current clinical recommendations suggest that copper control is essential for stabilization or improvement of hepatic, neurologic or psychiatric manifestations of WD. The concentration of circulating plasma total copper is expected to be low in WD due to decreased levels of Cp. In line with the efficacy assessments relied upon for approval of the copper chelators penicillamine and trientine, the measures of the primary endpoint for Studies WTX101-201 and WTX101-203 were based on assessing the control of plasma exchangeable copper via cNCC/$NCC_{corrected}$ calculations.

As copper concentrations are consistently low at baseline in treatment naïve patients with WD, it is difficult to justify using serial copper blood measures as an adequate monitoring tool for therapeutic efficacy. As plasma total copper concentrations are consistently low in WD, serial measurement of total copper has not previously been considered to be informative for monitoring treatment. However, the temporal patterns for both plasma total copper and molybdenum seen in Study WTX101-201 support the decoppering mechanism of action of ALXN1840. After the initial decoppering phase of approximately 24 weeks, participants with WD apparently entered a maintenance phase where tissue copper became less available and, thus, less TPC was formed, even though the ALXN1840 dose was generally maintained. Overall, ALXN1840 PK (plasma total molybdenum) and PD (plasma total copper) profiles changed coordinately and were highly correlated, with both PK and PD apparently dependent on formation of copper-albumin-TPC complexes. These observations support the ability of ALXN1840 to reduce copper overload in patients with WD. Results from the Phase 2 Study WTX101-201 demonstrate a rapid and significant ($p<0.0001$) reduction of mean serum $cNCC_{corrected}$ levels after initiation of treatment, with significant improvements in neurological status, as measured by UWDRS Part III ($p<0.0001$) and patient-reported disability, measured by UWDRS Part II ($p<0.001$), as well as a stabilization or improvement of hepatic status in most patients following 24 weeks of ALXN1840 treatment (Weiss, 2017). In the Extension Period of Study WTX101-201, 48-week follow up data indicate maintained overall improvement in disability as shown by mean reduction in the UWDRS Part II score and maintained overall improvement in neurologic status as shown by mean reduction in UWDRS Part III. Treatment with ALXN1840 was generally well tolerated with most reported AEs being mild (Grade 1) to moderate (Grade 2).

Approximately half of newly diagnosed patients with WD are younger than 18 years old (Ferenci, 2019). Standard treatments for WD are approved for use in children or adolescents, but significant unmet needs still exist with respect to efficacy, safety, and simplicity of dosing regimens. All currently available WD treatments are associated with adverse effects (such as neurological worsening) in a subset of patients, which can require adjustment, substitution, or even discontinuation of treatment. These adverse effects also reduce the patient's compliance with treatment, which by itself can lead to clinical deterioration and even death. All require multiple daily doses to achieve adequate copper control. The burden of multiple daily doses for standard treatments may negatively impact medical adherence and clinical outcomes, particularly among patients who discontinue treatment entirely. Once-daily dosing and the small tablet diameter of the 15 mg dose of ALXN1840 (5 mm) may increase therapeutic adherence.

2.3.2. Potential and Identified risks

In patients with WD, the most commonly reported AEs associated with multiple ALXN1840 dosing are reversible, dose-dependent, liver test elevations (transaminases) observed after

treatment initiation with doses of 30 mg per day or higher. In the Phase 2 Study WTX101-201, reversible liver test elevations were observed in 39% of patients. These elevations were generally mild to moderate, asymptomatic and normalized with dose adjustments. No initial drug-induced neurological worsening was observed upon treatment initiation with ALXN1840. As tetrathiomolybdate is a copper modulating agent, there is the risk of producing copper deficiency with prolonged dosing with ALXN1840. Changes in hematological parameters (thrombocytopenia and leukopenia), attributed by the Investigators to overtreatment and resultant copper deficiency, have been observed. Multiple-dose WD studies, like Study WTX101-301, therefore, involve frequent monitoring for these potential adverse hematological and hepatic effects of ALXN1840.

Details of potential safety risks related to the COVID-19 pandemic and mitigation measures are provided in Section 10.9.

2.3.3. Benefit/Risk Conclusions

Based on the efficacy results from Study WTX101-201 (lowering of free copper, stabilization or improvement of liver status and improvement in neurological symptoms) and the risk mitigation measures included in the protocol to account for the most common AEs reported in the study, Alexion considers that ALXN1840 has an acceptable benefit/risk in adult patients. The pathophysiology of copper overload does not differ substantially between adolescents and adults with WD, and the approved treatment options and therapeutic goal of copper control are also the same for adolescents and adults. Therefore, Alexion considers the acceptable benefit/risk extends to adolescent patients.

2.3.3.1. Pregnancy Exposure

No studies of ALXN1840 have been conducted in pregnant women. Pregnant or nursing female patients will be excluded from the clinical study. Patients enrolled in the study, and their spouses/partners, must use a highly effective method of contraception as required in Section 5.1. In the event of a pregnancy, the patient will be discontinued from study drug (ie, ALXN1840 or SoC; Section 7.1).

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the efficacy of ALXN1840 administered for 48 weeks, compared to standard of care (SoC), on copper control in WD patients aged 12 years and older	• Daily mean area under the effect-time curve (AUEC) of directly measured non-ceruloplasmin-bound copper (dNCC) from 0 to 48 weeks
Secondary	
• Establish the safety and tolerability of individualized dosing of ALXN1840	Incidence of • Adverse events/serious adverse events (AE/SAEs) • Clinical laboratory test data • Neurological and physical examination findings • 12-lead electrocardiogram (ECG) data • Vital signs
• Evaluate the effects of ALXN1840 on disability status	• Change from baseline in the Unified Wilson Disease Rating Scale (UWDRS) Part II total score
• Evaluate the effects of ALXN1840 on neurological status	• Change from baseline in UWDRS Part III total score and individual item/subscales (arising from a chair, gait, handwriting, and speech)
• Evaluate the global effects of ALXN1840 on global clinical symptoms	• Clinical Global Impression-Improvement Scale (CGI-I) • Change from baseline in Clinical Global Impression-Severity Scale (CGI-S)
• Evaluate the effects of ALXN1840 on hepatic status	• Change from baseline in Model for End-Stage Liver Disease (MELD) score
• Evaluate the efficacy of ALXN1840 administered for 48 weeks, compared to SoC, on copper control in WD patients aged 12 years and older	• Absolute change from baseline (Day 1) to 48 weeks in calculated NCC (cNCC) in plasma. • Percentage change from baseline in cNCC in plasma. For ALXN1840-treated patients, the cNCC in plasma will be corrected for the amount of copper bound to the ALXN1840 tripartite complex (TPC) ($cNCC_{corrected}$)
• Evaluate the effects of ALXN1840 on the cNCC responder rate	• cNCC responder rate at 48 weeks
Exploratory	
• Explore the effects of ALXN1840 on the individual patient's 3 most troublesome symptoms related to WD	• Individualized assessment of each patient's 3 most troublesome symptoms
• Explore the effects of ALXN1840 on hepatic fibrosis	• Change from baseline in the Fibrosis-4 (FIB 4) Index and by transient elastography
• Explore the effects of ALXN1840 on hepatic status	• Change from baseline in Modified Nazer Score
• Explore the effects of ALXN1840 on psychiatric symptoms	• Change from baseline in Brief Psychiatric Rating Scale-24 (BPRS-24)

• Explore the effects of ALXN1840 on the following Quality of Life (QoL)/Patient Reported Outcomes (PRO)	Change from baseline in QoL/PRO endpoint measures: • EuroQoL 5 Dimensions (EQ-5D) • Treatment Satisfaction Questionnaire for Medication-9 (TSQM-9)
• Explore the change in the timed 25F Walk Test	• Change from baseline in timed 25F Walk Test
• Explore the change in the 9-hole Peg Test (9-HPT)	• Change from baseline in 9-HPT
• Explore the change in the non-verbal Stroop Interference Test	• Change from baseline in non-verbal Stroop Interference Test
• Explore the change in the Digit Span Test.	• Change from baseline in Digit Span Test
• Explore other directly measured pharmacodynamics (PD) and biomarkers of ALXN1840	• Plasma total copper, plasma ultrafiltrate (PUF)-copper, dNCC, labile bound copper (LBC), ceruloplasmin (Cp), and ceruloplasmin-bound copper (CpC) concentration-time profiles in plasma • Daily mean AUEC of plasma dNCC (from 0 to 24 and 24 to 48 weeks) • Daily mean AUEC of LBC from 0 to 48 weeks • Daily mean AUEC of plasma total copper from 0 to 48 weeks • Absolute and percentage change from baseline (Day 1) to 48 weeks in dNCC • Absolute and percentage change from baseline (Day 1) to 48 weeks in LBC
• Explore ALXN1840 effect on initial decoppering phase compared to SoC based on directly measured pharmacokinetic (PK)/PD and biomarkers	• Time to first confirmed increase in plasma dNCC and total copper concentration • Time to minimum and maximum concentration of: – Plasma total copper – Plasma dNCC – Plasma LBC – Ratio plasma dNCC:total copper – Ratio plasma LBC:total copper – Urinary molybdenum – Ratio urinary molybdenum:copper – Ratio urinary molybdenum:dosed molybdenum – Plasma Cp – Plasma CpC – Ratio plasma Cp:total copper – Ratio plasma CpC:total copper – Ratio plasma CpC:Cp
• 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 measures: – Plasma total copper – Plasma dNCC – Plasma LBC – Ratio plasma dNCC: total copper

	– Ratio plasma LBC:total copper – Urinary molybdenum – Ratio urinary molybdenum:copper – Ratio urinary molybdenum:dosed molybdenum – Plasma Cp concentration – Plasma CpC concentration – Ratio plasma Cp:total copper – Ratio plasma CpC:total copper – Ratio plasma CpC:Cp
• Explore PK of ALXN1840	• Total molybdenum and PUF-molybdenum concentration-time profiles in plasma
• Evaluate the effects of ALXN1840 on the LBC responder rate	• LBC responder rate at 48 weeks
• Explore the change in 24-hour urinary copper and urinary molybdenum	• Change from baseline to 48 weeks in 24-hour urinary copper and urinary molybdenum
Extension Period	
• Long term safety and efficacy	• AEs, AESI, SAEs, laboratory tests (chemistry, hematology, coagulation, and urinalysis with microscopy), pregnancy testing in females of childbearing potential, physical examinations, vital signs, and ECGs. • CGI-I and the change from baseline in CGI-S • Change from baseline in MELD score • Change from baseline in UWDRS Part II total score • Change from baseline in UWDRS Part III total score and individual item/subscales (arising from a chair, gait, handwriting, and speech) • NCC/$NCC_{corrected}$ responder rate • LBC responder rate • Concentration-time profiles of the directly measured PK/PD and biomarkers

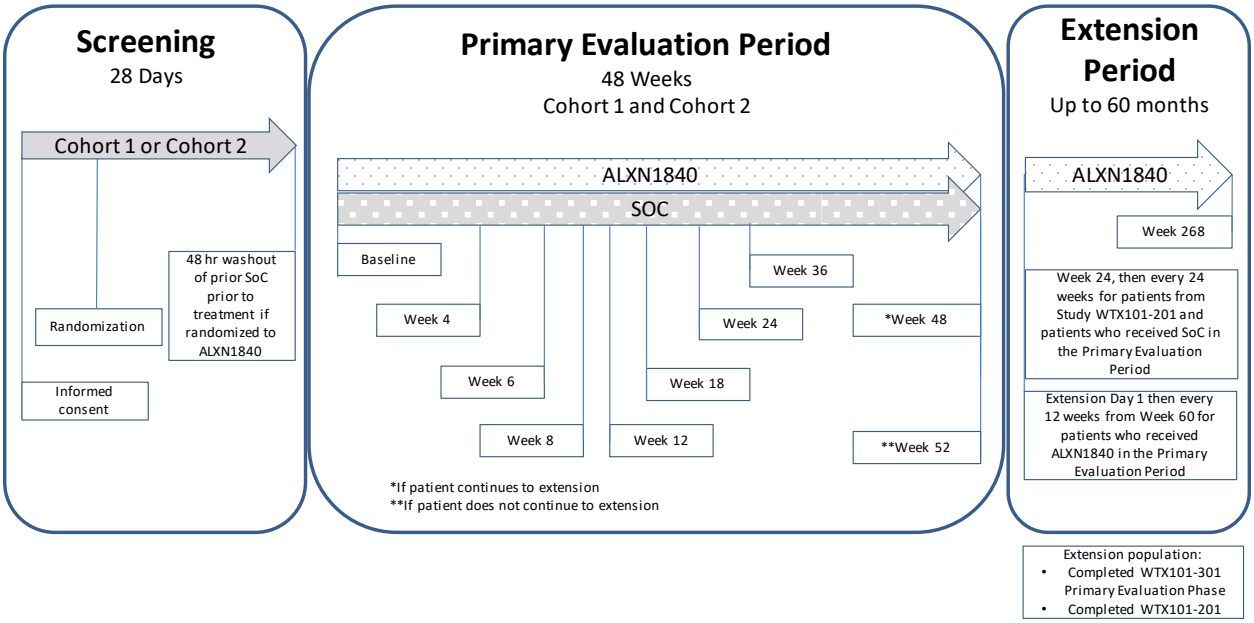
Abbreviations: 25F = 25-foot; 9-HPT = 9-hole peg test; AE = adverse event; AESI = adverse event of special interest; AUEC = area under the effect-time curve; BPRS-24 = Brief Psychiatric Rating Scale-24; CGI-I = Clinical Global Impression-Improvement Scale; CGI-S = Clinical Global Impression-Severity Scale; Cp = ceruloplasmin; CpC = ceruloplasmin-bound copper; ECG = electrocardiogram; EQ-5D(Y) = EuroQoL 5 Dimensions (Youth); FIB-4 = Fibrosis-4; LBC = labile bound copper; MELD = Model for End-stage Liver Disease; (d)(c)NCC = (directly measured) (calculated) non-ceruloplasmin-bound copper; $cNCC_{corrected}$ = calculated corrected NCC; PD = pharmacodynamics; PK = pharmacokinetics; PRO = Patient Reported Outcomes; PUF = plasma ultrafiltrate; QoL = quality of life; SAE = serious adverse event; SoC = standard of care; TPC = tripartite complex; TSQM-9 = Treatment Satisfaction Questionnaire for Medication-9; UWDRS = Unified Wilson Disease Rating Scale

4. STUDY DESIGN

4.1. Overall Design

Figure 1 provides a schematic view of the study design.

Figure 1: Schema for Study WTX101-301



Abbreviation: SoC = standard of care.

4.1.1. Primary Evaluation Period

This is a randomized, rater-blinded, multi-center study assessing the efficacy and safety of ALXN1840 versus SoC. In the Primary Evaluation Period, efficacy and safety will be assessed for an individualized ALXN1840 dosing regimen compared with SoC administered for 48 weeks in patients with WD who are aged 12 years and older (18 years and older in Germany). Approximately 180 patients will be enrolled globally.

Patients meeting all inclusion and no exclusion criteria will be enrolled into the study and studied as outpatients. Eligible patients with WD will be enrolled into 1 of 2 cohorts.

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

All enrolled patients will be randomized by cohort in a 2:1 ratio to treatment with ALXN1840 or SoC (either as continued therapy in Cohort 1 or as continued or initial therapy in Cohort 2). Treatments will be assigned randomly, stratified by cohort, utilizing an interactive voice/web response system.

Patients who are randomized to receive ALXN1840 will be required to withhold treatment with SoC for ≥ 48 hours immediately prior to first study assessment on Day 1. Patients who are randomized to ALXN1840 will receive ALXN1840 as delayed-release tablets for oral administration at doses ranging from 15 mg every other day (QOD) to 60 mg QD. Efficacy and safety assessments will be performed at scheduled visits, while AEs and concomitant medications will be monitored continuously throughout the study. Patients randomized to SoC will initiate treatment or continue treatment on their current regimen where possible, without compromising the safety of individual patients.

The Primary Evaluation Period will consist of an up to 28-day Screening Period, a 1-day Enrollment Visit, a 48-week Treatment Period, and a Follow-up Visit 4 weeks after the last dose for patients who do not elect to continue in the Extension Period.

4.1.2. Extension Period

Patients in Study WTX101-301 who have completed the 48-week Treatment Period and patients who completed participation in Study WTX101-201 will be offered the opportunity to participate in an up to 60-month Extension Period to evaluate the long-term safety and efficacy of ALXN1840.

If a patient from Study WTX101-201 qualifies for the Extension Period and chooses to participate, they must sign an additional informed consent form (ICF) for the Extension Period.

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

4.2. Scientific Rationale for Study Design

Control of exchangeable copper is essential for management of hepatic and neuropsychiatric manifestations in patients with WD. 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 TPCs, with a low risk for neurologic worsening due to copper exchange from chelators with a lower affinity for copper. Study WTX101-301 is the first prospective, randomized study to compare tetrathiomolybdate with penicillamine, trientine or zinc in WD.

The primary endpoint will integrate copper mobilization and elimination (ie, copper control) throughout the 48-week Primary Treatment Period by assessment of AUEC for plasma dNCC concentration. AUEC characterizes and measures the cumulative effect of ALXN1840. Measurement of dNCC in plasma is highly sensitive and accurate, requiring no special formulas or assumptions. As proposed, dNCC $AUEC_{0-48W}$ is an indirect measure of copper mobilization and elimination. Results from the Phase 2 Study WTX101-201 are strongly suggestive of rapid onset of TPC formation within hours following ALXN1840 administration, potent mobilization of copper from tissue into plasma persisting through Week 12, and nearly complete decoppering by Week 24. Over the course of 24-48 weeks of treatment with ALXN1840 in Study WTX101-201, the plasma dNCC concentration continued to gradually decrease to baseline. The gradual,

sustained reduction of plasma dNCC concentrations over time indicates that copper mobilized by ALXN1840 is not simply redeposited back into the tissue, as both plasma concentrations of tetrathiomolybdate (from a daily weighted average dose of 30 mg ALXN1840 administration) and circulating bodily albumin (the other 2 components of TPC) remained essentially constant and sufficiently available for TPC formation throughout the study. Thus, daily mean dNCC $AUEC_{0-48w}$ is suitable as a quantitative measure of ALXN1840 treatment effect (tissue decoppering) in WD based on its mechanism of action.

Measurement of the AUEC for dNCC as the primary outcome measure overcomes many of the limitations of the estimated cNCC approach. Calculated estimates of NCC rely on separate measurements of plasma total copper and ceruloplasmin protein. The amount of copper within Cp is further estimated based on an assumed ratio of 6 copper atoms per molecule of Cp, which may be an overestimate in WD. Overestimation of ceruloplasmin-bound copper (CpC) results in approximately 20% of samples yielding physiologically impossible negative values for cNCC. In patients treated with ALXN1840, estimation of cNCC requires additional correction for the presence of copper in the TPC. TPC copper cannot be measured directly but must instead be estimated based on the plasma concentration of molybdenum.

For the primary evaluation of efficacy and safety, a treatment period of 1 year was chosen to allow sufficient time for evaluation of changes in biochemical measures of copper, as well as changes in liver function and neurologic disability and an adequate evaluation of safety and tolerability.

Following the Primary Evaluation Period, patients randomized to SoC during the Primary Evaluation Period will switch to treatment with ALXN1840 in the Extension Period, providing further evaluation of changes in copper, liver function and neurologic dysfunction. The Extension Period of up to 5 additional years will allow further evaluation of the long-term efficacy, safety, tolerability, and clinical outcomes in patients treated with ALXN1840.

The phenotypic spectrum of WD was taken into account when selecting hepatic and neurologic secondary endpoints. The Model for End-Stage Liver Disease (MELD) score is a widely accepted composite score which reflects the severity of liver disease and is used to estimate expected survival in patients with acute or chronic liver failure (UNOS, 2015). The MELD score ranges from 6 (normal) to 40 (very severe liver failure). MELD scores for patients in Study WTX101-301 are expected to be nearly normal, as patients with decompensated liver disease are excluded. The MELD score is expected to remain stable or improve to a modest extent. The Nazer score is similar to the MELD score, but was developed specifically for liver disease associated with WD.

The UWDRS scoring system was developed specifically for the motor and movement disorders associated with chronic copper neurotoxicity in WD. Based on advice from the FDA, Alexion decided to assess some individual items/subscales of the UWDRS Part III (arising from a chair, gait, handwriting, and speech) in addition to the UWDRS Parts I, II, and III overall, to further define the range of burdensome signs and symptoms of WD, so as to further understand the assessment of treatment effects on patients with WD. The UWDRS scores for consciousness (Part I) and abnormal neurologic examination findings (Part III) will be determined by a trained neurologist rater who is blinded to study treatment randomization. These scores will be used to provide a rigorous dataset for evaluating changes from baseline.

Inclusion of adolescents ≥12 years in this protocol (except in Germany, where only patients aged 18 years and older are included) is justified by the natural history of WD. In a large European cohort of 1357 patients, the average age at diagnosis of WD was 19.8 years, and half of all patients were diagnosed before the age of 18 (Ferenci, 2019). Compared with adults, children and adolescents are more likely to present with hepatic symptoms rather than neuropsychiatric manifestations. The goal of treatment in adolescents is the same as in adults, namely prompt and effective removal of excess copper from tissues.

4.3. Justification for Dose

4.3.1. ALXN1840

ALXN1840 daily dosing intended for use in this study is based on the doses established as safe and effective in the previous WD studies performed with ALXN1840. Daily doses of 30 to 60 mg have been shown as effective in de-coppering newly diagnosed patients with WD or maintaining a normal copper level in patients with WD previously treated with SoC (Weiss, 2017). In patients with WD treated with ALXN1840, asymptomatic elevation hepatic transaminases and/or gamma glutamyltransferase were seen in 39% of patients. Elevation of liver enzymes was dose-dependent and reversible with interruption or dose reduction of ALXN1840. Therefore, the dose of ALXN1840 in the current study will start at 15 mg daily and will be limited to a maximum of 60 mg daily, the highest dose studied and considered to have a good safety profile in healthy volunteers. The intent is to individually titrate the dose of ALXN1840, as is done with the currently available chelators, to an appropriate dose based on cNCC levels adjusted for molybdenum plasma concentration, hematology values, and liver function tests. The dosing regimen for ALXN1840, therefore, includes the following features:

- Initial dosing QD as described in Section 6.2.3.1.
- Up titration design and individualized dosing as indicated by neurological and liver function testing, after Sponsor approval.

In line with currently available WD treatments, the dose of ALXN1840 will be adjusted in individual patients, depending on clinical response and safety, as appropriate, based on protocol specified guidelines. A detailed dosing guide for ALXN1840 dose modifications is outlined in Section 6.2.3.2 and Table 4.

4.3.2. Standard of Care

To the extent possible, without compromising the safety of individual patients, the type and dose of SoC medication should not be changed throughout the 48-week study period. Dose modification guidance is detailed in Section 6.2.3.4.

4.4. End of Study Definition

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

5. STUDY POPULATION

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

5.1. Inclusion Criteria

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

1. 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 Kayser-Fleischer rings, neurologic symptoms, serum ceruloplasmin below the reference range, Coombs-negative hemolytic anemia, elevated liver or urinary copper, and presence of mutations in the *ATP7B* gene, or other, as considered appropriate) may be used to confirm the diagnosis of WD.
2. 12 years of age or older at time of informed consent/assent (18 years and older in Germany).
3. Willing and able to give written informed consent and comply with the study visit schedule. For patients < 18 years of age (or below the age of adulthood under Japanese local law for patients in Japan), patient's legal guardian must be willing and able to give written informed consent and the patient 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 patients' Legally Acceptable Representative may provide informed consent if a patient is unable to do so.
4. Able to understand and willing to comply with study procedures, restrictions, and requirements, as judged by the Investigator.
5. Willing to withhold treatment with SoC for ≥ 48 hours immediately prior to first study assessment on Day 1.
6. Adequate venous access to allow collection of required blood samples
7. Willing to avoid use of vitamins and/or minerals containing copper, zinc, or molybdenum throughout the study duration
8. Willing to avoid intake of foods and drinks with high contents of copper throughout the study duration
9. Female patients of childbearing potential, if heterosexually active, must be willing to follow protocol-specified guidance for highly effective contraception starting at least 6 weeks before the Day 1 visit and continuing through 28 days after the last dose of study drug (either ALXN1840 or SoC). Male patients, if heterosexually active, must be willing to follow protocol-specified guidance for highly effective contraception beginning at the Day 1 visit and continuing through 90 days after the last dose of study drug (either ALXN1840 or SoC). See Section 6.6 for additional details.

5.1.1. Patients who have completed Study WTX101-201

Patients from Study WTX101-201 are eligible to roll over from that study to the Extension Period of Study WTX101-301 if they satisfy the below criteria.

1. The patient is willing and able to give written informed consent and comply with the study visit schedule.
2. Able to understand and willing to comply with study procedures, restrictions, and requirements, as judged by the Investigator.

5.2. Exclusion Criteria

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

1. Decompensated hepatic cirrhosis
2. MELD score > 13
3. Modified Nazer score > 7 (Dhawan, 2005)
4. Clinically significant GI bleed within past 3 months
5. Alanine aminotransferase > 2 × upper limit of normal (ULN) for patients treated for > 28 days with WD therapy (Cohort 1)
6. Alanine aminotransferase > 5 × ULN for treatment naïve patients or patients who have been treated for ≤ 28 days (Cohort 2)
7. Marked neurological disease requiring either nasogastric feeding or intensive inpatient medical care
8. Hemoglobin < 9 g/dL
9. Participation in a clinical study of an experimental or unapproved/unlicensed therapy during the screening period or within 4 weeks prior to informed consent
10. History of seizure activity within 6 months prior to informed consent
11. Pregnant (or women who are planning to become pregnant) or breastfeeding women
12. Known sensitivity to ALXN1840, ALXN1840 excipients (anhydrous di-calcium phosphate, anhydrous sodium carbonate), or any of the ingredients contained in ALXN1840 or related compounds
13. Active infection with hepatitis B virus (positive hepatitis B surface antigen) or C virus (patients with positive hepatitis C antibody result would require confirmation of active disease with a positive hepatitis C polymerase chain reaction test), or seropositivity for human immunodeficiency virus (HIV)
14. Previous treatment with tetrathiomolybdate
15. Any disease, disability, illness or abnormal laboratory values in the opinion of the Investigator, compromise patient safety or interfere with the collection or interpretation of study results

16. Patients with end-stage renal disease on dialysis (chronic kidney disease stage 5 [CKD 5]) or creatinine clearance < 30 mL/min
17. In the opinion of the Investigator, the patient and/or their legal guardian (in the case of adolescent patients or patients below the age of adulthood under Japanese local law for patients in Japan) is likely to be non-compliant or uncooperative during the study

5.3. Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but are not subsequently entered in the study due to failure to meet study entry criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements (Schulz, 2010) and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE) occurring during the screening period.

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

6. STUDY TREATMENTS

6.1. Treatment Groups

Patients in the Primary Evaluation Period will be randomized to either ALXN1840 or SoC treatment. Patients will be enrolled into 1 of 2 cohorts:

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

All patients in the Extension Period will receive treatment with ALXN1840.

6.2. Preparation/Handling/Storage/Accountability

6.2.1. Formulation and Packaging

6.2.1.1. ALXN1840

ALXN1840 will be supplied as white, round, delayed-release tablets for oral administration. Each tablet contains 15 mg of the bis-choline salt of tetrathiomolybdate, bis[2-hydroxyethyl) trimethyl-ammonium] tetrathiomolybdate, and the following excipients: tribasic calcium phosphate, sodium carbonate, sodium starch glycolate, and magnesium stearate. The tablets are coated with an inner pre-coat (Opadry 03K19229 clear) and outer enteric coat (Acryl-EZE white). Tablets are debossed on 1 side with a hexagon.

ALXN1840 will be supplied in treatment kits containing 28 tablets. The treatment kit consists of thermoform blister strips mounted into a cardboard wallet. Each treatment kit will have a unique identification number and be packaged and labelled in accordance with all applicable regulatory requirements. At a minimum, the treatment kit label will provide the following information: study Sponsor identification, batch number, directions for use, required storage conditions, caution statements (including “New Drug-Limited by Federal Law to Investigational Use” language), study identification, and expiry date. ALXN1840 must be stored, inventoried and the inventories carefully and accurately documented according to applicable state, federal and local regulations, ICH Guidelines, GCPs and study procedures.

The ALXN1840 treatment kits should be stored at refrigerated conditions, 2°C to 8°C (36°F to 46°F).

6.2.1.2. Standard of Care

Patients randomized to receive SoC treatment will continue their current therapy or initiate therapy with chelation 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.

6.2.2. Study Drug Preparation and Dispensing

Appropriately trained employees of the study site will administer ALXN1840 on Day 1 and will instruct patients on how to correctly dose themselves on the days when they take ALXN1840 at home. Additional details will be provided in the Pharmacy manual.

At each clinic visit, patients will be asked about their compliance with the agreed dosing regimen of ALXN1840 or SoC. Once compliance with ALXN1840 or SoC has been calculated, patients may be dispensed new ALXN1840 or SoC to cover dosing requirements until the next in-clinic visit if required. Drug accountability documentation for ALXN1840 and SoC will be kept at the individual clinical site including records of receipt and dispensing.

6.2.3. Study Drug Administration

6.2.3.1. ALXN1840

ALXN1840 will be administered orally at doses ranging from 15 mg QOD to 60 mg QD. ALXN1840 will be administered QD or QOD in the fasted state (1 hour before or 2 hours after meals). On study visit days where laboratory sampling is planned, patients will be asked to withhold any doses of ALXN1840 due to be taken prior to their visit, to allow laboratory samples to be taken pre-dose.

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 instructed based on cNCC levels adjusted for the amount of copper bound to the ALXN1840 TPC
- Safety monitoring: dose modification criteria are based on regularly scheduled assessments for recognized hematological effects of copper lowering, hepatic testing, and neurological test

6.2.3.2. Dose Modification for ALXN1840

In all patients, ALXN1840 will be administered at a 15 mg QD starting dose on Day 1 continuing for the first 4 weeks. After 4 weeks, up-titration to 30 mg QD may be performed after Sponsor approval, if the disease is not adequately controlled, taking into account the patient's clinical status and free blood copper levels, as measured by cNCC/$cNCC_{corrected}$, and none of the Dose Modification Criteria apply. Further dose increases are possible after Sponsor approval in 15 mg increments at least 4 weeks apart following the same aforementioned criteria. 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 Sponsor Medical Monitor.

When $cNCC_{corrected}$ levels have fallen to within the normal range (< 2.3 µmol/L), and/or the clinical status of the patient is stable or improved for 2 consecutive study visits, ALXN1840 dosage may be maintained or reduced at the discretion of the Investigator. To avoid over-treatment, the dose may be reduced at any time, at the discretion of the Investigator, guided by the following: if the patient's clinical status indicates possible over-treatment and/or

cNCC/cNCC$_{corrected}$ values are below the normal range. Specific criteria for dose modification of ALXN1840 are detailed in Table 4.

Table 4: ALXN1840 Dose Modifications for Individual Patients

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

Test	Result	Conditions	Action With ALXN1840 Dosing	Changes in Safety Monitoring[a]	Re-Challenge[b,c,d]
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 level.
	> 30% ↓ from baseline	None	Reduce dose to previous dose level if up-titration has occurred or reduce dose to 15 mg QOD if on 15 mg QD. No further dose ↑ until resolution of abnormality.	Weekly repeat testing	Not applicable.
Platelets	< 30,000 µL	None	Temporary interruption	Weekly repeat testing	At 15 mg QOD when platelets and other hematology parameters (neutrophils and hemoglobin) are at baseline level.
	> 30% ↓ from baseline	Platelets below normal range at baseline	Reduce dose to previous dose level if up-titration has occurred or reduce dose to 15 mg QOD if on 15 mg QD. No further dose ↑ until resolution of abnormality.	Weekly repeat testing	Not applicable.
Neutrophils	< 1.0×10^3/µL	None	Temporary interruption	Weekly repeat testing	At 15 mg QOD when neutrophils and other hematology parameters (hemoglobin and platelets) are at baseline level.
	> 30% ↓ from baseline	Neutrophils below normal range at baseline	Reduce dose to previous dose level if up-titration has occurred or reduce dose to 15 mg QOD if on 15 mg QD. No further dose ↑ until resolution of abnormality.	Weekly repeat testing	Not applicable.
Bilirubin	> 2 × ULN	Accompanied by ALT > 3 × ULN, indicative of liver injury.	Temporary interruption	Weekly repeat testing	At 15 mg QOD or less frequent, when bilirubin is below ULN. Re-challenge under these conditions requires approval of the Medical Monitor.

Test	Result	Conditions	Action With ALXN1840 Dosing	Changes in Safety Monitoring[a]	Re-Challenge[b,c,d]
UWDRS-III and clinical neurological assessment	Increase in UWDRS-III score from baseline as follows, AND is deemed clinically significant by the Investigator: Baseline UWDRS-III score < 20: ≥ 4 point increase OR Baseline UWDRS-III score ≥ 20: ≥ 6 point increase		Investigator and 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 UWDRS exam part I, II and III. Re-evaluate neurologic status, including complete UWDRS examination, no later than next study visit, even if not planned per the SoA.	Discuss with the 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. 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. A maximum of 3 re-challenges will be allowed for ALXN1840.
c. For re-challenges, patients who were on 15 mg QOD should be re-challenged at the 15 mg QOD dose.
d. The Investigator, in consultation with the Medical Monitor, may change dose and dose frequency in patients who require re-challenge.

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

6.2.3.3. Standard of Care

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

Similarly, to the extent possible, without compromising the safety of individual patients, the dosing of the SoC medication should remain consistent throughout the 48-week study period, unless required as part of the treatment (eg, titration of SoC initiated at the start of the study).

6.2.3.4. Dose Modification for Standard of Care

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 Sponsor Medical Monitor.

Specific criteria for dose modification of SoC if neurologic or psychologic worsening occurs are detailed in Table 5.

Table 5: Standard of Care Dose Modifications for Individual Patients

Test	Result and Conditions	Action With SoC Dosing	Changes in Safety Monitoring[a]	Re-Challenge[a,b,c]
UWDRS-III and clinical neurological assessment	Increase in UWDRS-III score from baseline as follows AND is deemed clinically significant by the Investigator: Baseline UWDRS-III score <20: ≥ 4 point increase OR Baseline UWDRS-III score ≥20: ≥6 point increase	Investigator and 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 exam. 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. A maximum of 3 re-challenges will be allowed.
b. For re-challenges, patients who were on 15 mg QOD should be re-challenged at the 15 mg QOD dose.
c. The Investigator, in consultation with the Medical Monitor, may change dose and dose frequency in patients who require re-challenge.

Abbreviations: QOD = every other day; SoA = Schedule of Activities; SoC = standard of care; UWDRS = Unified Wilson Disease Rating Scale.

6.2.3.5. ALXN1840 Administration During the Extension Period

All patients will be treated with ALXN1840 in the Extension Period. Patients who received ALXN1840 in the Primary Evaluation Period of Study WTX101-301 will continue to receive the same dose they received at last study visit in the Primary Evaluation Period; individualized dosing will be subsequently managed described in Section 6.2.3.1. Patients who transition from SoC in the Extension Period will be administered ALXN1840 as described in Section 6.2.3.1. Dose modification, if required, will be made as described in Section 6.2.3.2. Patients who received ALXN1840 in Study WTX101-201 will continue to receive the same dose they received at the last study visit in the Extension Period.

ALXN1840 treatment kits will be dispensed to patients as outlined in the Pharmacy manual. A sufficient number of kits should be dispensed to the patient to cover the need until the next visit, including the possible need for up titration.

6.3. Measures to Minimize Bias: Randomization and Blinding

Patients will be randomized after meeting all inclusion and none of the exclusion criteria. Randomization may be required on or before Day -2 to allow for SoC to be withheld for ≥ 48 hours for patients randomized to receive ALXN1840.

Patients will be randomized, stratified by cohort, via an interactive voice/web response system in a 2:1 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 patient's treatment assignment and no access to systems that could result in potential unblinding of treatment assignment. Both raters and patients 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. Treatment Compliance

Compliance with ALXN1840/SoC will be assessed by the study team at study visits. Changes in dose regimen (including any deviation from the prescribed dosing regimen), missed doses and drug interruptions will be recorded in the electronic data capture (EDC) system.

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

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

6.5. Prior and Concomitant Medications and/or Procedures

Any medications taken within 30 days prior to signing informed consent and throughout the duration of the study will be recorded in the source documents and on the appropriate electronic case report form (eCRF). Medications specific for WD taken at any time prior to the study will also be recorded.

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

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

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

- Gadolinium- and iodine-containing contrast media are known to interfere with tests on molybdenum. Gadolinium- and iodine-containing contrast media are requested not to be used within the 96 hours prior to molybdenum testing.

- Barium-containing contrast media are known to interfere with tests on copper. Barium-containing contrast media are requested not to be used within the 96 hours prior to copper testing.

6.5.1.1. Prohibited Medications

The following medications are prohibited during the study:

- Estrogens may interfere with biliary copper excretion. Patients must not initiate estrogen therapy or estrogen-containing contraception on or after the Day 1 visit. Detailed guidance on allowed contraceptive methods and medication are provided in Section 6.6.
- Vitamin E has been used as an adjunctive therapy in WD treatment regimens. Patients must not initiate use of vitamin E during the study.
- Use of an experimental or unapproved/unlicensed therapy.
- Patients must not use vitamins and/or minerals containing copper, zinc, or molybdenum.

6.6. Contraception Guidance

6.6.1. Guidance for Female Patients

Female patients of non-childbearing potential are exempt from contraception requirements. Non-childbearing potential for female patients is defined as any of the following:

- Prior to first menses
- Postmenopausal, as documented by amenorrhea for at least 1 year prior to the Day 1 visit and follicle stimulating hormone (FSH) serum levels consistent with postmenopausal status
- Permanent sterilization at least 6 weeks prior to the Day 1 visit:
  - Hysteroscopic sterilization
  - Bilateral tubal ligation or bilateral salpingectomy
  - Hysterectomy
  - Bilateral oophorectomy

The following text applies to all patients except those in Canada or Japan, for whom details are provided below. Female patients or female partners of male patients of childbearing potential (including breastfeeding females), if heterosexually active, must use a highly effective method of contraception starting at least 6 weeks before the Day 1 visit and continuing through 28 days after the last dose of study drug, including at least one of the below. Female patients must not donate eggs (ova, oocytes) for the purpose of reproduction during this period.

a. Intrauterine device (without copper) in place for at least 6 weeks
b. Progestogen-only hormonal contraception (either oral, injectable, or implantable) for at least 6 weeks

c. Intrauterine progestogen releasing system for at least 6 weeks

d. Bilateral tubal occlusion for at least 6 weeks

e. Combined (estrogen and progestogen containing) hormonal contraception (either oral, intravaginal, or transdermal) for at least 6 weeks. Estrogen-containing hormonal contraception is acceptable only if it has been used for at least 6 weeks immediately prior to the Day 1 visit. Estrogen-containing hormonal contraception may not be initiated during the study period; see Section 6.5.1.1.

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

The following applies to patients in Japan only:

A female patient of childbearing potential who is sexually active must use one of the highly effective contraceptive methods listed below, which are approved in Japan.

a. Intrauterine device or intrauterine progestogen-releasing system (without copper) in place for at least 6 weeks

b. Bilateral tubal occlusion for at least 6 weeks

c. Combined (estrogen and progestogen containing) hormonal contraception for at least 6 weeks. Estrogen-containing hormonal contraception is acceptable only if it has been used for at least 6 weeks immediately prior to the Day 1 visit. Estrogen-containing hormonal contraception may not be initiated during the study period; see Section 6.5.1.1.

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

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

- Barrier methods, such as male or female condoms, diaphragm, or cervical cap, used alone or in combination, are not acceptable.
- Spermicides or spermicidal sponges, used alone or in combination with barrier methods, are not acceptable.
- Withdrawal (coitus interruptus) is not acceptable.
- Lactational amenorrhea is not acceptable.

The following applies to patients in Canada only:

Female patients of childbearing potential must use two highly effective methods of contraception, or one effective plus one highly effective method, including at least one of the following highly effective methods:

g. Intrauterine device (without copper) in place for at least 6 weeks.

h. Progestogen-only hormonal contraception (either oral, injectable, or implantable) for at least 6 weeks.

i. Intrauterine progestogen releasing system for at least 6 weeks.

j. Bilateral tubal occlusion for at least 6 weeks.

k. Combined (estrogen and progestogen containing) hormonal contraception (either oral, intravaginal, or transdermal) for at least 6 weeks. Estrogen-containing hormonal contraception is acceptable only if it has been used for at least 6 weeks immediately prior to the Day 1 visit.

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

- Barrier methods, such as male or female condoms, diaphragm, or cervical cap, used alone or in combination, are acceptable in combination with a highly effective method.
- Spermicides must be used in combination with barrier methods, and such a combination is to be considered a single method.
- Withdrawal (coitus interruptus) is not acceptable.
- Lactational amenorrhea is not acceptable.

Sexual abstinence for female patients

- Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse. In this study, abstinence is only acceptable if consistent with the patient's preferred and usual lifestyle. Abstinent female patients who wish to initiate a highly effective method of contraception during the study must refrain from heterosexual intercourse for at least 6 weeks.
- Periodic abstinence (eg, calendar, symptothermal, or post-ovulation methods) is not considered a highly effective method of contraception for female patients.

6.6.2. Guidance for Male Patients With a Partner Who is a Woman of Childbearing Potential

- Male patients who have had a vasectomy greater than 6 months prior must use a condom during heterosexual intercourse. Male patients who have had a vasectomy less than 6 months prior must use a condom and spermicide during heterosexual intercourse.
- Male patients who have not had a vasectomy must use a condom and spermicide during heterosexual intercourse.
- Sexual abstinence for male patients
  - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse. In this study, abstinence is only acceptable if consistent with the patient's preferred and usual lifestyle. Abstinent male patients who become heterosexually active must use a condom and spermicide 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 patients.

- Male patients must not donate sperm from the Day 1 visit until 90 days after the last dose of study drug.
- No contraception/barrier is required for men with a male sexual partner.
- No contraception/barrier is required for men with a female sexual partner who is not of childbearing potential.

7. DISCONTINUATION OF STUDY INTERVENTION AND PATIENT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

Dose modification and reasons for interruption or discontinuation of dosing are detailed in Section 6.2.3.2 for ALXN1840 and Section 6.2.3.4 for SoC.

7.2. Patient Discontinuation/Withdrawal from the Study

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

- The patient or legal guardian (for adolescent patients, or patients below the age of adulthood under Japanese local law for patients in Japan) withdraws consent or requests discontinuation from the study for any reason, is lost to follow-up or dies.
- Occurrence of any medical condition or circumstance that exposes the patient to substantial risk and/or does not allow the patient to adhere to the requirements of the protocol.
- Occurrence of a decompensation cirrhosis event which is not responsive to standard treatment.
  - A decompensation cirrhosis event is defined as acute esophageal or gastric variceal bleeding, development of new overt hepatic encephalopathy, or substantive *de novo* ascites formation.
- Any SAE, clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition which indicates to the Investigator that continued participation is not in the best interest of the patient
- Patient becomes pregnant or is unwilling to comply with protocol requirements for highly effective contraception
  - Patients entering the Extension Period from Study WTX101-201 must follow the requirements for highly effective contraception as defined by the protocol for Study WTX101-301.
- Requirement to take prohibited concomitant medication
- Patient failure to comply with protocol requirements or study-related procedures

A participant must be withdrawn from this study if they receive an experimental or unapproved/unlicensed therapy.

See the SoA in Table 1, Table 2, and Table 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.

If a patient withdraws prematurely from the study due to the above criteria or any other reason, study staff should make every effort to complete the full panel of assessments scheduled for the Early Termination (ET) Visit. Patient withdrawal (including any reason for withdrawal, if provided by the patient) must be documented in the eCRF.

In the case of patients lost to follow-up, attempts to contact the patient must be made and documented in the patient's medical records.

7.3. Lost to Follow Up

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

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

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

8. STUDY PROCEDURES AND ASSESSMENTS

Study procedures and their timing are summarized in the Schedules of Activities in Section 1.2. The procedures to be performed at Screening and during the Primary Evaluation Period are detailed in Table 1. The procedures to be performed for patients who enter the Extension Period and were randomized to SoC are detailed in Table 2. The procedures to be performed for patients who enter the Extension Period and were either randomized to ALXN1840 in Study WTX101-301 or completed Study WTX101-201 are detailed in Table 3.

The end of study for each patient and for the overall study is detailed in Section 4.4.

8.1. Efficacy Assessments

The time points for all efficacy assessments are provided in the SoA (Section 1.2).

8.1.1. Assessment of Copper

Measurements of plasma dNCC concentration are the primary assessment for the efficacy of ALXN1840 treatment in WD. The AUEC for plasma dNCC concentration over time aims to quantify the dynamic tissue mobilization and decoppering effect of ALXN1840 based on preliminary analysis of Study WTX101-201 data. This assessment is also applicable to SoC treatments based on preliminary analysis of Study WTX101-203 data. In addition, plasma Cp, CpC, plasma total copper, and LBC will be measured with AUEC calculated for plasma total copper and LBC.

The LBC method measures exchangeable plasma copper that is not bound to either Cp or TPC.

8.1.2. Model for End-Stage Liver Disease

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

The MELD score 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 patient-reported review of daily activity items [disability], items 2 to 11), and UWDRS Part III (a detailed neurological examination, items 12 to 34).

The UWDRS Part I and Part III will be assessed by a 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 patient, family member, or caregiver (Czlonkowska, 2007; Leinweber, 2008). The UWDRS has not been formally evaluated in adolescents. However, the components of Part I (level of consciousness), Part II (patient or caregiver-reported disability) and Part III (neurologic

examination findings) are not fundamentally different between adults and adolescents. Patients aged 12 years and older are expected to be able to comply with UWDRS assessments.

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

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

The Clinical Global Impression-Severity scale (CGI-S) is a 7-point scale that requires the clinician to rate the severity of the patient's illness at the time of assessment, relative to the clinician's past experience with patients who have the same diagnosis. Considering total clinical experience, a patient is assessed on severity of illness at the time of rating as: 1, normal, not at all ill; 2, borderline ill; 3, mildly ill; 4, moderately ill; 5, markedly ill; 6, severely ill; or 7, extremely ill.

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

8.1.5. Three Most Troublesome Symptoms

Patients will be assessed for their 3 most troublesome symptoms of WD. Each patient, or the patient and caregiver, will identify their 3 most troublesome symptoms as well as the impact these symptoms have on their activities of daily living. In addition to collection via a paper questionnaire, the patient’s 3 most troublesome symptoms may also be recorded by the site staff via video for patients who provide separate informed consent. Note: this information is not required to be collected via video in the Extension Period of the study and also for patients who switch from SoC to ALXN1840 during the first year of the Extension Period.

8.1.6. Fibrosis-4 Index/Transient Elastography

The Fibrosis-4 (FIB-4) Index is a formula used to predict liver fibrosis based on standard biochemical values (alanine aminotransferase [ALT], aspartate aminotransferase [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.

8.1.7. Modified Nazer Score

The modified Nazer Score is an assessment of liver status and consists of a composite of 5 laboratory parameters: aspartate aminotransferase, international normalized ratio, 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.

8.1.8. Brief Psychiatric Rating Scale-24

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

8.1.9. EuroQoL 5 Dimensions

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

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

8.1.10. Treatment Satisfaction Questionnaire for Medication

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

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

8.1.11. Timed 25F Walk Test

The Timed 25-foot (25F) Walk Test is a quantitative mobility and leg function performance test based on a timed 25-foot walk. Scoring for the Timed 25F Walk Test is the average of the 2 trials. Patients may use assistive devices when doing this task.

8.1.12. Nine-Hole Peg Test

The 9-Hole Peg Test (9-HPT) is a brief, standardized, quantitative test of upper extremity function. Both the dominant and non-dominant hands are tested twice. The total time to complete the task is recorded. Two consecutive trials with the dominant hand are immediately followed by two consecutive trials with the non-dominant hand.

8.1.13. Non-Verbal Stroop Interference Test

In psychology, the Stroop effect is a demonstration of interference in the reaction time of a task. There will not be any verbal communication during this test. The test will be taught with nonverbal directions, using gestures and demonstration.

8.1.14. Digit Span Test

The complete Digit Span Test is measured for forward and reverse-order recall of digit sequences and digit span sequencing. Digit sequences are presented beginning with a length of 2 digits and 2 trials are presented at increasing list length. Testing ceases when the patient fails to accurately report either trial at 1 sequence length or when the maximal list length is reached (9 digits, 8 backwards).

8.2. Safety Assessments

The time points for all safety assessments are provided in the SoA (Section 1.2).

8.2.1. Physical Examination

A physical examination is required during screening and will include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, and musculoskeletal (including spine and extremities) systems. Unified Wilson Disease Rating Scale Part III is the neurological examination used in this study.

Note: A neurological examination will be conducted by a blinded neurologist for UWDRS Part III on Day 1 (see Section 8.1.3).

An abbreviated physical examination consists of a body system relevant examination based upon Investigator (or designee) judgment and patient symptoms. At least 1 body system must be checked for an abbreviated exam.

8.2.2. Vital Signs

Vital sign measurements will be taken after the patient has been resting for at least 5 minutes and will include systolic and diastolic blood pressure (BP; mm Hg), heart rate (beats/minute), respiratory rate (breaths/minute), height, weight, and temperature (°C or °F).

8.2.3. Electrocardiograms

Single 12-lead electrocardiograms (ECGs) will be obtained in triplicate, as outlined in the SoA (Section 1.2) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals.

Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

The Investigator or designee will be responsible for reviewing the ECG to assess whether the ECG is within normal limits and determine the clinical significance of the results. These assessments will be indicated on the eCRF.

8.2.4. Clinical Laboratory Evaluations

Clinical laboratory measures include chemistry, hematology, coagulation, and urinalysis (with microscopy). All protocol-required laboratory assessments, as defined in Section 10.2 (Appendix 2), must be conducted in accordance with the laboratory manual and the SoA (Section 1.2).

For the 24-hour urine sample, 500 mL will be considered the minimum acceptable sample size. Any amount < 500 mL will not be tested due to an insufficient sample collection.

Detailed procedures of sampling preparation, storage, and shipment will be described in a specific laboratory manual that will be provided to all sites.

8.2.5. Pregnancy Test

For females of childbearing potential, a serum or urine pregnancy test (ie, beta-human chorionic gonadotropin) will be performed according to the SoA (Section 1.2).

In addition to pregnancy tests detailed at the visits in the SoA, females of childbearing potential in Austria only 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 pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.4.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy) are considered SAEs.

Serum and urine pregnancy tests will only be performed for females of childbearing potential. Female patients of childbearing potential must not be pregnant nor breastfeeding and must have a negative serum pregnancy test at Screening. Positive urine pregnancy results will be confirmed by a serum pregnancy test.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE or SAE can be found in Section 10.3 (Appendix 3).

Adverse events will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

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

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

All events will be collected from the signing of the ICF until the follow-up contact specified in the SoA (Section 1.2).

Medical occurrences that begin before the start of ALXN1840/SoC but after obtaining informed consent will be recorded as pre-treatment AEs.

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

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

The method of recording, evaluating, and assessing causality of AEs and SAEs, and the procedures for completing and transmitting SAE reports are provided in Section 10.3 (Appendix 3).

8.3.2. Method of Detecting AEs and SAEs

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

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs and non-serious AEs of special interest (AESIs) (as defined in Section 8.3.6), will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Section 10.3 (Appendix 3).

8.3.4. Regulatory Reporting Requirements for SAEs

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

8.3.5. Pregnancy

Pregnancy data will be collected during this study for all female patients and female spouses/partners of male patients. Exposure during pregnancy (also referred to as exposure in utero) can be the result of either maternal exposure or transmission of drug product via semen following paternal exposure. Female patients who become pregnant during the study must withdraw from the study.

For all Alexion products, 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 patient discontinues study drug (ie, ALXN1840 or SoC) or withdraws from the study.

If a female patient or a patient's female partner becomes pregnant during the conduct of this study, the Investigator must submit the "Pregnancy/Breastfeeding Reporting and Outcome Form" to Alexion Global Drug Safety (GDS) via fax or email (Section 10.4). When the outcome of the pregnancy becomes known, the form should be updated and submitted to Alexion GDS. If additional follow-up is required, the Investigator will be requested to provide the information.

Exposure of an infant to an Alexion product during breastfeeding must also be reported (via the "Pregnancy/Breastfeeding Reporting and Outcome Form") and any AEs experienced by the infant must be reported to Alexion GDS or designee via email or facsimile (Section 10.4).

Pregnancy in itself is not regarded as an AE unless there is a suspicion that the investigational product 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, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy). Elective abortions without complications should not be reported as AEs.

8.3.6. Adverse Events of Special Interest

Any new neurological symptom or clinically significant worsening of an ongoing neurological symptom after initiation of study drug (ALXN1840 or SoC) will be designated to be an AESI, whether serious or non-serious.

If a patient 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 patient status: UWDRS Part III, non-verbal Stroop Interference Test, Digit Span Test, and the CGI-I and CGI-S. The Investigator or Sub Investigator can perform additional assessments or laboratory testing at their discretion.

Adverse events of special interest 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 drug (ALXN1840 or SoC). They will be blinded to the treatment given to the patient. All available relevant patient 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. Overdose

For patients receiving ALXN1840 an overdose is defined as any daily dose exceeding 60 mg.

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

Adverse events related to overdose of both ALXN1840 and SoC will be captured in the EDC system.

8.5. Pharmacokinetics, Pharmacodynamics, and Biomarkers

The PK/PD/Biomarker profiling visits are specified in the Schedules of Activities (Table 1, Table 2, and Table 3). The actual date and time (24-hour clock time) of each sample will be recorded. Pre-dose whole blood samples will be collected at each designated visit for the measurement of the following ALXN1840 PK, PD, and biomarker analysis:

8.5.1. Pharmacokinetics

Blood samples for PK analysis will be collected to measure plasma total molybdenum and plasma ultrafiltrate (PUF) molybdenum.

8.5.2. Pharmacodynamics

Blood samples will be collected to directly measure plasma total copper, PUF copper, dNCC, and LBC. Calculations may be performed for cNCC and $cNCC_{corrected}$, the latter of which is non-ceruloplasmin-bound and non-molybdenum-albumin-bound copper.

8.5.3. Biomarkers and Biobank Samples

Blood samples will be collected to measure plasma Cp and CpC.

Urine samples will be collected for analysis of urine copper and molybdenum.

Additional biomarker or biobank samples will be collected for the analysis of molybdenum and/or copper species associated with treatment.

Details of the use, analysis, and storage of biobank samples in the Netherlands are provided in Section 10.8.

Details including further handling and processing instructions and sampling time windows will be provided in the study laboratory manual.

8.6. Genetics

A blood sample for DNA isolation will be collected from patients who have consented to participate in the genetic analysis component of the study. Participation is optional. Patients 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.

8.7. Unscheduled Study Visits

Unscheduled Study 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 visit. If the Unscheduled Study Visit is for weekly repeat laboratory assessments as required in Table 1, these can be completed by a home healthcare nurse.

9. STATISTICAL CONSIDERATIONS

All statistical analyses will be performed by Alexion Pharmaceuticals or under the authority of Alexion Pharmaceuticals. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan (SAP), which will be finalized prior to database lock. Any deviations from the planned analysis as described in the SAP will be justified and recorded in the final study report.

Statistical analyses will be carried out using SAS®, Version 9.3 or later, SAS Institute, Cary, North Carolina, USA.

In general, continuous variables will be summarized by descriptive statistics (number of patients, mean, standard deviation [SD], minimum, median, and maximum). Categorical data will be summarized by absolute and relative frequencies.

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

9.1. Analysis Populations

9.1.1. Full Analysis Set

The Full Analysis Set includes all randomized patients who received at least 1 dose of randomized treatment. Patients will be analyzed as randomized.

9.1.2. Safety Analysis Set

The safety analysis will be performed on the Safety Analysis Set. This dataset includes all patients who received at least 1 dose of randomized treatment. Patients will be summarized according to the treatment actually received.

9.1.3. Per-Protocol Set

The Per-Protocol Set includes all patients who are randomized and had at least baseline and 48-week efficacy assessments for dNCC in the Primary Evaluation Period. Patients with major protocol deviations that are likely to impact the primary efficacy 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.

9.1.4. Extension Analysis Set

This dataset includes all patients who entered the Extension Period and received at least 1 dose of ALXN1840 in the Extension Period.

9.2. Statistical Methods

9.2.1. Analysis of Efficacy

9.2.1.1. Primary Efficacy Analysis

The primary estimand is the difference in daily mean dNCC AUEC from 0 to 48 weeks between ALXN1840 and SoC in patients with WD, regardless of less-than-complete adherence or use of another medication that affects plasma dNCC, with no benefit derived from treatment after death.

The AUEC for dNCC concentration will be calculated using the trapezoidal rule, and then divided by number of days to yield a mean daily AUEC plasma dNCC concentration from baseline to Week 48 (expressed as µmol/L and described as $AUEC_{0\text{-}48W}$).

The $AUEC_{0\text{-}48W}$ will be compared between ALXN1840 and SoC using an analysis of covariance (ANCOVA) statistical model; treatment arm, baseline plasma dNCC concentration, and cohort, will be included in the model. Tests will be performed at a significance level of 0.05 (2-sided).

Model-based estimates of the difference between randomized treatments (ALXN1840 – SoC) in $AUEC_{0\text{-}48W}$, along with a 2-sided 95% CI and p-value will be provided. If the lower 2-sided 95% CI exceeds 0 µM, superiority will be concluded.

Cohort 1: Patients previously treated for > 28 days

The supportive analysis of the primary endpoint within Cohort 1 will mirror that described for the overall population analysis except that the analysis will remove cohort from the model.

Cohort 2: Patients who are treatment naïve or previously treated for ≤ 28 days

The $AUEC_{0\text{-}48W}$ will be analyzed descriptively; there will be no formal statistical comparison made between the randomized treatment arms. The $AUEC_{0\text{-}48W}$ will be estimated using the same model terms as described for the analysis of Cohort 1 patients.

9.2.1.2. Secondary Efficacy Analysis

Key secondary endpoints and associated multiplicity testing will be adapted to regional expectations as agreed upon discussion with the US FDA and EMA CHMP (Table 6).

The secondary efficacy endpoints and the methods for analyzing them will be defined in more detail in the SAP.

Table 6: Analysis of Key Secondary Endpoints Customized for Specific Regional Health Authorities

	US FDA and Japan PMDA	EMA CHMP
Key secondary endpoints	• UWDRS Part II • Individual items/subscores from UWDRS Part III (arising from a chair, gait, handwriting, and speech)	• UWDRS Part II • UWDRS Part III • CGI-I and CGI-S • Percent change from baseline in cNCC/$cNCC_{corrected}$ • cNCC/$cNCC_{corrected}$ response rate

Abbreviations: CGI-I = Clinical Global Impression-Improvement Scale; CGI-S = Clinical Global Impression-Severity Scale; CHMP = Committee for Medicinal Products for Human Use; cNCC = calculated non-ceruloplasmin-

bound copper; $cNCC_{corrected}$ = calculated corrected NCC; EMA = European Medicines Agency; FDA = Food and Drug Administration; PMDA = Pharmaceuticals and Medical Devices Agency; UWDRS = Unified Wilson Disease Rating Scale.

9.2.2. Type I Error Control

A multiplicity adjustment will be applied to address the following two sources of multiplicity in this trial:

1. Analysis of the primary/key secondary endpoints.
2. Data-driven decision rule (sample size re-estimation rule) at the interim analysis.

The proposed multiplicity adjustment guarantees strong control of the overall Type I error rate control with respect to these sources of multiplicity at a two-sided alpha = 0.05.

The multiplicity adjustment relies on a prospectively defined multiple testing procedure. This procedure will be applied in conjunction with the combination function approach (Wassmer, 2016) at the interim and final analyses to ensure strong Type I error rate control. The combination function approach will be applied using the modification described in Sugitani et al. (Sugitani, 2016).

To address multiplicity induced by the first source of multiplicity in this trial, namely, multiplicity induced by the analysis of the primary/key secondary endpoints, a multiple testing procedure will be applied. This procedure is defined using the graphical method (Bretz, 2009).

To account for the second source of multiplicity (data-driven decision rule at the interim analysis), the multiple testing procedure will be applied separately to the two trial stages:

- Stage 1 includes all patients who are included in the interim database.
- Stage 2 includes all patients who are not included in the interim database.

The multiple testing procedure will account for the interim decision rule to support inferences at the final analysis for primary/key secondary endpoints. For example, if a decision is made to increase the sample size in the trial, the evidence of treatment effectiveness from the two trial stages will be pooled with pre-defined weights using the modified combination function principle. The standard analysis will be performed at the final analysis if the sample size is not adjusted at the interim analysis.

Let p denote the two-sided treatment effect p-values for the null hypotheses of interest computed from the Stage 1 data. Similarly, let q denote the two-sided treatment effect p-values for the null hypotheses computed from the Stage 2 data.

The combined p-value for each hypothesis is derived using the weighted inverse-normal combination function, ie,

$$c(x,y) = 1 - \Phi\left(\sqrt{w}\Phi^{-1}(1-x) + \sqrt{1-w}\Phi^{-1}(1-y)\right),$$

where $\Phi(x)$ denotes the cumulative distribution function of the standard normal distribution, and w and $1-w$ are the pre-defined weights assigned to Stages 1 and 2.

The combined p-value for the hypothesis H_i is computed as follows:

$r_i = c(p_i, q_i)$.

These combined p-values are equivalent to those derived from a weighted combination of test statistics from the two stages (Cui, 1999; Lehmacher, 1999).

The resulting combined p-values will then be passed to the multiple testing procedure to perform inferences at the final analysis, ie, the adjusted p-values will be computed for the null hypotheses and each null hypothesis will be rejected at the final analysis if its adjusted p-value does not exceed a one-sided $\alpha = 0.025$.

The proposed multiplicity adjustment guarantees overall Type I error rate control in the strong sense with respect to both sources of multiplicity in the adaptive study.

9.2.3. Efficacy Analyses Relating to Exploratory Objectives

The analysis methods for efficacy endpoints relating to exploratory objectives will be described in full in the SAP.

9.2.4. Efficacy Subgroup Analysis

For exploratory purposes, the primary and secondary efficacy endpoints will also be evaluated in clinically relevant subgroups. These subgroups will be described in full in the SAP.

9.2.5. Handling of Missing Data

An outline of how the primary endpoint will be analyzed is provided in Table 7.

Table 7: Analysis Outline for Primary Endpoint

Endpoint	Daily mean dNCC $AUEC_{0\text{-}48W}$, expressed as µM	
Analysis Method	Analysis of covariance (ANCOVA)	
Primary Analysis	**Population**	**How to handle missing data**
	Full Analysis Set	1. Patients who die during study o Baseline plasma dNCC concentration will be carried forward 2. Patients who drop out due to other reasons o Multiple imputation assuming missing not at random. ALXN1840 missing value will be imputed with multiple imputation based on the response for SoC participants (jump to reference method) 3. All other intermediate missing (including missing due to COVID-19 pandemic) o Use interpolation to fill out intermediate missing values
Sensitivity Analysis 1	**Population**	**How to handle missing data**
	Per Protocol Set	Per Protocol Set will only include patients who had at least baseline and 48-week assessments for plasma dNCC concentration, so only intermediate missing data. • Use available time points only to derive dNCC $AUEC_{0\text{-}48W}$ using trapezoidal rule. Equivalent to interpolation.
Sensitivity Analysis 2	**Population**	**How to handle missing data**
	Full Analysis Set	Tipping point analysis Use available time points only to derive dNCC $AUEC_{0\text{-}48W}$ using trapezoidal rule. Two-dimensional tipping point analysis will be applied to participants with missing data at Week 48 regardless of type of intercurrent events.

Abbreviations: $AUEC_{0-48W}$ = area under the effect-time curve from 0 to 48 weeks; dNCC= direct non-ceruloplasmin-bound copper.

Handling of Missing Data for Primary Analysis

For intermediate missing data, interpolation will be used to fill out missing values. For participants who die during study, their baseline plasma dNCC concentration will be carried forward. For participants who drop out due to other reasons, multiple imputation will be used to impute missing dNCC concentration assuming data are missing not at random. In this case, responses for both treatment groups will be imputed with multiple imputation based on the response for SoC participants (jump to reference method). Cohort, baseline, and previous visit value will be included in the imputation model. The following steps will be repeated:

Step 1: Missing values at each visit will be imputed 10 times via SAS PROC MI, and imputed values will be retained in the imputed datasets.

Step 2: Mean daily $AUEC_{0-48W}$ dNCC concentration will be derived using the trapezoidal rule (Yeh, 1978) and scaled by the number of days.

Step 3: ANCOVA analysis will performed for each of the 10 imputed datasets, with least square (LS) means (standard error [SE]) for each treatment arm and difference in LS means between studies (SE) saved from each of the 10 analyses.

Step 4: 10 set of analysis results will be combined using Rubin's rules (Rubin, 1987) via SAS PROC MIANALYZE. The treatment differences, CIs, and p-values were estimated by MODELEFFECTS and STDERR statement.

Tipping point analysis:

A tipping point analysis will be conducted for the primary endpoint, by splitting the patients into two subgroups: “observed” and “missing”. “Observed” are those patients with baseline and Week 48 assessment in plasma dNCC concentration, while “missing” refers to all other patients. An efficient two-dimensional tipping point analysis will be accomplished by performing two one-dimensional analyses: (a) vary assumptions about the missing outcomes in the ALXN1840 arm, while fixing those about the SoC arm, and (b) vary assumptions about the missing outcomes in the SoC arm, while fixing those in the ALXN1840 arm. The combination of assumed missing data values that maintain the statistically significant Superiority conclusion are bound by the two one-way tipping points (Gorst-Rasmussen, 2020).

Step 1: Within the “observed” subgroup, ANCOVA analysis will be performed on the daily mean dNCC $AUEC_{0-48W}$ with cohort and baseline plasma dNCC as covariates. The LS means and SEs for ALXN1840 and SoC, respectively, and the residual error estimate, will be extracted.

a. ALXN1840 varied, SoC fixed

Step 2:

i. For “missing” SoC patients, the daily mean dNCC $AUEC_{0-48W}$ is generated randomly as a deviate from a normal distribution with mean equal to the LS mean for “observed” SoC patients, and SD equal to the residual error estimate, as obtained in Step 1.

ii. For “missing” ALXN1840 patients, the LS mean for daily mean dNCC $AUEC_{0-48W}$ in Step 1 will be decreased by a small increment (δ=10%), to reflect a marginally worse AUEC0-48W value. For these patients, the daily mean dNCC $AUEC_{0-48W}$ will be

generated randomly as a deviate from a normal distribution with mean equal to (100 − δ)% of the LS mean for "observed" ALXN1840 patients, and SD equal to the residual error estimate, as obtained in Step 1.

iii. Combine "observed" and "missing" patients into a complete dataset. Analyze the complete dataset using ANCOVA with cohort and baseline plasma dNCC as covariates, to give LS means and SEs for ALXN1840 and SoC, with treatment effect estimate and associated SE.

Step 3:

i. Step 2 will be repeated 10 times for the same increment δ, giving rise to 10 sets of LS means, treatment effect estimates, and associated SEs.

ii. The 10 treatment effect estimates will be combined via PROC MIANALYZE using Rubin's method.

Step 4: Steps 2 and 3 will be repeated with larger increments (δ =20%, 30%,…, 90%) to reflect an even-poorer outcome with ALXN1840 treatment.

Step 5: The treatment effect estimates, associated SEs, and CIs generated for all increments (δ = 10%, 20%,…, 90%) will be summarized in a table, and the first point at which superiority fails (if it exists) will be highlighted.

b. ALXN1840 fixed, SoC varied

Step 2:

i. For "missing" ALXN1840 patients, the daily mean dNCC $AUEC_{0\text{-}48W}$ is generated randomly as a deviate from a normal distribution with mean equal to the LS mean for "observed" ALXN1840 patients, and SD equal to the residual error estimate, as obtained in Step 1.

ii. For "missing" SoC patients, the LS mean for daily mean dNCC $AUEC_{0\text{-}48W}$ in Step 1 will be increased by a small increment (δ=10%), to reflect a marginally better $AUEC_{0\text{-}48W}$ value. For these patients, the daily mean dNCC $AUEC_{0\text{-}48W}$ will be generated randomly as a deviate from a normal distribution with mean equal to (100 + δ)% of the LS mean for "observed" SoC patients, and SD equal to the residual error estimate, as obtained in Step 1.

iii. Combine "observed" and "missing" patients into a complete dataset. Analyze the complete dataset using ANCOVA with cohort and baseline total copper as covariates, to give LS means and SEs for ALXN1840 and SoC, with treatment effect estimate and associated SE.

Step 3:

i. Step 2 will be repeated 10 times for the same increment δ, giving rise to 10 sets of LS means, treatment effect estimates, and associated SEs.

ii. The 10 treatment effect estimates will be combined via PROC MIANALYZE using Rubin's method.

Step 4: Steps 2 and 3 will be repeated with larger increments (δ =20%, 30%,…, 200%) to reflect an even-better outcome with SoC treatment.

Step 5: The treatment effect estimates, associated SEs, and CIs generated for all increments (δ = 10%, 20%,…, 90%) will be summarized in a table, and the first point at which superiority fails (if it exists) will be highlighted.

9.2.6. Evaluation of Safety

Safety and tolerability over the course of the study period is a secondary endpoint and will not be subject to formal analysis. Rather, descriptive statistics will be used to summarize the safety data by treatment arm. The Safety Analysis Set dataset will be used for the evaluation of safety.

9.2.6.1. Adverse Events

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

Summary tables will include patient counts and percentages and will present separate tabulations for all AEs, AESIs, SAEs, AEs leading to treatment discontinuation or withdrawal, and AEs leading to death. No statistical comparison of the overall incidence of AEs will be done between arms.

9.2.6.2. Laboratory Assessments

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

9.2.6.3. Electrocardiogram

QT intervals will be corrected for heart rate according to Bazett (QTcB = QT/(RR1/2) and Fridericia (QTcF = QT/(RR1/3).

All corrected values will be tabulated according to the ICH E14 Guidelines as follows: QTc actual values: ≤450 ms, >450 to ≤480 ms, >480 to ≤500 ms, and >500 ms. ECG results will be tabulated.

9.2.6.4. Vital Signs

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

Abnormal vital sign results will be tabulated.

9.2.6.5. Physical Examination

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

9.2.7. Sample Size Determination

The original primary endpoint is copper control assessed as the percent change from baseline to 48 weeks in cNCC levels; for ALXN1840-treated patients, the cNCC level will be corrected for the amount of copper bound to the ALXN1840 TPC.

The hypothesis to be tested with regards to the primary endpoint is

$H_0: \mu_{ALXN1840} - \mu_{SoC} \geq \Delta$ vs $H_1: \mu_{ALXN1840} - \mu_{SoC} < \Delta$

where Δ=15% is the non-inferiority margin, μ_{ALXN1840} and μ_{SoC} represent 48-week mean percent change for ALXN1840 and SoC, respectively.

For patients who have been previously treated with SoC for >28 days (ie, corresponding to Cohort 1 in the present study), the NCC data in Study WTX101-201 gives a mean percent change in cNCC level at 24 weeks of 80% with estimated projected SD of 20% to 30% at 48 weeks. Based on this anticipated degree of variability, 90 Cohort 1 patients, randomized by cohort on a 2:1 basis, will provide between 60% and 91% power to rule out a difference of Δ = 15% in mean percent change in NCC values, ALXN1840 versus SoC, with a 1-sided Type I error of 2.5%.

The number of patients in Cohort 2 is based on feasibility only, and there is no supporting power calculation. The intent of Cohort 2 is to provide at least some randomized data in patients who are treatment naïve or have been previously treated with SoC for ≤ 28 days to descriptively assess within arm changes from baseline. No formal statistical comparisons are planned within Cohort 2 patients alone.

In relation to the overall analysis of cNCC percent change from baseline to 48 weeks, Study WTX101201 gives a mean percent change in cNCC level at 24 weeks of 78%. A total of 120 patients (90 patients in Cohort 1 and 30 patients in Cohort 2) will provide between 73% and 97% power to rule out a difference of Δ = 15%, in mean percent change in NCC values, ALXN1840 versus SoC, in the overall patient population, with a 1-sided Type I error of 2.5%.

Study WTX101-201 had a minimum cNCC value of 0.8 for study entry while this study has no minimum requirement. This may result in the entry of patients with negative baseline cNCC values into this study who will be non-evaluable for the primary analysis and/or have a smaller effect size. For these reasons, and to achieve a pooled safety database of at least 100 patients treated with ALXN1840 for at least 1 year pooling Studies WTX101-201 and WTX101-301, these numbers have been inflated by 25% to achieve a total of 150 evaluable patients (approximately 113 patients in Cohort 1 and 37 patients in Cohort 2).

To help ensure that at least 150 evaluable patients complete 48 weeks of treatment, approximately 180 patients (approximately 135 patients in Cohort 1 and approximately 45 patients in Cohort 2) will be enrolled in total, this will also provide additional safety and tolerability data.

The proposed 150 evaluable patients will provide adequate power (approximately 99%) for the new primary endpoint, namely, daily mean dNCC AUEC from 0 to 48 weeks. This power

calculation uses previously observed data on Cohort 1 patients. In Study WTX101-201, Cohort 1 patients treated with ALXN1840 showed AUEC of dNCC with a mean (SD) of 3.96 (2.047), while in Study WTX101-203, Cohort 1 patients treated with SoC showed a mean (SD) of 0.85 (0.425). With a significance level of 2.5% using a one-sided unequal variance t-test, 150 patients (100 to ALXN1840 and 50 to SoC) will provide >99% power to reject the null hypothesis of equal means.

Because the study size and power are sensitive to the assumptions used for effect size, variability, and withdrawal rates, a sample size re-estimation will be performed. Details of the sample size re-estimation are provided in Section 9.2.8.

9.2.8. Sample Size Re-estimation

A sample size re-estimation (SSR) will be performed to reassess the required size of the study population based on estimation of the original primary endpoint. Enrollment of patients will proceed without interruption while the analysis is ongoing. There are no plans to stop the study early for demonstration of noninferiority or superiority at the SSR. The sample size will not be reduced from the planned enrollment of 180 designed to achieve 150 evaluable patients and the maximum total number of patients enrolled may be increased to achieve up to 225 evaluable patients.

The SSR will be performed including approximately 31% of enrolled patients (eg, approximately the first 55 of the total 180 patients to be enrolled). It will be conducted after the last of these patients completes Week 48, or has withdrawn from the study, whichever comes first.

Based on the results of this re-estimation procedure, the study may need to enroll an estimated additional 75 evaluable patients, bringing the total to approximately 225 evaluable patients. The cap is non-binding and the analysis may lead to a different total number that may be higher or lower than that currently estimated.

The SSR will be based on a conditional power for noninferiority (CPni) using a promising zone with boundaries of ≥ 30% and < 80%. The CPni will be calculated using the results obtained at this interim analysis and will assume population mean percent change in cNCC equals the observed sample mean percent change in cNCC at the time of the SSR.

If the CPni is below 30%, or equal to or above 80%, (ie, outside the promising zone) then no increase in sample size will be made. If the CPni is within the promising zone then the sample size will be increased by the amount estimated needed to achieve a CPni of 80%. This decision rule is illustrated in Table 8.

The SSR will be repeated based on conditional power for superiority using the same boundaries and decision rules described for noninferiority.

The adaptive re-estimation methodology and practicalities will be documented in a pre-defined charter. An independent statistical center (ISC) will be established for creating the SSR report and will work with the existing DMC to review the SSR report and implement the sample size re-assessment in accordance with the SSR charter. The recommendations of the ISC/DMC to the Sponsor will be non-binding as the statistical adaptive algorithm should be seen as a guideline to aid decision making rather than as a definitive rule. Other criteria, such as secondary endpoints,

safety issues, feasible recruitment rates, withdrawal rates, and budgetary limits, can impact both independent recommendations by the ISC/DMC and decisions by the Sponsor.

Table 8: Criteria for Sample size Re-estimation

Criterion	Decision
CPni < 30%	Continue to N=150 evaluable
Promising zone: 30% ≤ CPni <80%	Increase to N=225 evaluable[a]
80% ≤ CPni	Continue to N=150 evaluable

[a] Decision is non-binding and N=225 may be exceeded to achieve CPni=80%
Abbreviation: CPni = conditional power for noninferiority.

9.2.9. Extension Period Analyses

Given the single arm, open-label nature of the Extension Period, data evaluation will be predominantly descriptive. All data collected in the Extension Period will be fully listed, with patient data from the antecedent parent study included to provide a full longitudinal profile over time for each patient. For Extension Period patients who received ALXN1840 in the antecedent parent study, their main baseline will be the baseline from that study; and for Extension Period patients who received SoC in the antecedent parent study, their main baseline will be the baseline from the Extension Period.

Full details of all planned analyses will be specified in an Extension SAP, which will be finalized prior to data lock of the Extension Period data. The Extension Period SAP will contain details of all the analyses including specifications for all tables, listings and figures. All statistical programming will be performed using SAS® software.

9.2.10. Other Analyses

Detailed population PK/PD analyses including the staged population PK/PD model development scheme during the treatment period will be described in the PK/PD Modeling and Simulation Analysis Plan, which will be finalized before database lock.

9.3. Data Monitoring Committee

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

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

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

9.4. Neurological Adverse Event Panel

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

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

9.5. Hepatic Adjudication Panel

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

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, substantial protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any substantial amendments to the protocol will require IRB/IEC and competent authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to the requirements of ICH guidelines and the IRB/IEC, all regional and national regulations as applicable (eg, CFR Title 21, Regulation [EU] No 536/2014 for clinical studies on medicinal products for human use, Directive 2001/20/EC), and all other applicable local regulations.

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

The Investigator or his/her representative will explain the nature of the study to the patient, their legal guardian (in the case of an adolescent patient, or a patient below the age of adulthood under Japanese local law for patients in Japan), or his/her legally authorized representative (if allowable per local regulations) and answer all questions regarding the study. If allowable by local regulations, a legally authorized representative may be able to provide informed consent on a patient's behalf if the patient is unable to provide informed consent.

Patients must be informed that their participation is voluntary. Patients, legal guardians of adolescent patients (or patients below the age of adulthood under Japanese local law for patients in Japan) or a patient's legally acceptable representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.

The Investigator must retain the original version of the signed ICF(s). A copy of the signed ICF(s) must be provided to the patient or the patient's legally authorized representative.

A patient who is rescreened is not required to sign another ICF unless an updated ICF is available.

10.1.4. Data Protection

Patients will be assigned a unique identifier by the Sponsor. Patient records or datasets that are transferred to the Sponsor will contain the identifier only; patient names or other information that would make the patient identifiable will not be transferred.

The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, appropriate IRB/IEC members, and inspectors from regulatory authorities.

10.1.5. Dissemination of Clinical Study Data

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

10.1.6. Data Quality Assurance

All patient data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 5 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.7. Source Documents

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

Data reported on the CRF or entered in the eCRF 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. Also, current medical records must be available. Source documents are filed at the Investigator's site.

10.1.8. Publication Policy

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

10.2. Appendix 2: Clinical Laboratory Tests

10.2.1. Chemistry

Table 9: Chemistry

Alanine aminotransferase	Albumin
Alkaline phosphatase	Bicarbonate
Aspartate aminotransferase	Total Calcium
Blood urea nitrogen	Glucose
Chloride	Lactate dehydrogenase
Creatinine[a]	Potassium
Gamma-glutamyl transferase	Total bilirubin
Creatine phosphokinase	Conjugated bilirubin
Magnesium	Uric acid
Sodium	Phosphate
Protein	Total cholesterol
Triglycerides	HDL cholesterol

[a] Including calculated creatinine clearance calculated by Cockcroft-Gault method for patients aged 18 years or older, and the Schwartz formula for patients < 18 years of age.

10.2.2. Coagulation

- Prothrombin time
- Partial thromboplastin time
- International normalized ratio

10.2.3. Endocrinology

- Follicle-stimulating hormone (For post-menopausal females only)

10.2.4. Hematology

Table 10: Hematology

Hematocrit	Hemoglobin
Platelets	Red blood cell count[a]
White blood cell count	Mean corpuscular volume
Mean cell hemoglobin	Mean cell hemoglobin concentration
Neutrophils	Lymphocytes
Monocytes	Eosinophils
Basophils	

[a] Including nucleated red blood cells.

10.2.5. Urinalysis

Table 11: Urinalysis

Bilirubin	Blood
Glucose	Ketones
Leukocytes	Microscopy
Nitrite	pH
Protein	Specific gravity
Urobilinogen	Red blood cells
Bacteria	Creatinine

10.2.6. Other Tests

Table 12: Other Tests

HIV, hepatitis B, and hepatitis C screen	Serum and urine pregnancy test
Ceruloplasmin	Total copper and total molybdenum
24-hour urine	PUF molybdenum and copper
24-hour urine copper and molybdenum	Labile bound copper

Abbreviation: PUF = plasma ultrafiltrate

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

Definition of Adverse Event

AE Definition
• An AE is any untoward medical occurrence in a participant 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 the study intervention, whether or not considered related to the 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. • "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.
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. • Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish drug effect. • A medication error (including intentional misuse, abuse, and overdose of the product) or use other than what is defined in the protocol is not considered an AE unless there is an untoward medical occurrence as a result of a medication error. • Cases of pregnancy that occur during maternal or paternal exposure to investigational product are to be reported within 24 hours of Investigator/site awareness. Data on fetal outcome and breastfeeding will be collected for regulatory reporting and safety evaluation.

Definition of Serious Adverse Event

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

A 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 patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
3. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
4. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
5. Is a congenital anomaly/birth defect
6. Other situations: • Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical 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.

Suspected Unexpected Serious Adverse Reactions

Suspected Unexpected Serious Adverse Reactions
Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the Investigator's Brochure version corresponding to the onset date of the event and that the Investigator identifies as related to investigational product or procedure. The United States Title 21 Code of Federal Regulations (CFR) 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidance documents or national regulatory requirements in participating countries require the reporting of SUSARs. Alexion has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidance documents. Suspected unexpected serious adverse reactions will be reported to the national competent authority and IRBs/IECs where applicable.

Recording and Follow-up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRF.
- It is not acceptable for the Investigator to send photocopies of the patient's medical records to Alexion or designee in lieu of completion of the AE/SAE report. If applicable, additional information such as relevant medical records should be submitted with a signed SAE cover page to Alexion GDS via email: [redacted] or facsimile: [redacted] In this case, all patient identifiers, with the exception of the patient number, will be redacted on the copies of the medical records before sending to GDS.
- 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 Severity

The Investigator will make an assessment of severity for each AE and SAE reported during the study and assign it to 1 of the following categories from National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5.0, published 27 Nov 2017. Each CTCAE term is a Lowest Level Term (LLT) per the MedDRA. Each LLT will be coded to a MedDRA Preferred Term:

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

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

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

Assessment of Causality

- The Investigator is obligated to assess the relationship between study drug and occurrence of each AE/SAE. An Investigator causality assessment must be provided for all AEs (both nonserious and serious). This assessment must be recorded in the eCRF and on any additional forms, as appropriate. The definitions for the causality assessments are as follows:
  - Not related: This relationship suggests that there is no causal association between the study drug and the reported event.
  - Related: This relationship suggests that there is causal association between the study drug and the reported event.

Adverse Event and Serious Adverse Event Recording

- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration will be considered and investigated.
- This protocol will use the current Investigator's Brochure as the Reference Safety Document. The expectedness and reporting criteria of an SAE will be determined by the Sponsor, based on the Reference Safety Document version that corresponds with the onset date of the event. The Investigator will also consult the Investigator's Brochure in his/her assessment.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to Alexion or designee. However, **it is very important that the Investigator**

AE and SAE Recording
always make an assessment of causality for every event before the initial transmission of the SAE data to Alexion GDS. • 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 or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a patient dies during participation in the study or during a recognized follow-up period, the Investigator will provide Alexion or designee with a copy of any post-mortem findings including histopathology. • The site will enter new or updated SAE data into the electronic system as soon as it becomes available, but no later than 24 hours. The Investigator will submit any updated SAE data to the GDS within 24 hours of awareness of the information.

Reporting of SAEs

SAE Reporting to Alexion GDS via an Electronic Data Collection Tool
• All SAEs will be recorded and reported to Alexion immediately and within 24 hours of awareness. • The primary mechanism for reporting an SAE to Alexion will be the EDC system. • If the electronic system is unavailable or site staff is unable to process the SAE via the EDC system 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 facsimile or email. Facsimile transmission or email may also be used in the event of electronic submission failure. • Email: [redacted] or Fax: [redacted] • 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 immediately with the new information and an updated SAE report should be submitted to Alexion Global Drug Safety (GDS) within 24 hours of Investigator/site awareness. • After the participant has completed the study, no new data or changes to existing data are expected to be entered in the EDC system.   o If a site receives a report of a new SAE from a study participant which the Investigator considers to be related to the study intervention, or the site receives updated data on a previously reported SAE after the EDC system has been taken offline, then the site can report this information on a paper Contingency Form for SAE Reporting via facsimile or email.
SAE Reporting to Alexion or Designee via Paper CRF
• If applicable, additional information such as relevant medical records should be submitted to Alexion GDS via the email address or fax number noted above. • All paper forms and follow-up information submitted to the Sponsor outside of the RAVE Safety Gateway (eg, discharge summary) should be kept in the appropriate section of the study file and MUST be accompanied by a cover page signed by the Investigator. • Paper source documents and/or reports should be kept in the appropriate section of the study file.

10.4. Appendix 4: Collection of Pregnancy Information

Pregnancy Testing

Women of childbearing potential should only be included after a confirmed menstrual period and a negative highly sensitive serum pregnancy test (see the SoA Section 1.2).

Additional pregnancy testing should be performed per the time points specified in the SoA (Section 1.2).

Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

Collection of Pregnancy Information

Pregnancy data will be collected during this study for all female patients and female spouses/partners of male patients. Any female patient who becomes pregnant during the study should be considered for discontinuation 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 patient or a male patient'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. 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, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy). Elective abortions without complications should not be reported as AEs.

10.5. Appendix 5: Genetics

Use/Analysis of DNA

- 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 and related diseases. 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 resolve issues with 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 or in a separate study summary.
- The Sponsor 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. Appendix 6: Abbreviations

Abbreviation	Definition
9-HPT	9-hole Peg Test
25F	25-foot
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AUEC	area under the effect-time curve
BfArM	Federal Institute for Drugs and Medical Devices in Germany
BPRS-24	Brief Psychiatric Rating Scale-24
CGI-I	Clinical Global Impression-Improvement Scale
CGI-S	Clinical Global Impression-Severity Scale
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
Cp	Ceruloplasmin
CpC	Ceruloplasmin-bound copper
CPni	Conditional power for noninferiority
CRF	Case report form
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTR1	Copper transporter 1
CYP	Cytochrome P450
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EMA	European Medicines Agency
EOS	End of Study
EQ-5D (Y)	EuroQoL 5 Dimensions (Y)
ET	Early Termination
FDA	Food and Drug Administration
FIB-4	Fibrosis-4
FSH	Follicle-stimulating hormone
GDS	Global Drug Safety
GI	Gastrointestinal
HIV	Human immunodeficiency virus
ICF	Informed consent form

Abbreviation	Definition
IEC	Institutional Ethics Committee
INR	International normalized ratio for prothrombin time
IRB	Institutional Review Board
ISC	Independent statistical center
LBC	Labile bound copper
LLT	Lowest level term
LS	Least-squares
MELD	Model for End-Stage Liver Disease
MT	Metallothionein
(d)(c)NCC	(directly measured) (calculated) non-ceruloplasmin-bound copper
$NCC_{corrected}$	Non-ceruloplasmin-bound copper in plasma corrected for the amount of copper bound to the ALXN1840 tripartite complex
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PRO	Patient Reported Outcomes
PUF	Plasma ultrafiltrate
QD	Once daily
QOD	Every other day
QoL	Quality of life
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SE	Standard error
SoA	Schedule of Activities
SoC	Standard of care
SSR	Sample size re-estimation
SUSAR	Suspected unexpected serious adverse reaction
TPC	Tripartite complex
TSQM-9	Treatment Satisfaction Questionnaire for Medication-9
ULN	Upper limit of normal
UMCU	University Medical Center Utrecht
UWDRS	Unified Wilson Disease Rating Scale
VAS	Visual Analogue Scale
WD	Wilson disease
WMO	Medical Research Involving Human Subjects Act

10.7. Appendix 7: Protocol Amendment History

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

DOCUMENT HISTORY	
Document	**Date**
Original Document	07 Nov 2017
Amendment 1	17 Jan 2019
Amendment 1.1 (Japan)	25 Mar 2019
Amendment 1.2 (Netherlands)	22 May 2019
Amendment 1.3 (Germany)	17 May 2019
Amendment 1.4 (Sweden)	21 May 2019
Amendment 1.5 (Germany)	10 Jul 2019
Amendment 1.6 (Austria)	30 Apr 2020
Amendment 2 (Global)	25 Mar 2021
Amendment 2.1 (UK)	16 Apr 2021
Amendment 3 (Global)	27 Apr 2022

10.7.1. Amendment 1, 17 Jan 2019

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

Overall Rationale for the Amendment:

Substantial changes and administrative changes to the protocol are detailed in the tables below.

Substantial Changes to the Protocol

Section # and Name	Description of Change	Brief rationale and/or clarifications
Title Page, Sponsor Signatory	Change of Sponsor (from Wilson Therapeutics AB to Alexion Pharmaceuticals Inc.), Medical Monitor (from [redacted] to [redacted]), and product code (from WTX101 to ALXN1840)	To reflect the legal and administrative integration of Wilson Therapeutics AB into Alexion Pharmaceuticals, Inc.
Section 1 Synopsis, Section 2.1 Study Rationale, Section 4.2, Scientific Rationale for Study Design, Section 8.1 Inclusion Criteria	To include adolescent patients (12 to 17 years old)	To expand the population who can receive ALXN1840 to include adolescents as well as adults, because approximately half of all patients are diagnosed before 18 years of age (Ferenci, 2019).
Section 1 Synopsis, Section 9.2.7 Sample Size Determination	To increase the sample size from 102 to 180 patients (targeting approximately 150 evaluable patients for up to 48 weeks), for enhanced statistical power to test for superiority versus Standard of Care	To enhance robustness for superiority testing of ALXN1840 versus Standard of Care and ensure that approximately 100 patients with 1 year of treatment will be available for the safety database.
Section 9.2.8 Sample Size Re-estimation	To add the sample size re-estimation	To confirm the appropriate sample size to test the hypothesis and allow for a possible increase in the sample size.

Section # and Name	Description of Change	Brief rationale and/or clarifications
Section 1 Synopsis, Section 4.3 Justification for Dose	Maximum daily dose permitted decreased from 90 mg to 60 mg	Results from Phase 1 and Phase 2 studies indicate that the ALXN1840 60 mg dose was well-tolerated in healthy volunteers, and it is anticipated to have an appropriate efficacy and safety profile in patients with Wilson Disease. Doses greater than 60 mg daily have not been tested in healthy volunteers.
Section 6.2.3.2 Dose Modification and Table 6	Changes in dose modification criteria and actions in individual patients for patients receiving ALXN1840	Provide more guidance on criteria that may prompt an increase or decrease in dosing of ALXN1840. Requirement for documentation of the rationale and decision-making for dose modification. To lower the re-challenge dose of ALXN1840 to 15 mg QOD to enhance safety.
Section 6.2.3.4 Dose Modification and Table 7	Changes in dose modification criteria and actions in individual patients for patients receiving Standard of Care	Provide more guidance on criteria that may prompt an increase or decrease in dosing of Standard of Care. Require documentation of the rationale and decision-making for dose modification.
Section 5.1. Inclusion Criteria	Criteria relating to contraception condensed into one criterion and new section, Section 6.6 Contraception Guidance, added	To clarify contraception guidance
Section 5.2 Exclusion Criteria	Criteria updated to exclude patients with creatinine clearance < 30 mL/min	The safety of ALXN1840 in patients with creatinine clearance < 30 mL/min has not yet been studied.
Section 9.5 Hepatic Adjudication Panel	Addition of an independent Hepatic Adjudication Panel to evaluate potential cases of drug-induced liver injury.	Elevations of liver enzymes and bilirubin were seen in 39% of patients treated with ALXN1840 in the Phase 2 Study WTX101-201. The Hepatic Adjudication Panel will provide additional review and recommendations to enhance patient safety.

Administrative Changes to the Protocol

Section # and Name	Description of Change	Brief Rationale and/or clarifications
Section 4.4 End of Study Definition	Text added on the end of the study	To define the end of the study
Section 5 Study Population	Addition of text on protocol waivers or exemptions	To clarify that prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted
Section 5.3 Screen Failure	Text added on screen failures	Section added to confirm definition of screen failures
Section 8.4 Overdose	Addition of language on overdose	To clarify what constitutes an overdose of study drug (ALXN1840 or Standard of Care)
Section 10.1 Appendix 1: Regulatory, Ethical, and Study Oversight Considerations	Text added or updated	Section added to comply with current Regulatory requirements and for compliance

Section # and Name	Description of Change	Brief Rationale and/or clarifications
Section 10.3 Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Revision of safety language, including update of adverse event reporting based on Reference Safety Information	To align with Alexion's current text on safety reporting
Section 10.5 Appendix 5: Genetics	Text added on the use, analysis, and storage of DNA samples	To add details of what analysis of genetic tests may be undertaken
All sections	Change of template	To align the protocol with Alexion's current protocol template
All sections	Minor editorial updates and corrections	For clarification, and to ensure accuracy and consistency throughout the protocol

10.7.2. Amendment 1.1 (Japan) 25 Mar 2019

Overall Rationale for the Amendment:

Substantial changes to the protocol were made based on feedback from the Japanese Pharmaceuticals and Medical Devices Agency. Substantial changes and administrative changes to the protocol are detailed in the tables below.

Substantial Changes to the Protocol

Section # and Name	Description of Change	Brief rationale and/or clarifications
Section 5.1 Inclusion Criteria Section 5.2 Exclusion Criteria Section 7.2 Patient Discontinuation/Withdrawal from the Study Section 10.1.3 Informed Consent Process	Change to reflect that the legal guardian of patients who are below the legal age for an adult in Japan must give consent to participate in or withdraw from the study	To reflect that the age where a subject becomes an adult in Japan is 20 years old, not 18 years old, as defined in the Global Study Protocol
Section 6.6.1 Guidance for Female Patients	Addition of text noting which methods of female contraception are authorized in Japan	To clarify which methods of female contraception are authorized in Japan

Administrative Changes to the Protocol

Section # and Name	Description of Change	Brief Rationale and/or clarifications
All sections	Minor editorial updates and corrections	For clarification, and to ensure accuracy and consistency throughout the protocol

10.7.3. Amendment 1.2 (Netherlands) 22 May 2019

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

Overall Rationale for the Amendment:

Substantial changes to the protocol were made based on requirements from the University Medical Center Utrecht, the Netherlands, to add details regarding biobank samples. These changes, and administrative changes to the protocol are detailed in the tables below.

Substantial Changes to the Protocol

Section # and Name	Description of Change	Brief rationale and/or clarifications
Section 8.5.3 Biomarkers and Biobank Samples Section 10.5 Appendix 5: Biobank Samples	Addition of an appendix detailing information on the management, storage, and analysis of biobank samples for the study site in the Netherlands	To include the Biobank Regulations from the University Medical Center Utrecht

Administrative Changes to the Protocol

Section # and Name	Description of Change	Brief Rationale and/or clarifications
All sections	Minor editorial updates and corrections	For clarification, and to ensure accuracy and consistency throughout the protocol

10.7.4. Amendment 1.3 (Germany) 17 May 2019

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

Overall Rationale for the Amendment:

A substantial change to the protocol was made in response to the requirement from the Federal Institute for Drugs and Medical Devices in Germany (BfArM) to include further justification as to why adolescent patients aged 12 to < 18 years should be included in this study, which currently only allows patients aged 18 years and above to enroll. In addition, details of the formula used to calculate creatinine clearance in patients < 18 years of age were added to the protocol. The changes to the protocol are detailed in the table below.

Substantial Change to the Protocol

Section # and Name	Description of Change	Brief rationale and/or clarifications
Section 2.3.2, Potential and Identified Risks	Text added relating to the maximum number of attempts to be made for blood samples and the failure escalation procedure	To ensure any risk associated with venous vessel access for blood samples are appropriately mitigated
Section 4.3.1, ALXN1840	Brief details of the PK results that support the proposed starting and maximum dose selection in patients aged 12 to <18 years is have been added.	To include justification of the dose for patients aged 12 to < 18 years.
Section 10.2.1, Chemistry Table 8 Chemistry	Text added to the footnote noting that the Schwartz formula is used to calculate creatinine clearance in patients < 18 years of age	To reflect that different methods are used to calculate creatinine clearance in patients < 18 years of age and those 18 years and older

10.7.5. Amendment 1.4 (Sweden) 21 May 2019

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

Overall Rationale for the Amendment:

This amendment was prepared to address requests by the Swedish Health Authority to provide clarification of when the primary efficacy analysis will be performed and to add details of the conclusions of the benefit/risk assessment. Some minor administrative changes were also made,

for clarity and consistency. Substantial changes and administrative changes to the protocol are detailed in the tables below.

Substantial Changes to the Protocol

Section # and Name	Description of Change	Brief rationale and/or clarifications
Section 2.3	Text added regarding the conclusions of the benefit/risk assessment.	To clarify the benefit/risk.
Synopsis Section 9.2.1.1, Primary Efficacy Analysis	Details added of when the primary efficacy analysis will be performed.	To ensure clarity regarding when the primary efficacy analysis will be performed.
Section 10.1.1	Added text on the competent authority	To confirm that protocol amendments should be approved by the competent authority, in addition to the IEC/IRB
Section 10.2.1, Chemistry Table 8 Chemistry	Text added to the footnote noting that the Schwartz formula is used to calculate creatinine clearance in patients < 18 years of age	To reflect that different methods are used to calculate creatinine clearance in patients < 18 years of age and those 18 years and older.

Administrative Changes to the Protocol

Section # and Name	Description of Change	Brief rationale and/or clarifications
All sections	Minor editorial updates and corrections	For clarification, and to ensure accuracy and consistency throughout the protocol

10.7.6. Amendment 1.5 (Germany) 10 Jul 2019

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

Overall Rationale for the Amendment:

The purpose of this amendment was to remove adolescents from the study in Germany, ie, patients aged 12 to 17 years of age in response to comments from the Federal Institute for Drugs and Medical Devices in Germany (BfArM) on Protocol Amendment 1. Only patients aged 18 years and older were to be enrolled in the study at sites in Germany, as per the original protocol dated 07 Nov 2017. This amendment only applied to Germany; other countries in the study were able to enroll patients aged 12 to 17 years under Protocol Amendment 1, if permitted by their respective regulatory authorities. Substantial changes to the protocol are detailed in the table below.

Substantial Changes to the Protocol

Section # and Name	Description of Change	Brief rationale and/or clarifications
Title Page Section 1.1 Synopsis Section 2.1, Study Rationale Section 2.3.1, Potential Benefits Section 3, Objectives and Endpoints Section 4.1.1, Primary Evaluation Period Section 4.2, Scientific Rationale for Study Design Section 5.1, Inclusion Criteria Section 8.1.3, Unified Wilson Disease Rating Scale (Parts I, II, and III) Section 8.1.9, EuroQoL 5 Dimensions	Removal of text relating to inclusion of patients aged 12 to 17 years in the study in Germany.	It has been decided not to include patients aged 12-17 years in Germany, in response to comments from BfArM. Note: this amendment only applies to Germany; other countries in the study will be able to enroll patients aged 12 to 17 years under Protocol Amendment 1, if permitted by their respective regulatory authorities.

10.7.7. Amendment 1.6 (Austria), 30 Apr 2020

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

Overall Rationale for the Amendment:

Substantial changes to the protocol and administrative changes are detailed in the tables below.

Substantial Changes to the Protocol

Section # and Name	Description of Change	Brief rationale and/or clarifications
Section 1.2 Schedule of Activities, Tables 3, 4, and 5 Section 8.2.5 Pregnancy Test	Addition of requirement for female subjects of childbearing potential to perform monthly pregnancy testing at their home throughout the study	It is a legal requirement in Austria to include monthly pregnancy tests in clinical studies
Section 1.2 Schedule of Activities, Table 5 only	Addition of text that patients who transferred from Study WTX101-201 do not need to attend visits at Weeks 60 and 84	These visits were not required for patients who had previously been in Study WTX101-201.
Section 1.2 Schedule of Activities, Table 4 only and Section 8.1.5 Three Most Troublesome Symptoms	Text added to clarify that videos of patients reporting their 3 most troublesome symptoms are not collected in the Extension Period of the study	Videos are not required for patients in the Extension Period
Section 8.3.1 Time Period and Frequency for Collecting AE and SAE Information	Text corrected to confirm that medical occurrences that occur after consent but before study drug are reported as pre-treatment adverse events	To clarify that medical occurrences that occur after consent is given but before administration of study drug should be reported as pre-treatment adverse events, not medical history
Section 9.2.7 Sample Size Determination	Numbers of patients revised to approximately 113 evaluable patients Cohort 1 and 37 evaluable patients in Cohort 2	To reflect the correct ratio of patients in Cohorts 1 and 2, ie, 3:1.

Administrative Changes to the Protocol

Section # and Name	Description of Change	Brief Rationale and/or clarifications
Section 1.2, Schedule of Activities, Tables 3, 4, and 5	Renumbering and editing of footnotes	To align and clarify footnotes, primarily because some had been misaligned when the previous amendment was prepared
Section 1.2, Schedule of Activities, Table 5	Add Extension Period Study Day and Week	To clarify the expected schedule and procedures for patients who transfer to this study from Study WTX101-201
Section 4.1 Overall Design	Revised Figure 1 as Weeks 18 and 24 were in an incorrect position and to clarify assessment time points for patients who enter the Extension Period	For clarification
All sections	Minor editorial updates and corrections	For clarification, and to ensure accuracy and consistency throughout the protocol

10.7.8. Amendment 2 (Global), 25 Mar 2021

This amendment is considered to substantially 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.

Overall Rationale for the Amendment:

The main reason for this amendment is to change the primary endpoint to reflect that a dynamic measure of tissue copper mobilization and elimination over time is a surrogate endpoint more likely to predict clinical benefit than point measurements of plasma calculated non-ceruloplasmin-bound copper (cNCC; the previous primary endpoint), because it will assess the treatment effect on tissue copper overload, the underlying cause of Wilson disease (WD).

This amendment includes additional changes in the identity and/or the testing order of other endpoints to support the assessment of ALXN1840 tissue decoppering effect and its potentially greater benefits on the clinical outcomes of WD compared with standard of care (SoC) treatment.

Substantial changes from protocol amendment 1 are detailed in Table 1.

Table 1: Substantial Changes to the Protocol

Section # and Name	Description of Change	Brief rationale and/or clarifications
Substantial Changes to the Protocol		
Section 1.1 Synopsis, Section 3 Objectives and Endpoints	Primary endpoint changed from: • Percentage change from baseline (Day 1) to 48 weeks in non-ceruloplasmin-bound Cu (NCC) in plasma. For ALXN1840-treated patients, the NCC in plasma will be corrected for the amount of Cu bound to the ALXN1840 tripartite complex (TPC) ($NCC_{corrected}$) to: • Daily mean area under the effect-time curve (AUEC) of directly measured non-ceruloplasmin-bound copper (dNCC) from 0 to 48 weeks	Based on results obtained from completed Phase 1 and Phase 2 studies, it was determined that an integrative measure of non-ceruloplasmin-bound copper mobilization and elimination over time is a more appropriate surrogate endpoint to assess the treatment effect on tissue copper overload than point measurements of blood species of copper (eg, total plasma copper, labile bound copper, and cNCC) , which do not reflect the underlying burden of copper overload in tissues, and, therefore, do not provide meaningful data to direct therapeutic decisions.
	The previous primary endpoint has been moved to become a secondary endpoint and expanded to include absolute change from baseline: • Absolute change from baseline (Day 1) to 48 weeks in cNCC in plasma. • Percentage change from baseline in cNCC in plasma. • For ALXN1840-treated patients, the cNCC in plasma will be corrected for the amount of copper bound to the ALXN1840 tripartite complex (TPC) ($cNCC_{corrected}$)	The endpoint of percentage change from baseline in cNCC may be highly variable when the baseline levels are close to zero. Analysis of both absolute and percentage change from baseline in cNCC will allow more meaningful interpretation of the effect of ALXN1840 and SoC on circulating copper concentrations.
	Additional secondary endpoint of assessment of UWDRS Part III individual items/subscales (arising from a chair, gait, handwriting, and speech) added to the secondary objective of "Evaluate the effects of ALXN1840 on neurological status"	Based on a recommendation by the US FDA, individual items/subscales of UWDRS Part III have been added to further define the range of functionally burdensome signs and symptoms of WD, so as to further understand the assessment of treatment effects on patients with WD.
	Additional endpoints added to the exploratory objective "Evaluate other directly measured PD and biomarkers of ALXN1840" Addition of exploratory objectives of "Explore ALXN1840 effect on initial decoppering phase compared to SoC based on directly measured PK/PD and biomarkers" and "Explore ALXN1840 effect on subsequent maintenance phase compared to SoC based on directly measured PK/PD and biomarkers"	The LBC assay was developed to provide a direct quantification of exchangeable copper in the NCC fraction, because the indirect method for estimating NCC concentrations is often associated with biologically implausible negative values. Therefore, newly developed endpoints have been added to reflect the additional assessments that will be performed relating to total copper concentration and LBC.

Section # and Name	Description of Change	Brief rationale and/or clarifications
	Extension Period endpoints aligned, so that the additional endpoints added to the primary, secondary, and exploratory objectives are also assessed.	To ensure appropriate additional endpoints are also assessed during the Extension Period of the study.
Section 1.1 Synopsis 2.1, Study Rationale 4.2 Scientific Rationale for Study Design	Revision of text on the rationale for the study	To align the study rationale with the change in primary endpoint.
Section 1.1 Synopsis Section 9.2.1.1 Primary Efficacy Analysis 9.2.1.2 Secondary Efficacy Analysis 9.2.2 Type I Error Control 9.2.5 Handling of Missing Data 9.2.7 Sample Size Determination	Revision of text relating to the statistical analysis of the primary endpoint and deletion of text relating to statistical analysis of the secondary endpoints	To align details of the statistical analysis with the change in primary endpoint. Details of the statistical analyses to be performed on the secondary endpoints will be described in the Statistical Analysis Plan.
Section 1.2 Schedule of Activities, Table 6 only	Addition of text to clarify that patients who transferred from Study WTX101-201 do not need to attend visits at Weeks 60 and 84	These visits were not required for patients who had previously been in Study WTX101-201.
Section 1.2 Schedule of Activities, Table 5 only, Section 8.1.5 Three Most Troublesome Symptoms	Text added to clarify that videos of patients reporting their 3 most troublesome symptoms are not required to be collected in the Extension Period of the study	Videos are not required for patients in the Extension Period and also for patients who switch from SoC to ALXN1840 during the first year of the Extension Period.
Section 1.2 Schedule of Activities, Table 5	Removal of the following assessments on Day 295: Plasma/serum PK/PD/biomarkers and biobank samples, UWDRS Parts I, II, and III, and administer/dispense ALXN1840	The Day 295 visit is performed via a phone call, so assessments are not performed.
Section 1.2 Schedule of Activities, Table 5 and Table 6	Addition of administer/dispense ALXN1840 on Days 1513, 1681, and 1849 (Table 5) and Day 1849 (Table 6)	To correct the SoA to when ALXN1840 is administered/dispensed.
Section 2.2.1 Wilson Disease 2.2.2 ALXN1840 2.3.1 Potential Benefits 4.2 Scientific Rationale for Study Design	Addition/update of the description of the proposed mechanism of action of ALXN1840	To include text on the proposed mechanism of action of ALXN1840.
Section 6.5.1.1 Prohibited Medications	Added text prohibiting the use of an experimental or unapproved/unlicensed therapy	To ensure that use of experimental or unapproved/unlicensed drugs is excluded during the study.
Section 7.2 Patient Discontinuation/ Withdrawal from the Study	Revision of the requirement that patients may be discontinued from the study if they enroll in a clinical study of an experimental or unapproved/unlicensed therapy to state that they must be withdrawn if they receive an experimental or unapproved/unlicensed therapy.	To clarify that if patients receive an experimental or unapproved/unlicensed therapy (eg, for treatment of COVID-19), they must be withdrawn from the study.
Section 8.1.1 Assessment of Copper	Added details of the assessment of copper using AUEC	To align with the change in primary endpoint.

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	Text corrected to confirm that medical occurrences that occur after consent but before study drug are recorded as pre-treatment adverse events	To clarify that medical occurrences that occur after consent is given but before administration of study drug should be reported as pre-treatment adverse events, not medical history.
Section 9.2.1.2 Secondary Efficacy Analysis	Text and table added defining key secondary endpoints according to regional expectations.	Following interactions with the US FDA and EMA CHMP, regional differences in the key secondary endpoints and associated multiplicity testing were agreed.
Section 9.2.5 Handling of Missing Data	Tipping point analysis replaced with a 2-dimensional tipping point analysis.	The US FDA requested a more comprehensive tipping point analysis that would allow assumptions about the missing outcomes on the 2 groups to vary independently rather than just applying the shift to the ALXN1840 group.
Section 9.2.7 Sample Size Determination	Numbers of patients revised to approximately 113 evaluable patients Cohort 1 and 37 evaluable patients in Cohort 2	To reflect the correct ratio of patients in Cohorts 1 and 2, ie, 3:1.
Section 10.2.1 Chemistry, Table 8 Chemistry	Total cholesterol and triglycerides added to the table of chemistry assessments	Routine lipid panel added for completeness.
	Text added to the footnote noting that the Schwartz formula is used to calculate creatinine clearance in patients < 18 years of age	To reflect that different methods are used to calculate creatinine clearance in patients < 18 years of age and those 18 years and older.
Section 10.3 Appendix 3: Definition of Adverse Event and Reporting of SAEs	Definition of an AE, and text on reporting of SAEs updated.	To be in-line with the definition in the latest Alexion approved protocol template.

Abbreviations: AE = adverse event; AUEC = area under the effect-time curve; (d)(c)NCC = (direct) (calculated) non-ceruloplasmin-bound copper; CHMP = Committee for Medicinal Products for Human Use; EMA = European Medicines Agency; FDA = Food and Drug Administration; LBC = labile bound copper; PD = pharmacodynamic; PK = pharmacokinetic; SAE = serious adverse event; SoC = standard of care; TPC = tripartite complex; UWDRS = Unified Wilson Disease Rating Scale, WD = Wilson disease.

Changes made in the country specific amendments 1.1, 1.2, 1.3, 1.4, 1.5, and 1.6, as well as urgent safety measures relating to the COVID-19 pandemic already implemented in the study and notified to Competent Authorities have also been incorporated into this amendment (Table 2). Minor administrative changes have also been made for clarification and consistency (Table 3).

Table 2: COVID-19 Urgent Safety Measures and Changes Incorporated from Country Specific Amendments and Administrative Change Letters

Section # and Name	Description of Change	Brief rationale and/or clarifications
Section 10.9, Appendix 9: COVID-19 Urgent Safety Measures	Appendix added detailing the provision of additional study procedures, laboratory assessments, safety monitoring and study drug dispensation that may be conducted as a result of the global COVID pandemic	To ensure that every effort is made to maintain patient safety in the setting of COVID-19 transmission while continuing treatment for Wilson disease.
Section 1.1, Synopsis Section 2.1, Study Rationale Section 4.1.1, Primary Evaluation Period Section 4.2, Scientific Rationale for Study Design Section 5.1, Inclusion Criteria	Addition of text stating that patients enrolled in Germany have to be 18 years of age or older	Only patients aged 18 years and older can be enrolled in Germany, as detailed in Amendment 1.5 (Germany) dated 10 Jul 2019, based on comments that were received from the Federal Institute for Drugs and Medical Devices in Germany (BfArM) on Protocol Amendment 1 dated 17 Jan 2019 and Amendment 1.3 (Germany) dated 17 May 2019.
Section 1.1, Synopsis Section 9.2.1.1, Primary Efficacy Analysis	Details added of when the primary efficacy analysis will be performed.	To ensure clarity regarding when the primary efficacy analysis will be performed, as requested by the Swedish Health Authority in Amendment 1.4 (Sweden) dated 21 May 2019.
Section 1.2 Schedule of Activities, Tables 4, 5, and 6 Section 8.2.5 Pregnancy Test	Addition of requirement for female subjects of childbearing potential to perform monthly pregnancy testing at their home throughout the study	Added as per Amendment 1.6 (Austria) dated 30 Apr 2020, because it is a legal requirement in Austria to include monthly pregnancy tests in clinical studies.
Section 2.3.3 Benefit/Risk Conclusions	Text added regarding the conclusions of the benefit/risk assessment.	To clarify the benefit/risk, as requested by the Swedish Health Authority in Amendment 1.4 (Sweden) dated 21 May 2019.
Section 5.1 Inclusion Criteria Section 5.2 Exclusion Criteria Section 7.2 Patient Discontinuation/Withdrawal from the Study Section 10.1.3 Informed Consent Process	Change to reflect that the legal guardian of patients who are below the legal age for an adult in Japan must give consent to participate in or withdraw from the study	To reflect that the age where a subject becomes an adult in Japan is 20 years old, not 18 years old, as defined in the Global Study Protocol, as previously detailed in Amendment 1.1 (Japan) dated 25 Mar 2019.
Section 6.6.1, Guidance for Female Patients	Addition of text on acceptable methods of contraception for female patients of childbearing potential in Japan, which differ from the methods accepted elsewhere	Added in response to a request from the Japan Health Authorities, as previously detailed in Amendment 1.1 (Japan) dated 25 Mar 2019.
Section 6.6.1, Guidance for Female Patients	Addition of text on acceptable methods of contraception for female patients of childbearing potential in Canada, which differ from the methods accepted elsewhere	Added in response to a request from Health Canada, previously detailed in Administrative Change Letter 7 (Canada) dated 24 Jul 2020.

Section # and Name	Description of Change	Brief rationale and/or clarifications
Section 8.5.3 Biomarkers and Biobank Samples Section 10.8 Appendix 8: Biobank Samples in the Netherlands	Addition of an appendix detailing information on the management, storage, and analysis of biobank samples for the study site in the Netherlands	To include the Biobank Regulations from the University Medical Center Utrecht, as previously detailed in Amendment 1.2 (Netherlands) dated 22 May 2019.
Section 10.1.1	Added text on the competent authority	To confirm that protocol amendments should be approved by the competent authority, in addition to the IEC/IRB, as detailed in Amendment 1.4 (Sweden) dated 21 May 2019.
Section 10.7 Appendix 7: Protocol Amendment History	Details of the previous protocol amendments, 1.1, 1.2, 1.3, 1.4, 1.5, and 1.6 added.	To include details of previous amendments.

Table 3: Administrative Changes to the Protocol

Section # and Name	Description of Change	Brief Rationale and/or clarifications
Section 1.2, Schedule of Activities, Tables 4, 5, and 6	Renumbering and editing of footnotes	To align and clarify footnotes, primarily because some had been misaligned when amendment 1 was prepared.
Section 1.2, Schedule of Activities, Table 6	Added Extension Period Study Days and Weeks	To clarify the expected schedule and procedures for patients who transfer to this study from Study WTX101-201.
Section 4.1 Overall Design	Revised Figure 1 as Weeks 18 and 24 were in an incorrect position and to clarify assessment time points for patients who enter the Extension Period	For clarification.
All sections	Minor editorial updates and corrections	For clarification, and to ensure accuracy and consistency throughout the protocol.

10.7.9. Amendment 2.1 (UK), 16 Apr 2021

This amendment is considered non-substantial and applies to the UK.

Overall Rationale for the Amendment:

The reason for this amendment is 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.

The change from protocol amendment 2 is detailed in Table 1.

Table 1: Change to the Protocol

Section # and Name	Description of Change	Brief rationale and/or clarifications
10.10 Appendix 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.

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

10.8. Appendix 8: Biobank Samples in the Netherlands

To fulfil the requirements set forth in the biobank regulations at the University Medical Center Utrecht (UMCU), the Netherlands, additional language is included here for this study to comply with the provisions of Article 10 of these regulations with regards to human biological material that was collected for the purpose of a specific study, subject to the Medical Research Involving Human Subjects Act (WMO), and that was not used (in full) for the study concerned.

This appendix has been specifically written to document details regarding PK, PD, genetic and biomarker blood samples that will be stored and may be used for future research on ALXN1840. This appendix should be reviewed in addition to the conditions and procedures as set forth in the body of the main study protocol.

10.8.1. Purpose of the Biobank Samples

Blood and urine samples collected for testing of PK, PD, future genetic research, and biomarkers will be frozen, stored and may be used for future research linked to WD and the potential activity of ALXN1840, subject to the WMO. The samples will be de-identified, allowing the samples to be used without the researchers knowing the patient's name or other personal identifiers.

10.8.2. Processing, Analyzing and Storage of the Samples

The process for collecting and handling the samples that are to be kept for future research is described in the study laboratory manual.

These samples will be stored frozen at Alexion Pharmaceuticals, Inc. (100 College Street, New Haven, CT 06510 USA) or its designee for a maximum of 5 years after all data have been collected for the study (10 years for samples for genetic analysis). Cells will not be amplified to immortal (stem) cells and cell lines.

In case of exceptional circumstances that something is discovered when analyzing the samples that could be in the patient's interest, it will be reported to the biobank committee at UMCU. The committee will review all relevant information, and will discuss with the treating physician and/or the patient's general practitioner, and the Medical Cluster Head from the Department of Gastroenterology. They will decide if the patient will be informed about these findings by the treating physician.

This process is also explained in the informed consent form and the patient and/or his/her parents/guardians will provide consent for the use and storage of these samples and to be informed about any relevant findings.

10.8.3. Release of the samples

The terms for management of the samples are:

1. Approval from the Medical Ethics Committee at UMCU as delegated by the Reviewing Committee Biobanking at UMCU.
2. Executive Board approval at UMCU for the study including the biobanking.
3. Samples may not be used for research other than specified in the ethical review application, unless obtaining a new approval by the Medical Ethics Committee at UMCU.

4. In case of future use of the samples, prior permission will be sought from the person at UMCU responsible for the biobank as described on the registration form.

Samples are received, handled, analyzed, retained, and disposed in accordance with the Study WTX101-301 protocol, applicable laboratory standard operating procedures, and Alexion standard operating procedures.

10.8.4. Procedures for coding and storage of personal data and biomaterial

Personal data

Patients receive a unique study code that will not identify the patient. The code linking personal identifiers to the samples will be kept by the investigator in a secure location at the study site. Patient initials and full Date of Birth information will not be used on any documents outside the hospital. The laboratories involved in the shipment or testing of samples do not have access to this information. These data are only accessible to the investigator and members of the research team in the hospital where the patient is treated.

Samples will be labelled with a unique study number, sample number (code) and the study code described above.

Alexion, and authorized representatives on behalf of Alexion, such as study monitors, as well as the Medical Ethics Committee, Health inspection, and other competent authorities, will have access to the source documents and other data traceable to individual patients at the hospital.

The investigator and Alexion will store the patient's data for at least 25 years after the end of the study, in accordance with applicable EU laws and national guidelines.

Biomaterial

a. During the research

Biomaterial (blood samples and urine) from patients will be coded so that Alexion and their designees can store and analyze the samples without knowing the patient's name or other personal identifiers. The patient's biomaterial will receive a unique study number not linked to the person as described above.

b. After conclusion of the research

Blood samples for PK, PD, and biomarkers may be stored for a maximum of 5 years after the study, and samples for future genetic research for 10 years, and may be used for future research linked to the potential activity of ALXN1840. The blood samples will be discarded according to the standard procedures of the laboratory.

All other blood and urine samples collected during the study will be destroyed after the tests described in the protocol have been performed.

10.8.5. Consent procedure

Where required by local regulations, explicit consent for the biobank storage and future research is required, and patients and/or their parents/guardians (where applicable) are specifically asked for their consent for retention and analysis of the biomaterial for future use for the purposes described in the informed consent form. In case the samples would be used for other purposes than described in the informed consent form, the patient's (and/or parents/guardians) further

consent will first be obtained. In addition, where required by local regulations, there is a separate withdrawal consent process for patients and/or their parents/guardians who initially consented to the storage of their samples for future use, but who change their mind during or after the study.

10.9. Appendix 9: COVID-19 Urgent Safety Measures

The COVID-19 pandemic has the potential to restrict access to ALXN1840 and SoC treatment and safety monitoring visits for study patients. 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 13). These include visits at the patient's home, by an investigator or home healthcare provider, in-person, by telephone or by video conference, at another study site located near the patient's home, or an alternative center located near the patient'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.

Patients 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 patients receiving ALXN1840 or SoC. The risk to benefit assessment favors continuity of treatment for WD, when possible.

An Urgent Safety Measure was notified to both competent authorities and IRBs/ECs, where applicable. Informed consents forms were updated as necessary to permit release of medical records for patients transferring to another study site and to enable remote data verification where permitted.

The future of this pandemic is uncertain. These changes in the conduct of the study are effective but are intended to be temporary. Alexion intends to revert back to the original measures described in the current protocol after the end of the pandemic period. Alexion is making every effort to maintain patient 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 13: COVID-19 Clinical Study Mitigation Measures (Optional and Temporary) for Study WTX101-301

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, patient 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.
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, patient study visits may need to be completed remotely at the patient'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 patient'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, patient study visits may need to be completed remotely at another study site located near the patient's home, or an alternative center located near the patient'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 patient	Due to COVID-19 pandemic restrictions, patient study visits may need to be completed remotely at the patient'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 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 patient	Due to COVID-19 pandemic restrictions, patient study visits may need to be completed remotely at the patient'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 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.

Table 13: COVID-19 Clinical Study Mitigation Measures (Optional and Temporary) for Study WTX101-301

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 patient	Due to COVID-19 pandemic restrictions, patient study visits may need to be completed remotely at the patient'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 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, patient study visits may need to be completed remotely at the patient'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, patient study visits may need to be completed remotely at the patient's home, by site staff or home healthcare provider. This alternative temporary measure will limit impact of the pandemic on the parameter assessment.
MELD 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 patient	Due to COVID-19 pandemic restrictions, patient study visits may need to be completed remotely at the patient'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 patient's home. This alternative temporary measure will limit impact of the pandemic on the parameter assessment.

Table 13: COVID-19 Clinical Study Mitigation Measures (Optional and Temporary) for Study WTX101-301

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 copper and molybdenum	PI/Sub-I/SC/Other certified staff	Home Healthcare Provider		Courier may be used for shipment of lab kits from site to patient	Due to COVID-19 pandemic restrictions, patient study visits may need to be completed remotely at the patient'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 patient	Due to COVID-19 pandemic restrictions, patient study visits may need to be completed remotely at the patient'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 patient'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, patient 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. .
UWDRS I & III	Video by Neurologist if feasible				Due to COVID-19 pandemic restrictions, patient 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.
BPRS	Site staff Phone/Video				Due to COVID-19 pandemic restrictions, patient 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, patient 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.
25F Walk Test	Home visit by site staff if feasible				Due to COVID-19 pandemic restrictions, patient 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.
9-HPT	Home visit by site staff if feasible				Due to COVID-19 pandemic restrictions, patient 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.

Table 13: COVID-19 Clinical Study Mitigation Measures (Optional and Temporary) for Study WTX101-301

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	
Digit Span	Home visit by site staff if feasible				Due to COVID-19 pandemic restrictions, patient 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.
3 Most Troublesome Symptoms	Patient to complete	Home healthcare provider may provide completed questionnaire to site		Courier may be used for shipment of questionnaires from site to patient	Due to COVID-19 pandemic restrictions, patient study visits may need to be completed remotely at the patient's home, by site staff or home healthcare provider This alternative temporary measure will limit impact of the pandemic on the parameter assessment.
EQ-5D	Patient to complete	Home healthcare provider may provide completed questionnaire to site		Courier may be used for shipment of questionnaires from site to patient	Due to COVID-19 pandemic restrictions, patient study visits may need to be completed remotely at the patient's home, by site staff or home healthcare provider. This alternative temporary measure will limit impact of the pandemic on the parameter assessment.
TSQM-9	Patient to complete	Home healthcare provider may provide completed questionnaire to site		Courier may be used for shipment of questionnaires from site to patient	Due to COVID-19 pandemic restrictions, patient study visits may need to be completed remotely at the patient'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, patient study visits may need to be completed remotely at the patient's home, by site staff or home healthcare provider. This alternative temporary measure will limit impact of the pandemic on the re-consent of patients if needed.

a. Critical for safety monitoring

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