TITLE PAGE

STATISTICAL ANALYSIS PLAN

Primary Evaluation Period

Version Number: 1.0

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

Protocol Number: ALXN1840-WD-302

Protocol Amendment Number: 3 (Global)

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

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

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Version Date: 21 June 2022

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VERSION HISTORY

This Statistical Analysis Plan (SAP) for Study ALXN1840-WD-302 is based on Protocol Amendment 3 (Global), dated 08 Mar 2022.

SAP Version	Version Date	Change	Rationale
1.0	21 Jun 2022	Not applicable	Original version

More details are provided in Section 6.5.

APPROVAL SIGNATURES

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1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes the statistical methods for analyzing data for Protocol ALXN1840-WD-302 ("A multicenter, randomized, controlled, open-label, rater-blinded study to evaluate efficacy, safety, pharmacokinetics, and pharmacodynamics of ALXN1840 versus standard of care in pediatric participants with Wilson disease"). Standard data presentation instructions, and table, figure, and listing specifications are contained in the Data Presentation Plan in a separate document.

This SAP describes the analytical plan for the randomized Primary Evaluation Period (Period 1). A separate SAP will be generated for the nonrandomized, exploratory, open-label Extension Period (Period 2).

1.1. Objectives and Estimand(s) and/or Endpoint(s)

Objectives Period 1: Up to Week 48	**Estimand(s) and/or Endpoint(s)**
Primary	
• To evaluate the efficacy of ALXN1840 administered for 48 weeks, compared to standard of care (SoC), on Cu control in participants with Wilson disease (WD) aged 3 to < 18 years of age at the time of enrollment	• Treatment: ALXN1840 and SoC • Population: pediatric participants with WD who meet all inclusion and no exclusion criteria • Variable: Percent change from baseline (Day 1) to 48 weeks in non-ceruloplasmin-bound Cu (NCC) in plasma. For ALXN1840-treated participants, the NCC in plasma will be corrected for the amount of Cu bound to the ALXN1840 tripartite (tetrathiomolybdate-Cu-albumin) complex ($NCC_{corrected}$). • Intercurrent event: For participants who die or discontinue early for any reason, a while-on-treatment strategy will be applied reflecting that missing data will not be imputed. For participants who use another medication that affects plasma-calculated NCC (cNCC)/cNCC corrected for Cu bound in tripartite (tetrathiomolybdate-Cu-albumin) complexes ($cNCC_{corrected}$), the treatment policy strategy will be applied. • Summary measure: Comparison of the percent change from baseline (Day 1) to 48 weeks in cNCC/$cNCC_{corrected}$ in plasma between treatment groups
Secondary	
• Evaluate the safety and tolerability of ALXN1840 administered for up to 48 weeks	• Incidence of adverse events (AEs)/serious adverse events (SAEs), adverse events of special interest (AESIs), tolerability, clinical laboratory test data (including liver function tests), neurological and physical examination findings, 12-lead electrocardiogram (ECG) data, and vital signs.
• Evaluate pharmacodynamics (PD) and biomarkers of ALXN1840 vs SoC administered for 48 weeks	• Area under the effect-versus-time curve (AUEC) for directly measured NCC (dNCC) • AUEC for plasma total Cu

Objectives Period 1: Up to Week 48	**Estimand(s) and/or Endpoint(s)**
	• Biomarkers: observed, absolute, and percent changes of ceruloplasmin-bound Cu (CpC) and ceruloplasmin
• Evaluate the effects of ALXN1840 and SoC on the NCC responder rate	• cNCC/cNCC$_{corrected}$ responder rate
• Evaluate the effects of ALXN1840 and SoC on participant-reported disability status	• Change from baseline to Week 48 in the Unified Wilson Disease Rating Scale (UWDRS) Part II total score
• Evaluate the effects of ALXN1840 and SoC on rater-blinded neurological status	• Change from baseline in UWDRS Part III total score or individual items/subscales, as appropriate
• Evaluate pharmacokinetics (PK) of ALXN1840 administered for 48 weeks	Estimation of PK parameters and accumulation ratios: • PK: maximum observed concentration (C_{max}), time to C_{max} (t_{max}), trough (predose) concentration observed at the start of the dosing interval (C_{trough}), and area under the plasma concentration-versus-time curve from time 0 to the end of the dosing interval (AUC_{tau}) on Day 1, Day 43 (Week 6), and Day 337 (Week 48) for plasma total Mo and plasma ultrafiltrate (PUF) Mo concentrations, accumulation ratio of Day 43 to Day 1 and Day 337 to Day 1 based on C_{max}, C_{trough}, and AUC_{tau} • Derived secondary PK parameters such as apparent total body clearance (CL/F) and apparent volume of distribution (V_d/F; as appropriate)
• Evaluate the effects of ALXN1840 and SoC on global clinical symptoms as assessed by the Investigator	• Clinical Global Impression-Improvement Scale (CGI-I) • Change from Baseline to Week 48 in Clinical Global Impression-Severity scale (CGI-S)
• Evaluate the effects of ALXN1840 and SoC on hepatic status	• Change from Baseline to Week 48 in Model for End-Stage Liver Disease (MELD) score (ages 12 years and older) or Pediatric End-Stage Liver Disease (PELD) score (ages 3 to < 12 years) • Change from Baseline to Week 48 in modified Nazer score
Exploratory	
• Evaluate the effects of ALXN1840 and SoC on hepatic fibrosis	• Change from Baseline to Week 48 in the Fibrosis-4 (FIB-4) Index and by transient elastography
• Evaluate the effects of ALXN1840 and SoC on psychiatric symptoms	• Change from Baseline to Week 48 in Brief Psychiatric Rating Scale-24 (BPRS-24) and Brief Psychiatric Rating Scale for Children (BPRS-C9)
• Evaluate the effects of ALXN1840 and SoC on quality of life (QoL)/patient-reported outcomes	• Change from Baseline to Week 48 in QoL/patient-reported outcome endpoint measures: – EuroQoL 5 Dimensions (EQ-5D) or EuroQoL 5 Dimensions-Youth (EQ-5D-Y) – Pediatric Quality of Life Inventory (PedsQL™) NOTE: These tests will be administered by parent/proxy for participants unable to complete them independently.

Objectives Period 1: Up to Week 48	Estimand(s) and/or Endpoint(s)
• Evaluate participant satisfaction of treatment with ALXN1840 and SoC	• Change from Baseline to Week 48 in Treatment Satisfaction Questionnaire for Medication-9 (TSQM-9) NOTE: This questionnaire will be administered by parent/proxy for participants unable to complete them independently.
• Evaluate the effects of ALXN1840 and SoC on 24-hour fecal Cu and fecal Mo	• Change from Baseline to Week 6 in 24-hour fecal Cu and fecal Mo
• Evaluate the effects of ALXN1840 and SoC on 24-hour urinary Cu and urinary Mo	• Change from Baseline to Week 48 in 24-hour urinary Cu and urinary Mo
• Explore other directly measured PD and biomarkers of ALXN1840	• Daily mean AUEC of dNCC and plasma total Cu from 0 to 24 weeks and from 24 to 48 weeks • Observed, absolute and percent changes of Cu levels (total Cu, PUF Cu, labile-bound Cu [LBC])
• Explore ALXN1840 effect on initial decoppering phase compared to SoC based on directly measured PK/PD and biomarkers	• Time to first confirmed increase in plasma dNCC and total Cu concentration • Time to minimum and maximum concentration of: – Plasma total Cu – Plasma dNCC – Plasma LBC – Ratio plasma dNCC:total Cu – Ratio plasma LBC:total Cu – Plasma ceruloplasmin – Plasma CpC – Ratio plasma ceruloplasmin:total Cu – Plasma CpC:total Cu – 24-hour urinary Mo – Ratio urinary Mo:Cu – Ratio 24-hour urinary Mo:dosed Mo
• Explore ALXN1840 effect on subsequent maintenance phase compared to SoC based on directly measured PK/PD and biomarkers	• Time for return to predose baseline for the following PK/PD parameters: – Plasma total Cu – Plasma dNCC – Plasma LBC – Ratio plasma dNCC:total Cu – Ratio plasma LBC:total Cu – Plasma ceruloplasmin concentration – Plasma CpC concentration – Ratio plasma ceruloplasmin:total Cu – Ratio plasma CpC:total Cu – 24-hour urinary Mo – Ratio urinary Mo:Cu – Ratio urinary Mo:dosed Mo

1.2. Study Design

This is a multicenter, randomized, controlled, open-label, rater-blinded study designed to assess the efficacy, safety, PK, and PD of ALXN1840 versus SoC in pediatric participants aged 3 to < 18 years with a confirmed diagnosis of WD, who meet prespecified laboratory parameters and

do not have decompensated cirrhosis. PK measured by plasma total Mo and PUF Mo, and PD measured by plasma total Cu and LBC will be determined for all participants.

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

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

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

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

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

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

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

- For participants aged 12 to < 18 years: ALXN1840 will be administered at a starting dose of 15 mg/day. Dose escalation is not permitted. Individualized doses ranging from 15 mg/day every other day to 15 mg/day are allowed. Doses < 15 mg every other day may be considered, with approval of the Alexion Medical Monitor.
- For participants aged 3 to < 12 years, a lower starting dose of 2.5 mg/day will be administered for at least 4 weeks based on scaling of the starting dose of 15 mg/day in the ongoing Study WTX101-301. Dose escalation is permitted but not required. The dose may be increased in increments of 2.5 mg daily with the permission of the Alexion Medical Monitor, depending on the participant's clinical status,

cNCC/cNCC$_{corrected}$ concentrations, and safety laboratory results. Dose increases must occur at least 4 weeks apart and may only occur if no dose modification (reduction or interruption) criteria apply. Participants who require doses of 15 mg daily may use the 15-mg adult tablet. The maximum dose for children aged < 12 years is 15 mg/day.

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

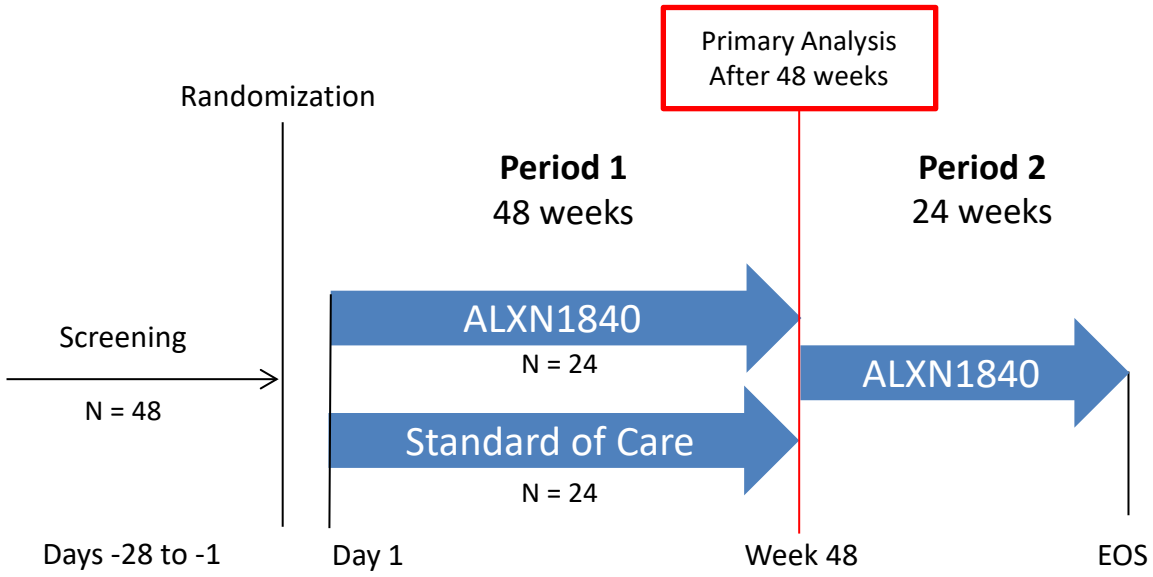
- Clinical criteria: dose-titration based on hepatic and neurological status
- cNCC/cNCC$_{corrected}$: dose-titration based on cNCC/cNCC$_{corrected}$ concentrations. The reference range for cNCC is 0.8 to 2.3 μM.
- Safety monitoring: Dose modification criteria are based on regularly scheduled assessments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

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

The primary analysis will be performed after 48 weeks, and the final analysis after completion of Period 2. Interim analyses of data may be performed to support regulatory submissions. The interim analyses will be descriptive only and will be performed to assess safety data only; they will not include formal hypothesis testing and will not be used to adapt the study. The efficacy data available at the time of primary analysis will also be used in an efficacy extrapolation to develop evidence for ALXN1840 efficacy on Cu control for pediatric participants (ages 3 to < 18 years) with WD using adult/adolescent participant data from Studies WTX101-301 and ALXN1840-WD-302. Full details of the extrapolation exercise will be provided in the Study ALXN1840-WD-303 SAP.

An independent Data Monitoring Committee (DMC), comprising experts in relevant fields with no direct relationship to the study, will be appointed by Alexion. The specific responsibilities of the DMC will be described in the DMC Charter.

1.2.1. Study Schematic



2. STATISTICAL HYPOTHESES

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

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

3. SAMPLE SIZE DETERMINATION

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

The proposed sample size for this study was assessed for its adequacy for the extrapolation Study ALXN1840WD-303 via simulation using the proposed Bayesian hierarchical model. To explore the performance of the design, 3 distinct states of efficacy were considered in each of the populations with respect to the mean 48-week percent change from baseline in cNCC/cNCC$_{corrected}$:

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

Given the 2 populations (adult population: adults in Study WTX101-301, and pediatric population: pediatrics in Study ALXN1840-WD-302 plus adolescents from Study WTX101-301), there are 9 possible combinations representing potential underlying scenarios. For each of these scenarios, 5000 studies were simulated and the proportion of studies that claim noninferiority in the pediatric participant population was estimated. Statistical power is captured in scenarios in which ALXN1840 is either superior or equivalent to SoC in the pediatric participant population. Type I error is captured in scenarios in which ALXN1840 is inferior to SoC in the pediatric participant population. Table 1 shows the simulation results assuming an SD of 30% (absolute) on the 48-week change in cNCC/cNCC$_{corrected}$.

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

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

Table 1: Simulated Power for Pediatric Extrapolation Study ALXN1840-WD-303 Primary Analysis

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

4. ANALYSIS SETS

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

Population	Description
Screened	All participants who sign the informed consent form
Enrolled	All participants who agree to participate in the study following completion of the informed consent process and who satisfy the inclusion/exclusion criteria and are randomized.
Safety Analysis Set	All participants who receive at least 1 dose of ALXN1840 or SoC treatment. Participants will be analyzed according to the study intervention they actually received.
Full Analysis Set (FAS)	All participants who receive at least 1 dose of ALXN1840 or SoC treatment. Participants will be analyzed as randomized.
Per Protocol Analysis Set (PPS)	All participants who receive at least 1 dose of ALXN1840 or SoC treatment and have both baseline and Week 48 cNCC/cNCC$_{corrected}$ concentrations. Participants with major protocol deviations that are likely to impact the primary endpoint analysis will be excluded from the PP Analysis Set. Major protocol deviations and the PP Analysis Set will be defined, documented, and agreed within Alexion prior to database lock.
Extension Analysis Set	This dataset includes all participants who enter Period 2 and receive at least 1 dose of ALXN1840 in Period 2.
PK/PD Analysis Set	All participants who have sufficient plasma samples to enable the calculation of PK parameters and provide PK/PD profiles

5. STATISTICAL ANALYSES

5.1. General Considerations

The evaluations of PK, PD, safety, and efficacy of ALXN1840 and SoC in the Primary Evaluation Period of this study will be summarized descriptively using summary statistics. A separate SAP will be generated for the nonrandomized, exploratory, open-label Extension Period.

A separate analysis and report will present the results of the Bayesian extrapolations and statistical testing of the efficacy of ALXN1840 compared with SoC in pediatrics (Study ALXN1840-WD-303).

Missing data will not be imputed.

Summary statistics will be computed and displayed by treatment group, cohort, age group, and visit, where applicable and if sample size allows. Descriptive statistics for continuous variables will minimally include the number of participants, mean, SD, minimum, median, and maximum. For categorical variables, frequencies and percentages will be presented. Graphical displays will be provided as appropriate.

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

All prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary version from September 2021 or later. AE severity will be evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (published 27 Nov 2017) (NCI, 2017). System Organ Class and Preferred Term for medical history will be coded using the most up-to-date version of the Medical Dictionary for Regulatory Activities (MedDRA), version 24.1 or higher.

Summaries of study and participant characteristics (eg, demographics and baseline characteristics, medical history, and protocol deviations) are described in Section 6.2.

5.2. Study Participants

The number and percentage of all participants enrolled, randomized, and included in the FAS and PP, Safety, PK, and PD analysis sets will be summarized. The reasons for exclusion from the analysis sets will also be provided. Frequency counts and percentages of participants excluded prior to randomization will be provided for participants who failed to meet study entry requirements during Screening at the start of the study.

The number and percentage of participants who completed or prematurely discontinued from the study will be described by randomized treatment group within each cohort, for rollover participants, and overall. For participants who discontinued the study, the number and percentage will be summarized by their reason for premature discontinuation and withdrawal of consent. A summary of participants will be provided by region, country, and site. Additionally, a summary of participants who did not meet inclusion or who met exclusion criteria will be provided.

Descriptive statistics of the number of days in the study will be summarized. The date of the first and last use of study medications in each period and the study termination date will be listed. Individual reasons for premature discontinuation and withdrawal of consent from the study will

be presented in a listing. All enrolled participants will be listed, indicating their analysis set along with the reason for exclusion. A listing of screen failure participants will also be provided. Additionally, a listing of the inclusion/exclusion criteria and a listing of participants and the inclusion criteria they failed to meet and the exclusion criteria they met will be provided.

5.3. Primary Analysis

The primary analysis will be based on the FAS. The primary endpoint will also be assessed on the PP Analysis Set.

5.3.1. Estimands and/or Endpoint(s)

The primary estimand is the percent change from baseline (Day 1) to 48 weeks in cNCC/$cNCC_{corrected}$ in plasma between ALXN1840 and SoC in pediatric participants with WD, regardless of less-than-complete adherence or use of another medication that affects plasma cNCC with no imputation for missing data after discontinuation or death.

cNCC will be calculated as follows (EASL, 2012; Roberts, 2008):

$$\text{cNCC}[\mu\text{mol/L}] = \frac{\text{Plasma total Cu } [\mu\text{g/L}] - 3.15 * \text{ceruloplasmin}[\text{mg/L}]}{63.5\ [\mu\text{g}/\mu\text{mol}]}$$

For ALXN1840-treated participants, the cNCC in plasma will be corrected for the amount of Cu bound to the ALXN1840 tripartite (tetrathiomolybdate-Cu-albumin) complex (ie, $cNCC_{corrected}$) using the square root-based cNCC correction method as determined based on data from Study WTX101-201 as follows (Plitz, 2017):

$$\text{cNCC}_{\text{corrected}} = (\sqrt{\text{cNCC}} - 0.993\sqrt{\text{Mo}})^2$$

In the calculation of cNCC and $cNCC_{corrected}$, the following rules apply:

- For plasma total Cu concentration values < lower limit of quantification (LLOQ), cNCC will be considered missing.
- Serum ceruloplasmin concentration values < LLOQ are set to 0.
- Plasma total Mo concentration values < LLOQ are set to 0.
- In cases where cNCC calculation produces a negative result, cNCC will be considered missing and $cNCC_{corrected}$ will not be derived.
- $cNCC_{corrected}$ will be set to 0 when $0.993\sqrt{\text{Mo}} > \sqrt{\text{cNCC}}$.

5.3.2. Main Analytical Approach

The primary endpoint, the percent change from Baseline (Day 1) to 48 weeks in cNCC/$cNCC_{corrected}$ concentrations, will be analyzed by treatment group within each cohort and overall using descriptive summary statistics.

Missing data will not be imputed.

Subgroup analysis may be performed (eg, age group, sex, cohort, and randomization stratification) if sample sizes permit.

5.3.3. Sensitivity Analysis

No sensitivity analyses are planned.

5.3.4. Supplementary Analyses

No supplementary analyses are planned.

5.4. Secondary Analysis

Analyses of secondary efficacy endpoints will be based on the FAS.

5.4.1. Key Secondary Estimand(s) and/or Endpoint(s)

Not applicable.

5.4.2. Other Secondary Analysis

All secondary efficacy endpoints will be summarized by treatment group within each cohort and overall using descriptive statistics.

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

cNCC responder

A cNCC/cNCC$_{corrected}$ responder is defined as a participant who achieved or maintained normalized cNCC/cNCC$_{corrected}$ concentration (0.8 to 2.3 µM) (Brewer, 2009) within (at or before) 48 weeks or reached a reduction of at least 25% in cNCC/cNCC$_{corrected}$ within 48 weeks. Thus, a participant will be considered a cNCC/cNCC$_{corrected}$ responder if they meet at least one of the following criteria:

- Achieved normalized cNCC/cNCC$_{corrected}$ concentration for 2 consecutive measurements within 48 weeks for participants who had elevated concentration at baseline
- Maintained normalized cNCC/cNCC$_{corrected}$ concentration within 48 weeks for participants who had normal concentration at baseline
- Reached a reduction of at least 25% in cNCC/cNCC$_{corrected}$ for 2 consecutive measurements within 48 weeks

A nonresponder will be defined as a participant who did not meet the responder criteria.

UWDRS (Part I, II, and III)

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

The UWDRS Part I and Part III will be assessed by a neurologist who is blinded, while UWDRS Part II may be reported to a nonblinded member of the study team by the participant, family member, or caregiver (Czlonkowska, 2007; Leinweber, 2008). The UWDRS has not been formally evaluated in children. However, the components of Part I (level of consciousness), Part II (participant or caregiver-reported disability), and Part III (neurologic examination findings) are not fundamentally different between adults and children. Participants aged 12 years and older are expected to be able to comply with UWDRS assessments without modification (Rohay, 2020). The UWDRS assessments should be conducted to the greatest extent feasible in children < 12 years.

CGI-S and CGI-I

The Clinical Global Impression (CGI) rating scales are commonly used measures of symptom severity, treatment response, and the efficacy of treatments in treatment studies of adult and pediatric participants with mental disorders. Although originally developed for participants with mental disorders (Guy, 1976), the CGI rating scales have been adapted to use generalized language (Busner, 2007), which supports their application to any clinically assessed disease setting.

Clinical Global Impression-Severity Scale

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

Clinical Global Impression-Improvement Scale

The CGI-I is a 7-point scale that requires the clinician to assess how much the participant's illness has improved or worsened relative to a baseline state at the beginning of the intervention and rated as follows: 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; or 7, very much worse. Transformed CGI-I is derived as CGI-4, and it ranges between -3 (very much improved) and 3 (very much worse) with 0 indicating no change.

MELD and PELD Scores

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 to 40, with higher values indicating more advanced disease) uses the participant's values for serum bilirubin, serum creatinine, and the international normalized ratio (INR) for prothrombin time to predict survival. The initial MELD score, $MELD_{(i)}$, is calculated according to the following formula:

$MELD_{(i)} = 3.78 \times \ln(\text{serum bilirubin [mg/dL]}) + 11.2 \times \ln(\text{INR}) + 9.57 \times \ln[\text{serum creatinine (mg/dL)}] + 6.43$

Creatinine, bilirubin, and INR values less than 1.0 are set to 1.0 and creatinine values greater than 4.0 are set to 4.0 when calculating $MELD_{(i)}$. Additionally, creatinine, bilirubin, and INR are

rounded to the 10th decimal place prior to performing the calculation. The initial MELD score is then rounded to the nearest integer. The maximum MELD score is 40.

In participants with a $MELD_{(i)}$ score > 11, the serum sodium is also taken into account (UNOS, 2015), and MELD is recalculated as follows:

$MELD = MELD_{(i)} + 1.32 \times (137\text{-sodium[mmol/L]}) - 0.033 \times MELD_{(i)} \times (137\text{-sodium[mmol/L]})$

Sodium values less than 125 mmol/L will be set to 125 and values greater than 137 mmol/L will be set to 137.

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

The PELD score is based on the following formula and will be calculated by a central laboratory:

$PELD = 4.80 \times \ln(\text{bilirubin[mg/dL]}) + 18.57 \times \ln(\text{INR}) - 6.87 \times \ln(\text{albumin[g/dL]}) + 4.36$ (if participant under 12 months) + 6.67 (if history of growth failure positive)

The bilirubin, albumin and INR values less than 1.0 are set to 1.0.

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

Modified Nazer Score

The modified Nazer score is an assessment of liver status and consists of a composite of 5 laboratory parameters: aspartate aminotransferase (AST), INR, bilirubin, albumin, and white blood cell count. The score has a total range of 0 to 20, and lower values indicate a healthier liver status (Dhawan, 2005). If any of the 5 parameters required to compute the modified Nazer score are unavailable at any given visit, the modified Nazer score will not be derived for that visit. The score for an individual analyte (bilirubin, AST, INR, leukocytes, and albumin) should be derived from Table 2, and all 5 scores will be added to obtain the final score.

The modified Nazer score will be calculated by a Central Laboratory.

Table 2: Modified Nazer Score

Score	Billirubin (µmol/L)	AST (IU/L)	INR	Leukocytes (10^9/L)	Albumin (g/L)
0	0-100	0-100	0-1.29	0-6.7	> 44
1	101-150	101-150	1.3-1.6	6.8-8.3	34-44
2	151-200	151-300	1.7-1.9	8.4-10.3	25-33
3	201-300	301-400	2.0-2.4	10.4-15.3	21-24
4	> 300	> 400	> 2.4	> 15.3	< 21

Abbreviations: AST = aspartate aminotransferase; INR = international normalized ratio

5.5. Tertiary/Exploratory Analysis

All exploratory endpoints will be summarized by treatment group within each cohort and overall using descriptive statistics using the FAS.

FIB-4 Index and Transient Elastography

The FIB-4 Index (Vallet-Pichard, 2007) is a formula used to predict liver fibrosis based on standard biochemical values (alanine aminotransferase [ALT], AST, and platelet count) and age. The FIB-4 Index will be calculated by a central laboratory. The formula is as follows:

Age (years) × AST (U/L)/[Platelets (10^9/L × sqrt (ALT (U/L))]

Transient elastography is a noninvasive 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 using a sonogram. If any of the parameters required to compute the FIB-4 Index are unavailable at any given visit, the FIB-4 Index will be set to missing for that visit.

Brief Psychiatric Rating Scale-24

The BPRS-24 (Ventura, 1993) is a 24-item instrument for adolescents aged 12 to < 18 years 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, and social worker) who has completed the training required to administer the instrument.

The BPRS-24 will be obtained at Day 1, Week 12, Week 24, Week 36, and Week 48/Early Termination. The total score across the 24 items will be used as the endpoint for analysis. A minimum of 20/24 items are required to be completed at any given visit; the total score will then be taken for the nonmissing items and scaled up to the 24-item score for the purpose of data summary and analysis. If fewer than 20/24 items are completed at any given visit, the BPRS-24 total score will be set to missing for that visit.

Brief Psychiatric Rating Scale for Children

The BPRS-C9 is a 9-item instrument for children aged 3 to < 12 years.

The BPRS-C9 will be obtained at Day 1, Week 12, Week 24, Week 36, and Week 48/Early Termination. The presence and severity of symptoms are rated on a scale ranging from 1 (not present) to 6 (extremely severe). As with the BPRS-24, the BPRS-C9 can be performed by a qualified person who has been appropriately trained. A minimum of 7/9 items are required to be completed at any given visit.

EuroQoL-5 Dimensions

The EQ-5D (EuroQol Group, 2015) consists of 2 different assessments: the EQ-5D-5-Level Descriptive System and the EuroQoL visual analog scale (EQ VAS). The descriptive system comprises measures of health-related QoL state and consists of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels of severity: no problems, slight problems, moderate problems, severe problems, or extreme problems. The EQ VAS records the participant's self-rated health on a vertical EQ VAS.

Together, this can be used as a quantitative measure of health outcome that reflects the participant's own judgement.

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

EuroQoL 5 Dimensions-Youth

The EQ-5D-Y (Wille N, 2010). was introduced as a more comprehensible instrument suitable for children and adolescents. The wording was changed to be more suitable for children and adolescents, the most severe label for the mobility dimension was changed from "confined to bed" to "a lot of problems walking about" to increase the applicability and sensitivity of the mobility dimension. and the instructions for the EQ VAS task were simplified, making the task easier to complete and to score.

Pediatric Quality of Life Inventory

The PedsQL™ Measurement Model is a modular approach to measuring health-related QoL in healthy children and adolescents and those with acute and chronic health conditions.

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

Scales:

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

Summary Scores:

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

Treatment Satisfaction Questionnaire for Medication

The TSQM-9 is used to assess the overall level of satisfaction or dissatisfaction with medication participants are taking (Atkinson, 2004; Atkinson, 2005; Bharmal, 2009). This composite scale comprises 3 items on the TSQM-9 survey:

- Overall, how confident are you that taking this medication is a good thing for you?
- How satisfied are you that good things about this medication outweigh the bad things?

- Taking all things into account, how satisfied or dissatisfied are you with this medication?

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

Urinary and Fecal Cu Excretion

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

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

The purpose of these assessments is to assess the change from Baseline in urinary and fecal Cu excretion in participants with WD who are treated with ALXN1840 or SoC.

Urinary and Fecal Mo

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

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

The purpose of these assessments is to assess the change from Baseline in urinary and fecal Mo in participants with WD who are treated with ALXN1840 or SoC.

5.6. Other Safety Analyses

All safety analyses will be performed on the Safety Analysis Set.

Safety analyses will include all AEs, ECGs, clinical laboratory data, physical examinations, and vital sign measurements using descriptive statistics. No inferential statistical analyses are planned for the safety parameters of this study.

5.6.1. Study Duration, Treatment Compliance, and Exposure

Study duration will be summarized for all enrolled participants by treatment within each cohort. Treatment compliance and exposure will be summarized for the Safety Analysis Set by treatment within each cohort. Supportive listings will also be provided.

Study Duration

Study duration is defined as the time from informed consent to the end of the Primary Evaluation Period (ie, Week 48) or study discontinuation date, whichever occurs first.

Treatment Compliance

The treatment compliance is defined as:

Compliance (%) = (number of dose received)/(total number of dose scheduled) × 100.

Furthermore, the compliance will be summarized in the following ways:

- Compliance (%)

- Compliance (< 80%, ≥ 80%)

Treatment compliance will be summarized using descriptive statistics by visit, by randomized treatment within cohort and overall. Compliance up to Week 48 (Primary Evaluation Period) will be summarized for all participants. If a participant prematurely discontinues during the Primary Evaluation Period, his or her compliance will be based on the period up to the point of discontinuation from the study. Additionally, drug interruptions or missed doses as the result of a physician decision or AE will be factored into the number of doses scheduled, whereas drug interruptions or missed doses for any reason will be factored into calculating the number of doses received. A supporting listing will also be produced.

Exposure

The number of participants exposed to the study intervention will be summarized in terms of counts for the overall duration of the study, and by periods specified in the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use E3 guideline. The number of participants will also be summarized by the following mean daily dose groups:

1. ≤ 2.5 mg
2. > 2.5 mg to ≤ 5 mg
3. > 5 mg to ≤ 7.5 mg
4. > 7.5 mg to ≤ 10 mg
5. > 10 mg to ≤ 12.5 mg
6. > 12.5 mg to ≤ 15 mg

This summary will be for the overall duration and in each specified time period, as follows:

- 1 day or less
- 2 days to 1 week
- 1 week to 1 month
- 1 month to 6 months
- 6 months to 1 year
- > 1 year

The duration (days) of exposure to treatment will be calculated as follows:

date of the last exposure to treatment – date of the first dose + 1.

Patient-years of exposure will be derived individually for each participant. Patient-years will be defined for each participant as the total time (in years) from first dose to the last available dose of study drug. Dose adjustments and/or interruptions will not be factored into this derivation.

Results will be analyzed using descriptive statistics and the frequency and percentage of participants in the following dose categories:

1. ≤ 2.5 mg
2. > 2.5 mg to ≤ 5 mg

3. > 5 mg to ≤ 7.5 mg
4. > 7.5 mg to ≤ 10 mg
5. > 10 mg to ≤ 12.5 mg
6. > 12.5 mg to ≤ 15 mg

The gap in drug exposure will not be included in the calculation of duration of exposure. Dosing will be described by mean daily dose, final daily dose, minimum daily dose, maximum daily dose, and total accumulative dose.

- Mean daily dose = sum (each dose × each dose frequency × each period)/total treatment period
- Final daily dose is defined as the last dispensed dose in titration studies
- Minimum daily dose is defined as the minimum daily dose over the Treatment Period
- Maximum daily dose is defined as the maximum daily dose over the Treatment Period
- Total cumulative dose is the sum of doses over the total Treatment Period

The dosing regimen was individualized. The mean daily dose (mg), minimum daily dose (mg), and maximum daily dose (mg) will be summarized using descriptive statistics. All available dosing data will be presented in a listing. Where available, reasons for dose adjustment will also be presented in a listing.

Listings of exposure, drug interruptions, and missed doses will also be presented.

Relationships to duration of study therapy and dose of study therapy may be explored along with examination within relevant subgroups, eg, WD severity at study entry prior, prior therapies received, age, and sex. WD severity at study entry may be assessed by the following:

- Cirrhosis status (yes, no)
- MELD/PELD score at baseline above (>) or below (≤) median
- Modified Nazer score at baseline above (>) or below (≤) median
- Total bilirubin (μmol/L) > upper limit of normal (ULN)
- Platelets (10^9/L) < lower limit of normal (LLN)
- UWDRS Part II total score at baseline > 0 or = 0
- UWDRS Part III total score at baseline > 0 or = 0
- CGI-S at baseline above (>) or below (≤) median
- LBC (μmol/L) at baseline above (>) or below (≤) median
- Leukocytes (10^9/L) < LLN
- Neutrophils (10^9/L) < LLN

Prior therapies received may be assessed as follows:

- Cohort 1 will be categorized by prior SoC, where prior SoC is defined as the most recent treatment prior to or at time of Screening (whichever is later) and is categorized as penicillamine, trientine hydrochloride, zinc, or combination. This cohort will have participants who have received SoC therapy for > 28 days prior to enrollment in the study.
- Cohort 2 will be categorized into participants who are treatment naïve and those who have received SoC therapy for ≤ 28 days prior to enrollment in the study.

5.6.2. Adverse Events

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

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

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

The incidence of AEs and SAEs will be summarized by System Organ Class and Preferred Term for each treatment and overall and by relationship to study intervention. AEs will also be summarized by treatment and, overall, by severity. SAEs and AEs resulting in withdrawal from the study will be listed.

5.6.2.1. AEs by System Organ Class and Preferred Term

The number of TEAEs and the number and percentage of participants with events will be presented by System Organ Class and Preferred Term. Percentages will be based on the Safety Analysis Set. System Organ Class will be listed in descending frequency as will PTs within each System Organ Class. If needed, terms will also be ordered alphabetically.

Treatment-emergent SAEs, treatment-emergent non-SAEs, TEAEs leading to withdrawal of study drug, TEAEs leading to death, treatment-emergent AESIs, pretreatment adverse events

(PTAEs), and TEAEs occurring in ≥ 5% or ≥ 10% of participants will be summarized using the same approach.

5.6.2.2. AEs by System Organ Class

The number of TEAEs and the number and percentage of participants with events will be presented by System Organ Class. Patients are counted once in each System Organ Class. Percentages will be based on the total number of treated participants in the treatment cohort.

5.6.2.3. AEs by Preferred Term

The number of TEAEs and the number and percentage of participants with events will be presented by Preferred Term. Patients are counted once in each Preferred Term. Percentages will be based on the total number of treated participants in the treatment cohort.

5.6.2.4. AEs by System Organ Class, Preferred Term, and Relationship

The number of TEAEs and the number and percentage of participants with events will be presented by System Organ Class and Preferred Term as described in Section 5.6.2.1 and by relationship (related, not related). If a participant has more than 1 occurrence of an AE, the strongest relationship to study treatment will be used in the summary table. If the relationship to study drug is missing, the AE will be assumed to be related. A similar analysis will be conducted for treatment-emergent SAEs.

The number of related TEAEs and the number and percentage of participants with related TEAEs will be summarized by System Organ Class and Preferred Term and separately by Preferred Term only. The same analyses will be produced for related treatment-emergent SAEs.

Lastly, the number of TEAEs by System Organ Class, Preferred Term, and relationship, without considering the highest relationship, will be analyzed. A similar analysis will be conducted for treatment-emergent SAEs.

5.6.2.5. AEs by System Organ Class, Preferred Term, and Severity

The number of TEAEs and the number and percentage of participants with events will be presented by System Organ Class, Preferred Term, and severity. If a participant has more than 1 occurrence of an AE, the highest severity reported will be used. If severity is missing, the AE will be assumed to be severe. The number of TEAEs by System Organ Class, Preferred Term, and severity, without taking into account the highest severity, will also be analyzed.

Additionally, a summary of related TEAEs by System Organ Class, Preferred Term, and severity using the highest severity will be presented.

5.6.2.6. Deaths, Other SAEs, and AESIs

SAEs and AESIs will be reportable from the time the participant signs the informed consent through the EOS Visit or until the Investigator and Alexion Pharmaceuticals determine that follow-up is no longer necessary.

Any new neurological symptom or clinically significant worsening of an ongoing neurological symptom after initiation of study intervention (ALXN1840 or SoC) will be designated an AESI, whether serious or nonserious. This includes all AEs in the MedDRA System Organ Class

"Nervous system disorders" or any AE where the "Is this an AESI?" check box is checked in the case report form (CRF).

AESIs 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 participant. All available relevant participant information will be provided to this panel to aid in their assessment. The assessment of AESIs by the panel will be independent of and in addition to the usual assessments of the AE, including assessments of severity (intensity) and causality, by both the Principal Investigator and Alexion. A summary and listing of assessments given by the Neurological Adverse Event Panel will be presented.

A separate independent Hepatic Adjudication Panel, comprising experts in hepatology and drug-induced liver injury, will be appointed by the Sponsor. 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. A summary and listing of assessments given by the Hepatic Adjudication Panel will be presented.

5.6.2.7. Other Significant Adverse Events

Other significant TEAEs encompass those for abnormal liver function tests (also known as hepatic events), hematopoietic cytopenias, and dyslipidemia. These include any new AE, or worsening of an ongoing AE, after initiation of study drug therapy that meet the criteria described below:

- Hepatic events: All AEs in the "Drug related hepatic disorder" Standardized MedDRA Queries (SMQ) (comprehensive search) or any AE where the "Is this a Hepatic AE?" check box is ticked.
- Hematopoietic cytopenias: All AEs in the "Haematopoietic cytopenias" SMQ
- Dyslipidemia: All AEs in the "Dyslipidaemia" SMQ

5.6.3. Additional Safety Assessments

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

Clinically Significant Laboratory Test Abnormalities

The following laboratory tests will be graded according to the National Cancer Institute CTCAE V5.0 at ADaM level.

- **Hematology:** Absolute neutrophil count (neutrophil) (NEUT), total leukocytes (Leukocytes) (WBC), hemoglobin (HGB), platelet count (PLAT), and lymphocytes (LYM). Grading for all of these hematology laboratory parameters is based on decreased levels).

- **Coagulation:** International normalized ratio (INR)
- **Chemistry:** Alanine aminotransferase (ALT), albumin (ALB), alkaline phosphatase (ALP), aspartate aminotransferase (AST), total bilirubin (BILI), creatinine (CREAT), gamma-glutamyl transferase (GGT), glucose (GLUC) (only grading for hypoglycemia, no grading for hyperglycemia), creatine kinase (CK), cholesterol (CHOL), non-high density lipoprotein (non-HDL-C), low-density lipoprotein (LDL-C), high-density lipoprotein (HDL-C), very low density lipoprotein (VLDL), and triglycerides (TRIG)

Laboratory toxicity grade 0 will be derived for the shift table as any nonmissing results outside the range of the National Cancer Institute CTCAE criteria. Laboratory tests with missing either LLN or ULN or both will not be graded. Abnormal laboratory tests values will be summarized by National Cancer Institute CTCAE Laboratory Toxicity Grade. Shift from baseline tables of the number and percentage of participants in each of the National Cancer Institute CTCAE categories will also be presented for each treatment group for each parameter and visit time window (scheduled visits only). An overall shift summary will also be provided comparing baseline to worst postdose toxicity observed across all scheduled visits.

Lipid profile plots will be produced for individual participants, showing total cholesterol, HDL-C, non-HDL-C, LDL-C, VLDL, and triglycerides, and ALT as a multiple of the respective baseline (BLN) values and a multiple of ULN values.

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

5.6.3.1. Evaluation of Drug-Induced Serious Hepatotoxicity

A Hy's law case refers to an increase in aminotransferase > 3× the reference ULN, with bilirubin > 2× ULN. Possible Hy's law cases can be visualized with use of evaluation of drug-induced serious hepatotoxicity (eDISH) plots, a log-log scatter plot where the x-axis is the peak postbaseline ALT as a multiple of ULN, and the y-axis is the peak postbaseline total bilirubin as a multiple of ULN (Guo, 2009).

The following series of figures, adapted from Tesfaldet et al (2016), will be produced for each treatment group (ALXN1840 and SoC) separately for the Safety Analysis Set.

1. Distribution of ULN of liver serum enzymes, showing the ULN reference values used in each test (bilirubin, ALT, AST, and ALP) and their respective frequencies in percentiles
2. Distribution of baseline liver serum enzymes for each test by cohort
3. Distribution of baseline liver serum enzymes (×ULN) for each test by cohort
4. Status of baseline liver serum enzymes as function of ULN. Baseline status categorized as normal, > 1 ×, > 1.5 ×, > 2 ×, > 3 ×, > 5 ×, and > 10 ×
5. eDISH plot by treatment group
6. eDISH plot by quadrant

7. Panel of eDISH quadrant shift plots at baseline. Patients will be color coded to correspond to the quadrant to which they belong in the eDISH plot. The data presented in the panel will correspond to each participant's baseline value as a multiple of the ULN.
8. Panel of shift plots by eDISH quadrants. Patients will be color coded to correspond to the quadrant to which they belong in the eDISH plot. The data will be presented as multiples of the baseline value (BLN) rather than the ULN. The shift in peak postbaseline laboratory value will be compared to each participant's baseline value.
9. Panel of eDISH shift plots by eDISH quadrants. The panels will represent the on-treatment eDISH quadrants, whereas the colored symbols will represent the eDISH quadrants of the baseline values (not postbaseline) as multiples of ULN.
10. Time course of liver tests as × BLN and × ULN.

5.7. Other Analyses

5.7.1. PK and PD Analyses

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

5.7.1.1. PK/PD Sampling Schedule

At the Day 1, Week 6 (Day 43), and Week 48 (Day 337) Visits, serial blood samples will be collected for plasma PK/PD/biomarker concentrations at the following time points: predose at 0 hours and at 2, 4, 8, and 24 hours postdose. Samples collected within ± 10% in minutes or 30 minutes of the scheduled time, whichever is less, will not be considered a protocol deviation.

5.7.1.2. Plasma PK Parameters

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

PK:

- C_{max}
- t_{max}
- C_{trough}
- AUC_{tau}

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

5.7.1.3. Handling of Missing Data

Missing concentration data for all participants who are administered scheduled study treatments will be considered as noninformative missing and will not be imputed. No concentration estimates will be provided for missing sample values.

For the derivation of area under the plasma concentration-versus-time curve and for the individual plasma concentration-versus-time curves, the following rules will apply:

- Concentration values below the assay's lower limit of quantification (BLQ) in predose Day 1 samples will be treated as 0.
- The sampling time of predose samples relative to dosing will also be treated as 0.
- BLQs between 2 quantifiable samples will be set to missing.
- The first BLQ after the last measurable sample will be set to missing; any subsequent BLQs will be set to 0.

For the plasma concentrations summary, the following rules will apply:

- All BLQ values will be set to 0.
- No further imputation will be applied to any missing values.

5.7.1.4. Plasma PK Concentration and PK Parameter Data

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

PK parameters derived from plasma concentrations of total Mo and PUF Mo (if measured) will be presented in data listings and summarized separately using the following descriptive statistics: number of participants, arithmetic mean, geometric mean, SD, arithmetic coefficient of variation, geometric mean coefficient of variation, median, minimum, and maximum.

Individual and mean C_{trough} for total Mo versus day will be plotted on both linear and semi-logarithmic scales. Time to reach steady state will be graphically assessed by plotting mean C_{trough} versus study day in both linear and semilogarithmic scales. In addition, attainment of steady state will be assessed via a stepwise, linear trend test. This approach involved an examination of C_{trough} over time by conducting a linear regression of C_{trough} versus time and calculating a 95% confidence interval around the slope estimate, and a first instance where 0 was included in the 95% confidence interval would indicate that the steady state was achieved.

Urinary and Fecal Mo

24-hour urinary Mo will be assessed at Baseline, Week 6, Week 24, and Week 48 in all participants. 24-hour fecal Mo will be assessed at Baseline and Week 6 in all participants. This assessment is optional. The purpose of these assessments is to assess the change from Baseline in urinary and fecal Mo in participants with WD who are treated with ALXN1840 or SoC.

5.7.1.5. PD Parameters

For PD (total and PUF [if measured] Cu, dNCC, LBC, and cNCC/$cNCC_{corrected}$) and biomarker endpoints (CpC), concentration-versus-time data will be listed and summarized with descriptive statistics and plotted. The same analyses will be conducted on the absolute, change from Baseline, and percent changes from Baseline of these concentration-versus-time data.

Observed, absolute, and percent changes of molar ratio of CpC to ceruloplasmin have been added as an exploratory endpoint and will be summarized.

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

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

PD parameters derived from plasma concentrations of total Cu, dNCC, and LBC will be presented and summarized by analyte and day similar to PK parameters.

5.7.1.6. Urinary and Fecal Cu Excretion

24-hour urinary and 24-hour fecal Cu excretion-versus-time data will be listed and summarized with descriptive statistics and plots. The same analyses will be conducted on the absolute, change from Baseline, and percent changes from Baseline of these concentration-versus-time data.

5.7.2. Subgroup Analyses

For exploratory purposes, the primary and secondary efficacy endpoints will also be summarized in clinically relevant subgroups. As a general rule, a subgroup is analyzed only if the number of participants is ≥ 3 in each treatment group.

- Age in years group (≥ 3 to < 12, ≥ 12 to < 18)
- Sex (Male, Female)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, Unknown)
- Race (White, Black or African American, Asian, American Indian or Alaska native, Native Hawaiian or other Pacific Islander, Other)
- Country/Region (US, EU, UK, Germany, Japan, Rest of the World)
- Body mass index (BMI) group (< 25 kg/m^2, 25 to 30 kg/m^2, > 30 kg/m^2)

- UWDRS Part II total score at Baseline (> 0, = 0)
- UWDRS Part III total score at Baseline (> 0, = 0)
- Cirrhosis at Baseline (Yes, No)
- Psychiatric symptoms at Baseline (Yes, No; at least 1 symptom present on BPRS-24 and BPRS-C9)
- Renal function status at Baseline
  - G1
  - G2
  - G3a/G3b/G4/G5 combined
- ALT at Baseline (> ULN, ≤ ULN)

5.8. Interim Analyses

The primary analysis will be performed after 48 weeks, and the final analysis will be performed after completion of Period 2. Interim analyses of data may be performed to support regulatory submissions. These will primarily focus on analyzing safety endpoints only, and the safety summaries described in Section 5.6 may be performed. These analyses will be descriptive only; they will not include formal hypothesis testing and will not be used to adapt the study.

The efficacy data available at the time of primary analysis will also be used in an efficacy extrapolation to develop evidence for ALXN1840 efficacy on Cu control for pediatric participants (ages 3 to < 18 years) with WD using adult/adolescent participant data from Studies WTX101-301 and ALXN1840-WD-302. Full details of the extrapolation exercise will be provided in the Study ALXN1840-WD-303 SAP.

5.8.1. DMC or Other Review Board

An independent DMC, comprising experts in relevant fields with no direct relationship to the study, will be appointed by Alexion. The specific responsibilities of the DMC will be described in the DMC Charter.

A separate independent Neuro Event Adjudication Panel, comprising independent experts in relevant fields, will be appointed by Alexion. As detailed in the Neuro Event Adjudication Panel Charter (maintained separately from the study protocol), the Neuro Event Adjudication Panel will review and monitor study data for neurological SAEs that may impact safety, effectiveness, and study conduct and make recommendations regarding study continuation, changes to the study population, and/or modification to study procedures. The specific responsibilities are described in the Neuro Event Adjudication Panel Charter.

A separate independent Hepatic Adjudication Panel, comprising experts in hepatology and drug-induced liver injury, will be appointed by Alexion. As detailed separately in the Hepatic Adjudication Panel Charter (maintained separately from the study protocol), the Hepatic Adjudication Panel will review and monitor study data for abnormalities of liver tests and liver function that may impact safety, effectiveness, and study conduct and make recommendations

regarding study continuation, changes to the study population, and/or modification to study procedures. The specific responsibilities are described in the Hepatic Adjudication Panel Charter.

6. SUPPORTING DOCUMENTATION

6.1. Appendix 1: Technical Specifications for Derived Variables

The following derived data will be calculated prior to analysis.

Adverse Events

The analysis of AEs is described in detail in Section 5.6.2 .

TEAEs are adverse events with start dates and start times onset or after the date and time of the first study intervention dose or existing events that worsened in severity after the first dose of randomized treatment. If the start date of an AE is partially or completely missing and the end (stop) date and time of the AE does not indicate that it occurred prior to the first dose, then the determination of treatment-emergent status will be based on the following:

- If the start year is after the year of the first study intervention dose, then the AE is treatment emergent; else
- If the start year is the same as the year of the first study intervention dose and
  - The start month is missing, then the AE is treatment emergent; else if
  - The start month is present and is the same or after the month of the first study intervention dose, then the AE is treatment-emergent; else
- If the start date is completely missing, then the AE is treatment emergent.

All other AEs are considered PTAEs.

Percentages are based on the total number of treated participants in the particular treatment group.

Age

Age will be presented as the number of years between the date of birth and the reference date. For age at enrollment, the reference date will be the date of signing the informed consent form.

The following formula should be followed for the calculation of age, if needed:

Age (year) = FLOOR([reference date – date of birth]/365.25), where the FLOOR( ) function returns the integer part of the result.

In cases where only the month and year are provided for a date, the day for the date will be imputed as 15. The missing month will be imputed as June. In cases where the day is observed but the month is missing, the date will be imputed as June 15. In instances when the imputed reference date is earlier than the birth date, the birth date will be used as the reference date.

Analysis Relative Day

Analysis relative day is the day relative to the first dosing day. It will be calculated as analysis date – first dose date + 1 if the analysis date is after the first dose date; otherwise, it will be calculated as first dose date – analysis date.

Baseline Value

Baseline is defined as the last nonmissing value collected on or prior to the first dose.

Body Mass Index

BMI is derived as follows: weight (kg)/[height (cm)/100]^2

Change from Baseline

Change from baseline will be calculated as postbaseline assessment value – baseline assessment value when both values are not missing.

Percent change from baseline is calculated as change from baseline/baseline × 100.

If either the baseline or the postbaseline value is missing, the change from baseline and/or percent change from baseline is set to missing. Additionally, if the baseline is 0, the percent change from baseline will be missing.

Medications and Therapies

Concomitant medications/therapies are any events with administration dates and times on or after the date and time of the first study drug dose. If the start date of a medication or therapy is partially or completely missing and the end (stop) date and time of the medication/therapy does not indicate that it occurred prior to the first dose, then the determination of concomitant status will be based on the following:

If the start year is after the year of the first study drug dose, then the medication/therapy is concomitant; else, if the start year is the same as the year of the first study drug dose and the start month is missing, then the medication/therapy is concomitant. If the start month is present and is the same or after the month of the first study drug dose, then the medication/therapy is concomitant. If the start date is completely missing, then the medication/therapy is concomitant.

All other medications/therapies are considered prior medications/therapies and could occur from 30 days prior to informed consent up through the Screening Period and prior to the first dose.

UWDRS

As described in Section 5.4.2, UWDRS has 3 subscores. The algorithms for calculating the subscores are given below. The UWDRS total score will be the sum of the 3 subscores.

UWDRS Part I: Consciousness; maximum score of 3

Set to Question 1, range 0 to 3.

UWDRS Part II total score: Disability; maximum score of 40

- Calculate the sum of Questions 2 to 11; each question has range 0 to 4.
- If all 10 items are populated, the subscore will be the sum calculated above. If 8 or 9 items are populated, prorate the score by dividing by the number of answered items and multiplying by 10. This is done in order to estimate the value the participant could have achieved if they had answered all the questions. If less than 8 items are populated, the score will not be derived.

UWDRS Part III total score: Neurological status; maximum score of 175

- Calculate the following new scores for Questions 12 to 34:
  - Question 12: range 0 to 4; set to Q12A
  - Question 13: range 0 to 6;

    If Q13 = 0 then set to 0;
    else if Q13 = 1 then do;
    if Q13A > 2 then set to Q13A
    else set to Q13A + Q13B
    end;
  - Question 14: range 0 to 1; set to Q14
  - Question 15: range 0 to 16; set to Q15A + Q15B + Q15C + Q15D
  - Question 16: range 0 to 4; set to Q16
  - Question 17: range 0 to 20; set to Q17A + Q17B + Q17C + Q17D + Q17E
  - Question 18: range 0 to 8; set to Q18A + Q18B
  - Question 19: range 0 to 8; set to Q19A + Q19B
  - Question 20: range 0 to 4; set to Q20
  - Question 21: range 0 to 16; set to Q21A1 + Q21A2 + Q21B1 + Q21B2
  - Question 22: range 0 to 8; set to Q22A + Q22B
  - Question 23: range 0 to 8; set to Q23A + Q23B
  - Question 24: range 0 to 8; set to Q24A + Q24B
  - Question 25: range 0 to 4; set to Q25
  - Question 26: range 0 to 8; set to Q26A + Q26B
  - Question 27: range 0 to 4; set to Q27
  - Question 28: range 0 to 10

Visit Windowing

In analysis of data summarized by study visit, all data collection will be reassigned a study visit where data are scheduled for collection based on the actual days relative to baseline. All visits will be assigned a target study day; for the determination of target days, weeks will be assumed to have 7 days. Baseline will have a target study day of 1. Thus, Week 4 would have a target day of $4 \times 7 + 1 = 29$. For each assessment, the postbaseline period will be divided using the scheduled visit's target days. The lower bound of each visit interval will be evaluated as the midpoint between the target day and the previous visit's target day in the following manner: study day interval lower bound = target study day – ([target study day – last target study day]/2). If more than 1 value is mapped to the same scheduled visit, the closer of those values will be considered for summarization. Visit windows are intended to be contiguous such that all data collected at all postbaseline visits, whether scheduled or unscheduled, will map to 1 of the visits.

The visit displayed on participant data listings will be reflective of the scheduled visit label as reported on the CRF. Study days relative to baseline will be displayed for each visit so it is apparent which visit the data may have been reassigned to in the summaries.

6.2. Appendix 2: Study and Participant Characteristics

Disposition of Participants

The number and percentage of all participants enrolled, randomized, included in the FAS and PP, Safety, PK, and PD analysis sets will be summarized. The reasons for exclusion from the analysis sets will also be provided. Frequency counts and percentages of participants excluded prior to randomization will be provided for participants who failed to meet study entry requirements during Screening at the start of the study.

The number and percentage of participants who completed or prematurely discontinued from the study will be described by randomized treatment group within each cohort, for rollover participants and overall. For participants who discontinued the study, the number and percentage will be summarized by their reason for premature discontinuation and withdrawal of consent. A summary of participants will be provided by region, country, and site. Additionally, a summary of participants who did not meet inclusion or who met exclusion criteria will be provided.

Descriptive statistics of the number of days in the study will be summarized. The date of the first and last use of study medications in each period and the study termination date will be listed. Individual reasons for premature discontinuation and withdrawal of consent from the study will be presented in a listing. All enrolled participants will be listed, indicating their analysis set along with the reason for exclusion. A listing of screen failure participants will also be provided. Additionally, a listing of the inclusion/exclusion criteria and a listing of participants and the inclusion criteria they failed to meet and the exclusion criteria they met will be provided.

All demographic and baseline characteristics information will be summarized on the FAS. Summary statistics will be presented by randomized treatment within cohort, for rollover participants and overall. Continuous variables will be presented using descriptive statistics, and categorical variables will be presented using frequencies and percentages. Age will be calculated relative to the date of informed consent and will be summarized as both a continuous and categorical variable. Time since WD treatment start date (months) will be calculated as months occurring between the date of informed consent and the start date from WD treatment history CRF and will be summarized using descriptive statistics. Listings will also be provided.

Demographics

The following demographic variables will be summarized:

- Age (years)
- Age in years group (3 to < 12, 12 to < 18)
- Sex (Male, Female)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown)
- Race (White, Black or African American, Asian, American Indian or Alaska native, Native Hawaiian or other Pacific Islander, Other)

- Country/Region (US, UK, Germany, Japan, Rest of the World)
- Height (cm)
- Weight (kg)
- BMI (kg/m^2)

Disease Characteristics

The following disease characteristics will be summarized:

- Time since WD treatment start date (months)
- Cumulative duration of prior WD treatment (months)
- Prior WD therapy: (i) zinc monotherapy versus penicillamine or trientine (± zinc); (ii) zinc monotherapy versus penicillamine (± zinc) versus trientine (± zinc)
- Cirrhosis (Yes, No)
- CGI severity
- Psychiatric symptom (Yes, No; at least 1 symptom present on BPRS-24 and BPRS-C9)
- cNCC and dNCC
- Plasma total Cu
- Plasma total Mo
- PUF-Cu
- PUF-Mo
- Cp
- CpC
- 24-hour urinary Cu concentration
- 24-hour urinary Mo concentration
- LBC
- MELD score
- Modified Nazer score
- UWDRS Part II total score (original score and FDA-suggested score)
- UWDRS Part III total score
- UWDRS Part III Functional Subscale (original score and FDA-suggested score)
- UWDRS Part III individual symptoms (original score and FDA-suggested score of arising from a chair, gait, speech, and handwriting)
- UWDRS activities of daily living subgroup at baseline

- EQ VAS
- EQ-5D-5 levels

In addition, the following baseline laboratory measures will be summarized:

- ALT
- ALT groups (> 2× ULN, ≤ 2× ULN)
- Albumin
- AST
- Total and direct bilirubin
- Total bilirubin groups (> ULN, ≤ ULN)
- Gamma-glutamyl transferase (GGT)
- INR
- Platelets
- Leukocytes
- Creatinine
- Total cholesterol, high-density lipoprotein, low-density lipoprotein
- Triglycerides
- Renal function status at baseline
  - Normalized glomerular filtration rate (GFR) (mL/min/1.73 m^2)
    - G1: GFR > 90 mL/min/1.73 m^2
    - G2: GFR 60 to 89 mL/min/1.73 m^2
    - G3a: GFR 45 to 59 mL/min/1.73 m^2
    - G3b: GFR 30 to 44 mL/min/1.73 m^2
  - Absolute GFR (mL/min)
    - G1: GFR ≥ 90 mL/min
    - G2: GFR 60 to < 90 mL/min
    - G3: GFR 30 to < 60 mL/min

Renal function status at baseline:

Participants will be classified into 4 different stages of kidney disease based on normalized GFR estimated from the serum concentration of creatinine at baseline. Participants will also be classified based on the absolute GFR (EMA/CHMP/83874/2014).

For children and adolescent participants (age < 18 years), the equation provided by Schwartz (2009) ("bedside" formula) provides a better estimate of the normalized GFR (Frequently Asked Questions, National Kidney Foundation, 2014):

Normalized GFR (mL/min/1.73 m^2) = 0.41 × [Height (cm)/Scr (mg/dL)]

The relationship between normalized GFR and absolute GFR can be obtained using body surface area (BSA), as presented in Frequently Asked Questions, National Kidney Foundation, 2014:

Absolute GFR (mL/min) = Normalized GFR (mL/min/1.73 m^2) × BSA/1.73

For young and adolescent participants, BSA can be determined using the formula by Haycock et al, 1978, and also presented in Schwartz (2009):

Age < 18 years: BSA (m^2) = 0.024265 × (Weight [kg])$^{0.5378}$ × (Height [cm])$^{0.3964}$

Participants with end-stage renal disease on dialysis (chronic kidney disease Stage 5) or estimated glomerular filtration rate < 30 mL/min/1.73 m^2 are excluded from the study.

Protocol Deviations

All protocol violations will be determined and appropriately categorized prior to database lock. The number and percentage of participants with any important/not important protocol violations, as well as the number and percentage of participants with violations within each category, will be presented. A listing will also be provided.

Medical History

Medical history will be summarized by counts and percentages and displayed by System Organ Class and Preferred Term within each System Organ Class. System Organ Class and Preferred Term will be coded using the most up-to-date version of the MedDRA, version 24.1 or higher, available at the start of the study. This dictionary will be used throughout the life of the study and will not be updated during study conduct. The number and percentage of participants will be presented for ongoing conditions and previous conditions separately by System Organ Class and Preferred Term. A by-participant listing will also be created.

All details of WD diagnosis will be listed in full. WD treatment history will be summarized by counts and percentages for Cohort 1 and Cohort 2 by prior SoC, where prior SoC is defined as the later of the treatment at the time of Screening or the most recent treatment prior to Screening and is categorized as penicillamine, trientine hydrochloride, zinc, or combination.

Prior and Concomitant Medications

The WHO Drug Dictionary version from September 2021 or later will be used to code the medications. Medications will be summarized by Anatomical Therapeutic Chemical (ATC) level 3 class and generic drug name.

Prior and concomitant medications will be summarized for the FAS by randomized treatment within treatment cohort, for rollover participants and overall. The number and percentage of participants receiving any concomitant medication will be summarized, as well as the number and percentage receiving any concomitant medication by ATC drug class and generic drug name. Participants reporting use of more than 1 medication at each level of summarization (any medication received, ATC class, and generic drug name) will be counted only once. ATC class terms will be displayed by descending order of incidence, as well as generic drug names within each ATC class. Prior medications used to treat WD and an additional analysis of all prior medications will be summarized similarly.

Prior medications will be defined as medications that were discontinued prior to the start of study drug. Concomitant medications will be defined as medications that either started prior to the first dose of study drug and were continuing at the time of the first dose of study drug or started on or after the date of the first dose of study drug. If it cannot be determined whether a medication was stopped prior to the start of study drug dosing due to partial or missing medication start or end date, it will be considered a concomitant medication.

Prior and concomitant medications will be presented in a by-participant data listing by participant and medication name.

6.3. Appendix 3: Instrument Scoring Details

Not applicable

6.4. Appendix 4: Additional Details on Statistical Methods

To maintain study integrity and minimize bias in this open-label study, draft tables, listings, and figures will be produced with blinded treatment assignments for review prior to database lock for the Primary Evaluation Period.

Analysis Considerations Related to COVID-19

On 11 Mar 2020, Coronavirus Disease 2019 (COVID-19) was declared a pandemic by the WHO. This section summarizes additional analysis considerations to assess the potential impact of COVID-19 (Meyer, 2020). The following additional sensitivity and supplementary analyses will be included to assess the impact of the pandemic disruption on the study and to address pandemic-related data missingness.

1. The summary of participant disposition will include COVID-19 related discontinuations and withdrawals.
2. A summary of known COVID-19 exposure or diagnosis during the Primary Evaluation Period will be provided by treatment group using the Safety Analysis Set.
3. A summary of COVID-19 related important protocol deviations during the Primary Evaluation Period will be provided. A by-participant listing of all protocol deviations will be provided.
4. A summary of the number and percentage of participants who missed a study visit or had a modified study visit during the Primary Evaluation Period, along with the reasons (COVID-19 related/not), will be provided by treatment group and by visit using the FAS and Safety Analysis Set. For participants who had a modified study visit, the method for the different assessments will be summarized.
5. Alternative data collection methods required during the pandemic may introduce additional variability. Two sensitivity analyses will be performed to assess this possibility. Descriptive statistics for the primary and key secondary endpoints by visit (and by randomized treatment and cohort) can be calculated, with the visits split into the categories described below. In the sensitivity analysis, each visit for each participant will be categorized as either “collected as planned” or “modified.”
6. Missing data on the primary endpoint due to any COVID-19 related reasons will be handled as described in Section 5.3.2, where no imputation will be performed.

6.5. Appendix 5: Changes to Protocol-planned Analyses

- NCC or NCC/$NCC_{corrected}$ has been clearly specified as dNCC or cNCC/$NCC_{corrected}$ in the SAP.
- Observed, absolute, and percent changes of molar ratio of CpC to ceruloplasmin have been added as an exploratory endpoint.
- Assessing change from Baseline in urinary and fecal Mo Urinary and Fecal Mo
  - 24-hour urinary Mo will be assessed at Baseline, Week 6, Week 24, and Week 48 in all participants.

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

6.6. Appendix 6: List of Abbreviations

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC_{tau}	area under the plasma concentration-versus-time curve from time 0 to the end of the dosing interval
AUEC	area under the effect-versus-time curve
BLQ	below the assay's lower limit of quantification
BMI	body mass index
BPRS-24	Brief Psychiatric Rating Scale-24
BPRS-C9	Brief Psychiatric Rating Scale for children
BSA	body surface area
CE_{max}	maximum observed effect after dosing
CGI	Clinical Global Impression
CGI-I	Clinical Global Impression-Improvement scale
CGI-S	Clinical Global Impression-Severity scale
CL/F	apparent total body clearance
C_{max}	maximum observed concentration
cNCC	calculated non-ceruloplasmin-bound Cu
$cNCC_{corrected}$	calculated non-ceruloplasmin-bound Cu corrected for Cu bound in tripartite (tetrathiomolybdate-Cu-albumin) complexes
COVID-19	Coronavirus Disease 2019
CpC	ceruloplasmin-bound Cu
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	trough (predose) concentration observed at the start of the dosing interval
DMC	Data Monitoring Committee
dNCC	directly measured non-ceruloplasmin-bound Cu
ECG	electrocardiogram
eDISH	evaluation of drug-induced serious hepatotoxicity
EQ-5D	EuroQoL 5 Dimensions
EQ-5D-Y	EuroQoL 5 Dimensions-Youth
EQ VAS	EuroQoL visual analogue scale
FAS	Full Analysis Set
FIB-4	fibrosis-4
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
INR	international normalized ratio
LBC	labile-bound Cu
LLN	lower limit of normal
LLOQ	lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End-Stage Liver Disease
NCC	non-ceruloplasmin-bound Cu
$NCC_{corrected}$	non-ceruloplasmin-bound Cu in plasma corrected for the amount of Cu bound to the ALXN1840 tripartite (tetrathiomolybdate-Cu-albumin) complex
PD	pharmacodynamic(s)
PedsQL	Pediatric Quality of Life Inventory
PELD	Pediatric End-stage Liver Disease

Abbreviation	Definition
PK	pharmacokinetic(s)
PPS	Per Protocol
PTAE	pretreatment adverse events
PUF	plasma ultrafiltrate
QoL	quality of life
SAE	serious adverse event
SAP	Statistical Analysis Plan
SMQ	Standardized MedDRA Queries
SoC	standard of care
$t_{½}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
TE_{max}	time after dosing at which the maximum effect was observed
t_{max}	time to maximum observed concentration
TSQM-9	Treatment Satisfaction Questionnaire for Medication-9
ULN	upper limit of normal
UWDRS	Unified Wilson Disease Rating Scale
V_d/F	apparent volume of distribution
WD	Wilson Disease
WHO	World Health Organization

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