Clinical trial results:
A Phase 2, Multi-centre, Open-label, Study to Evaluate the Efficacy and Safety of WTX101 Administered for 24 Weeks in Newly Diagnosed Wilson Disease Patients Aged 18 and Older with an Extension Phase of 36 Months

Summary

EudraCT number	2014-001703-41
Trial protocol	DE AT PL GB
Global end of trial date	07 November 2018
Results information	
Result version number	v1 (current)
This version publication date	31 January 2021
First version publication date	31 January 2021

Trial information

Trial identification	
Sponsor protocol code	WTX101-201
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	Alexion Pharmaceuticals, Inc.
Sponsor organisation address	121 Seaport Boulevard, Boston, MA, United States, 02210
Public contact	European Clinical Trial Information, Alexion Pharmaceuticals, Inc., 33 147100615, clinicaltrials.eu@alexion.com
Scientific contact	European Clinical Trial Information, Alexion Pharmaceuticals, Inc., 33 147100615, clinicaltrials.eu@alexion.com

Notes:

Paediatric regulatory details	
Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 June 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 November 2018
Global end of trial reached?	Yes
Global end of trial date	07 November 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the efficacy of ALXN1840 (formerly WTX101) for 24 weeks on non-ceruloplasmin-bound copper (NCC) concentrations adjusted for molybdenum (Mo) plasma concentration in participants newly diagnosed Wilson Disease (WD) who were aged 18 and older and who had NCC concentrations within or above the reference range at the time of enrolment in the study.

Protection of trial subjects:

This study was conducted in accordance with International Council on Harmonisation (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the countries in which the study was conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 August 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 8
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	United States: 12
Worldwide total number of subjects	29
EEA total number of subjects	17

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	29
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants meeting all inclusion and no exclusion criteria were enrolled into the study and studied as outpatients.
Participants who completed the 24-week treatment period and had favorable safety profiles and WD control were offered the opportunity to participate in the Extension Period.

Pre-assignment

Screening details:

Participants enrolled as pre-treated with other de-coppering agents were required to undergo a 48-hour washout from their previous WD treatment just prior to initiation of study treatment.

Pre-assignment period milestones

Number of subjects started	29
Number of subjects completed	28

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 1

Period 1

Period 1 title	24-Week Treatment Period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	ALXN1840 24-Week Treatment Period

Arm description:

Treatment Period: ALXN1840 at individualized doses ranging from 15 to 60 milligrams (mg) per day. Dose increases or dose reductions were dependent on the individual non-ceruloplasmin-bound copper (NCC) concentrations adjusted for Mo plasma concentration. ALXN1840 may have been administered every other day, once daily, or twice daily, depending on individualized dosing regimen, for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	ALXN1840
Investigational medicinal product code	
Other name	WTX101
Pharmaceutical forms	Capsule, Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Individualized oral doses of ALXN1840. Initially, ALXN1840 was administered as uncoated capsules. Following a protocol amendment, ALXN1840 was administered as enteric coated tablets.

Number of subjects in period 1[1]	ALXN1840 24-Week Treatment Period
Started	28
Received at Least 1 Dose of Study Drug	28
Completed	22
Not completed	6
Physician decision	1
Adverse event, non-fatal	3
Participant was unable to come	1
Protocol deviation	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: One participant was enrolled but not treated.

Period 2

Period 2 title	Extension Period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	ALXN1840 Extension Period

Arm description:

Extension Period: Participants continued the same ALXN1840 daily dose maintained at Week 24 of the Treatment Period and the same dosing regimen. During the Extension Period, no up-titration was made unless NCC concentrations adjusted for Mo plasma concentration did not remain stable within (or below) the reference range.

Arm type	Experimental
Investigational medicinal product name	ALXN1840
Investigational medicinal product code	
Other name	WTX101
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Individualized oral doses of ALXN1840.

Number of subjects in period 2	ALXN1840 Extension Period
Started	22
Received at Least 1 Dose of Study Drug	22
Completed	0
Not completed	22
Participant Withdrew for Personal Reasons	1
Lost to follow-up	1

Continued into Study WTX101-301 extension	19
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	24-Week Treatment Period
Reporting group description:	
Participants who were enrolled and received at least 1 dose of study drug.	

Reporting group values	24-Week Treatment Period	Total	
Number of subjects	28	28	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	28	28	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	34.1		
standard deviation	± 11.86	-	
Gender categorical Units: Subjects			
Female	15	15	
Male	13	13	
Race Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	2	2	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	0	0	
White	26	26	
More than one race	0	0	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	ALXN1840 24-Week Treatment Period

Reporting group description:

Treatment Period: ALXN1840 at individualized doses ranging from 15 to 60 milligrams (mg) per day. Dose increases or dose reductions were dependent on the individual non-ceruloplasmin-bound copper (NCC) concentrations adjusted for Mo plasma concentration. ALXN1840 may have been administered every other day, once daily, or twice daily, depending on individualized dosing regimen, for 24 weeks.

Reporting group title	ALXN1840 Extension Period

Reporting group description:

Extension Period: Participants continued the same ALXN1840 daily dose maintained at Week 24 of the Treatment Period and the same dosing regimen. During the Extension Period, no up-titration was made unless NCC concentrations adjusted for Mo plasma concentration did not remain stable within (or below) the reference range.

Subject analysis set title	ALXN1840 Every Other Day
Subject analysis set type	Full analysis

Subject analysis set description:

Participants who received at least 1 dose of ALXN1840 administered at 15 mg every other day and from whom pharmacokinetic (PK) parameters could be derived.

Subject analysis set title	ALXN1840 15 mg Daily
Subject analysis set type	Full analysis

Subject analysis set description:

Participants who received at least 1 dose of ALXN1840 administered at 15 mg per day and from whom PK parameters could be derived.

Subject analysis set title	ALXN1840 30 mg Daily
Subject analysis set type	Full analysis

Subject analysis set description:

Participants who received at least 1 dose of ALXN1840 administered at 30 mg per day and from whom PK parameters could be derived.

Subject analysis set title	ALXN1840 60 mg Daily
Subject analysis set type	Full analysis

Subject analysis set description:

Participants who received at least 1 dose of ALXN1840 administered at 60 mg per day and from whom PK parameters could be derived.

Primary: Percentage Of Participants With Normalized Concentrations Of NCC

End point title	Percentage Of Participants With Normalized Concentrations Of NCC[1]

End point description:

Normalized concentrations of NCC was defined as who achieving or maintaining normalized levels of NCC (0.8 to 2.3 micromole [µmol]l/liter [L]]) adjusted for molybdenum (Mo) plasma concentration or reaching a reduction of at least 25% in NCC corrected for Mo if above the normal reference range at the time of enrollment. NCC was calculated by subtracting the amount of copper (Cu) bound to ceruloplasmin (CP) from the total plasma Cu concentration. Post-baseline NCC values were adjusted (corrected) to account for Cu bound in tripartite complexes with ALXN1840 and albumin. Descriptive statistics are reported

End point type	Primary

End point timeframe:

Week 24

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As per protocol, statistical analysis was not performed. Descriptive statistics are included.

End point values	ALXN1840 24-Week Treatment Period			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: Percentage of participants				
number (confidence interval 95%)	85.7 (70.8 to 97.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In NCC Concentrations Adjusted For Mo Plasma Concentration At Week 24

End point title	Change From Baseline In NCC Concentrations Adjusted For Mo Plasma Concentration At Week 24

End point description:

The change from Baseline in NCC adjusted for Mo plasma concentration over 24 weeks were analyzed and descriptive statistics are reported. Change from baseline = (Baseline NCC concentrations) - (Week 24 NCC concentrations adjusted for Mo plasma concentration). Least square means and their 95% confidence intervals (CIs) were calculated using a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM) with fixed effects for Baseline, cohort, visit, Baseline-by-visit, and cohort-by-visit interaction.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	ALXN1840 24-Week Treatment Period			
Subject group type	Reporting group			
Number of subjects analysed	21[2]			
Units: µmol/L				
least squares mean (confidence interval 95%)	-2.56 (-3.13 to -1.98)			

Notes:

[2] - Had analyzable data at the specified timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Time To Normalization Of NCC Adjusted For Mo Plasma Concentration In Participants With Elevated Baseline NCC

End point title	Time To Normalization Of NCC Adjusted For Mo Plasma Concentration In Participants With Elevated Baseline NCC

End point description:

For time to normalization of NCC adjusted for Mo plasma concentration, a Kaplan-Meier approach was

used where participants not normalized were censored at the latest observed time point. To achieve a normalized NCC concentration, participants must have demonstrated 2 consecutive measures within the normal range (0.8 to 2.3 µmol/L). Analyses includes all data up to the last assessment in the extension period for participants who reached the event of normalization of NCC corrected concentrations. Last Assessment is a summary of the last available post-baseline result for each participant. Analyses includes all data up to the last assessment in the extension period; up to Week 176. The analysis included participants who did not normalize. The values for these participants were censored to be the time of last observation in the Kaplan-Meier analysis.

End point type	Secondary

End point timeframe:

Up to last assessment (up to Week 176)

End point values	ALXN1840 24-Week Treatment Period			
Subject group type	Reporting group			
Number of subjects analysed	16[3]			
Units: days				
median (inter-quartile range (Q1-Q3))	147.5 (37.0 to 211.0)			

Notes:

[3] - Subset of participants with elevated baseline NCC.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Neurological Status Using The Unified Wilson's Disease Rating Scale (UWDRS) (Neurological Subscore; Part I) At Week 24

End point title	Change From Baseline In Neurological Status Using The Unified Wilson's Disease Rating Scale (UWDRS) (Neurological Subscore; Part I) At Week 24

End point description:

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: a) dystonic b) ataxic, c) Parkinsonian syndrome. The UWDRS is designed to comprise 3 parts:
• UWDRS I (consciousness, item 1): maximum score of 3
• UWDRS II (disability, items 2 to 11): maximum score of 40
• UWDRS III (neurological status, items 12 to 34): Maximum score of 175
The UWDRS total score is the sum of the 3 subscores. UWDRS I and III was assessed by a Neurologist, while UWDRS II was reported by the participant or caregiver.
Change from baseline was calculated as: Baseline score - Week 24 score. A decrease in score from baseline indicates an improvement in condition. The UWDRS Part 1 mean scores are reported.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	ALXN1840 24-Week Treatment Period			
Subject group type	Reporting group			
Number of subjects analysed	22[4]			
Units: score on a scale				
arithmetic mean (standard deviation)	0.0 (± 0.0)			

Notes:

[4] - Had analyzable data at the specified timepoint

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Neurological Status Using The Unified Wilson's Disease Rating Scale (UWDRS) (Neurological Subscore; Parts II, III, And Total Score) At Week 24

End point title	Change From Baseline In Neurological Status Using The Unified Wilson's Disease Rating Scale (UWDRS) (Neurological Subscore; Parts II, III, And Total Score) At Week 24

End point description:

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: a) dystonic b) ataxic, c) Parkinsonian syndrome. The UWDRS is designed to comprise 3 parts:
• UWDRS I (consciousness, item 1): maximum score of 3
• UWDRS II (disability, items 2 to 11): maximum score of 40
• UWDRS III (neurological status, items 12 to 34): Maximum score of 175
The UWDRS total score is the sum of the 3 subscores. UWDRS I and III was assessed by a Neurologist, while UWDRS II was reported by the participant or caregiver.
Change from baseline was calculated as: Baseline score - Week 24 score. A decrease in score from baseline indicates an improvement in condition.
The UWDRS Parts II and III and total score are reported.
Least square means and their 95% CIs were calculated using an REML-based MMRM with fixed effects for Baseline, cohort, visit, Baseline-by-visit, and cohort-by-visit interaction.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	ALXN1840 24-Week Treatment Period			
Subject group type	Reporting group			
Number of subjects analysed	22[5]			
Units: score on a scale				
least squares mean (confidence interval 95%)				
UWDRS Part II	-2.5 (-4.6 to -0.4)			
UWDRS Part III	-5.75 (-10.74 to -0.77)			
Total Score	-8.23 (-15.42 to -1.04)			

Notes:

[5] - Had analyzable data at the specified timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Psychiatric Status Using Mini International Neuropsychiatric Interview (M.I.N.I.) Tracking At Week 24

End point title	Change From Baseline In Psychiatric Status Using Mini International Neuropsychiatric Interview (M.I.N.I.) Tracking At Week 24

End point description:

The M.I.N.I. is a psychiatric diagnostic interview instrument with only "yes" or "no" answers. The M.I.N.I. is designed to "track" severity of symptoms in relation to baseline data. The following components are presented: Major Depressive Episode (n=22), Suicidality Tracking Scale (n=23), Manic/Hypomanic Episode (n=21), Panic Disorder (n=23), Agoraphobia (n=22), Social Anxiety Disorder (n=22), Obsessive Compulsive Disorder (n=23), Post Traumatic Stress Disorder (n=22), Alcohol Use Disorder (n=22), Substance Use Disorder (n=23), Psychotic Disorders (n=22), Anorexia Nervosa (n=23), Bulimia Nervosa (n=23), Binge Eating Disorder (n=22), Generalized Anxiety Disorder (n=23), and Antisocial Personality Disorder (n=20).
Change from baseline = Baseline score - Week 24 score. Decrease in score indicates decrease in symptoms. Least square means and 95% CIs were calculated using an REML-based MMRM with fixed effects for Baseline, cohort, visit, Baseline-by-visit, and cohort-by-visit interaction.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	ALXN1840 24-Week Treatment Period			
Subject group type	Reporting group			
Number of subjects analysed	23[6]			
Units: score on a scale				
least squares mean (confidence interval 95%)				
Major Depressive Episode Standardized	-0.39 (-0.62 to -0.16)			
Suicidality Tracking Scale Standardized	-0.07 (-0.09 to -0.04)			
Manic/Hypomanic Episode Standardized	-0.09 (-0.23 to 0.05)			
Panic Disorder Standardized	-0.28 (-0.35 to -0.21)			
Agoraphobia Standardized	-0.58 (-0.70 to -0.46)			
Social Anxiety Disorder Standardized	-0.35 (-0.52 to -0.18)			
Obsessive Compulsive Disorder Standardized	-0.04 (-0.14 to 0.05)			
Post Traumatic Stress Disorder Standardized	-0.24 (-0.35 to -0.13)			

Alcohol Use Disorder Standardized	0.0 (-0.03 to 0.03)			
Substance Use Disorder Standardized	-0.02 (-0.10 to 0.05)			
Psychotic Disorders Standardized	0.00 (-0.06 to 0.07)			
Anorexia Nervosa Standardized	0.04 (-0.07 to 0.15)			
Bulimia Nervosa Standardized	0.0 (-0.12 to 0.13)			
Binge Eating Disorder Standardized	0.04 (-0.06 to 0.14)			
Generalized Anxiety Disorder Standardized	-0.37 (-0.59 to -0.16)			
Antisocial Personality Disorder Standardized	-0.06 (-0.12 to 0.00)			

Notes:

[6] - Had analyzable data at the specified timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Clinical Symptoms As Assessed By The Investigators On The Clinical Global Impression (CGI) Scale Items 1 (Severity Of Illness) And 2 (Global Improvement) At Week 24

End point title	Change From Baseline In Clinical Symptoms As Assessed By The Investigators On The Clinical Global Impression (CGI) Scale Items 1 (Severity Of Illness) And 2 (Global Improvement) At Week 24

End point description:

CGI Severity scale (CGI-S) is a 7-point scale where the investigator rated the severity of the participant's illness at the time of assessment, relative to the investigator's past experience with participants who have the same diagnosis. Considering total clinical experience, a participant was assessed on severity of illness at the time of rating as: 1, normal, not at all ill; 2, borderline ill; 3, mildly ill; 4, moderately ill; 5, markedly ill; 6, severely ill; or 7, extremely ill. The CGI Improvement scale (CGI-I) is a 7 point scale where the clinician assessed how much the participant's illness 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. Change from baseline = Baseline score - Week 24 score. Decrease in CGI-S score and increase in CGI-I score indicates improvement.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	ALXN1840 24-Week Treatment Period			
Subject group type	Reporting group			
Number of subjects analysed	22[7]			
Units: score on a scale				
least squares mean (confidence interval 95%)				

Week 24 CGI-S Week 24 CGI-I	-0.1 (-0.6 to 0.3) -0.8 (-1.3 to 0.3)			

Notes:

[7] - Had analyzable data at the specified timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Quality Of Life (QoL)/Patient Reported Outcome (PRO) Assessed By The European Quality Of Life 5 Dimensions (EQ-5D) Visual Analogue Scale (VAS) At Week 24

End point title	Change From Baseline In Quality Of Life (QoL)/Patient Reported Outcome (PRO) Assessed By The European Quality Of Life 5 Dimensions (EQ-5D) Visual Analogue Scale (VAS) At Week 24

End point description:

The EQ-5D VAS records the participant's self-rated health as indicated on a 20 centimeter (cm) vertical VAS with endpoints labelled "the best health you can imagine" (20 cm) and "the worst health you can imagine" (0 cm) on a scale from 0 to 100, with higher scores for higher quality of life. Change from baseline = Baseline score - Week 24 score. An increase in score indicates improvement. Least square means and their 95% CIs were calculated using an REML-based MMRM with fixed effects for Baseline, cohort, visit, Baseline-by-visit, and cohort-by-visit interaction.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	ALXN1840 24-Week Treatment Period			
Subject group type	Reporting group			
Number of subjects analysed	23[8]			
Units: score on a scale				
least squares mean (confidence interval 95%)	11.3 (5.1 to 17.6)			

Notes:

[8] - Had analyzable data at the specified timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Quality Of Life (QoL)/Patient Reported Outcome (PRO) Assessed By The EQ5D Descriptive System UK Health Index Scores At Week 24

End point title	Change From Baseline In Quality Of Life (QoL)/Patient Reported Outcome (PRO) Assessed By The EQ5D Descriptive System UK Health Index Scores At Week 24

End point description:

The EQ-5D-5L Descriptive System provides a simple descriptive profile and a single index value for health status (UK Health Index Score) consisting of 5 dimensions (mobility, self-care, usual activities,

pain/discomfort, anxiety/depression), each of which can have 1 of 5 responses that represent 5 levels of severity (no problems, slight problems, moderate problems, severe problems, extreme problems). The participant was asked to indicate his/her health state for each of the 5 dimensions. This decision resulted in a 1-digit number expressing the level selected for that dimension. Digits for the 5 dimensions were combined in a 5-digit number describing the participant's health state.
Change from baseline = Baseline score - Week 24 score. An increase in score indicates improvement. Least square means and their 95% CIs were calculated using an REML-based MMRM with fixed effects for Baseline, cohort, visit, Baseline-by-visit, and cohort-by-visit interaction.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	ALXN1840 24-Week Treatment Period			
Subject group type	Reporting group			
Number of subjects analysed	23[9]			
Units: score on a scale				
least squares mean (confidence interval 95%)	0.0439 (-0.0341 to 0.1219)			

Notes:

[9] - Had analyzable data at the specified timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: QoL/PRO Assessed By The 8-Item Medication Adherence Scale (MMAS-8) At Week 24

End point title	QoL/PRO Assessed By The 8-Item Medication Adherence Scale (MMAS-8) At Week 24

End point description:

The MMAS-8 is a scale used to evaluate adherence to medication. The first 7 questions are yes or no questions. For Questions 1 through 4, 6, and 7, yes takes a value of 0 and no takes a value of 1. For Question 5, yes takes a value of 1 and no takes a value of 0. Question 8 has to be remapped as follows: 4 = 1, 3 = 0.75, 2 = 0.5, 1 = 0.25, 0 = 0. The total score was calculated by adding values for Questions 1 through 8 and thus has a maximum value of 8 (maximum adherence to medication). If 7 of the 8 questions were answered, the total score was pro-rated by dividing by 7 and multiplying by 8. If less than 7 questions were answered, the total score was not derived. Least square means and their 95% CIs were calculated using an REML-based MMRM with fixed effects for Baseline, cohort, visit, Baseline-by-visit, and cohort-by-visit interaction.

End point type	Secondary

End point timeframe:

Week 24

End point values	ALXN1840 24-Week Treatment Period			
Subject group type	Reporting group			
Number of subjects analysed	23[10]			
Units: score on a scale				
arithmetic mean (confidence interval 95%)	7.59 (7.29 to 7.88)			

Notes:

[10] - Had analyzable data at the specified timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: QoL/PRO Assessed By The Treatment Satisfaction Questionnaire For Medication (TSQM-9) At Week 24

End point title	QoL/PRO Assessed By The Treatment Satisfaction Questionnaire For Medication (TSQM-9) At Week 24

End point description:

The TSQM-9 was used to assess the overall level of satisfaction or dissatisfaction with medication participants were taking. This composite scale is comprised of 2 items on the TSQM-9 survey:
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 domain scores (effectiveness score, convenience score, global satisfaction score) range from 0 to 100 with higher scores representing greater satisfaction for the domain.

End point type	Secondary

End point timeframe:

Week 24

End point values	ALXN1840 24-Week Treatment Period			
Subject group type	Reporting group			
Number of subjects analysed	23[11]			
Units: score on a scale				
arithmetic mean (confidence interval 95%)				
Effectiveness	69.81 (58.90 to 80.72)			
Convenience	83.57 (77.62 to 89.53)			
Global Satisfaction	75.47 (62.77 to 88.16)			

Notes:

[11] - Had analyzable data at the specified timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Hepatic Laboratory Measure Alanine Aminotransferase (ALT) At Week 24

End point title	Change From Baseline In Hepatic Laboratory Measure Alanine Aminotransferase (ALT) At Week 24

End point description:

Assessed by laboratory measurements. Change from baseline = Baseline ALT level- Week 24 ALT level.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	ALXN1840 24-Week Treatment Period			
Subject group type	Reporting group			
Number of subjects analysed	23[12]			
Units: U/L				
arithmetic mean (standard deviation)	-2.0 (± 23.71)			

Notes:

[12] - Had analyzable data at the specified timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Hepatic Laboratory Measure Aspartate Aminotransferase (AST) At Week 24

End point title	Change From Baseline In Hepatic Laboratory Measure Aspartate Aminotransferase (AST) At Week 24

End point description:

Assessed by laboratory measurements. Change from baseline = Baseline AST level- Week 24 AST level.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	ALXN1840 24-Week Treatment Period			
Subject group type	Reporting group			
Number of subjects analysed	23[13]			
Units: U/L				
arithmetic mean (standard deviation)	-10.3 (± 28.18)			

Notes:

[13] - Had analyzable data at the specified timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Hepatic Laboratory Measure International Normalized Ratio (INR) At Week 24

End point title	Change From Baseline In Hepatic Laboratory Measure International Normalized Ratio (INR) At Week 24

End point description:

Assessed by laboratory measurements. Change from baseline = Baseline INR - Week 24 INR.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	ALXN1840 24-Week Treatment Period			
Subject group type	Reporting group			
Number of subjects analysed	22[14]			
Units: ratio				
arithmetic mean (standard deviation)	-0.05 (± 0.148)			

Notes:

[14] - Had analyzable data at the specified timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Hepatic Laboratory Measure Bilirubin At Week 24

End point title	Change From Baseline In Hepatic Laboratory Measure Bilirubin At Week 24

End point description:

Assessed by laboratory measurements. Change from baseline = Baseline bilirubin level- Week 24 bilirubin level.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	ALXN1840 24-Week Treatment Period			
Subject group type	Reporting group			
Number of subjects analysed	23[15]			
Units: µmol/L				
arithmetic mean (standard deviation)	-0.7 (± 4.30)			

Notes:

[15] - Had analyzable data at the specified timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Exchangeable Cu At Week 24

End point title	Change From Baseline In Exchangeable Cu At Week 24

End point description:

Assessed by laboratory measurements. Change from baseline = Baseline Exchangeable Cu level- Week 24 Exchangeable Cu level.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	ALXN1840 24-Week Treatment Period			
Subject group type	Reporting group			
Number of subjects analysed	22[16]			
Units: ng/mL				
arithmetic mean (standard deviation)	-25.1 (± 56.64)			

Notes:

[16] - Had analyzable data at the specified timepoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In Speciation Profiling (Mo, Cu, And Protein Complex Profiling Using Size Exclusion Chromatography) At Week 24

End point title	Change From Baseline In Speciation Profiling (Mo, Cu, And Protein Complex Profiling Using Size Exclusion Chromatography) At Week 24

End point description:

Due to low chromatographic resolution of data, quantitative analysis for speciation profiling, as had been planned in the protocol, was not feasible.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	ALXN1840 24-Week Treatment Period			
Subject group type	Reporting group			
Number of subjects analysed	0[17]			
Units: NA				
number (not applicable)				

Notes:

[17] - Quantitative analysis for speciation profiling was not feasible.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline In 24-Hour Urinary Mo And Cu At Week 24

End point title	Change From Baseline In 24-Hour Urinary Mo And Cu At Week 24

End point description:

Assessed by laboratory measurements. Change from baseline = Baseline 24-hour urinary Mo or Cu level - Week 24 24-hour urinary Mo or Cu level.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	ALXN1840 24-Week Treatment Period			
Subject group type	Reporting group			
Number of subjects analysed	20[18]			
Units: µg/day				
arithmetic mean (confidence interval 95%)				
Mo	1561.1 (1093.8 to 2028.4)			
Cu	-28.1 (-107.1 to 51.0)			

Notes:

[18] - Had analyzable data at the specified timepoint

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Area Under The Curve From Time 0 to 24 (AUC0-24) Of Plasma Total Mo On Day 1 And Week 12

End point title	PK: Area Under The Curve From Time 0 to 24 (AUC0-24) Of Plasma Total Mo On Day 1 And Week 12

End point description:

PK blood sampling occurred on Day 1, Week 12, and Week 24 at the following serial PK sampling time-

points: 0, 1, 2, 3, 4, 5, 6, 8, and 12 (10 to 12) hours post-dose.

End point type	Secondary

End point timeframe:

0, 1, 2, 3, 4, 5, 6, 8, and 12 (10 to 12) hours post-dose on Day 1 and Week 12

End point values	ALXN1840 Every Other Day	ALXN1840 15 mg Daily	ALXN1840 30 mg Daily	ALXN1840 60 mg Daily
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	0[19]	4[20]	16[21]	6[22]
Units: h*ng/mL				
arithmetic mean (standard deviation)				
Day 1	()	2872.6 (± 943.4)	4796.7 (± 3464.8)	3138.7 (± 3090.3)
Week 12	()	7873.6 (± 3361.1)	9157.1 (± 2521.4)	11342.5 (± 4706.7)

Notes:

[19] - No participants had analyzable PK data.

[20] - n=3 for Day 1 and n=4 for Week 12

[21] - n=16 for Day 1 and n=12 for Week 12

[22] - n=2 for Day 1 and n=6 for Week 12

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Area Under The Curve From Time 0 to 24 (AUC0-24) Of Plasma Total Mo On Week 24

End point title	PK: Area Under The Curve From Time 0 to 24 (AUC0-24) Of Plasma Total Mo On Week 24

End point description:

PK blood sampling occurred on Week 24 at the following serial PK sampling time-points: 0, 1, 2, 3, 4, 5, 6, 8, and 12 (10 to 12) hours post-dose.

End point type	Secondary

End point timeframe:

0, 1, 2, 3, 4, 5, 6, 8, and 12 (10 to 12) hours post-dose on Week 24

End point values	ALXN1840 Every Other Day	ALXN1840 15 mg Daily	ALXN1840 30 mg Daily	ALXN1840 60 mg Daily
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1[23]	3	8	5
Units: h*ng/mL				
arithmetic mean (standard deviation)	5668.7 (± 0)	4593.6 (± 1260.0)	7884.3 (± 3157.2)	8890.2 (± 5801.6)

Notes:

[23] - Note: Since only 1 participant was analyzed, standard deviation was unable to be calculated.

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Maximum Concentration (Cmax) Of Plasma Total Mo On Day 1 And Week 12

End point title	PK: Maximum Concentration (Cmax) Of Plasma Total Mo On Day 1 And Week 12

End point description:

PK blood sampling occurred on Day 1 and Week 12 at the following serial PK sampling time-points: 0, 1, 2, 3, 4, 5, 6, 8, and 12 (10 to 12) hours post-dose.

End point type	Secondary

End point timeframe:

0, 1, 2, 3, 4, 5, 6, 8, and 12 (10 to 12) hours post-dose on Day 1 and Week 12

End point values	ALXN1840 Every Other Day	ALXN1840 15 mg Daily	ALXN1840 30 mg Daily	ALXN1840 60 mg Daily
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	0[24]	6	19[25]	6[26]
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 1	()	202.7 (± 114.5)	304.8 (± 202.9)	167.6 (± 144.6)
Week 12	()	393.0 (± 177.3)	505.5 (± 159.4)	607.3 (± 257.3)

Notes:

[24] - No participants had analyzable PK data.

[25] - n=19 for Day 1 and n=13 for Week 12

[26] - n=3 for Day 1 and n=6 for Week 12

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Maximum Concentration (Cmax) Of Plasma Total Mo At Week 24

End point title	PK: Maximum Concentration (Cmax) Of Plasma Total Mo At Week 24

End point description:

PK blood sampling occurred on Week 24 at the following serial PK sampling time-points: 0, 1, 2, 3, 4, 5, 6, 8, and 12 (10 to 12) hours post-dose.

End point type	Secondary

End point timeframe:

0, 1, 2, 3, 4, 5, 6, 8, and 12 (10 to 12) hours post-dose on Week 24

End point values	ALXN1840 Every Other Day	ALXN1840 15 mg Daily	ALXN1840 30 mg Daily	ALXN1840 60 mg Daily
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	1[27]	4	10	7
Units: ng/mL				
arithmetic mean (standard deviation)	364.0 (± 0)	359.0 (± 163.7)	447.7 (± 200.4)	489.9 (± 293.4)

Notes:

[27] - Note: Since only 1 participant was analyzed, standard deviation was unable to be calculated.

Statistical analyses

No statistical analyses for this end point

Secondary: Extension Period: Percentage Of Participants With Normalized Concentrations Of NCC

End point title	Extension Period: Percentage Of Participants With Normalized Concentrations Of NCC

End point description:

Normalized concentrations of NCC was defined as who achieving or maintaining normalized levels of NCC (0.8-2.3 µM) adjusted for Mo plasma concentration or reaching a reduction of at least 25% in NCC corrected for Mo if above the normal reference range at the time of enrollment. NCC was calculated by subtracting the amount of Cu bound to Cp from the total plasma Cu concentration. Post-baseline NCC values were adjusted (corrected) to account for Cu bound in tripartite complexes with ALXN1840 and albumin. Last Assessment is a summary of the last available post-baseline result for each participant. Analyses includes all data up to the last assessment in the extension period; up to Week 176.

End point type	Secondary

End point timeframe:

Up to last assessment (up to Week 176)

End point values	ALXN1840 24-Week Treatment Period			
Subject group type	Reporting group			
Number of subjects analysed	28			
Units: Percentage of participants				
number (confidence interval 95%)	92.9 (81.0 to 99.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Extension Period: Change From Baseline In NCC Levels Adjusted For Mo Plasma Concentration

End point title	Extension Period: Change From Baseline In NCC Levels Adjusted For Mo Plasma Concentration

End point description:

The change from Baseline in NCC adjusted for Mo plasma concentration over 176 weeks were analyzed.

Last Assessment is a summary of the last available post-baseline result for each participant. Analyses includes all data up to the last assessment in the extension period, up to Week 176. Change from baseline = (Baseline NCC concentrations) - (last assessment [up to Week 176] NCC concentrations adjusted for Mo plasma concentration). Least square means and their 95% CIs were calculated using an REML-based MMRM with fixed effects for Baseline, cohort, visit, Baseline-by-visit, and cohort-by-visit interaction.

End point type	Secondary

End point timeframe:

Baseline, last assessment (up to Week 176)

End point values	ALXN1840 24-Week Treatment Period			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: µmol/L				
least squares mean (confidence interval 95%)	-2.92 (-3.45 to -2.39)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Day 1 after dosing up to last assessment (up to Week 176), mean duration of treatment of 693.1 days	
Adverse event reporting additional description:	
Participants who were enrolled and received at least 1 dose of study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups	
Reporting group title	ALXN1840

Reporting group description:

Treatment Period: ALXN1840 at individualized doses ranging from 15 to 60 milligrams (mg) per day. Dose increases or dose reductions were dependent on the individual non-ceruloplasmin-bound copper (NCC) concentrations adjusted for Mo plasma concentration. ALXN1840 may have been administered every other day, once daily, or twice daily, depending on individualized dosing regimen, for 24 weeks. Extension Period: Participants continued the same ALXN1840 daily dose maintained at Week 24 of the Treatment Period and the same dosing regimen. During the Extension Period, no up-titration was made unless NCC concentrations adjusted for Mo plasma concentration did not remain stable within (or below) the reference range.

Serious adverse events	ALXN1840		
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 28 (39.29%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic enzyme increased			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Hepato-lenticular degeneration			

subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Neurological decompensation			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Agranulocytosis			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Gait disturbance			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	1 / 28 (3.57%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Abnormal behaviour			

subjects affected / exposed	1 / 28 (3.57%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Adjustment disorder				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Affective disorder				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mania				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Personality disorder				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychotic disorder				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Back pain				
subjects affected / exposed	1 / 28 (3.57%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	ALXN1840		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 28 (92.86%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	10 / 28 (35.71%)		
occurrences (all)	15		
Aspartate aminotransferase increased			
subjects affected / exposed	9 / 28 (32.14%)		
occurrences (all)	11		
Gamma-glutamyltransferase increased			
subjects affected / exposed	8 / 28 (28.57%)		
occurrences (all)	9		
Hepatic enzyme increased			
subjects affected / exposed	6 / 28 (21.43%)		
occurrences (all)	18		
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Liver function test increased			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 28 (21.43%)		
occurrences (all)	11		
Tremor			

subjects affected / exposed occurrences (all) Dysgeusia subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all)	5 / 28 (17.86%) 6 2 / 28 (7.14%) 2 2 / 28 (7.14%) 2		
Blood and lymphatic system disorders Leukopenia subjects affected / exposed occurrences (all)	 3 / 28 (10.71%) 12		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	 6 / 28 (21.43%) 6		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 4 / 28 (14.29%) 4 3 / 28 (10.71%) 3 2 / 28 (7.14%) 6 2 / 28 (7.14%) 2		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	 3 / 28 (10.71%) 4		
Skin and subcutaneous tissue disorders Rash			

subjects affected / exposed	4 / 28 (14.29%)		
occurrences (all)	4		
Dry skin			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Erythema			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	4		
Depression			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Insomnia			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	4		
Sleep disorder			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Depressed mood			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	4 / 28 (14.29%)		
occurrences (all)	5		
Arthralgia			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Dupuytren's contracture			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Muscle spasms			

subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	3		
Myalgia			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Neck pain			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Plantar fasciitis			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	8 / 28 (28.57%)		
occurrences (all)	8		
Sinusitis			
subjects affected / exposed	3 / 28 (10.71%)		
occurrences (all)	3		
Influenza			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	4		
Tonsillitis			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		
Upper respiratory tract infection			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	3		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 28 (7.14%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 December 2014	• The 8-item Medication Adherence Questionnaire was replaced with the MMAS-8. • Number of planned study sites was increased. • Clarified that over the counter medication also had to be recorded as concomitant medication on the CRF. • Clarified that UWDRS (Parts I, II, and III), M.I.N.I. Tracking, CGI scale item 1, and EQ-5D had to be filled in within 24 hours prior to the first dose of study drug on Day 1. • Copper endpoints for serial assessment were changed from NCC, Mo, and exchangeable Cu to Cp, total and exchangeable Cu, and Mo. • Window periods for PK sampling were further specified. • Planned volume of blood to be collected by Week 24 was markedly decreased. • Creatinine phosphokinase was added to the laboratory measures. • Lactate dehydrogenase measurement, hematology parameters, coagulation parameters, pregnancy testing, follicle stimulating hormone, urinalysis, and analyses for Cp, total and exchangeable Cu, and total Mo were added to Screening. • A urine pregnancy test was added to Day 1 (prior to dosing). • Investigators' obligations in relation to AE intensity assessment were further specified. • In relation to the informed consent form process, clarified that under certain circumstances, the signature of an impartial witness could be accepted. • Time windows for scheduled visits were defined.
27 February 2015	• Dosing of ALXN1840 during the Initiation Period was changed to 30 mg once daily (QD) from Day 1 for the first 6 weeks with the option to up-titrate to 30 mg twice daily (BID) upon review of the Day 43 NCC concentrations adjusted for Mo plasma concentration. • Dosing of ALXN1840 upon entry into the Maintenance Period was changed to 30 mg QD. • Dosing of ALXN1840 during the Maintenance Period in case NCC concentrations adjusted for Mo plasma concentration did not remain stable within the reference range was changed from re-initiation of BID daily dosing with the current dose (eg, 120 mg QD was increased to 120 mg BID) with potential, subsequent increases by 30 mg BID up to a maximum dose of 150 mg BID to up-titration to a maximum dose of 30 mg BID. • Off-site Visits were added in Weeks 7, 9, and 11. • Number of drug kits dispensed was reduced at some time points. • 24-hour urinary Mo was added as an evaluation criterion. • Planned volume of blood to be collected by Week 28 was increased by approximately 100 mL. • Time frame for reporting and follow-up of serious adverse events that were suspected to be drug-related was increased from the participant's study termination to up to 30 days after the participant's study termination.

22 May 2015	• A 12-month Extension Period was added to the study. • Primary objective was changed to "to evaluate the efficacy of ALXN1840 administered for 24 weeks on NCC concentrations adjusted for Mo plasma concentration in newly diagnosed WD patients aged 18 and older with NCC concentrations above the reference range at the time of enrollment". •Secondary objective/efficacy endpoint was added: Evaluate the durability, and establish long-term safety and efficacy of ALXN1840 in a 12-month Extension Period. • Long term safety and tolerability of ALXN1840 obtained in the Extension Period was added as a safety endpoint. • Minimum starting dose of ALXN1840 was changed from 30 mg QD to 15 mg QD. • Formulation of study drug was changed from uncoated capsules containing 30 mg of bis-choline tetrathiomolybdate to enteric coated tablets containing 15 mg of bis-choline tetrathiomolybdate. • Mode of administration of study drug was changed from fed state to fasted state. • Number of drug kits dispensed was increased at some time points. • Clarified that, during the Extension Period, no up-titration was to be made unless NCC concentrations adjusted for Mo plasma concentration did not remain stable within (or below) the reference range. If the NCC concentration was above the reference range, up-titration of study drug might have been performed (ie, from 30 mg QD to 30 mg BID, or from 15 mg QD to 30 mg QD). • Stopping rules/dose modification criteria were modified. • Blood samples for the measurement of plasma concentrations of total and free Cu were added to the study. • Definition of the Maintenance Period was changed • Clarified that Off-site Visits could either be conducted by a visiting nurse or at the primary institution. • Safety monitoring guidelines were revised.
11 September 2015	• Primary objective was changed to "to evaluate the efficacy of ALXN1840 for 24 weeks on NCC adjusted for Mo plasma concentration in newly diagnosed WD patients aged 18 and older with NCC concentrations within or above the reference range at the time of enrollment in the study". • Primary endpoint was changed to "the proportion of successful patients who achieve or maintain normalized concentrations of NCC (0.8 - 2.3 µM) adjusted for Mo plasma concentration or reach a reduction of at least 25% in NCC corrected for Mo if above the reference range at the time of enrollment". • Primary efficacy variable was changed to "change from Baseline in NCC adjusted for Mo plasma concentration over 24 weeks". • Clarified that, as the objective of the trial was going to be analyzed using primarily descriptive statistics, no formal power calculations had been done. • Clarified that, for participants with normal Cu concentration at Baseline, maintenance within the reference range was considered a success. • Inclusion Criterion 5 was changed to "NCC concentrations within or above the reference range (0.8 – 2.3 µM)". • Exclusion Criterion 1 was changed to "Treatment for greater than 24 months for WD with chelation therapy … or Zn therapy". • Starting dose of ALXN1840 in the Initiation Period was clarified. • Clarified that doses of ALXN1840 15 mg QD could be reduced to 15 mg QOD throughout the study. • Participants no longer had to be symptomatic with neurological, hepatic, or combined neurological and hepatic presentation to be eligible for enrollment. • Clarified that participants could enter the study into the Maintenance Period (ie, without participating in the Initiation Period), if their Screening NCC concentrations were within the reference range. • Reference range for NCC concentrations adjusted for Mo plasma concentration was specified to be 0.8 – 2.3 µM.

18 March 2016	• Extension Period was extended from 12 months to 36 months and clarified, for each participant, that the main study would end approximately 28 weeks after initiation of treatment on study Day 1. • Dosing scheme for ALXN1840 was changed from QD dosing in the morning and BID dosing (in the morning and in the evening) to QD dosing (in the morning) during the Initiation Period, because previous work in oncology with bis-choline tetrathiomolybdate had shown that both BID and QD dosing were effective in de-coppering and maintaining a de-coppered status and QD dosing was considered easier for the participants. • Clarified that, after review of NCC concentrations in Week 6, ALXN1840 might have been up-titrated as soon as in Week 8. • Clarified that participants remained in the Initiation Period until they met the criteria for the Maintenance Period (meaning that the length of the Initiation Period was individualized). • Exclusion Criterion 9 was corrected from "Severe anemia with a hemoglobin < 9 mg/dL" to "Severe anemia with a hemoglobin < 9 g/dL". • Clarified that, at each Clinic Visit, participants did not only have to return unused medication, but also empty kits so that compliance could be calculated. • A urine sample for measurement of urinary creatinine was added to Screening, Day 1, all Clinic Visits (prior to dosing), and the End of Study Visit. • Laboratory tests for all periods of the study were further specified. • It was further specified what did not constitute an AE.
27 October 2017	• A description of the calculation of NCC concentrations adjusted for Mo plasma concentration was added based on a proposal by the American Association for the study of Liver Diseases and European WD practice guidelines.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to low chromatographic resolution of data, quantitative analysis for speciation profiling, as had been planned in the protocol, was not feasible.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28988934