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

Summary

EudraCT number	2017-004135-36
Trial protocol	GB DE CZ FR AT ES HU PL PT SE BE DK NL
Global end of trial date	30 June 2023

Results information

Result version number	v1
This version publication date	18 October 2023
First version publication date	18 October 2023

Trial information

Trial identification

Sponsor protocol code	WTX101-301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03403205
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Alexion Pharmaceuticals Inc.
Sponsor organisation address	100 College Street, New Haven, CT, United States, 06510
Public contact	Alexion Europe SAS European Clinical Trial Information, Alexion Pharmaceuticals Inc., +33 787148158, clinicaltrials.eu@alexion.com
Scientific contact	Alexion Europe SAS European Clinical Trial Information, Alexion Pharmaceuticals, Inc., +33 787148158, clinicaltrials.eu@alexion.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-002232-PIP02-19
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 February 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 February 2021
Global end of trial reached?	Yes
Global end of trial date	30 June 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to evaluate the efficacy of ALXN1840 administered for 48 weeks, compared to standard of care (SoC), on copper control in participants with Wilson Disease aged 12 years and older.

Protection of trial subjects:

This study was conducted in accordance with the protocol and with the following:
• Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
• Applicable International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines
• Applicable laws and regulations

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 February 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	60 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 54
Country: Number of subjects enrolled	Poland: 25
Country: Number of subjects enrolled	Russian Federation: 23
Country: Number of subjects enrolled	Germany: 23
Country: Number of subjects enrolled	Austria: 16
Country: Number of subjects enrolled	Hungary: 8
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	Turkey: 5
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Czechia: 2
Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	Serbia: 1
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Japan: 13

Country: Number of subjects enrolled	Korea, Republic of: 5
Country: Number of subjects enrolled	China: 4
Country: Number of subjects enrolled	New Zealand: 3
Country: Number of subjects enrolled	Taiwan: 3
Country: Number of subjects enrolled	Canada: 2
Country: Number of subjects enrolled	Singapore: 2
Country: Number of subjects enrolled	Australia: 2
Worldwide total number of subjects	207
EEA total number of subjects	85

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)	18
Adults (18-64 years)	185
From 65 to 84 years	4
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study consists of 2 periods: Primary Evaluation Period (PEP) and Extension Period. Participants who completed the 48-week PEP were offered the opportunity to continue treatment in an up to 60-month Extension. A total of 214 participants were randomized; 207 participants were treated.

Pre-assignment

Screening details:

Participants were randomized, stratified by cohort, in 2:1 ratio to ALXN1840 or continued treatment with Standard of Care (SoC) in Cohort 1 or as continued or initial therapy in Cohort 2. Results through the end of 48-week Primary Evaluation Period has been reported. Results from the Extension Period will be reported after the completion of study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor[1]

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1: ALXN1840

Arm description:

Participants in Cohort 1 (who received SoC therapy, that is, chelation therapy with penicillamine or trientine, zinc therapy, or a combination of both chelation and zinc therapy for >28 days) received titrated doses of ALXN1840 orally for up to 48 weeks.

Arm type	Experimental
Investigational medicinal product name	ALXN1840
Investigational medicinal product code	WTX101
Other name	Tiomolibdic acid Tiomolibdate choline Bis-choline tetrathiomolybdate
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

ALXN1840 was administered per schedule specified in the arm description.

Arm title	Cohort 1: SoC Therapy

Arm description:

Participants in Cohort 1 (who received SoC therapy, that is, chelation therapy with penicillamine or trientine, zinc therapy, or a combination of both chelation and zinc therapy for >28 days) continued to receive SoC therapy for up to 48 weeks according to the local package label.

Arm type	Active comparator
Investigational medicinal product name	SoC Medication
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Soc medication was administered per schedule specified in the arm description.

Arm title	Cohort 2: ALXN1840

Arm description:	
Participants in Cohort 2 (who were treatment naïve or who received SoC therapy for ≤28 days) received titrated doses of ALXN1840 orally for up to 48 weeks.	
Arm type	Experimental
Investigational medicinal product name	ALXN1840
Investigational medicinal product code	WTX101
Other name	Tiomolibdic acid Tiomolibdate choline Bis-choline tetrathiomolybdate
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
ALXN1840 was administered per schedule specified in the arm description.	
Arm title	Cohort 2: SoC Therapy
Arm description:	
Participants in Cohort 2 (who were treatment naïve or who received SoC therapy for ≤28 days) received SoC therapy for up to 48 weeks according to the local package label.	
Arm type	Active comparator
Investigational medicinal product name	SoC Medication
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Soc medication was administered per schedule specified in the arm description.	

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: Assessor was the only role blinded for this study.

Number of subjects in period 1	Cohort 1: ALXN1840	Cohort 1: SoC Therapy	Cohort 2: ALXN1840
Started	104	56	33
Completed PEP, Enter Extension	89 [2]	49 [3]	28 [4]
Completed PEP, not into Extension	4 [5]	3 [6]	1 [7]
Completed	93	52	29
Not completed	11	4	4
Adverse event, serious fatal	1	-	1
Consent withdrawn by subject	4	2	2
Adverse event, non-fatal	4	-	1
Protocol Deviation	-	1	-
Pregnancy	1	-	-
Lost to follow-up	1	1	-

Number of subjects in period 1	Cohort 2: SoC Therapy
Started	14
Completed PEP, Enter Extension	12 [8]
Completed PEP, not into Extension	1 [9]
Completed	13
Not completed	1

Adverse event, serious fatal	-
Consent withdrawn by subject	1
Adverse event, non-fatal	-
Protocol Deviation	-
Pregnancy	-
Lost to follow-up	-

Notes:

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: These are number of participants who completed PEP but not entered in extension.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: These are number of participants who completed PEP but not entered in extension.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: These are number of participants who completed PEP but not entered in extension.

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: These are number of participants who completed PEP and entered in extension.

[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: These are number of participants who completed PEP and entered in extension.

[7] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: These are number of participants who completed PEP and entered in extension.

[8] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: These are number of participants who completed PEP but not entered in extension.

[9] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: These are number of participants who completed PEP and entered in extension.

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1: ALXN1840
Reporting group description:	
Participants in Cohort 1 (who received SoC therapy, that is, chelation therapy with penicillamine or trientine, zinc therapy, or a combination of both chelation and zinc therapy for >28 days) received titrated doses of ALXN1840 orally for up to 48 weeks.	
Reporting group title	Cohort 1: SoC Therapy
Reporting group description:	
Participants in Cohort 1 (who received SoC therapy, that is, chelation therapy with penicillamine or trientine, zinc therapy, or a combination of both chelation and zinc therapy for >28 days) continued to receive SoC therapy for up to 48 weeks according to the local package label.	
Reporting group title	Cohort 2: ALXN1840
Reporting group description:	
Participants in Cohort 2 (who were treatment naïve or who received SoC therapy for ≤28 days) received titrated doses of ALXN1840 orally for up to 48 weeks.	
Reporting group title	Cohort 2: SoC Therapy
Reporting group description:	
Participants in Cohort 2 (who were treatment naïve or who received SoC therapy for ≤28 days) received SoC therapy for up to 48 weeks according to the local package label.	

Reporting group values	Cohort 1: ALXN1840	Cohort 1: SoC Therapy	Cohort 2: ALXN1840
Number of subjects	104	56	33
Age Categorical Units: participants			
≥12 years - <18 years	10	4	2
≥18 years - <65 years	92	50	31
≥65 years	2	2	0
Sex: Female, Male Units: participants			
Female	46	30	9
Male	58	26	24
Race/Ethnicity, Customized Units: Subjects			
Asian	19	13	5
Black or African American	1	2	0
White	80	41	27
Other	3	0	0
Unknown	0	0	1
Not Reported	1	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	2	2	0
Not Hispanic or Latino	101	54	32
Unknown or Not Reported	1	0	1

Reporting group values	Cohort 2: SoC Therapy	Total	
Number of subjects	14	207	

Age Categorical Units: participants			
≥12 years - <18 years	2	18	
≥18 years - <65 years	12	185	
≥65 years	0	4	
Sex: Female, Male Units: participants			
Female	3	88	
Male	11	119	
Race/Ethnicity, Customized Units: Subjects			
Asian	0	37	
Black or African American	0	3	
White	12	160	
Other	2	5	
Unknown	0	1	
Not Reported	0	1	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	2	6	
Not Hispanic or Latino	11	198	
Unknown or Not Reported	1	3	

End points

End points reporting groups

Reporting group title	Cohort 1: ALXN1840
Reporting group description:	
Participants in Cohort 1 (who received SoC therapy, that is, chelation therapy with penicillamine or trientine, zinc therapy, or a combination of both chelation and zinc therapy for >28 days) received titrated doses of ALXN1840 orally for up to 48 weeks.	
Reporting group title	Cohort 1: SoC Therapy
Reporting group description:	
Participants in Cohort 1 (who received SoC therapy, that is, chelation therapy with penicillamine or trientine, zinc therapy, or a combination of both chelation and zinc therapy for >28 days) continued to receive SoC therapy for up to 48 weeks according to the local package label.	
Reporting group title	Cohort 2: ALXN1840
Reporting group description:	
Participants in Cohort 2 (who were treatment naïve or who received SoC therapy for ≤28 days) received titrated doses of ALXN1840 orally for up to 48 weeks.	
Reporting group title	Cohort 2: SoC Therapy
Reporting group description:	
Participants in Cohort 2 (who were treatment naïve or who received SoC therapy for ≤28 days) received SoC therapy for up to 48 weeks according to the local package label.	

Primary: Daily Mean Area Under The Effect-time Curve (AUEC) of Directly Measured Non-ceruloplasmin-bound Copper (dNCC) from 0 to 48 Weeks (dNCC AUEC0-48W)

End point title	Daily Mean Area Under The Effect-time Curve (AUEC) of Directly Measured Non-ceruloplasmin-bound Copper (dNCC) from 0 to 48 Weeks (dNCC AUEC0-48W)
End point description:	
dNCC is the directly quantified copper not bound to ceruloplasmin, obtained by inductively coupled plasma mass spectrometry after immunocapture and removal of ceruloplasmin. Baseline was defined as last non-missing value on or before first study drug administration. Least square (LS) mean and standard error (SE) was calculated using analysis of covariance (ANCOVA). Full analysis set included all randomized participants who received at least 1 dose of randomized treatment.	
End point type	Primary
End point timeframe:	
Baseline to Week 48	

End point values	Cohort 1: ALXN1840	Cohort 1: SoC Therapy	Cohort 2: ALXN1840	Cohort 2: SoC Therapy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	104	56	33	14
Units: micromoles (µmol)*hours (hr)/liter (L)				
least squares mean (standard error)	2.50 (± 0.150)	0.87 (± 0.204)	4.76 (± 0.319)	0.96 (± 0.487)

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis was performed using ANCOVA model, which included treatment, cohort, and baseline value. Missing imputation was performed: 1) for intermediate missing, interpolation was used to fill out missing values. 2) For participants who die, baseline dNCC was carried forward from discontinuation to week 48. 3) For others, multiple imputation was used to impute missing dNCC assuming data were missing not at random.

Comparison groups	Cohort 1: ALXN1840 v Cohort 1: SoC Therapy
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 [1]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	1.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.14
upper limit	2.13
Variability estimate	Standard error of the mean
Dispersion value	0.254

Notes:

[1] - Test was performed at a significance level of 0.05.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Analysis was performed using ANCOVA model, which included treatment, cohort, and baseline value. Missing imputation was performed: 1) for intermediate missing, interpolation was used to fill out missing values. 2) For participants who die, baseline dNCC was carried forward from discontinuation to week 48. 3) For others, multiple imputation was used to impute missing dNCC assuming data were missing not at random.

Comparison groups	Cohort 2: ALXN1840 v Cohort 2: SoC Therapy
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 [2]
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	3.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.65
upper limit	4.94
Variability estimate	Standard error of the mean
Dispersion value	0.584

Notes:

[2] - Test was performed at a significance level of 0.05.

Secondary: Number of Participants With Treatment-emergent Adverse Events (TEAEs)

End point title	Number of Participants With Treatment-emergent Adverse Events (TEAEs)

End point description:

An AE was any untoward medical occurrence in a participant administered the study drug and which did not necessarily have a causal relationship with this treatment. TEAEs were 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. A summary of all Serious Adverse Events and Other Adverse Events (nonserious) regardless of causality is located in the 'Reported Adverse Events' Section. Safety analysis set included all participants who received at least 1 dose of randomized treatment.

End point type	Secondary

End point timeframe:

Baseline up to Week 48

End point values	Cohort 1: ALXN1840	Cohort 1: SoC Therapy	Cohort 2: ALXN1840	Cohort 2: SoC Therapy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	104	56	33	14
Units: participants	89	41	30	12

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in the Unified Wilson Disease Rating Scale (UWDRS) Part II Total Score at Week 48

End point title	Change From Baseline in the Unified Wilson Disease Rating Scale (UWDRS) Part II Total Score at Week 48

End point description:

The UWDRS comprises 3 parts: UWDRS Part I (level of consciousness, item 1), UWDRS Part II (a patient-reported review of daily activity items [disability], items 2 to 11 [10 items in total]), and UWDRS Part III (a detailed neurological examination, items 12 to 34 [23 items in total]). The UWDRS Part II total score was calculated as the sum of Question 2 to Question 11 (each question has range 0 [none] to 4 [severe]). The UWDRS Part II total score ranges from 0 (no disability) to 40 (severe disability), with lower score indicating improvement in condition and a better outcome. Change from baseline was calculated as: postbaseline assessment value – baseline assessment value when both values were not missing. Full analysis set included all randomized participants who received at least 1 dose of randomized treatment. Here, 'Overall number of participants analyzed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	Cohort 1: ALXN1840	Cohort 1: SoC Therapy	Cohort 2: ALXN1840	Cohort 2: SoC Therapy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	92	50	29	12
Units: units on a scale				
arithmetic mean (standard deviation)	-0.7 (± 2.75)	0.0 (± 2.31)	-0.5 (± 3.23)	-1.8 (± 4.63)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in UWDRS Part III Total Score at Week 48

End point title	Change From Baseline in UWDRS Part III Total Score at Week 48

End point description:

The UWDRS comprises 3 parts: UWDRS Part I (level of consciousness, item 1), UWDRS Part II (a patient-reported review of daily activity items [disability], items 2 to 11 [10 items in total]), and UWDRS Part III (a detailed neurological examination, items 12 to 34 [23 items in total]). The UWDRS Part I and III was assessed by a neurologist who was blinded to the treatment randomization. The UWDRS Part III total score was calculated as the sum of Question 12 to Question 34. The UWDRS Part III total score ranges from 0 (normal) to 175 (severe disease), with lower score indicating improvement in condition and a better outcome. Change from baseline was calculated as: postbaseline assessment value – baseline assessment value when both values were not missing. Full analysis set included all randomized participants who received at least 1 dose of randomized treatment. Here, 'Overall number of participants analyzed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	Cohort 1: ALXN1840	Cohort 1: SoC Therapy	Cohort 2: ALXN1840	Cohort 2: SoC Therapy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	91	49	28	11
Units: units on a scale				
arithmetic mean (standard deviation)	-2.24 (± 7.458)	-1.59 (± 6.188)	-2.06 (± 9.843)	1.55 (± 5.889)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in UWDRS Part III Functional Subscale Score at Week 48

End point title	Change From Baseline in UWDRS Part III Functional Subscale Score at Week 48

End point description:

UWDRS Part III Functional Subscale consists of speech, handwriting, arising from chair, and gait from UWDRS Part III. The standardized score of the first 3 items ranges from 0 (normal) to 10 (worst), and standardized transformed score of gait ranges from 0 (normal) to 10 (worst). The average of these scores was used to create the Part III Functional Subscale with a range of 0 (normal) - 10 (worst) with higher scores indicating more functional disability. Full analysis set included all randomized participants who received at least 1 dose of randomized treatment. Here, 'Overall number of participants analyzed' =

participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	Cohort 1: ALXN1840	Cohort 1: SoC Therapy	Cohort 2: ALXN1840	Cohort 2: SoC Therapy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	91	49	28	11
Units: units on a scale				
arithmetic mean (standard deviation)	-0.165 (± 0.7620)	-0.102 (± 0.5467)	-0.090 (± 0.8464)	0.227 (± 0.4214)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in UWDRS Part III Individual Items/Subscales (Speech, Handwriting, Arising From a Chair, and Gait) Score at Week 48

End point title	Change From Baseline in UWDRS Part III Individual Items/Subscales (Speech, Handwriting, Arising From a Chair, and Gait) Score at Week 48

End point description:

UWDRS Part III individual items speech, handwriting, arising from chair, and gait are reported here. For speech (Question 12), original score ranges from 0 (normal) to 4 (unintelligible). For handwriting (Question 20), original score ranges from 0 (normal) to 4 (cannot hold a pen). For arising from chair (Question 27), original score ranges from 0 (normal) to 4 (unable to arise without help). For gait (Question 29), the original score (range: 0 [normal] to 10 [severe condition]) was calculated by summing subscores (0 [normal] to 4 [severe]) of Part A (Right and Left Leg dystonia), B (Ataxia), and C (Parkinsonism). Full analysis set included all randomized participants who received at least 1 dose of randomized treatment. Here, 'Overall number of participants analyzed' = participants evaluable for this endpoint. 'n' = participants evaluable for specified category.

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	Cohort 1: ALXN1840	Cohort 1: SoC Therapy	Cohort 2: ALXN1840	Cohort 2: SoC Therapy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	91	49	28	11
Units: units on a scale				
arithmetic mean (standard deviation)				
Speech (n=91,49,28,11)	-0.1 (± 0.50)	0.0 (± 0.35)	-0.1 (± 0.52)	0.1 (± 0.54)
Handwriting (n=91,48,28,11)	-0.2 (± 0.63)	-0.1 (± 0.48)	0.1 (± 0.60)	0.2 (± 0.40)
Arising from a chair (n=91,49,28,11)	0.0 (± 0.45)	-0.1 (± 0.56)	0.0 (± 0.27)	0.0 (± 0.00)
Gait (n=91,49,28,11)	-0.03 (± 1.317)	0.00 (± 1.141)	-0.18 (± 0.945)	0.23 (± 0.754)

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression-Improvement Scale (CGI-I) Score at Week 48

End point title	Clinical Global Impression-Improvement Scale (CGI-I) Score at Week 48

End point description:

The CGI-I is a 7-point scale where the clinician assessed how much 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. Full analysis set included all randomized participants who received at least 1 dose of randomized treatment. Here, 'Overall number of participants analyzed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Week 48

End point values	Cohort 1: ALXN1840	Cohort 1: SoC Therapy	Cohort 2: ALXN1840	Cohort 2: SoC Therapy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	92	50	27	12
Units: units on a scale				
arithmetic mean (standard deviation)	3.4 (± 0.89)	3.8 (± 0.80)	3.1 (± 1.06)	3.2 (± 1.34)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Clinical Global Impression Severity Scale (CGI-S) Score at Week 48

End point title	Change From Baseline in Clinical Global Impression Severity Scale (CGI-S) Score at Week 48

End point description:

The CGI-S is a 7-point scale where the investigator rated severity of 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 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. Full analysis set included all randomized participants who received at least 1 dose of randomized treatment. Here, 'Overall number of participants analyzed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	Cohort 1: ALXN1840	Cohort 1: SoC Therapy	Cohort 2: ALXN1840	Cohort 2: SoC Therapy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	89	47	27	11
Units: units on a scale				
arithmetic mean (standard deviation)	-0.4 (± 0.79)	-0.1 (± 0.73)	-0.6 (± 1.11)	-0.5 (± 1.21)

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Model for End-Stage Liver Disease (MELD) Score at Week 48

End point title	Change From Baseline in Model for End-Stage Liver Disease (MELD) Score at Week 48

End point description:

The MELD score uses the participant’s values for bilirubin, creatinine, and the international normalized ratio (INR). The initial MELD score (MELD[i]) is calculated according to the following formula:
MELD(i) = 3.78*ln[serum bilirubin (mg/dL)] + 11.2*ln[INR] + 9.57*ln[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 MELD score ranges from 6 (least sick) - 40 (most sick), with higher values indicating more advanced disease. Full analysis set included all randomized participants who received at least 1 dose of randomized treatment. Here, 'Overall number of participants analyzed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	Cohort 1: ALXN1840	Cohort 1: SoC Therapy	Cohort 2: ALXN1840	Cohort 2: SoC Therapy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	86	49	28	11
Units: units on a scale				
arithmetic mean (standard deviation)	-0.1 (± 1.85)	0.1 (± 1.32)	-0.7 (± 1.61)	0.2 (± 1.25)

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute Change From Baseline in Calculated Non-Ceruloplasmin Bound Copper (cNCC) or Calculated Non-Ceruloplasmin Bound Copper Corrected

(cNCCcorrected) in Plasma at Week 48

End point title	Absolute Change From Baseline in Calculated Non-Ceruloplasmin Bound Copper (cNCC) or Calculated Non-Ceruloplasmin Bound Copper Corrected (cNCCcorrected) in Plasma at Week 48

End point description:

cNCC = Plasma Total Copper (Cu) [micrograms (µg)/L]−(3.15*ceruloplasmin [milligrams (mg)/L])/63.5 [µg/µmol]
For ALXN1840-treated participants, cNCC in plasma corrected for amount of Cu bound to ALXN1840 tripartite complex (TPC)
cNCCcorrected = (√cNCC− 0.993)2√Mo, (Mo= molybdenum).
In calculation of cNCC and cNCCcorrected following rules apply:
- For plasma total Cu concentration <lower limit of quantification (LLOQ), cNCC was considered missing (LLOQ = 20 nanograms [ng]/mL);
- Serum ceruloplasmin concentration values <LLOQ are set to 0 (LLOQ = 22.5 mg/L);
- Plasma total Mo concentration values <LLOQ are set to 0 (LLOQ = 1 ng/L);
- If cNCC calculation produces a negative result, cNCC was considered missing and cNCCcorrected was not derived;
- cNCCcorrected was set to 0 when 0.993√Mo > √cNCC.

Full analysis set: all randomized participants who received at least 1 dose of study drug. 'Overall number of participants analyzed'= participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	Cohort 1: ALXN1840	Cohort 1: SoC Therapy	Cohort 2: ALXN1840	Cohort 2: SoC Therapy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	63	29	26	10
Units: µmol/L				
arithmetic mean (standard deviation)	-0.72 (± 1.107)	0.64 (± 2.769)	-1.95 (± 1.536)	-1.51 (± 2.361)

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in cNCC or cNCCcorrected in Plasma at Week 48

End point title	Percent Change From Baseline in cNCC or cNCCcorrected in Plasma at Week 48

End point description:

cNCC [µmol/L] = Plasma Total Cu [µg/L]−(3.15*ceruloplasmin [mg/L])/63.5 [µg/µmol]
For ALXN1840-treated participants, cNCC in plasma was corrected for amount of Cu bound to the ALXN1840 TPC using square root-based cNCC correction method:
cNCCcorrected = (√cNCC− 0.993)2√Mo, where Mo = molybdenum.
In calculation of cNCC and cNCCcorrected following rules apply:
- For plasma total Cu concentration values <LLOQ, cNCC was considered missing (LLOQ = 20 ng/mL);
- Serum ceruloplasmin concentration values <LLOQ are set to 0 (LLOQ = 22.5 mg/L);
- Plasma total Mo concentration values <LLOQ are set to 0 (LLOQ = 1 ng/L);
- In cases where cNCC calculation produces a negative result, cNCC was considered missing and cNCCcorrected was not derived;
- cNCCcorrected was set to 0 when 0.993√Mo > √cNCC.

Full analysis set included all randomized participants who received at least 1 dose of randomized

treatment. Here, 'Overall number of participants analyzed' = participants evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 48

End point values	Cohort 1: ALXN1840	Cohort 1: SoC Therapy	Cohort 2: ALXN1840	Cohort 2: SoC Therapy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	60	28	26	10
Units: percent change				
arithmetic mean (standard deviation)	-7.7 (± 263.20)	104.6 (± 292.11)	-64.0 (± 42.88)	-44.3 (± 68.82)

Statistical analyses

No statistical analyses for this end point

Secondary: cNCC/cNCCcorrected Responder at Week 48

End point title	cNCC/cNCCcorrected Responder at Week 48

End point description:

cNCC/cNCCcorrected responder was defined as participants who achieved or maintained normalized cNCC/cNCCcorrected concentration (0.8-2.3 µmol) within (at or before) 48 weeks or reached a reduction of at least 25% in cNCC/cNCCcorrected within 48 weeks. Thus, a participant was considered a cNCC/cNCCcorrected responder if they met at least 1 of the following criteria:
- Achieved normalized cNCC/cNCCcorrected concentration for 2 consecutive measurements within 48 weeks, for participants who had elevated cNCC concentrations at baseline;
- Maintained normalized cNCC/cNCCcorrected concentration within 48 weeks, for participants who had normal cNCC concentrations at baseline;
- Reached a reduction of at least 25% in cNCC/cNCCcorrected for 2 consecutive measurements within 48 weeks.

Full analysis set included all randomized participants who received at least 1 dose of randomized treatment.

End point type	Secondary

End point timeframe:

Week 48

End point values	Cohort 1: ALXN1840	Cohort 1: SoC Therapy	Cohort 2: ALXN1840	Cohort 2: SoC Therapy
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	104	56	33	14
Units: participants	101	39	33	13

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline up to Week 48	
Adverse event reporting additional description:	
Safety analysis set included all participants who received at least 1 dose of randomized treatment.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups	
Reporting group title	Cohort 1: ALXN1840
Reporting group description:	
Participants in Cohort 1 (who received SoC therapy, that is, chelation therapy with penicillamine or trientine, zinc therapy, or a combination of both chelation and zinc therapy for >28 days) received titrated doses of ALXN1840 orally for up to 48 weeks.	
Reporting group title	Cohort 2: SoC Therapy
Reporting group description:	
Participants in Cohort 2 (who were treatment naïve or who received SoC therapy for ≤28 days) received SoC therapy for up to 48 weeks according to the local package label.	
Reporting group title	Cohort 2: ALXN1840
Reporting group description:	
Participants in Cohort 2 (who were treatment naïve or who received SoC therapy for ≤28 days) received titrated doses of ALXN1840 orally for up to 48 weeks.	
Reporting group title	Cohort 1: SoC Therapy
Reporting group description:	
Participants in Cohort 1 (who received SoC therapy, that is, chelation therapy with penicillamine or trientine, zinc therapy, or a combination of both chelation and zinc therapy for >28 days) continued to receive SoC therapy for up to 48 weeks according to the local package label.	

Serious adverse events	Cohort 1: ALXN1840	Cohort 2: SoC Therapy	Cohort 2: ALXN1840
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 104 (13.46%)	0 / 14 (0.00%)	4 / 33 (12.12%)
number of deaths (all causes)	1	0	1
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Transitional cell carcinoma			
subjects affected / exposed	1 / 104 (0.96%)	0 / 14 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lipoma			

subjects affected / exposed	1 / 104 (0.96%)	0 / 14 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatocellular carcinoma			
subjects affected / exposed	1 / 104 (0.96%)	0 / 14 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Venous thrombosis limb			
subjects affected / exposed	0 / 104 (0.00%)	0 / 14 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumothorax spontaneous			
subjects affected / exposed	1 / 104 (0.96%)	0 / 14 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspiration			
subjects affected / exposed	0 / 104 (0.00%)	0 / 14 (0.00%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pleural effusion			
subjects affected / exposed	0 / 104 (0.00%)	0 / 14 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 104 (0.00%)	0 / 14 (0.00%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Persistent depressive disorder			
subjects affected / exposed	1 / 104 (0.96%)	0 / 14 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Paranoia			
subjects affected / exposed	1 / 104 (0.96%)	0 / 14 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device malfunction			
subjects affected / exposed	0 / 104 (0.00%)	0 / 14 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 104 (0.96%)	0 / 14 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Gastrostomy tube site complication			
subjects affected / exposed	0 / 104 (0.00%)	0 / 14 (0.00%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intentional overdose			
subjects affected / exposed	1 / 104 (0.96%)	0 / 14 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial bones fracture			
subjects affected / exposed	1 / 104 (0.96%)	0 / 14 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 104 (0.00%)	0 / 14 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Hepato-lenticular degeneration			

subjects affected / exposed	2 / 104 (1.92%)	0 / 14 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Balance disorder			
subjects affected / exposed	1 / 104 (0.96%)	0 / 14 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	2 / 104 (1.92%)	0 / 14 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dystonia			
subjects affected / exposed	0 / 104 (0.00%)	0 / 14 (0.00%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic encephalopathy			
subjects affected / exposed	1 / 104 (0.96%)	0 / 14 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Neurological decompensation			
subjects affected / exposed	0 / 104 (0.00%)	0 / 14 (0.00%)	1 / 33 (3.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 104 (0.00%)	0 / 14 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	1 / 104 (0.96%)	0 / 14 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			

subjects affected / exposed	1 / 104 (0.96%)	0 / 14 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 104 (0.00%)	0 / 14 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 104 (0.00%)	0 / 14 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varices oesophageal			
subjects affected / exposed	1 / 104 (0.96%)	0 / 14 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hypertransaminasaemia			
subjects affected / exposed	1 / 104 (0.96%)	0 / 14 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver disorder			
subjects affected / exposed	0 / 104 (0.00%)	0 / 14 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bursitis			
subjects affected / exposed	1 / 104 (0.96%)	0 / 14 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhabdomyolysis			
subjects affected / exposed	0 / 104 (0.00%)	0 / 14 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Muscle spasms			
subjects affected / exposed	0 / 104 (0.00%)	0 / 14 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 104 (0.00%)	0 / 14 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 104 (0.00%)	0 / 14 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 104 (0.96%)	0 / 14 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 104 (0.96%)	0 / 14 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epididymitis			
subjects affected / exposed	1 / 104 (0.96%)	0 / 14 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 104 (0.96%)	0 / 14 (0.00%)	0 / 33 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Cohort 1: SoC Therapy		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 56 (10.71%)		
number of deaths (all causes)	0		
number of deaths resulting from			

adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Transitional cell carcinoma			
subjects affected / exposed	0 / 56 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lipoma			
subjects affected / exposed	0 / 56 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatocellular carcinoma			
subjects affected / exposed	0 / 56 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Venous thrombosis limb			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pneumothorax spontaneous			
subjects affected / exposed	0 / 56 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Aspiration			
subjects affected / exposed	0 / 56 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Suicidal ideation			

subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Persistent depressive disorder				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Paranoia				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Product issues				
Device malfunction				
subjects affected / exposed	1 / 56 (1.79%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Blood creatine phosphokinase increased				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Gastrostomy tube site complication				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intentional overdose				
subjects affected / exposed	0 / 56 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Facial bones fracture				

subjects affected / exposed	0 / 56 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rib fracture			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Hepato-lenticular degeneration			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Balance disorder			
subjects affected / exposed	0 / 56 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	0 / 56 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dystonia			
subjects affected / exposed	0 / 56 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatic encephalopathy			
subjects affected / exposed	0 / 56 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Neurological decompensation			
subjects affected / exposed	0 / 56 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Epilepsy			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	0 / 56 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	0 / 56 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Varices oesophageal			
subjects affected / exposed	0 / 56 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hypertransaminasaemia			
subjects affected / exposed	0 / 56 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Liver disorder			

subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Bursitis			
subjects affected / exposed	0 / 56 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rhabdomyolysis			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Muscle spasms			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cystitis			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	0 / 56 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	0 / 56 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Epididymitis			
subjects affected / exposed	0 / 56 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cellulitis			
subjects affected / exposed	0 / 56 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Cohort 1: ALXN1840	Cohort 2: SoC Therapy	Cohort 2: ALXN1840
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 104 (44.23%)	7 / 14 (50.00%)	16 / 33 (48.48%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	19 / 104 (18.27%)	1 / 14 (7.14%)	1 / 33 (3.03%)
occurrences (all)	24	1	1
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 104 (6.73%)	3 / 14 (21.43%)	4 / 33 (12.12%)
occurrences (all)	7	3	5
Tremor			
subjects affected / exposed	6 / 104 (5.77%)	1 / 14 (7.14%)	4 / 33 (12.12%)
occurrences (all)	8	2	4
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	9 / 104 (8.65%)	1 / 14 (7.14%)	4 / 33 (12.12%)
occurrences (all)	12	1	4
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	6 / 104 (5.77%)	2 / 14 (14.29%)	2 / 33 (6.06%)
occurrences (all)	6	2	2
Infections and infestations			
Nasopharyngitis			

subjects affected / exposed	11 / 104 (10.58%)	2 / 14 (14.29%)	4 / 33 (12.12%)
occurrences (all)	14	2	4
Upper respiratory tract infection			
subjects affected / exposed	8 / 104 (7.69%)	0 / 14 (0.00%)	1 / 33 (3.03%)
occurrences (all)	9	0	1

Non-serious adverse events	Cohort 1: SoC Therapy		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 56 (32.14%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	8		
Tremor			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	3		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 56 (3.57%)		
occurrences (all)	2		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 56 (1.79%)		
occurrences (all)	1		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	10 / 56 (17.86%)		
occurrences (all)	12		
Upper respiratory tract infection			
subjects affected / exposed	3 / 56 (5.36%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 January 2019	It included following changes: • Documented the transition of Sponsor from Wilson Therapeutics AB to Alexion Pharmaceuticals, Inc.; • Expanded age range to include adolescent participants (12 to 17 years old) as well as adults; • Increased the sample size from 102 to 180 participants (targeting approximately 150 evaluable participants for up to 48 weeks) for enhanced statistical power to test for superiority versus SoC; • Added sample size re-estimation; • Decreased maximum daily dose permitted from 90 mg to 60 mg; • Changed dose modification criteria and actions in individual participants for participants receiving ALXN1840; • Changes in dose modification criteria and actions in individual participants for participants receiving SoC; • Criteria updated to exclude participants with creatinine clearance <30 mL/min; • Addition of an independent Hepatic Adjudication Panel to evaluate potential cases of drug-induced liver injury.
25 March 2021	It included following changes: • Implemented a change in the primary endpoint of the study which did not impact the study conduct; • Implemented provisions for study procedures, laboratory assessments, safety monitoring and study dispensation that may be conducted because of the global COVID-19 pandemic.
27 April 2022	It included following changes: • Diagnosis of Wilson disease was expanded to include historical diagnosis; • Addition of text to clarify that Alexion approval is needed to increase the dose of ALXN1840; • Addition of dose modification rules for increased triglycerides and total cholesterol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported