SYNOPSIS

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

Study Number: WTX101-301

Regulatory Agency Identifier Numbers:

IND Number: 119006

EudraCT: 2017-004135-36

NCT number: NCT03403205

Pediatric Investigational Plan Number: EMEA-002232-PIP02-19-M01

Study Phase: 3

Name of Study Intervention: ALXN1840 (bis-choline tetrathiomolybdate [[INN]: tiomolibdic acid; United States Accepted Names [USAN]/ Japanese Accepted Names [JAN]: tiomolibdate choline], formerly ATN-224 and WTX101)

Name of Sponsor/Company: Alexion Pharmaceuticals, Inc

Number of Study Sites and Countries: This study was conducted at 57 study centers that screened and randomized participants in 22 countries (Austria, Australia, Canada, Czech Republic, Denmark, France, Germany, Hong Kong, Hungary, Israel, Japan, New Zealand, Poland, Russia, Serbia, Singapore, South Korea, Spain, Taiwan, Turkey, UK, and US).

Publications:

Poujois A, Hedera P, Bega D, et al. Neurological manifestations of Wilson disease in treatment-naive patients and in patients receiving standard of care. European Journal of Neurology. 2021;28 (Suppl. 1), 133–134.

Weiss KH, Schilsky M, Czlonkowska A, et al. Efficacy and safety of ALXN1840 versus standard of care in Wilson disease: primary results from an ongoing phase 3, randomized, controlled, rater-blinded trial. J Hepatol. 2022;77(S1):GS001.

Study Period:

This Final CSR is for the study period from 15 Feb 2018 (first participant signed informed consent) to 30 Jun 2023 (end of study; last participant last visit). This report presents the final analysis of long-term efficacy, PD, PK, and safety results for participants in the Study WTX101-301 Extension Period.

Objectives, Endpoints, Statistical Methods and Results

The Study WTX101-301 Extension Period exploratory objectives and endpoints that are described in this report are listed below:

Exploratory Objectives	Exploratory Endpoints	Statistical Analyses
Evaluate the long-term efficacy of ALXN1840 on copper control in WD participants aged 12 years and older	• Daily mean AUEC of dNCC at every 48-week block throughout the Extension Period	• Trapezoidal rule in the formula • ANCOVA
Establish the safety and tolerability of individualized dosing of ALXN1840	• AEs/SAEs/AESI • Clinical laboratory test data • Neurological and physical examination findings • 12-lead ECG data • Vital signs	• Descriptive statistics
Evaluate the effects of ALXN1840 on disability status	• Change from baseline in the UWDRS Part II total score at every 48-week block throughout the Extension Period	• MMRM
Evaluate the effects of ALXN1840 on disability status in WD participants aged 12 years and older	• Change from baseline in the UWDRS Part II total score	• MMRM
Evaluate the effects of ALXN1840 on neurological status in WD participants aged 12 years and older	• Change from baseline in UWDRS Part III total score • Change from baseline in UWDRS Part III individual item/subscales (arising from a chair, gait, handwriting, and speech)	• MMRM
Evaluate the long-term effects of ALXN1840 on global clinical symptoms in WD participants aged 12 years and older	• CGI-I	• MMRM
	• Change from baseline in CGI-S	• MMRM
Evaluate the long-term effects of ALXN1840 on hepatic status in WD participants aged 12 years and older	• Change from baseline in MELD score	• MMRM
Evaluate the long-term effects of ALXN1840 on the cNCC responder rate in WD participants aged 12 years and older	• cNCC/cNCC$_{corrected}$ responder rate	• Logistic regression
To characterize the long-term safety and tolerability of	• AEs, SAEs, and AESIs	• Descriptive statistics

Exploratory Objectives	Exploratory Endpoints	Statistical Analyses
individualized dosing of ALXN1840 in WD participants aged 12 years and older	• Clinical laboratory test data • Neurological and physical examination findings • 12-lead ECG data • Vital signs	
Explore other directly measured PK, PD, and biomarkers of ALXN1840	• Concentration-time profiles of the directly measured PK, PD, and biomarkers	• Descriptive statistics

Abbreviations: AE = adverse event; AESI = adverse event of special interest; ANCOVA = analysis of covariance; AUEC = area under the effect-time curve; CGI-I = Clinical Global Impression-Improvement Scale; CGI-S = Clinical Global Impression-Severity Scale; cNCC = calculated non-ceruloplasmin-bound copper; dNCC = directly measured non-ceruloplasmin-bound copper; ECG = electrocardiogram; MELD = Model for End-stage Liver Disease; MMRM = mixed-effect model for repeated measures; PEP = Primary Evaluation Period; PD = pharmacodynamic; PK = pharmacokinetic; SAE = serious adverse event; SAP = statistical analysis plan; UWDRS = Unified Wilson's Disease Rating Scale; WD = Wilson disease

Methodology:

Study WTX101-301 was a Phase 3, randomized, rater-blinded, multicenter study designed to assess the efficacy and safety of ALXN1840 versus standard of care (SoC) in participants with Wilson disease (WD) aged 12 years and older (18 years and older in Germany). The study had 2 cohorts: participants who had received prior SoC treatment for WD for > 28 days (Cohort 1) and participants who were treatment-naïve or had received SoC treatment for WD for ≤ 28 days (Cohort 2) prior to starting the Primary Evaluation Period. Participants were randomized by cohort in a 2:1 ratio to receive either ALXN1840 or SoC during a 48-week Primary Evaluation Period.

The Extension Period was a single-arm, open-label period of up to 60 months to assess the long-term efficacy and safety of ALXN1840 in participants with WD aged 12 years and older (18 years and older in Germany).

Participants in Study WTX101-301 who completed the 48-week Primary Evaluation Period and participants who completed participation in Study WTX101-201 were offered the opportunity to participate in the Study WTX101-301 Extension Period.

Study WTX101-201 was a Phase 2, open-label, non-controlled study assessing the efficacy and safety of an individualized ALXN1840 dosage regimen administered for 24 weeks in participants with WD aged 18 and older.

All participants in the Study WTX101-301 Extension Period received treatment with ALXN1840 as enteric-coated delayed-release tablets for oral administration at doses ranging from 15 mg qod to 60 mg qd. Efficacy and safety assessments were performed at scheduled visits, while AEs and concomitant medications were monitored continuously throughout the study.

Results from the Study WTX101-301 Primary Evaluation Period and Study WTX101-201 are presented in separate CSRs.

Number of Participants (planned and analyzed):

Planned: 197 participants (178 participants from Study WTX101-301 and 19 participants from Study WTX101-201)

Analyzed: A total of 197 participants were included in the Extension Analysis Set (EAS) and 178 participants were included in the Long-term Safety and Efficacy Set (LTS). For reference: the EAS includes all participants who entered the Extension Period (both participants who completed the Study WTX101-301 Primary Evaluation Period and participants who completed Study WTX101-201) and received at least 1 dose of ALXN1840 in the Extension Period.

The LTS includes all participants who finished the Primary Evaluation Period of Study WTX101-301, entered the Extension Period, and received at least 1 dose of ALXN1840 in the Extension Period. Study WTX101-201 rollover participants were not included in this set.

Diagnosis and Main Criteria for Inclusion and Exclusion:

To be eligible for participation in the Study WTX101-301 Extension Period, participants must have completed the 48-week Primary Evaluation Period in Study WTX101-301 or completed participation in Study WTX101-201.

Study WTX101-301 enrolled male and female participants ≥ 12 years of age (≥18 years of age in Germany) who had an established diagnosis of WD. Participants were excluded from the study if they had any significant medical history of advanced or end-stage renal, liver, or neurological disease.

Study WTX101-201 enrolled male and female participants ≥ 18 years of age with a diagnosis of WD and who had not received SoC treatment for WD for > 24 months. Participants were excluded from the study for significant medical history of advanced or end stage renal, liver, or neurological disease.

Study Interventions, Dose, Mode of Administration, and Batch Number(s):

ALXN1840 was administered orally in a fasted state (1 hour before or 2 hours after meals) at doses ranging from 15 mg qod to 60 mg qd. Dosing of ALXN1840 was individualized based on safety evaluation and hepatic and neurological status and based on the parameters outlined in the protocol.

Batch numbers:

ALXN1840: GCS512943, GCS514143, L0607495, L0608752, GCS515975, GCS516001, GCS516707, GCS518087, GCS518204, GCS514142, GCS519991, GCS522542, and GCS524207

Duration of Study Intervention: Up to 60 months during the Extension Period.

Summary of Results and Conclusions:

This final clinical study report presents the results of the Extension Period through the end of the study (21 Sep 2023). Results for the Primary Evaluation Period were presented in the Study WTX101-301 Interim CSR dated 15 Jun 2023.

A total of 197 participants were enrolled in the Study WTX101-301 Extension Period; 178 participants who had completed the Study WTX101-301 Primary Evaluation Period and 19 participants who had completed Study WTX101-201. As of the end of the study, 1 participant completed the Extension Period and 196 (99.5%) participants had withdrawn from the study during the Extension Period: 144 participants withdrew from the study due to study termination by the Sponsor, 18 participants withdrew consent, 11 participants due to AEs, 4 participants due to physician decision, 2 due to pregnancy, 1 participant due to protocol deviation, 1 participant died, and 14 due to "other" reasons.

Demographic and Baseline Characteristics:

In the total population, 56.9% of participants were male, 79.2% of participants were White, and the mean age was 35.2 years. The majority (175 [88.8%]) of participants were ≥ 18 to < 65 years old and 14 (7.1%) participants were ≥ 12 to < 18 years old at the time of entering the Extension Period. In the EAS total population, 65 (36.5%) participants had cirrhosis reported at Baseline and 98 (59.0%) participants had psychiatric symptoms at Baseline (note: data pertaining to prior history of cirrhosis and Baseline psychiatric symptoms for participants who had completed Study WTX101-201 were not included in the Extension Period Analysis).

Exposure:

During the Extension Period, the mean duration of ALXN1840 treatment for all participants in the EAS was 1023.47 days; mean average daily dose of ALXN1840 was 14.62 mg (range: 5.0 mg to 60 mg).

For the LTS total population, the mean duration of ALXN1840 treatment was 1168.17 days and the maximum exposure to ALXN1840 treatment was 1898 days.

Efficacy Results:

<u>During Extension Period</u>

- Daily mean dNCC remained stable for the total population through the end of study
- UWDRS Part II and Part III scores remained stable or improved in each of the treatment groups
- CGI-S scores remained stable in the total population

<u>During ALXN1840 Treatment</u>

- Daily mean dNCC AUEC during the first 48 weeks of ALXN1840 treatment for the participants who had received SoC during the Primary Evaluation Period (SoC/ALXN1840 group) showed that they had similar mobilization of copper as the ALXN1840/ALXN1840 group (p = 0.7522)
  - Daily mean dNCC increased during the 4 to 8 weeks of ALXN1840 treatment and then declined from peak values; it stabilized after about 24 weeks and throughout long-term ALXN1840 treatment
- UWDRS Part II and Part III scores remained stable or improved in the total population

- CGI-S scores improved through the end of study
- BPRS-24 total scores decreased over time
- Liver stiffness, as measured by transient elastography, remained stable

Safety Results:

During Extension Period

- Mean duration of ALXN1840 treatment during the Extension Period for all participants was 1023.47 days; maximum duration was 1849 days.
- As of the end of study, 85.8% of participants experienced at least 1 AE during the Extension Period; the most frequently reported AEs (≥ 5% of all participants) were COVID-19 (53 [26.9%]); ALT increased (27 [13.7%]); nasopharyngitis (20 [10.2%]); headache (17 [8.6%]); fatigue and nausea (12 [6.1%] each); and urinary tract infection (11 [5.6%]).
- Overall, 62 (31.5%) participants had 1 or more AEs with the worst severity of Grade 1; 66 (33.5%) participants had 1 or more AEs with the worst severity of Grade 2; 39 (19.8%) participants experienced 1 or more AEs with the worst severity of Grade 3; 1 participant experienced 1 or more AEs with the worst severity of Grade 4 severity; and 1 participant experienced 1 AE with the worst severity of Grade 5 severity.
- A total of 63 (32.0%) of participants had AEs that were assessed by the Investigator as related to ALXN1840.
- One participant died due to acute hepatic failure during the Extension Period; the event was assessed by the Investigator as not related to ALXN1840.
- Overall, 44 (22.3%) participants experienced 1 or more SAEs during the Extension Period. Five participants had SAEs (ALT increased, hepatic failure, herpes simplex hepatitis, hepatic enzyme increase, and neurological symptom) that were assessed as related to ALXN1840 by the Investigator.
- A total of 14 (7.1%) participants had 1 or more AEs leading to discontinuation of ALXN1840 and/or study withdrawal.
- A total of 49 (24.9%) participants experienced 1 or more neurological events; these were generally nonserious, mild or moderate in severity, and the majority resolved or improved without dose modifications. The most frequently reported (> 5% total participants) neurological events were headache and tremor.
- A total of 63 (32.0%) participants experienced hepatic events; these were generally mild or moderate in severity, nonserious, and reversible with dose modification.
  - Hepatic events reported in > 2 participants included ALT increased (27 [13.7%]); GGT increased (9 [4.6%]); AST increased (8 [4.1%]); hypertransaminasemia (5 [2.5%]); hepatic enzyme increased (7 [3.6%]); thrombocytopenia (4 [2.0%]); and liver function test increased (3 [1.5%]).

  - 39 (19.8%) participants experienced hepatic AEs that were assessed by the Investigator as related to ALXN1840.
  - 9 participants had hepatic AEs that led to discontinuation of ALXN1840 and/or study withdrawal.
- A total of 24 (12.2%) participants experienced hematologic AEs; these were generally mild or moderate in severity and nonserious.
  - Hematologic AEs experienced by > 2 participants included neutropenia (8 [4.1%]), thrombocytopenia (6 [3.0%]), neutrophil count decreased (5 [2.5%]), anemia (5 [2.5%]), and leukopenia (3 [1.5%]).
  - 15 (7.6%) participants experienced hematologic AEs that were assessed by the Investigator as related to ALXN1840.
  - 2 (1.0%) participants had nonserious hematologic AEs (thrombocytopenia and neutropenia) that led to discontinuation of ALXN1840.
- Most lipid abnormalities were mild or moderate in severity and none resulted in clinically significant outcomes; 9 (4.6%) experienced AEs of dyslipidemia.
- 2 participants became pregnant during the Extension Period; both participants gave birth without delivery complications.
- There were no clinically meaningful findings in the vital sign measurements, ECGs, or other observations related to safety in the Extension Period.

<u>During ALXN1840 Treatment</u>

- As of the end of study, the mean duration of ALXN1840 treatment for the total population was 1168.17 days; maximum exposure was 1898 days.
- Overall, 93.8% of participants in the LTS experienced at least 1 AE during ALXN1840 treatment (569.3 patient-years); the most frequently reported AEs (≥ 10% of all participants) were COVID-19 (25.3%), ALT increased (21.3%), nasopharyngitis (16.9%), headache (11.8%), and fatigue (11.2%).
- Overall, 58 (32.6%) participants had 1 or more AEs with worst severity of Grade 1, 70 (39.3%) participants had 1 or more AEs with worst severity of Grade 2, 36 (20.2%) participants had 1 or more AEs with worst severity of Grade 3, 2 (1.1%) participants had 1 or more AEs with worst severity of Grade 4, and 1 participant experienced 1 AE with the worst severity of Grade 5 severity.
- A total of 91 (51.1%) of participants had AEs that were assessed as related to ALXN1840 by the Investigator.
- 1 participant in the LTS population died due to acute hepatic failure during ALXN1840 treatment; event was assessed by the Investigator as not related to ALXN1840. Although not part of the LTS population, 2 participants died during the WTX101-301 Primary Evaluation Period; both events were assessed as not related to ALXN1840 by the Investigators (1 participant with baseline cirrhosis died of hepatic encephalopathy and 1 participant died of acute aspiration).

- A total of 44 (24.7%) participants experienced 1 or more SAEs during ALXN1840 treatment. Six (3.4%) participants had SAEs (ALT increased, hepatic failure, herpes simplex hepatitis, hepatic enzyme increased, neurological symptom, and paranoia) that were assessed as related to ALXN1840 by the Investigator
- A total of 14 (7.9%) participants had an AE leading to discontinuation of ALXN1840 and/or study withdrawal.
- A total of 66 (37.1%) participants experienced neurological events; these were generally nonserious, mild or moderate in severity, and the majority resolved or improved without dose modifications. The most frequently reported (> 5% total participants) neurological events were headache and tremor.
- A total of 82 (46.1%) participants experienced hepatic events; these were generally mild or moderate in severity, nonserious, and reversible with dose modification.
  - Hepatic events reported in > 2 participants included ALT increased (38 [21.3%]); GGT increased and AST increased (10 [5.6%] each); hepatic enzyme increased (9 [5.1%]); liver function test increased (6 [3.4%]); hypertransaminasemia (5 [2.8%]), hepatic function abnormal (6 [3.4%] each); and thrombocytopenia and liver disorder (3 [1.7%] each).
  - 59 (33.1%) participants experienced hepatic AEs that were assessed by the Investigator as related to ALXN1840
  - 9 participants had hepatic AEs that led to discontinuation of ALXN1840 and/or study withdrawal.
- A total of 26 (14.6%) participants experienced hematologic AEs; these were generally mild or moderate in severity and nonserious.
  - Hematologic AEs experienced by > 2 participants included neutropenia (10 [5.6%]); anemia (8 [4.5%]); thrombocytopenia and neutrophil count decreased (5 [2.8%] each); and leukopenia (4 [2.2%]).
  - 18 (10.1%) participants experienced hematologic AEs that were assessed by the Investigator as related to ALXN1840.
  - 2 (1.1%) participants had hematologic AEs (thrombocytopenia and neutropenia) that led to discontinuation of ALXN1840.
- Most lipid abnormalities were mild or moderate in severity and none resulted in clinically significant outcomes; 9 (5.1%) participants experienced AEs of dyslipidemia.
- 2 participants became pregnant; both participants gave birth without delivery complications.
- There were no clinically meaningful findings in the vital sign measurements, ECGs, or other observations related to safety.

Pharmacokinetics

- Following initiation of ALXN1840 treatment in the SoC/ALXN1840 group, the median trough plasma total molybdenum concentration at Week 4 increased from Baseline by approximately 134-fold; peaked at Week 8 and, after an approximately 14% decrease from the peak at Week 18, maintained at essentially the same level through Week 168 (or through Week 264 for the ALXN1840/ALXN1840 group).
- The median trough PUF molybdenum concentration at Week 4 increased from Baseline by approximately 5-fold and remained within a narrow range through Week 168 in the SoC/ALXN1840 group and through Week 264 in the ALXN1840/ALXN1840 group.
- The mean trough PUF molybdenum concentrations were < 10% of those for plasma total molybdenum during long-term treatment, indicating that more than 90% of plasma molybdenum was present in the form of protein-bound thiomolybdate such as thiomolybdate-copper-albumin tripartite complexes.
- The median 24-hour urinary molybdenum output at Week 4 increased from Baseline by approximately 10-fold and remained at essentially the same level throughout the 264 weeks of treatment with some variability in the SoC/ALXN1840 group and in the ALXN1840/ALXN1840 group.
- For those in the ALXN1840/ALXN1840 group, all of the above ALXN1840 surrogate PK measurements remained relatively stable from the Primary Evaluation Period levels throughout the Extension Period.

Pharmacodynamics

- Following initiation of ALXN1840 treatment in the SoC/ALXN1840 group, the median trough plasma total copper concentration increased at Week 4 with the peak occurring at Week 6, which was approximately 2.1-fold that at Baseline, then gradually reduced to approximately 1.8-fold that of Baseline beginning from Week 18 and remained at relatively stable levels through Week 264.
- Once the SoC/ALXN1840 group started receiving ALXN1840, they showed a similar profile for plasma total copper concentration as the ALXN1840/ALXN1840 group during the Primary Evaluation Period. This further supports the observation in the Primary Evaluation Period that participants who had received SoC prior to the start of ALXN1840 treatment had residual tissue copper to be mobilized.
- In contrast to plasma total copper, mean and median PUF copper remained relatively similar to Baseline concentrations throughout the 264 weeks of treatment.
- Similar to plasma total copper, the median trough plasma LBC and dNCC concentrations increased at Week 4 with the peak occurring at Week 6, which was approximately 2-fold and 4.3-fold, respectively, that of the Baseline, then gradually declined to approximately 1.7-fold and 3.4-fold that of Baseline beginning at Week 12 and Week 24, respectively, and remained at that level throughout the 264 weeks of treatment.

- The ALXN1840/ALXN1840 participants tended to have slightly higher plasma LBC and dNCC concentrations relative to the SoC/ALXN1840 participants. This difference is likely due to the ALXN1840/ALXN1840 group including participants who were treatment-naïve or had previously received ≤ 28 days of WD therapy before starting ALXN1840 treatment.
- Together with plasma total copper and plasma LBC, plasma dNCC increase after ALXN1840 treatment is a reflection of tissue copper mobilization into the plasma or the systemic circulation.
- The median 24-hour urinary copper output for the 2 cohorts combined increased from Baseline by approximately 16% at Week 4 and beginning from Week 12, maintained at a greater (approximately 46% over Baseline) but relatively stable level throughout the rest of the 264 weeks of treatment.
- For those in the ALXN1840/ALXN1840 group, all the above ALXN1840 PD measurements remained relatively stable from the Primary Evaluation Period levels throughout the Extension Period.

Biomarkers

- Following initiation of ALXN1840 treatment, plasma Cp and CpC concentration-time profiles were relatively stable and did not appear to vary from Baseline throughout the 264 weeks of treatment.
- These data also support the hypothesis that ALXN1840 treatment does not perturb CpC biology and indicate that ALXN1840 does not decopper CpC in participants with WD.

Conclusions:

- Results from the Extension Period demonstrated a sustained treatment effect with up to 5 years of ALXN1840 treatment.
- Mobilization of copper from tissue occurred by 4 weeks after initiation of ALXN1840 treatment, reached higher steady state level compared to Baseline at Week 24, and remained stable during long-term ALXN1840 treatment.
  - The initial level of mobilization of copper from tissue was higher in treatment-naïve or minimally treated participants.
  - Participants who switched from SoC to ALXN1840 treatment during the Extension Period showed a similar increase in copper mobilization as the participants that received ALXN1840 during the Primary Evaluation Period.
- Clinical improvement in neurologic parameters and stability or improvement in psychiatric parameters was observed during long-term ALXN1840 treatment.
  - Participants who switched from SoC to ALXN1840 treatment during the Extension Period showed similar improvement over time compared to participants who received ALXN1840 during the Primary Evaluation Period.

- Long-term ALXN1840 treatment was well tolerated and the safety profile was consistent over time.
  - Elevations in liver enzymes, lipid abnormalities, and neutropenia generally occurred within the first 4 to 12 weeks of treatment and were primarily mild to moderate in severity, manageable with dose modifications, and did not result in clinically significant outcomes.
  - Neurological events were generally mild to moderate and resolved without dose modifications.
- ALXN1840 PK/PD concentration-time profiles in the SoC/ALXN1840 group were similar to those observed for the ALXN1840/ALXN1840 group.
- Increases in plasma total copper and plasma LBC, plasma dNCC concentrations after ALXN1840 treatment is a reflection of tissue copper mobilization into the plasma or the systemic circulation.
- ALXN1840 treatment did not cause chronic depletion of ceruloplasmin (Cp) protein or removal of Cp copper in participants with WD.

Date and Version of This Report: 1.0 **Date:** 20 Dec 2023