ALXN1840 shows rapid and sustained improvement in copper mobilization from tissues, potentially closing treatment gaps for Wilson disease community

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FoCus Phase III trial evaluates new approach to copper mobilization for patients with Wilson disease who have not seen meaningful innovation in decades

In Wilson disease, excess copper build-up in organs and tissues can lead to liver disease as well as neurological and psychiatric symptoms

WILMINGTON, Del., June 23, 2022 – Detailed results from the positive FoCus Phase III trial in Wilson disease showed that ALXN1840, an investigational once-daily, oral medicine, met its primary endpoint demonstrating three-times greater copper mobilization from tissues compared to the standard of care (SoC) arm (Least Square Mean Difference [LSM Diff] 2.18 µmol/L; p< 0.0001), including in patients who had been treated previously for an average of 10 years.[1]

In the trial, people taking ALXN1840 experienced rapid copper mobilization, with a response at four weeks and sustained through 48 weeks.[1]

Results from the trial will be presented on June 23 at the 2022 International Liver Congress (ILC) in London.

Wilson disease is a rare and progressive genetic condition in which the body's pathway for removing excess copper is compromised. This may result in the accumulation of copper in a person's liver, brain or other vital organs . Damage from excess copper build-up in tissues and organs may lead to symptoms of liver, neurological and psychiatric diseases, which may be irreversible.[2,3,4] Even after SoC treatment is initiated, some patients experience worsening of disease, especially of neurologic symptoms.[3,4]

Change in neurological scale scores and clinician-reported functional assessments with ALXN1840 treatment were also evaluated in a post-hoc analysis as secondary endpoints in the Phase III trial.[1]

In patients who were symptomatic at baseline, there were greater improvements in neurological scores for those treated with ALXN1840 compared to SoC (Unified Wilson Disease Rating Scale [UWDRS] part II symptomatic ALXN1840 -1.7, SoC -0.8; UWDRS Part III symptomatic ALXN1840 -2.91, SoC -1.31). However, there were no significant differences between treatment groups observed at 48 weeks.[1]

Most patients in the trial had low symptom scores at baseline, so there was minimal room for total score improvement (UWDRS Part II ALXN1840 -0.6, SoC -0.3; UWDRS Part III ALXN1840 -2.20, SoC -1.02).[1] As people with Wilson disease experience a highly varied degree of symptoms[4], this total score may not reflect the extent of disease severity.

ALXN1840 was well tolerated and the long-term safety and efficacy of ALXN1840 is being assessed in an up to 60-month extension period.[1]

Professor Karl Heinz Weiss, MD, Director of the Department of Internal Medicine at Salem Medical Center Heidelberg and investigator in the FoCus Phase III trial, said: "These data from the largest global trial in Wilson disease to date show significant copper mobilization from the tissues with ALXN1840, even in patients who were on standard of care for over a decade on average. These results have the potential to reframe the way doctors can think about the disease given that current therapies focus on removing copper from the blood. We are also encouraged by initial neurological improvement with ALXN1840 in those who were symptomatic and believe that assessing individual patient experiences may provide a better understanding of the impact on daily life."

Marc Dunoyer, Chief Executive Officer, Alexion, said: "Many people with Wilson disease continue to experience symptoms even after years of intervention with current therapies, illuminating an urgent need to re-evaluate the standard of care. Applying our 30 years of experience in rare disease clinical development, Alexion has conducted rigorous scientific research to bring fresh thinking to Wilson disease around the importance of copper mobilization from the tissues. These data further our efforts to potentially introduce a novel treatment for patients who have gone decades without meaningful innovation."

Summary of efficacy and safety results[i]

The primary endpoint gauged the daily mean Area Under the Effect Curve (AUEC) for directly measured non-ceruloplasmin-bound copper (dNCC)[ii] over 48 weeks. The dNCC parameter includes copper bound in an inert complex with ALXN1840.[1]

Statistic	Cohort 1[iii] Treatment-experienced		Cohort 2[iii] Naïve/minimally treated		Total	
	ALXN 1840 N = 104	SoC N= 56	ALXN 1840 N = 33	SoC N = 14	ALXN 1840 N = 137	SoC N = 70
n[iv]	91	51	27	12	118	63
Mean (Standard Deviation)	2.68 (2.118)	0.72 (0.643)	4.58 (2.526)	1.09 (0.484)	3.12 (2.347)	0.79 (0.629)
LSM[v] (Standard Error)	2.50 (0.150)	0.87 (0.204)	4.76 (0.319)	0.96 (0.487)	3.18 (0.167)	1.00 (0.219)
LSM Difference (SE)	1.64 (0.254)		3.79 (0.584)		2.18 (0.244)	
p-value	<0.0001		<0.0001		<0.0001	

i. Results analyzed using ANCOVA model, model included treatment, cohort, and baseline value. For cohort analysis, analysis was performed on each cohort using ANCOVA model, cohort term was removed from model. Analysis results were combined using Rubin's rules.
ii. Daily Mean AUEC for dNCC measured in µmol/L.
iii. Cohort 1= Prior WD Treatment >28 days; Cohort 2= Treatment Naïve or Prior WD Treatment ≤ 28 days.
iv. Patient numbers for calculation of mean; all patients were included in the calculation of LSM, LSM difference and p values.
v. LSM is a statistical method that determines the line of best fit for a dataset.

Most adverse events (AEs) were not considered serious (ALXN1840, 85.4%; SoC, 75.7%) and/or were not considered related to trial treatment (ALXN1840, 77.4%; SoC, 75.7%). The most common AE associated with ALXN1840 was a reversible increase in alanine aminotransferase levels (ALXN1840, 14.6%; SoC, 2.9%). Two deaths were also reported but were unrelated to ALXN1840.[1]

In addition to the Phase III trial, two ongoing mechanistic trials in Wilson disease are also underway. Alexion is working closely with health authorities worldwide and intends to submit these data for review.

Notes

Wilson disease

Wilson disease is an inherited condition in which the body's pathway for removing excess copper is compromised. Over time, that results in the build-up of excess copper levels in the liver, brain and other organs leading to damage that greatly impacts patients.[2]

Although the disease is present at birth, the age of diagnosis occurs between five to 35 years.[3,4] People can develop a wide range of symptoms, including liver disease and/or psychiatric or neurological symptoms.[2,3,4]

FoCus

FoCus (301) is a pivotal Phase III, randomized, controlled, rater-blinded trial designed to evaluate the efficacy and safety of ALXN1840 versus SoC in patients with Wilson disease aged 12 years and older. The primary endpoint assessed copper mobilization over 48 weeks, defined as daily mean AUEC for dNCC. In the trial, 214 patients were enrolled in one of two cohorts on a 3:1 basis (treatment-experienced:treatment-naïve). Each cohort was then randomized 2:1 (ALXN1840:SoC). The first cohort enrolled 161 patients who received SoC (chelation therapy with penicillamine or trientine, zinc therapy or a combination of both chelation and zinc therapy) for more than 28 days and the second cohort enrolled 53 patients who were

treatment-naïve or had received SoC for 28 days or less.[1,5] Key secondary endpoints assessed over the 48-week period included change in neurological function as measured by the UWDRS Part II and III.[1]

ALXN1840

ALXN1840 is a potential new once-daily, oral medicine in development for the treatment of Wilson disease. This investigational, novel molecule is designed to selectively and tightly bind to and remove copper from the body's tissues and blood. ALXN1840 has been granted Orphan Drug Designation in the United States and orphan designation in the European Union for Wilson disease.

Alexion

Alexion, AstraZeneca Rare Disease, is the group within AstraZeneca focused on rare diseases, created following the 2021 acquisition of Alexion Pharmaceuticals, Inc. As a leader in rare diseases for 30 years, Alexion is focused on serving patients and families affected by rare diseases and devastating conditions through the discovery, development and commercialization of life-changing medicines. Alexion focuses its research efforts on novel molecules and targets in the complement cascade and its development efforts on hematology, nephrology, neurology, metabolic disorders, cardiology and ophthalmology. Headquartered in Boston, Massachusetts, Alexion has offices around the globe and serves patients in more than 50 countries. For more information, please visit www.alexion.com.

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