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HEALTH TECHNOLOGY BRIEFING
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Bis-choline tetrathiomolybdate for Wilson's disease

NIHRIO ID	3300	**NICE ID**	9950
Developer/Company	Alexion Pharma UK	**UKPS ID**	655106

Licensing and market availability plans	Currently in phase III clinical development

SUMMARY

Bis-choline tetrathiomolybdate is in clinical development for the treatment of Wilson's disease (WD). WD is a genetic disorder that prevents the body from removing extra copper, causing copper to build up in the liver, brain, eyes, and other organs. The copper overload in WD is either treated with chelators or zinc. Despite current therapies, there are several situations in which current medications cannot avoid an unsatisfactory outcome.

Bis-choline tetrathiomolybdate, through oral administration, is expected to rapidly attach to copper and to a protein called albumin in the bloodstream. This prevents copper to be taken up by the organs and is eliminates it from the body. Therefore, the damaging effects of copper are expected to be reduced. In comparison to current treatments, bis-choline tetrathiomolybdate provides an alternative copper-protein binding mechanism. If licenced, bis-choline tetrathiomolybdate will offer an additional treatment option for WD patients.

PROPOSED INDICATION

Bis-choline tetrathiomolybdate is indicated for the treatment of patients with Wilson's disease (WD).[1]

TECHNOLOGY

DESCRIPTION

Bis-choline tetrathiomolybdate (Decuprate, ATN-224, WTX101, ALXN1840) is a novel copper-protein binding agent with a unique mechanism of action, under investigation for WD, involving impaired copper transport.[2] Bis-choline tetrathiomolybdate targets hepatic intracellular copper and reduces plasma non-ceruloplasmin-bound copper (NCC) by forming tripartite complexes with albumin and increasing biliary copper excretion.[3]

Bis-choline tetrathiomolybdate is currently in both phase II and phase III clinical trials for patients with WD. In the ongoing phase III clinical trial (NCT03403205), participants will receive oral bis-choline tetrathiomolybdate tablets at doses ranging from 15mg every other day (QOD) to 60mg daily (QD).[1,4-6]

INNOVATION AND/OR ADVANTAGES

Treatment of the copper overload in WD is either accomplished with chelators (penicillamine or trientine) or zinc, with the use of zinc limited to patients who are presymptomatic or stable after de-coppering with chelators. However, even with several drugs available, there are a number of situations in which current medications cannot prevent an unsatisfactory outcome. First, in patients presenting with severe hepatic disease, and especially in those with impending liver failure, chelators might be too slow to control the damaging effect of unbound copper on liver cells, and a transplant might be unavoidable. Second, chelators can induce a worsening of symptoms in patients presenting with neurological disease, which is not always reversible. Finally, even without worsening, a substantial proportion of patients with neurological symptoms will not fully recover.[7]

In contrast to current treatments, bis-choline tetrathiomolybdate provides an alternative copper-protein binding mechanism by forming a tripartite complex with copper and albumin. Bis-choline tetrathiomolybdate thereby detoxifies excess copper in both liver and blood and promotes copper clearance through biliary excretion (the body's natural route of elimination). Bis-choline tetrathiomolybdate has a 10,000-fold higher affinity for copper than other chelators and addresses the underlying cause of the disease.[8]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Bis-choline tetrathiomolybdate does not currently have Marketing Authorisation in the EU/UK for any indication.

PATIENT GROUP

DISEASE BACKGROUND

Wilson's disease (WD) is a genetic disorder that prevents the body from removing extra copper, causing copper to build up in the liver, brain, eyes, and other organs. Mutations of a gene called ATP7B cause WD. Normally, the liver releases extra copper into bile, which carries the copper, along with other toxins and waste products, out of the body through the digestive tract. In WD, the liver releases less copper into bile, and extra copper stays in the body. The ATP7B mutations that cause's WD are inherited. These mutations are autosomal recessive, meaning that a person must inherit two ATP7B genes with mutations, one from each parent, to have WD. People who have one ATP7B gene without a mutation and one ATP7B gene with a mutation do not have WD, but they are carriers of the disease.[9]

Without treatment, high copper levels can cause life-threatening organ damage. Newer studies of people's genes suggest that WD may be more common than previous studies have suggested. A study in the United Kingdom found that about 1 in 7,000 people have gene mutations that cause WD compared to 1 in 30,000 people previously reported.[10]

Symptoms typically develop between the ages 5 and 40 years. However, some people develop symptoms at younger or older ages. Doctors have found the first symptoms of WD in infants as young as 9 months and in adults older than 70 years.[10]

The symptoms of WD vary. WD is present at birth, but the symptoms don't appear until the copper builds up in the liver, the brain, or other organs. Some may not have symptoms of WD before they are diagnosed with the disease and treated. If there are symptoms, the symptoms may be related to the following:[9]

- liver (e.g. hepatitis, inflammation, or acute liver failure)
- nervous system and mental health (e.g. problems with speech, tremors, anxiety, depression, etc.)
- eyes (e.g. Kayser-Fleischer rings);
- or other organs (e.g. haemolytic anaemia, bones and joints, kidney)

CLINICAL NEED AND BURDEN OF DISEASE

The study conducted by Bandmann et al. in 2015 suggested a higher rate of prevalence in the UK population compared to the 1984 estimate. The 2015 estimate suggests a prevalence rate of 1 in 7,000 in the UK, whereas the 1984 estimate was 1 in 30,000.[11] Based on the mid-2019 estimate of the UK population (66.8 million), the estimated number of patients who may have WD would be around 9,543.[11,12]

Death records in England, extracted from the Office for National Statistics (ONS) mortality data between 2008-2018, identified 52 patients with WD; 65% were male, with a mean age of 45.5 years (range 17–82). Complications related to cirrhosis or liver failure were assigned as the underlying cause of death (UCOD) in 44%. Hepatocellular carcinoma (HCC) was the UCOD in 5.8%. Of the 21% of patients who were recorded as having a liver transplant, transplant complications or graft failure were recorded as a cause of death in 8%. Sepsis was mentioned on the death certificate in 42% and recorded as the UCOD in 21%.[13]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

In the hospital setting, WD patients will be treated either by a hepatologist, a gastroenterologist or a haematologist. If there are other conditions or problems caused by WD, additional specialists may be involved. These are likely to be a neurologist (brain) or nephrologist (kidneys).[14] Psychiatrists may also be involved to manage psychiatric symptoms.[15]

CURRENT TREATMENT OPTIONS

Treatment for WD is aimed at removing the excess copper from the body and preventing it from building up again. This is primarily therapy with de-coppering or chelating agents. With early detection and successful treatment, it is possible for the patient to enjoy a healthy life.[14]

Currently available medical regimens include copper chelators, for example D-penicillamine or trientine, acting to increase copper excretion and zinc salts, which reduce copper uptake.[16] Additionally, liver transplantation is indicated in selected cases.[17]

PLACE OF TECHNOLOGY

If licensed, bis-choline tetrathiomolybdate will offer an additional treatment option for patients with WD.

CLINICAL TRIAL INFORMATION

Trial	NCT04573309, EudraCT-2020-001104-41; Copper and Molybdenum Balance in Participants With Wilson Disease Treated With ALXN1840 **Phase II** - Recruiting **Location(s):** UK **Estimated primary completion date:** September 2021
Trial design	Single group assignment, open-label
Population	N = 10 (planned), subjects with diagnosis of WD by Leipzig Criteria > 4, aged 18 years and older
Intervention(s)	Participants will be orally administered bis-choline tetrathiomolybdate at a dose of 15 milligrams (mg)/day on Day 1 through Day 28 and then increased to 30 mg/day on Day 29 through Day 39
Comparator(s)	-
Outcome(s)	Primary outcome(s): • Mean Daily Copper Balance: Day 1 through Day 8 (bis-choline tetrathiomolybdate 15 mg) and Day 31 through Day 35 (bis-choline tetrathiomolybdate 30 mg);

	• Steady state: Day 25 through Day 28 (bis-choline tetrathiomolybdate 15 mg) and Day 36 through Day 39 (bis-choline tetrathiomolybdate 30 mg) See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	NCT04422431, EudraCT-2019-003711-60; Copper Concentration and Histopathologic Changes in Liver Biopsy in Participants With Wilson Disease Treated With ALXN1840 **Phase II** – Not yet recruiting **Location(s):** EU (including the UK), United States, and other countries **Primary completion date:** August 2022
Trial design	Single group assignment, open label, pathologist-blinded
Population	N = 28 (planned), diagnosis of WD by Leipzig Criteria ⩾4, aged 18 years and older
Intervention(s)	Drug: Bis-Choline Tetrathiomolybdate Participants will be initiated at 15 milligrams (mg) once daily, then the dose will be increased to 30 mg once daily at Week 6.
Comparator(s)	-
Outcome(s)	Primary outcome(s): Change From Baseline At Week 48 In Liver Cu Concentration [Time Frame: Baseline, Week 48]
Results (efficacy)	-
Results (safety)	-

Trial	**NCT03403205, EudraCT-2017-004135-36**; Efficacy and Safety of ALXN1840 (Formerly Named WTX101) Administered for 48 Weeks Versus Standard of Care in Patients With Wilson Disease With an Extension Period of up to 60 Months **Phase III –** Active, not recruiting **Location(s):** EU (including the UK), Canada, United States, and other countries **Estimated primary completion date:** February 2021
Trial design	Randomised, parallel assignment, rater-blind
Population	N = 215; aged 12 years and older; subjects with established diagnosis of Wilson disease by Leipzig-Score = or > than 4.
Intervention(s)	Bis-choline tetrathiomolybdate administered orally in 15 mg tablets
Comparator(s)	Drug: Standard of Care (SoC) Therapy Depending on the site/region, subjects randomized to receive SoC treatment will receive trientine, penicillamine,

	zinc, or a combination of these medicines, administered according to standard regimens at the discretion of the investigator.
Outcome(s)	Primary outcome(s): Evaluate the efficacy of ALXN1840 using SoC as comparator and copper as the control assessed in terms of the percentage change from baseline (Day 1) to 48 weeks in non-ceruloplasmin-bound copper levels [Time Frame: Change from baseline (Day 1) to 48 weeks]
Results (efficacy)	-
Results (safety)	-

Trial	**NCT02273596**; Efficacy and Safety Study of WTX101 (ALXN1840) in Adult Wilson Disease Patients **Phase II** - Completed **Location(s):** EU (including the UK) and United States **Study completion date:** November 2018
Trial design	Multi-centre, open-label, single group assignment
Population	N = 28; aged 18 years or older; subjects with newly established diagnosis of WD by Leipzig-Score ⩾ 4 documented by testing.
Intervention(s)	Individualized oral doses of bis-choline tetrathiomolybdate (15-60mg per day).
Comparator(s)	**-**
Outcome(s)	Primary outcome(s): • Percentage Of Participants With Normalized Concentrations Of non-ceruloplasmin-bound copper (NCC) [Time Frame: Week 24] • Change From Baseline In NCC Concentrations Adjusted For Mo Plasma Concentration At Week 24 [Time Frame: Baseline, Week 24]
Results (efficacy)	At 24 weeks, 20 (71%, 95% CI 51·3-86·8; p<0·0001) of 28 patients met the criteria for treatment success: 16 (57%) treated with WTX101 either achieved or maintained normalised $NCC_{corrected}$ concentrations and 4 (14%) had at least a 25% reduction from baseline $NCC_{corrected}$. Mean $NCC_{corrected}$ was reduced by 72% from baseline to week 24 (least squares mean difference -2·4 µmol/L [SE 0·4], 95% CI -3·2 to -1·6; p<0·0001).[3]
Results (safety)	No cases of paradoxical drug-related neurological worsening were recorded. Liver function was stable in all patients, although reversible increased concentrations of asymptomatic alanine or aspartate aminotransferase, or γ-glutamyltransferase, without increased bilirubin, occurred in 11 (39%) of 28 patients who received at least 30 mg/day. 11 serious adverse events were reported in seven (25%) patients and included psychiatric disorders (six events in four patients), gait disturbance (one event), elevated liver

	aminotransferases (two events in two patients, one with agranulocytosis), and decline in neurological functioning (one event, likely due to natural disease progression although causality could not be ruled out). The seven serious adverse events categorised as psychiatric disorders and as gait disturbance were assessed as unlikely to be related to the study drug, whereas the remaining four events were possibly or probably related.[3]

ESTIMATED COST

The cost of bis-choline tetrathiomolybdate is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

No relevant guidance identified

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. Clinical Commissioning Policy: Trientine for Wilson disease (all ages). 170094P. December 2018.

OTHER GUIDANCE

- European Association for the Study of the Liver (EASL) Clinical Practice Guidelines: Wilson's disease. 2012.[18]

ADDITIONAL INFORMATION

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