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HEALTH TECHNOLOGY BRIEFING FEBRUARY 2021

Mavorixafor for WHIM syndrome

NIHRIO ID	13467	**NICE ID**	9873
Developer/Company	X4 Pharmaceuticals Inc	**UKPS ID**	Not applicable

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Mavorixafor (X4P-001) is in clinical development for the treatment of WHIM syndrome in patients aged 12 years and above. WHIM stands for warts (skin growths), hypogammaglobulinemia (low level of antibodies), infections and myelokathexis (a condition where immune cells are trapped in the bone marrow preventing them from fighting infections). Patients with WHIM syndrome have mutations (changes) in the gene for the CXCR4 receptor, which plays a role in the movement of blood cells into and from the bone marrow. Because of these mutations, the CXCR4 receptor is hyperactive and, as a consequence, blood cells (particularly neutrophils) are retained in the bone marrow, leading to low levels of neutrophils in the blood. There are no licenced therapies to treat WHIM syndrome.

Mavorixafor is an oral drug expected to reduce the activity of the CXCR4 receptor and allow neutrophils to be released from the bone marrow into the blood stream, thereby helping the body to fight infections. If licenced, mavorixafor would provide the first targeted treatment option for WHIM syndrome in patients aged 12 years and above, whose care is currently limited to the treatment of the different symptoms of WHIM syndrome.

PROPOSED INDICATION

Treatment of WHIM syndrome in patients aged 12 years and above.[1]

TECHNOLOGY

DESCRIPTION

Mavorixafor (X4P-001; X4P-001-RD) is a selective, small molecule antagonist of C-X-C chemokine receptor type 4 (CXCR4) that binds allosterically to the extracellular region of the receptor and inhibits C-X-C motif chemokine 12 stimulation of different intracellular variants of CXCR4.[2] Patients with WHIM syndrome have mutations in the gene for the CXCR4 receptor. Because of these mutations, the CXCR4 receptor is hyperactive and, as a consequence, blood cells (particularly neutrophils) are retained in the bone marrow, leading to low levels of neutrophils in the blood. Mavorixafor is expected to reduce the activity of the CXCR4 receptor and allow neutrophils to be released from the bone marrow into the blood stream. This increases the levels of neutrophils in the blood thereby helping the body to fight infections.[3]

In the phase III clinical trial (NCT03995108) participants will receive mavorixafor 400 milligrams orally, once daily for 52 weeks.[1]

INNOVATION AND/OR ADVANTAGES

Currently, there are no approved therapies for the treatment of WHIM syndrome. Care is currently limited to the treatment of the different symptoms of WHIM syndrome. The care of WHIM patients is mainly focused on the prevention and management of infections. None of these treatments, however, have been clinically proven to be effective for treating WHIM syndrome nor do they address the underlying cause of this multi-faceted disease, the genetic defect of the CXCR4 receptor.[4]

Mavorixafor is being developed as a first-in-class, oral, allosteric inhibitor of CXCR4 for the treatment of WHIM syndrome.[4] A phase II study (NCT03005327) demonstrated that mavorixafor 400 mg once-daily mobilizes neutrophil and lymphocytes in adult patients with WHIM syndrome and provides preliminary evidence of clinical benefit for patients on long-term therapy. The study also observed an average 75% reduction in the number of cutaneous warts, a main symptom of WHIM syndrome.[5]

Mavorixafor may be considered a highly specialised technology (HST) due to its small potential patient population.[6]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Mavorixafor is not currently licensed in the UK for any indication.

In July 2019, Orphan Designation was granted by the European Commission to Mavorixafor for the treatment of WHIM syndrome.[3]

In December 2020 X4 Pharmaceuticals received Rare Pediatric Disease Designation from the FDA for Mavorixafor for the treatment of WHIM Syndrome.[7]

X4 Pharmaceuticals was granted Fast Track Designation in October 2020 and Breakthrough Therapy Designation in November 2019 both by the FDA for Mavorixafor for the treatment of WHIM Syndrome.[8,9]

Mavorixafor is in phase II clinical trials for renal cell carcinoma.[10]

PATIENT GROUP

DISEASE BACKGROUND

WHIM syndrome is a rare congenital immune deficiency. WHIM stands for warts (skin growths), hypogammaglobulinemia (low level of antibodies), infections and myelokathexis (a condition where immune cells are trapped in the bone marrow preventing them from fighting infections).[3]

Individuals with WHIM syndrome are more susceptible to potentially life-threatening bacterial infections. To a lesser degree, they are also predisposed to viral infections. Affected individuals are particularly susceptible to human papillomavirus (HPV), which can cause skin and genital warts and can potentially lead to cancer. Patients with WHIM syndrome also have extremely low levels of certain white blood cells called neutrophils, which play a role in helping the body fight off infection, especially bacterial and fungal infections.[11]

The mutation that causes WHIM syndrome is inherited as an autosomal dominant trait, whereby only a single copy of an abnormal gene is necessary for the disease to appear. In most cases, WHIM syndrome is caused by mutations in the gene that creates the CXCR4 chemokine receptor however in some cases individuals do not have a detectable mutation in the CXCR4 gene, and their disorder may have other genetic causes.[11]

Generally, symptoms first appear in early childhood when most children with WHIM syndrome experience repeated bacterial infections that can be mild or severe, but usually respond promptly to antibiotic therapy. The number and frequency of infections can vary greatly from one child to another. Common infections include recurrent middle ear infections, infection of the skin and underlying tissue (cellulitis, impetigo, folliculitis, and abscess), bacterial pneumonia, sinusitis, septic arthritis, dental cavities, and infection of the gums.[11] More than 80% of the patients develop, by the age of 30 years old, widespread HPV-induced warts that are often difficult to treat, generally starting on hands and feet.[12]

CLINICAL NEED AND BURDEN OF DISEASE

In 2019, it was estimated that WHIM syndrome affected less than 0.001 in 100,000 people in the European Union.[3] This equates to an estimated prevalence in the UK of fewer than 66 people, using the 2019 mid-year population estimates.[13]

WHIM affected individuals may live well into adulthood. Major risk factors include intractable multifocal dysplastic HPV-induced lesions and invasive genital cancer, and liver failure. By the age of 40, the cancer risk is of about 30%.[12,14]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The treatment of WHIM syndrome is directed toward the specific symptoms that are apparent in each individual. Treatment may require the coordinated efforts of a team of specialists. Pediatricians, immunologists, hematologists, dermatologists, and other healthcare professionals may need to systematically and comprehensively plan an affected child's treatment.[15]

Treatment of WHIM syndrome may include immunoglobulin replacement therapy, granulocyte colony stimulating factor (G-CSF), or granulocyte macrophage colony stimulating factor (GM-CSF), to bolster production and maturation of neutrophils and reduce the incidence of infection. Vaccinations against HPV should be strongly considered in patients with WHIM syndrome given the established safety of the vaccine and the severity of HPV infections in these patients.[11]

CURRENT TREATMENT OPTIONS

There are no NICE approved treatments for WHIM syndrome.

PLACE OF TECHNOLOGY

If licenced, mavorixafor would provide the first targeted treatment option for WHIM syndrome in patients 12 years and above, whose care is currently limited to the treatment of the different symptoms of WHIM syndrome.

CLINICAL TRIAL INFORMATION

Trial	**X4P-001-103;** NCT03995108, 2019-001153-10; A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Mavorixafor in Patients With WHIM Syndrome With Open-Label Extension **Phase III** - Recruiting **Location(s):** EU countries (not including UK) Australia, Israel, Republic of Korea, and United States **Primary completion date:** September 2021
Trial design	Randomised, parallel assignment, double blind
Population	N = 28 (planned), a genotype-confirmed mutation of chemokine (C-X-C motif) receptor 4 (CXCR4) consistent with WHIM phenotype, aged 12 years and older.
Intervention(s)	Randomised period: mavorixafor provided as four 100 mg capsules once daily for 52 weeks. Open-label period: mavorixafor 400mg once daily orally until commercial availability or study termination
Comparator(s)	Matched placebo.
Outcome(s)	Primary outcome(s); • Randomized Period: Time (in Hours) Above Absolute Neutrophil Count (ANC) Threshold of 500 Cells/Microliter (µL) [Time Frame: Time 0 (pre-dose, up to 15 minutes prior), 30, 60, and 90

	min (each ± 5 min) and 2, 3, 4, 8, 12, 16, and 24 hours (each ± 15 min) post-dose at Baseline, Weeks 13, 26, 39, and 52] • Open-Label Period: Percentage of Participants With Adverse Events (AEs) [Time Frame: From Day 1 (end of randomized period) up to end of study (30 days post-treatment in open-label period [Week 56 of open-label period])] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Trial	**X4P-001-MKKA; NCT03005327;** A Phase 2, Open-Label, Multi-Center Trial of Mavorixafor in Patients With WHIM Syndrome **Phase II** - Active, not recruiting **Location(s):** Australia and United States **Primary completion date:** December 2022
Trial design	Single group assignment, open label
Population	N = 15 (planned), a genotype-confirmed mutation of chemokine receptor type 4 (CXCR4) consistent with WHIM syndrome, aged 18 years and older.
Intervention(s)	Initial treatment phase: mavorixafor at 50mg once daily orally or a higher dose, with potential escalation based on area under the curve for absolute neutrophil count and absolute leukocyte count (AUCANC/ALC) values to a maximum total daily dose of 400 mg. Extension Phase: all participants will receive mavorixafor; the dose will not exceed 400 mg.
Comparator(s)	No comparator.
Outcome(s)	Only include primary outcome(s); • Mean area under the curve for absolute neutrophil count and absolute leukocyte count (AUCANC and/or AUCALC) [Time Frame: Time 0 (-15 minutes [min] pre-dose), 30, 60, and 90 min (each ± 5 min) and 2, 3, 4, 8, 12, 16, and 24 hours (each ±15 min) at Weeks 5, 13, and 21] See trial record for full list of other outcomes.
Results (efficacy)[5]	• At a median follow up of 16.5 months, we observed dose-dependent increases of absolute neutrophil counts (ANC) and absolute lymphocyte counts (ALC). At doses at or above 300 mg per day, ANC was maintained above 500 cells/µL for a median of 12.6 hours, and ALC above 1000 cells/µL for up to 16.9 hours. • Continued follow-up on the extension study demonstrated a decreased yearly infection rate from 4.63 [95%CI 3.3,6.3] events in the 12 months prior to the trial to 2.27 [95%CI 1.4, 3.5] events for patients on effective doses. • An average 75% reduction in the number of cutaneous warts was observed.
Results (safety)[5]	• Seven patients (87.5%) experienced ≥1 treatment emergent adverse event (TEAE). Three patients experienced 11 grade 1 related TEAEs: nausea (4 events), nasal dryness (2 events), dry mouth (2 events), dyspepsia (1 event), conjunctivitis (1 event),

	and dermatitis psoriasiform rash (1 event). TEAE frequency did not increase with dose. • Mavorixafor was well tolerated with no treatment-related serious adverse events.

ESTIMATED COST

The cost of mavorixafor is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

No relevant guidance identified.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

No relevant guidance identified.

OTHER GUIDANCE

- The American Society of Haematology. How I treat warts, hypogammaglobulinemia, infections, and myelokathexis syndrome. 2017.[16]
- The American Academy of Allergy, Asthma & Immunology (AAAAI) and the American College of Allergy, Asthma & Immunology (ACAAI). Practice parameter for the diagnosis and management of primary immunodeficiency. 2015.[17]

ADDITIONAL INFORMATION

X4 Pharmaceuticals Inc did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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