Risk management plan (RMP) in the EU – in integrated format

EU Risk Management Plan for Xolremdi (mavorixafor)

RMP version to be assessed as part of this application:

RMP Version number: 1.0

Data lock point for this RMP: 06 September 2024

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Rationale for submitting an updated RMP: Not applicable for initial marketing authorisation application submission

Summary of significant changes in this RMP: Not applicable

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Details of the currently approved RMP: Not applicable

QPPV name: Sanja Prpic

QPPV oversight: The content of this RMP has been reviewed and approved by the marketing authorisation applicant´s QPPV. The electronic signature is available on file.

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Part I: Product(s) Overview

Table Part I.1 – Product(s) Overview

Active substance(s) **(INN or common name)**	Mavorixafor
Pharmacotherapeutic group(s) (ATC Code)	Antineoplastic and Immunomodulating agents, Immunostimulants, Immunostimulants, Other immunostimulants, ATC code: L03AX24
Marketing Authorisation <Holder> <Applicant>	X4 Pharmaceuticals (Austria) GmbH
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Xolremdi
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Synthetic, chemical
	Summary of mode of action: Mavorixafor is an orally active inhibitor of CXCR4
	Important information about its composition: NA
Hyperlink to the Product Information	Module 1.3, Summary of Product Characteristics (SmPC)
Indication(s) in the EEA	Current: Xolremdi is indicated in patients, 12 years and older, for the treatment of WHIM syndrome (warts, hypogammaglobulinemia, infections and myelokathexis), to increase the number of circulating mature neutrophils and lymphocytes.
	Proposed (if applicable): NA
Dosage in the EEA	Current: The recommended dose of Xolremdi for all adults and adolescent patients 12 years and older weighing over 50 kg is 400 mg (four 100 mg capsules) once daily, administered orally. The recommended dose for all patients weighing ≤50 kg is 300 mg (three 100 mg capsules) once daily, administered orally.

	Proposed (if applicable): NA
Pharmaceutical form(s) and strengths	Current (if applicable): 100 mg hard capsules
	Proposed (if applicable): NA
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

WHIM (Warts, Hypogammaglobulinemia, Immunodeficiency, Myelokathexis) Syndrome

Incidence and prevalence:

WHIM syndrome is an extremely rare disorder and its exact prevalence and incidence in the general population is unknown.

National registries

The first reported prevalence of WHIM syndrome was based on the French Severe Congenital Neutropenia Registry, a national registry set up in 1993 with longstanding expertise in congenital neutropenia, which identified 7 patients and one foetus in their 2011 registry report and had calculated an incidence rate at birth for the period 1990 to 2006 of 0.23 per 1,000,000 (1 million) births and the 95% confidence interval limits were 0.0019 to 0.29 per 1,000,000 (1 million) births (equivalent to 0.0023 per 10,000 births) (Beaussant-Cohen et al., 2012).

Literature review

Literature searches are also relevant in estimating the number of affected patients. The Orphanet Report Series, Number 1, November 2023 identified 65 cases of WHIM syndrome worldwide based on data pooled from registries, national/international health institutes and agencies, MEDLINE searches, medical texts, grey literature, and Orphanet collaborating experts (Orphanet, 2023).

To better understand the WHIM syndrome clinical picture, a review of 109 case studies within the medical literature, including 2 cohort studies (Beaussant-Cohen et al., 2012 [8 patients] and Dotta et al., 2016 [21 patients]), was carried out by the Sponsor's Medical Affairs team in March 2018 and presented at the NORD Rare Diseases and Orphan Products Breakthrough Summit, Washington, DC, USA, 15-16 October, 2018 (Ebrahim et al., 2018). There were 88 distinct cases with patient-specific data identified in literature in addition to the cohort of 21 patients described by Dotta et al. (2016) . Data for all reported cases of WHIM syndrome, from 1964 to 2018, were summarised (Ebrahim et al., 2018, X4 Case Study).

The Orphanet identifies WHIM syndrome as an orphan disease, with a prevalence of <1 per 1,000,000 (1 million) individuals (Orphanet, 2024).

Conclusion on prevalence data

The prevalence of WHIM syndrome is best estimated using data from country specific patient-registries. No ethnic backgrounds have been identified as being at higher risk for WHIM syndrome, and, therefore, the prevalence observed in a country specific epidemiological study can be reasonably extrapolated to the broader European Union population.

Accordingly, prevalence is best estimated using the French registry data which in 2014 was calculated as 0.0016 per 10,000 individuals in the European Union, corresponding to 80 patients with WHIM syndrome in the European Union, and that this estimation is still valid today. More recent data from the French Severe Congenital Neutropenia Registry in 2018 report a total of 14 French patients, which corresponds to a prevalence in France of 0.002 per 10,000 inhabitants and extrapolates to an estimated total number of 106 patients with WHIM syndrome in Europe. This coincides with 2 orphan drug designations that have been granted to other sponsors for the treatment of WHIM syndrome (EU/3/14/1403 and EU/3/14/1384); and both report a prevalence of approximately 0.002 per 10,000 people in the European Union. This supports the results of the Sponsor's calculation.

Demographics of the population in the proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

The case dataset, from the targeted literature review, showed that the diagnosis of WHIM syndrome may occur at any age; patients have been diagnosed prenatally or as late as the age of 75 years (Ebrahim et al., 2018, X4 Case Study). Of the 88 patients, 79 patients had reported age at diagnosis. Among these, about 50% were diagnosed as adults (aged >18 years), and about 70% of these adults were aged 18 to 39 years at diagnosis. All other patients had received paediatric diagnoses, primarily before or at the age of 12 years. There was a predominance of female patients (61%) compared with male patients (33%) (sex was not reported for 6%). Family history contributed to the diagnosis of approximately one-third of cases. Family history is especially important for very early diagnosis and initiation of supportive care: of the 14 patients who were less than 7 years old at diagnosis, approximately 50% had a relative affected with WHIM syndrome.

A recent study of the disease progression of WHIM syndrome in an international cohort of 66 patients evaluated 57 unique, previously unreported cases of WHIM syndrome and 9 individual case reports which had been reported previously (Geier et al., 2022). The cohort does not have major overlaps with any prior reports from academic centres with high expertise in Europe (Italy, France) or the National Institutes of Health in the USA. The cohort includes nearly twice as many children (n=43, aged <18 years) as adults (n=23, aged >18 years). The median age at diagnosis was 5.5 years (range 2 weeks to 51 years). There was a predominance of female patients (62%) compared with male patients (38%). The diagnosis of the majority of patients was prompted by clinical signs related to WHIM (79%), rather than via positive family history (20%) and/or newborn screening for severe combined immunodeficiency (1.5%). In 71% of patients, both genetic testing and diagnostic bone marrow biopsy were used to confirm WHIM diagnosis. In 26% of patients, diagnosis of WHIM syndrome was confirmed solely based on genetic testing, and the remaining 2 patients were diagnosed by bone marrow biopsy and clinical signs only. Only 22.7% of patients in this cohort presented with all 4 features of the WHIM acronym. The majority of patients were Non-Hispanic White (69.7%). A further 19.7% of patients were Asian/Pacific Islander, 4.5% were of unknown race, and 3% each were Hispanic White and African American.

The main existing treatment options:

Effective therapies addressing the primary physiopathology of the disease should ideally reverse the natural history of infections and warts and reduce the risk of long-term complications such as malignancies.

There are currently no therapies approved for the treatment of patients with WHIM syndrome. Current off-label therapeutic options for patients with WHIM syndrome include G-CSF, parenteral Ig therapy, antibiotic prophylaxis, and haematopoietic stem cell transplantation (Badolato et al., 2017). In addition, plerixafor (Mozobil SmPC, 2024), a parenteral CXCR4 inhibitor, was being investigated in patients with WHIM syndrome (McDermott et al., 2023).

Standard of care treatment is currently limited to incomplete prevention or management of infection using G-CSF, which selectively increases neutrophil counts, and parenteral Ig therapy, which raises Ig levels but has no impact on circulating leukocytes or immune responses. In a recent study of 18 patients with WHIM syndrome, approximately 50% of patients received antibiotic prophylaxis, whereas granulocyte colony stimulating factor (G-CSF) and immunoglobulin (Ig) treatments were used in 72% and 55% of patients, respectively (Dotta et al., 2019).

G-CSF

No placebo-controlled studies of G-CSF for the treatment of WHIM syndrome have been conducted and use is therefore based on extrapolation of data from patients with severe congenital neutropenia (Badolato et al., 2017). Although G-CSF does correct neutropenia, based on several case studies, there is no evidence that G-CSF reduces infection rates (Badolato et al., 2017, Dotta et al., 2019) and it has been reported that patients tend to withdraw from G-CSF due to the lack of efficacy of the treatment against infections. For example, in one report, 3 patients who had long-term treatment showed no benefit and therefore discontinued treatment (Beaussant-Cohen et al., 2012). Moreover, G-CSF treatment does not correct lymphopenia and monocytopenia and does not affect warts in patients with WHIM syndrome (Badolato et al., 2017) and may also not be an appropriate therapy for patients with lymphopenia as it is reported to inhibit lymphopoiesis by inhibiting committed progenitor cells (Day et al., 2015; Winkler et al., 2013). In addition, G-CSF enhances expansion of lymphoid-biased, short-term hematopoietic stem cells (HSC) and does not have a direct effect on purified myeloid-biased, long-term HSC (Chen and Rudolf, 2021). In a recent case study of WHIM syndrome patients, 88 % (15 of 17) patients had been diagnosed with lymphopenia suggesting G-CSF use is inappropriate in a significant percentage of the WHIM syndrome population (Dotta et al., 2019). G-CSF is also associated with potentially serious safety issues including hypersensitivity reactions, pulmonary adverse events, glomerulonephritis, capillary leak syndrome, splenomegaly and splenic rupture, malignant cell growth, thrombocytopenia, leukocytosis and immunogenicity (Filgrastim SmPC, 2023). Bone pain may also be experienced and has been reported to be treatment limiting (Badolato et al., 2017, Heusinkveld et al., 2017).

Prophylactic IgG

As for G-CSF, no clinical trials with IV Ig therapy have been conducted in patients with WHIM syndrome, although there is some evidence of efficacy based on individual case studies (Heusinkveld et al., 2017). Prophylactic Ig therapy has been reported to reduce the number of pulmonary infections and, when started in early childhood, may reduce the risk of bronchiectasis (Beaussant-Cohen et al., 2012). IgG therapy is associated with potential risks including infusion reactions, hypersensitivity, thromboembolism, acute renal failure, aseptic meningitis syndrome, haemolytic anaemia and transfusion related acute lung injury (EMA, 2021). In addition, Ig therapy is administered either subcutaneously (SC) or IV which is in burdensome on the patient.

HSCT

A small number of patients have been successfully treated with allogeneic haematopoietic stem cell transplantation (HSCT). However, the application of HSCT in patients with WHIM syndrome is limited by the availability of immunologically-matched donors. HSCT is also invasive and carries with it significant risks that may not be appropriate in patients with a non-life threatening or disabling level of infections (Heusinkveld et al., 2019).

Commercially available CXCR4 injectable antagonist

The only agent that blocks the CXCR4 receptor approved in the EU, plerixafor (Mozobil SmPC, 2024), is an injectable stem cell mobilising agent. It is not approved for the treatment of WHIM syndrome. In an investigator-initiated Phase 3 trial in 20 patients with WHIM syndrome, plerixafor was non-superior to G-CSF based on the difference in a total infection severity score (a weighted composite of predefined infection frequency and severity parameters [number of infections, presence or absence of fever, sterile versus nonsterile site of infection, route of administration of antibiotics, and level of care needed]). Exploratory endpoints suggested that plerixafor may be non-inferior to G-CSF for durably increasing the ANC and may have an advantage over G-CSF for elevating the ALC, for wart regression, and for limiting bone pain. There were several limitations with this crossover study design including, subjective classification of infections, co-administration of Ig and prophylactic antibiotics in some patients, potential for carry over effects, and low dose of G-CSF (McDermott et al., 2023). Plerixafor is associated with potential for allergic and vasovagal reactions as well as potential effects on the spleen (Mozobil SmPC, 2024).

In addition, plerixafor is not clinically practical as a long-term treatment for WHIM syndrome as it does not have ideal properties for a chronic disease treatment:

- Plerixafor is not orally bioavailable and must be administered by SC injection.
- Plerixafor has a short half-life (~3- to 5 hours) and WHIM syndrome patients are required to self-administer twice daily to achieve a sustained effect.
- Plerixafor is not formulated to be administered at the lower doses required for treating WHIM syndrome.

A second injectable stem cell mobilising agent which was not evaluated in patients with WHIM syndrome, motixafortide, has recently been approved in the US (Aphexda® USPI, 2023) but is not available in the EU at this time.

Antibiotics and antivirals

Antibiotics and antivirals are used extensively in patients with WHIM syndrome to treat and prevent recurrent infections. However, despite frequent administration of antibiotics and antivirals, patients with WHIM syndrome continue to experience frequent, recurrent, and severe infections as these therapies do not treat the underlying mechanism of disease (Kawai and Malech, 2009, Beaussant-Cohen et al., 2012). Additionally, frequent use of antibiotics often leads to resistance and pathogen persistence, exemplified by the long duration of infections seen in these patients, and the frequent alternation of antibiotic therapies (Heusinkveld et al., 2017, Kawai and Malech, 2009, Mohammadinejad et al., 2015, Huemer et al., 2020).

Management of chronic HPV infections characteristic of WHIM syndrome has been particularly problematic. Neither standard methods (cauterisation, laser therapy) nor more aggressive approaches (surgical removal, interferon, cidofovir, imiquimod) have proven effective. Anecdotal experience with Gardasil vaccine suggests that long-term efficacy may be limited (Handisurya et al., 2010).

Overall, there is a great unmet need for an effective therapy that addresses the underlying pathogenic mechanism of neutropenia and lymphopenia leading to frequent, recurrent, severe, and lengthy infections.

Conclusions on unmet medical needs

Current approved treatments focus on correcting neutropenia, hypogammaglobulinemia, and/or treating bacterial infections and do not address lymphopenia, high rates of infection nor the increased risk of malignancy. In practice, each patient's course of treatment is largely dependent upon attempting symptomatic management.

Antibiotics and antivirals provide only symptomatic treatment and may lead to pathogen resistance (Heusinkveld et al., 2017, Kawai and Malech, 2009, Mohammadinejad et al., 2015, Huemer et al., 2020). Although G-CSF does correct neutropenia, based on several case studies, there is no evidence that G-CSF reduces infection rates and some evidence suggests that patients withdraw from G-CSF as a result of lack of efficacy (Badolato et al., 2017; Dotta et al., 2019). Moreover, G-CSF treatment does not correct lymphopenia and monocytopenia and does not affect warts in patients with WHIM syndrome (Badolato et al., 2017). In addition, treatment-limiting adverse events, including bone pain, have been described in patients receiving G-CSF (Badolato et al., 2017, Heusinkveld et al., 2017). Additional, less common, treatment-limiting complications of G-CSF include myelofibrosis and an increased risk of leukaemia (Avalos et al., 2011; Lyman et al., 2018).

Administration of Ig therapies raises Ig levels but has no impact on circulating leukocytes or immune responses. There is limited evidence of long-term effectiveness (Badolato et al., 2017). IgG is also administered SC or IV which is burdensome to patients.

Plerixafor is being investigated for the treatment in WHIM syndrome but was non-superior to G-CSF based on the difference in a total infection severity score (McDermott et al., 2023). Plerixafor is also unsuitable for long-term treatment due to the route of administration and half-life which would be overly burdensome for patients.

HSCT has been used successfully in a small number of WHIM syndrome patients but is associated with significant risks and is reliant on the availability of a suitable donor (Heusinkveld et al., 2019).

Independent of side effects and treatment burden on patients, the inability of available therapies to prevent bacterial infection presents a significant challenge to patient quality of life. Missed school or work may diminish psychosocial function, and repeated infections can cause progressive lung damage, leading to bronchiectasis, and in some cases, dependence on supplemental oxygen (Heusinkveld et al., 2017). Though individual infections are often resolved, the impact of repeated infection on patient health and functioning can be substantial.

In conclusion, current treatments for WHIM syndrome are non-specific, burdensome for patients due to the route of administration and side effects, do not address the primary underlying defects, and have limited effectiveness to mitigate infections and little to no effectiveness to control HPV-infection and related risk of malignancy (Kawai et al., 2009, Beaussant-Cohen et al., 2012). The challenges and limitations of the currently available treatment options illustrate that the primary underlying drivers of morbidity in WHIM syndrome remain unaddressed. In particular, there is a great unmet need for an effective therapy that addresses the underlying pathogenic mechanism of neutropenia and lymphopenia leading to frequent, recurrent, severe, and lengthy infections and that is convenient for patients to administer considering the chronic nature of the disease.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

WHIM syndrome is a rare, autosomal dominant, combined primary immunodeficiency syndrome caused by inherited gain of function (GOF) mutations altering the CXC chemokine receptor Type 4 (CXCR4) receptor (Online Mendelian Inheritance in Man [OMIM], 2021). Repeated bacterial infections are the most common clinical manifestations, whereas neutropenia, secondary to myelokathexis (i.e., the abnormal retention of mature neutrophils in the bone marrow), lymphopenia, and hypogammaglobulinemia are common laboratory findings. Additionally, patients present with low numbers of circulating monocytes.

The natural history of WHIM syndrome has been characterised in 2 recently published studies: A study of the long-term outcomes of WHIM syndrome in an international cohort of 18 patients (Dotta et al., 2019) and a study of the disease progression of WHIM syndrome in an international cohort of 66 patients (Geier et al., 2022).

Dotta et al., (2019) showed that the clinical features first manifest at 2.2±2.6 years of age, whereas the disease diagnosis was often delayed until 12.5±10.4 years of age. The most common presentation was severe bacterial infection (78%). Pneumonia recurrence was observed in 61% of patients and was complicated with bronchiectasis in 27%. Skin warts were observed in 61% of patients at a mean age of 11 years, whereas human papilloma virus (HPV)-related malignancies manifested in 16% of patients (Dotta et al., 2019). Similarly, Geier et al., (2022) showed that 70% of symptomatic patients had their first initial WHIM clinical manifestation before the age of 1 year, and 96% had it before the age of 5 years; and infections were the most common initial clinical manifestation of WHIM syndrome (88%), dominated by upper and lower respiratory tract infection (49%), followed by otitis media (23%), and skin infections (13%).

Overall, infections were seen in 92% of patients in the Geier et al., (2022) study. The pattern of infections varies between individual patients but typically includes sites such as the upper and lower respiratory tract (e.g., otitis media, sinusitis, bronchitis, and pneumonia) along with the skin and underlying tissue (cellulitis, impetigo, folliculitis, and abscess). In addition, infections of joints (septic arthritis), gums (periodontitis), bone (osteomyelitis), urinary tract, and central nervous system (meningitis) have been reported (Beaussant-Cohen et al., 2012, Heusinkveld et al., 2017; Dotta et al., 2019). Clinical onset is most often observed in early childhood and is usually marked by an increase in the frequency and severity of both gram-negative and gram-positive bacterial infections as well as viral infections.

Although infection normally resolves in response to antibiotics and may not require hospitalisation, increased frequency and severity of recurrent and chronic infections in WHIM syndrome is associated with significant morbidity (Beaussant-Cohen et al., 2012, Heusinkveld et al., 2017; Geier et al., 2022). Specific examples include:

- Repeated pulmonary infections leading to bronchiectasis and further complicated by respiratory failure, lung collapse (atelectasis), heart failure, as well as infection due to unusual organisms such as Pseudomonas, Stenotrophomonas, and atypical mycobacteria (NORD, 2016; Kawai et al., 2009; Heusinkveld et al., 2017). In a review of case report literature, 39% of patients were reported to have suffered from pneumonia on at least 1 occasion, with 17% reported to have had numerous repeated episodes (Ebrahim et al., 2018). Similarly, Geier et al., (2022) reported that pneumonia was experienced by 63% of patients. Infection-associated end organ damage, including bronchiectasis and bronchiectasis due to recurrent pneumonias was experienced by 20% of patients.
- Additional infections reported in a review by Heusinkveld et al., 2017 include extracellular gram-positive and gram-negative pathogens, including Proteus mirabilis (n=3), Haemophilus influenzae (n=9), Pseudomonas aeruginosa (n=4), Streptococcus pneumonia (n=8), and Staphylococcus aureus (n=8).

- Recurrent ear infections leading to hearing loss and delayed speech development (Liu et al., 2012); otitis media was experienced by 68% of patients and hearing loss due to recurrent otitis by 20% of patients (Geier et al., 2022).
- Recurrent gum infections leading to tooth loss (Brenchley et al., 2024).

In the 2 recent natural history studies by Dotta et al., (2019) and Geier et al., (2022), 100% and 98% of patients, respectively, had severe neutropenia (ANC <500/µL per National Cancer Institute, 2017). Lymphopenia was detected in 88% of patients in both studies and hypogammaglobulinemia was detected in and 58% and 65% of patients, respectively. Neutropenia and lymphopenia are believed to be the major contributors to the susceptibility to infections (Dale et al., 2020).

The risk of infection in patients with cancer affected by neutropenia is substantially linked to the duration of severe neutropenia (Bodey et al., 1966, Hsieh et al., 2007). The longer the duration of neutropenia, the higher the risk of infection. In the Bodey study in patients with leukaemia and severe neutropenia (ANC <100/µL), active infections were present on 53% of the days studied (Bodey et al., 1966). The percentage of time suffering from active infections decreased sharply with increasing neutrophil levels, and the plateau was reached at ANC levels above 1,000/µL (Cadavid, 2021). Another important development linking neutropenia to risk of infection came from studies of patients receiving chemotherapy that causes acute neutropenia (Centers for Disease Control and Prevention [CDC], 2022).

A longitudinal analysis of laboratory values for 35 untreated patients with WHIM syndrome (that neither received G-CSF or CXCR4 antagonists) showed progressive neutropenia in 20 patients (57%) and progressive lymphopenia in 25 patients (71%) (Geier et al., 2022). Patients with WHIM syndrome displayed moderate leucopoenia prior to age 4 weeks until age 1 year which progressively worsened reaching a median WBC count of 830 cells/mm^3 (n=8) at age 10 years (from 3920 cells/mm^3 [n=5] at birth). Neutropenia varied through life; however, there was a trend towards a progressive loss of neutrophils with a median ANC count of 197 cells/mm^3 (n=8) at age 5 years (from 540 cells/mm^3 [n=6] at birth). Patients with WHIM syndrome displayed progressive lymphopenia in early childhood, with an ALC count of 787 cells/mm^3 (n=13) at age 5 years (from 2350 cells/mm^3 [n=4] at birth).

The high rate of repeated, often severe infections can significantly impact quality of life. Absence from school or work due to repeated hospitalisation for severe infections may weaken psychosocial functioning in patients with WHIM syndrome. This can also be impacted by the sequelae of such infections. For example, the need for supplemental oxygen following bronchiectasis and potential delayed speech development in children as a result of repeated ear infections has been observed (Heusinkveld et al., 2017; Heusinkveld et al., 2019; Geier et al., 2022).

Patients with WHIM syndrome are particularly susceptible to HPV-related disease. HPV- related manifestations were seen in 42% of patients in the Geier et al., (2022) study. In a recent cohort study of 18 patients, skin warts occurred in 61% of patients (11/18), with a median age at onset of 10 years (range 5 to 19 years) (Dotta et al., 2019). These warts are classically reported to be refractory to treatment. Skin warts affect the hands or feet, face, arms or legs and may proliferate extensively. Patients may develop ano-genital warts (condylomata acuminate) with a high risk of malignant transformation (Beaussant-Cohen et al., 2012). Approximately 20 to 25% of patients have genital-anal condyloma acuminata that may progress to invasive cancer (Beaussant-Cohen et al., 2012). Patients are susceptible to anorectal carcinoma, and female patients may develop significant cervical and vulvar dysplasia that progresses to invasive genital cancer. In the case dataset, anogenital warts were found in 18% (n=20) of patients (plus 1 possible case), with 4 cases of cervical dysplasia. None of the currently available treatments are able to prevent HPV infection or substantially reduce the burden of lesions (Heusinkveld et al., 2017). In addition to widespread susceptibility to HPV, multiple case studies document infection with varicella zoster virus (n=8), oral herpes simplex virus (HSV) (n=7),

and cytomegalovirus (n=1), as well as Epstein-Barr virus+ B-cell lymphoma (n=2), rubeola (n=1), and rubella (n=2) (Heusinkveld et al., 2017, Badolato et al., 2017).

Cohort level data and literature reviews show that patients with WHIM syndrome also have an increased risk of malignancy including HPV-induced cancer and lymphoma with an overall cancer risk that has been estimated to be of 30% by the age of 40 (Beaussant-Cohen et al., 2012).

The disease is associated with significant morbidity and mortality and has been recognised by the US FDA Center for Drug Evaluation and Research (CDER) as a 'severely debilitating or life-threatening hematologic disorder' for which there are no approved treatments directed at the primary pathophysiology of the syndrome (FDA CDER, 2019) and mavorixafor has received orphan drug designation in the EU (EU/3/19/2183) in recognition of the rare and chronically debilitating nature of the disease as well as the potential for life-threatening infections.

Important co-morbidities:

There are currently no expected co-morbidities and co-medications in the target population for this rare immunodeficiency disorder with an estimated prevalence of <1 per 1,000,000 (1 million) individuals. No ethnic backgrounds have been identified as being at higher risk for WHIM syndrome and the diagnosis of WHIM syndrome may occur at any age. Comorbidities have been identified that are a result of the high rate of severe infections experienced by patients with WHIM syndrome and have been described above.

A recent review based on analysis of all 105 published cases of WHIM syndrome noted that WHIM syndrome patients usually appear quite well in between infectious events, and comorbidities rarely include reports of immunologically-mediated disease (Heusinkveld et al., 2019). The dataset included 1 report of diabetes mellitus (Type 1), 4 reports of possible allergic reactions (IgG, Levaquin, strawberries and vancomycin) and 1 report of asthma. There were no other descriptions of autoimmunity, food allergy or allergy to common aero-allergens. In addition, there were no cases reported of myocardial infarction, angina, hypertension or stroke. This apparent comorbidity deficit could be due to a reporting bias because of the focus in the papers on WHIM phenotypes, or in part to the relatively narrow age distribution of the cohort (only 9 patients over age 40). Apart from HPV-associated squamous cell carcinoma, EBV+ B cell lymphoma and 2 cases of EBV-negative cutaneous lymphoma, only 2 other defined cancers were reported among the 105 patients with WHIM syndrome: a melanoma and a basal cell carcinoma. There were no paediatric cases of cancer, and no cases of common epithelial cancers (colon, breast, lung).

Part II: Module SII – Non-clinical part of the safety specification

Toxicity

Mavorixafor was tested in repeat-dose toxicity studies up to 28 days in rats and 39-weeks in dogs. Although AMD11070PHB was never used in clinical studies, the 26-week study in rats with this salt form provides supportive chronic toxicity data in rat. The NOAEL in the pivotal 4-week repeat-dose rat study with mavorixafor was 125 mg/kg/day with bone marrow hypocellularity observed at a higher dose of 250 mg/kg/day. Based on the total $AUC_{0\text{-last}}$, the exposures at the NOAEL in the 28-day study in female and male rats were 0.3-fold and 0.2-fold, respectively, compared to the exposure at the recommended human dose of mavorixafor at 400 mg once daily (mean $AUC_{0\text{-}24}$: 13970 ng*h/mL), while the safety margins based on unbound drug in plasma were 1.4-fold and 1.0-fold, respectively. In the pivotal 39-week repeat dose toxicology study in dogs, the NOAEL after oral capsule dosing in beagle dogs was determined to be 34.1 mg/kg/day in females and 11.4 mg/kg/day in males. Based on

the total AUC_{0-24}, the exposures at the NOAEL in the 39-week study in females and males were 3.3-fold and 0.7-fold, respectively, compared to the exposure at the recommended human dose of mavorixafor at 400 mg once daily, while the safety margins based on unbound drug in plasma were 13.5-fold and 1.9-fold, respectively. The NOAEL in males was lower due to adverse effects on the testes (seminiferous tubule degeneration/atrophy) in male animals at 34.1 mg/kg/day. No testicular changes were observed in a prior 13-week study in dogs (Study X4P-001-TOX-018) at the 70 mg/kg/day dose. No testicular changes were observed in the 26 week study, with 6 week recovery in juvenile dogs (X4P-001-TOX-033). Potential risk of testicular toxicity in dogs with chronic treatment was communicated to male subjects in the Phase 3 clinical study. Testicular assessments were performed in Study X4P-001-103 only. In this study, testicular ultrasounds were normal throughout the duration of the study and local testicular evaluation showed generally similar results between treatment groups. Across all mavorixafor clinical studies, TEAEs reported within SOC reproductive system and breast disorders were very infrequently reported, and all events occurring in mavorixafor-treated patients were deemed unrelated or unlikely related to drug. The significance to humans of the testicular toxicity findings in animal studies is unclear. The TEAE and testicular assessments in the clinical trials to date do not show evidence of testicular toxicity associated with mavorixafor treatment. Testicular toxicity is included in this RMP as an important potential risk.

Accumulation of pigment consistent with lipofuscin in multiple organs (liver, kidney, gallbladder, salivary gland, pyloric stomach) was observed at doses of 3.8 mg/kg/day and above in dogs. Liver necrosis observed in a 13-week toxicity study in dogs at doses ≥10 mg/kg/day was not replicated in the 39-week chronic toxicity study up to the highest dose tested (34.1 mg/kg) wherein the exposure achieved was nearly 4-fold that of the 13-week study. No patient in either of the two WHIM syndrome studies experienced clinically significant abnormalities in ALT, AST, or alkaline phosphatase (ALP) enzyme levels and no incidences of drug -induced liver injury in patients with WHIM syndrome or chronic neutropenia have been reported.

There was no evidence of mavorixafor related liver injury in oncology studies (X4P-001-RCCB, -RCCA, -MELA, and -204 studies). Findings consistent with drug induced hepatic injury have not been observed in studies conducted in healthy human volunteers.

Overall, there is no evidence of mavorixafor related hepatic injury, including in patients with WHIM syndrome. The significance to humans of the hepatotoxicity findings in animal studies is unclear. However, the number of patients and duration of exposure are limited, therefore hepatoxicity is included in this RMP as an important potential risk.

The 26-week rat study conducted with the para-hydroxybenzoate (PHB) salt form of mavorixafor, referred to as AMD11070PHB, provides supportive data for the chronic toxicity of mavorixafor in rats. Significant findings in the 26-week rat study of AMD11070PHB included retinal degeneration, with dose-related increases in both incidence and severity; a single male rat had this change at the low dose [40 mg/kg/day free base equivalent (FBE)]. Related findings reported as "retinal atrophy" were described only in the high-dose group (200 mg/kg/day FBE). Overall, retinal changes appeared to decrease among animals in the 4-week recovery group. These studies used albino rats, which are known to have increased sensitivity to ambient light-induced retinopathy; consequently, the clinical implications of these findings are uncertain. No retinal findings were observed in rats given AMD11070PHB for 13 weeks, in rats given X4P-001 (freebase) for 4 weeks, or in dogs given either drug form for up to 13 weeks. Dogs administered mavorixafor for 39 weeks exhibited retinal changes which were determined to be non-adverse. Close monitoring for eye toxicities and regularly scheduled ophthalmologic examinations were included in the clinical studies with mavorixafor. An extensive review of the data was also performed by an independent central review and an external ocular expert.

Following thorough analysis of the data in patients with WHIM syndrome and all other clinical studies conducted by X4 Pharmaceuticals, there has been no clinical evidence of retinal degeneration and atrophy. The significance of the initial non-clinical findings of retinal degeneration and atrophy to humans is not certain. Importantly, the retinal changes observed in initial non-clinical studies have not been reported in subsequent non-clinical studies, or in clinical studies with mavorixafor. Therefore, the likelihood of retinal adverse reactions with mavorixafor is low.

The most commonly occurring eye-related TEAEs across all mavorixafor studies were dry eye and ocular/conjunctival hyperaemia. These mild and generally short-lived events were reported more frequently in the oncology studies and healthy subject studies, with infrequent reports in patients with WHIM syndrome. Retinal degeneration and atrophy is included as an important potential risk of mavorixafor.

Based on the exposures observed at the NOAEL in the pivotal repeat-dose toxicity studies of mavorixafor in rat and dogs, the safety profile of mavorixafor supports use in the intended population.

Mavorixafor was not genotoxic in any of the standard in vitro or in vivo assays (bacterial reverse mutation, chromosome aberration, or rat micronucleus).

Tolerability and preliminary embryofoetal development studies were conducted in rabbits (X4P-001-TOX-022) and rats (X4P-001-TOX-023), respectively. Due to the poor tolerability observed at sub-clinical exposures in preliminary embryofoetal development studies in animals, a weight of evidence assessment was conducted to evaluate the risk of mavorixafor administration on pregnancy and embryofoetal development. A literature search revealed that CXCR4 is critical during normal embryonic, foetal, and neonatal development. Potential inhibition of the pathway by mavorixafor is anticipated to result in significant developmental toxicity. In mice, CXCR4-/- knockout is embryo lethal and causes multiple developmental toxicities, most notably in the hematopoietic, cardiovascular and nervous systems (Ma et al., 1998, Zou et al., 1998). CXCR4-deficient mice have severely reduced B-lymphopoiesis, reduced myelopoiesis in foetal liver, and a virtual absence of myelopoiesis in bone marrow. The cerebellum develops abnormally with an irregular external granule cell layer, ectopically located Purkinje cells, and numerous chromophilic cell clumps of abnormally migrated granule cells within the cerebellar anlage (Ma et al.,1998). The phenotype of an SDF-1 (CXCR4 ligand)/CXCR4 knock-out mouse is comparable to that of a mouse exhibiting DiGeorge syndrome, with defects in heart development and mental retardation (Escot et al., 2016). DiGeorge syndrome, is the most common human genetic deletion syndrome (22q11.2 deletion), resulting in mental disorders, craniofacial dysmorphogenesis, thymus hypoplasia, and congenital heart defects caused by cardiac outflow anomalies. Additionally, $CXCR4^{-/-}$ mice display impaired vascularization in various organs, including the intestines, stomach, and heart. The latter is a ventricular septal defect that occurs during embryogenesis (Tachibana et al., 1998). Furthermore, the approved CXCR4 antagonist Mozobil® (plerixafor) has known effects on foetal development in animal models. According to the drug label, plerixafor is teratogenic in animals and may cause foetal harm when administered to a pregnant woman. In contrast to mice with targeted deletion of CXCL12 or CXCR4, which die between embryonic days 15 and 18 of gestation, $CXCR4^{+/1013}$ (heterozygous knockout) mice are viable and their development appears normal. Histologic analyses of $CXCR4^{+/1013}$ mice showed no apparent morphologic abnormality in the myocardium architecture, cerebellum organization, Peyer patches architecture and distribution, and Malpighi's glomerulus structure in the kidney. Together with the fact that $CXCR4^{+/1013}$ mice display no alterations in weight and growth rate, these data indicate that the gain of CXCR4 function has no deleterious developmental effect (Balabanian et al., 2012). Based on the weight of evidence assessment and given the low potential margins (fractional margins) that can be achieved in test species of rats and rabbits, it is concluded that adequate testing cannot be achieved and definitive studies for embryofoetal development at low doses are not appropriate.

Based on the available literature, mavorixafor is expected to adversely affect embryo-foetal development when administered during pregnancy. Therefore, mavorixafor is contraindicated during pregnancy, and it is recommended that women of reproductive potential should use effective contraception during treatment and for three weeks after the final dose. Furthermore, it is recommended that male patients with female partners of childbearing potential should use condoms during treatment and for 3 weeks after the final dose. Embryo-foetal toxicity is included as an important potential risk in this RMP.

It is not known whether mavorixafor is excreted in human milk. Because many drugs are excreted in human milk, subjects should not breastfeed during treatment, and for 3 weeks after the final dose of mavorixafor. A decision must be made whether to discontinue breastfeeding during treatment and for three weeks after the final dose, or to discontinue Xolremdi therapy, considering the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Definitive juvenile toxicity studies in rats were not feasible as the exposures at the LOAEL in juvenile rats were below the clinical exposure levels. X4 believes that although definitive juvenile rat toxicity studies are not feasible, the 9-month chronic toxicity study initiated using dogs 5.5 to 6.5 months of age is sufficient to address the non-clinical safety for treatment of 8 to 12-year-old paediatric patients. This age in dogs is considered to be developmentally relevant to humans approximately 8 years of age and above. In particular, organ systems of potential importance to paediatric populations treated with mavorixafor (see subsequent discussion), including the endocrine and nervous systems and the eye, complete maturation during the same approximate postnatal period in humans and dogs (beginning around 7 to 8 years of age in humans and 5 to 6 months of age in Beagle dogs), according to ICH S11 Guideline (2020). Information obtained from this study is considered of particular relevance to paediatric populations due to the postnatal maturations of the organ systems involved included the lack of drug-related adverse CNS effects, as evaluated by a dedicated neurological examination and brain histopathology, at doses up to and including the highest dose tested, 34.1 mg/kg/day. This is considered important due to the role of the CXCR4 receptor in development of CNS structure and function (Ma et al., 1998). While children as young as 2 months of age have been treated with a single high dose (0.24 mg/kg/d) of plerixafor for stem cell mobilization, there is no data on chronic use of a CXCR4 inhibitor in paediatric patients (Vettenranta et al., 2012; Aabideen et al., 2011). The juvenile toxicity study in dogs, conducted in accordance with the agreed EU paediatric investigation plan, supports the use of mavorixafor down to 2 years of age. No further measures are proposed as part of this RMP.

Mavorixafor is not immunosuppressive at doses up to 250 mg/kg/day in rats and not cytotoxic to granulocyte-macrophage, erythroid, or multipotential progenitor cells up to a concentration of 10 µM (3500 ng/mL). No phototoxicity risks are expected for humans based on MEC values.

Safety pharmacology

Secondary pharmacodynamic studies identified several off-target receptors inhibited by mavorixafor, with IC_{50} values ranging from 0.52 µM (182 ng/mL) to 16.2 µM (5662 ng/mL). These IC_{50} values are well above the IC_{50} values for CXCR4 binding of <20 nM. There is no evidence of secondary pharmacologic effects in vivo with mavorixafor in either non-clinical or clinical studies to date.

In vitro measurements of hERG mediated potassium current showed no significant change in the presence of mavorixafor at measured concentrations of 3.9 µM (1363 ng/mL) and a modest (32%) inhibition of hERG at measured concentration of 13.28 µM (4648 ng/mL). In addition, the 13-week repeat dose study in dogs with AMD11070PHB at doses up to 50 mg/kg FBE and 39-week study in dogs with mavorixafor at doses up to 34.1 mg/kg/day, showed no toxicologically significant changes in ECG. Mavorixafor shortened, rather than lengthened, the APD in isolated dog Purkinje fibres at 10 µM

(3495 ng/mL) and 100 µM (34948 ng/mL) concentrations. There are extensive data with no evidence of effects on QT interval from a Phase 3 clinical study; however, greater than 10ms prolongation of QTc was observed at supratherapeutic doses in a thorough QT study (study X4P-001-106). A potentially relevant effect on QT could, therefore, be possible in the event of a drug-drug interaction. This has, however, been appropriately addressed in the SmPC and package leaflet (PIL).

No adverse effects on CNS or respiratory function were observed in rats up to the highest tested dose of 1000 mg/kg. With the exception of increased heart rate, there were no test article related effects on cardiac function parameters in dogs administered a single dose of mavorixafor at 50, 150 and 400 mg/kg.

Other toxicity-related information or data

In vitro assay results in HLM suggest that CYP2D6 and CYP3A4 were the major CYP enzymes contributing to the metabolism of mavorixafor. Therefore, inhibitors or inducers of CYP3A4 and CYP2D6 may potentially affect the PK of mavorixafor.

In vitro studies suggest that mavorixafor may be an inhibitor of transporters P-gp, OAT1, OCT2, and MATE1. Data from an in vitro screening assay suggest that mavorixafor is subject to active transport and may be a substrate for P-gp.

Two Phase 1 clinical studies have been conducted to assess potential DDIs with mavorixafor: Study X4P-001-108 (evaluation of a drug interaction between mavorixafor and the combined oral contraceptive) and Study X4P-001-109 (evaluation of drug interactions of mavorixafor with cytochrome P450 enzymes and drug transporters).

Mavorixafor is a substrate of CYP3A4. Concomitant use of strong CYP3A4 inhibitors may result in increased mavorixafor exposure. Therefore, concomitant use of mavorixafor with strong CYP3A4 inhibitors should be done with caution. A reduction in daily dosage of mavorixafor is recommended when co-administered with a strong CYP3A4 inhibitor.

Mavorixafor is a strong inhibitor of CYP2D6 and there is potential for DDIs when mavorixafor is co-administered with certain drugs metabolised by the CYP2D6 isoenzyme. Co-administration of mavorixafor with medications highly dependent on CYP2D6 for clearance and that have a narrow therapeutic index is contraindicated. A clinical DDI study between mavorixafor as a DDI object and a CYP2D6 precipitant PI will be conducted as a post-marketing commitment.

The potential for DDI risk is appropriately labelled in the SmPC and therefore DDIs are not included as risks within this RMP.

Part II: Module SIII – Clinical trial exposure

All tables included in this section provide data from X4-Sponsored clinical trials only; data from 12 patients included in the clinical trial run by Abbisko are not included.

Table SIII.1: Duration of exposure

Cumulative for all indications (person time)		
Duration of exposure	Patients	Person time (patient years)
<6 m	274	23.5
6 m to <12 m	36	23.0
12 m to <24 m	26	38.5

24 m to <36 m	15	36.2
36 m to <48 m	11	39.0
≥48 m	6	26.0
Total	368	186.3
WHIM Syndrome		
Duration of exposure	Patients	Person time (patient years)
<6 m	7	1.9
6 m to <12 m	3	2.2
12 m to <24 m	8	12.4
24 m to <36 m	10	24.6
36 m to <48 m	6	21.6
≥48 m	4	17.4
Total for indication	38	79.9
Chronic Neutropenia Disorders		
Duration of exposure	Patients	Person time (patient years)
<6 m	28	3.0
6 m to <12 m	15	7.8
12 m to <24 m	0	0
24 m to <36 m	0	0
36 m to <48 m	0	0
≥48 m	0	0
Total for indication	43	10.8
Healthy Volunteer		
Duration of exposure	Patients	Person time (patient years)
<6 m	172	4.8
6 m to <12 m	0	0
12 m to <24 m	0	0
24 m to <36 m	0	0
36 m to <48 m	0	0
≥48 m	0	0
Total for indication	172	4.8
Oncology		
Duration of exposure	Patients	Person time (patient years)
<6 m	67	13.8
6 m to <12 m	18	13.0
12 m to <24 m	18	26.1
24 m to <36 m	5	11.7
36 m to <48 m	5	17.4
≥48 m	2	8.6
Total for indication	115	90.7

Table SIII.2: Age group and gender

All Indications				
Age group	Patients		Person time (patient years)	
	M	F	M	F
<18 years	8	11	16.9	17.1
≥18 to <65 years	156	128	65.2	51.5
≥65 years	48	17	28.8	6.9
Total	212	156	110.9	75.4
WHIM Syndrome				
Age group	Patients		Person time (patient years)	
	M	F	M	F
<18 years	7	8	16.4	16.6
≥18 to <65 years	6	15	12.7	33.7
≥65 years	1	1	0.4	0.1
Total	14	24	29.5	50.4
Chronic Neutropenia Disorders				
Age group	Patients		Person time (patient years)	
	M	F	M	F
<18 years	1	3	0.5	0.5
≥18 to <65 years	14	23	4.2	5.1
≥65 years	2	0	0.5	0
Total	17	26	5.2	5.6
Healthy Volunteers				
Age group	Patients		Person time (patient years)	
	M	F	M	F
<18 years	0	0	0	0
≥18 to <65 years	90	81	2.7	2.1
≥65 years	0	1	0	0.04
Total	90	82	2.7	2.1
Oncology				
Age group	Patients		Person time (patient years)	
	M	F	M	F
<18 years	0	0	0	0
≥18 to <65 years	46	9	45.6	10.6
≥65 years	45	15	27.8	6.7
Total	91	24	73.5	17.3

Table SIII.3: Dose

All Indications		
Dose of exposure	Patients	Person time (patient years)
200mg BID	12	5.5

50mg QD	2	8.6
100mg QD	2	1.1
200mg QD	26	37.7
300mg QD	2	7.5
400mg QD	273	119.9
600mg QD	9	5.8
800mg QD	30	0.08
1000mg QD	6	0.02
1200mg QD	6	0.02
Total	368	186.3
WHIM Syndrome		
Dose of exposure	Patients	Person time (patient years)
50mg QD	2	8.6
100mg QD	2	1.1
200mg QD	8	17.3
300mg QD	2	7.5
400mg QD	24	45.4
Total	38	79.9

Chronic Neutropenia Disorders		
Dose of exposure	Patients	Person time (patient years)
200mg QD	2	1.0
400mg QD	41	9.8
Total	43	10.8
Healthy Volunteers		
Dose of exposure	Patients	Person time (patient years)
200mg BID	8	0.05
400mg QD	122	4.7
800mg QD	30	0.08
1000mg QD	6	0.02
1200mg QD	6	0.02
Total	172	4.8
Oncology		
Dose of exposure	Patients	Person time (patient years)
200mg BID	4	5.5
200mg QD	16	19.4
400mg QD	86	60.0
600mg QD	9	5.8
Total	115	90.7

Table SIII.4: Ethnic origin

All Indications		
Ethnic origin	Patients	Person time (patient years)
Hispanic or Latino	72	9.9
Not Hispanic or Latino	289	173.3
Missing/Not Reported/Unknown	7	3.1
Total	368	186.3
WHIM Syndrome		
Ethnic origin	Patients	Person time (patient years)
Hispanic or Latino	1	0.08
Not Hispanic or Latino	37	79.9
Missing/Not Reported/Unknown	0	0
Total	38	79.9

Chronic Neutropenia Disorders		
Ethnic origin	Patients	Person time (patient years)
Hispanic or Latino	2	0.5
Not Hispanic or Latino	37	10.3
Missing/Not Reported/Unknown	4	0.01
Total	43	10.8
Healthy Volunteers		
Hispanic or Latino	62	1.9
Not Hispanic or Latino	110	2.9
Missing/Not Reported/Unknown	0	0
Total	172	4.8
Hispanic or Latino	62	1.9
Oncology		
Ethnic origin	Patients	Person time (patient years)
Hispanic or Latino	7	7.4
Not Hispanic or Latino	105	80.2
Missing/Not Reported/Unknown	3	3.1
Total	115	90.7

Part II: Module SIV – Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Criterion 1

Reason for exclusion: Participant was pregnant or breastfeeding

Is it considered to be included as missing information?: **No**

Rationale: The proposed SmPC includes that mavorixafor is contraindicated during pregnancy and it is recommended that women of reproductive potential should be advised to use effective contraception during treatment and for three weeks after the final dose. It is recommended that male patients with female partners of childbearing potential should use condoms during treatment and for 3 weeks after the final dose. Furthermore, a decision must be made whether to discontinue breastfeeding during treatment and for three weeks after the final dose, or to discontinue mavorixafor therapy, considering the benefit of breastfeeding for the child and the benefit of therapy for the woman. The risk of embryo-foetal toxicity is included as an important potential risk on the basis of non-clinical data with other products of the same class.

Criterion 2

Reason for exclusion: Participant had a known history of positive serology or viral load for HIV or a known history of AIDS

Is it considered to be included as missing information?: **No**

Rationale: Patients with HIV or AIDS are unlikely to have a different benefit risk or increased safety risk compared to participants included in the clinical studies.

Criterion 3

Reason for exclusion: Participant had a positive test result for hepatitis C or hepatitis B

Is it considered to be included as missing information?: **No**

Rationale: Patients with hepatitis C or hepatitis B are unlikely to have a different benefit risk or increased safety risk compared to participants included in the clinical studies.

Criterion 4

Reason for exclusion: Participant had an estimated glomerular filtration rate based on the Modification of Diet in Renal Disease of ≤29 mL/min/1.73 m^2 (Stage 4 or 5 chronic kidney disease)

Is it considered to be included as missing information?: **No**

Rationale: The data generated in patients with creatinine clearance in the range of 30 to 89 mL/minute (mild-to-moderate renal impairment) suggest that renal impairment does not have a significant effect on the total clearance of mavorixafor. The pharmacokinetics of mavorixafor have not been studied in patients with severe renal impairment or end stage renal disease (ESRD). The proposed SmPC includes that mavorixafor use in patients with severe renal impairment or ESRD is not recommended.

Criterion 5

Reason for exclusion: Participant had serum aspartate aminotransferase (AST) >2.5×upper limit of normal (ULN), serum alanine aminotransferase (ALT) >2.5×ULN, or total bilirubin >1.5×ULN (unless due to Gilbert's syndrome, in which case total bilirubin ≥3.0×ULN and direct bilirubin >1.5×ULN)

Is it considered to be included as missing information?: **No**

Rationale: Use in patients with hepatic impairment is appropriately mitigated in the SmPC. A hepatic impairment PK study is ongoing and results will be provided as a post-marketing commitment.

Criterion 6

Reason for exclusion: Participant had recently used another product to treat WHIM (e.g., plerixafor, antibiotics, G-CSF/GM-CSF or glucocorticoid

Is it considered to be included as missing information?: **No**

Rationale: The recent use of another product to treat WHIM is not expected to impact safety. The exclusion criterion was included to ensure the efficacy assessment for mavorixafor was not biased by other products.

Criterion 7

Reason for exclusion: Participant had, within 2 weeks prior to Day 1, received any medication that was prohibited, based on potential for drug-drug interactions

Is it considered to be included as missing information?: **No**

Rationale: The proposed SmPC provides guidance on identified drug-drug interactions including a contra-indication for use in combination with medicines that are highly dependent on CYP2D6 clearance.

Criterion 8

Reason for exclusion: Participant had a clinically diagnosed active infection (excluding warts) that had the potential to raise the ANC

Is it considered to be included as missing information?: **No**

Rationale: The presence of an active infection is not expected to impact safety. The exclusion criterion was included to ensure the efficacy assessment for mavorixafor was not biased by a raised ANC due to an infection.

Criterion 9

Reason for exclusion: Participant had a medical history of haematological malignancies

Is it considered to be included as missing information?: **No**

Rationale: Patients with haematological malignancies are unlikely to have a different benefit risk or increased safety risk compared to participants included in the clinical studies.

Criterion 10

Reason for exclusion: Participant had corrected QT interval using Fridericia's formula of >450 ms.

Is it considered to be included as missing information?: **No**

Rationale: The proposed SmPC includes appropriate warning that a dose- or concentration-dependent QTc interval prolongation has been observed with mavorixafor and that a dose reduction may be considered in patients with risk factors for QTc prolongation and/or when used concomitantly with medicinal product with a known potential to prolong the QTc interval, QTc assessment and monitoring is required and provides recommendations on dose reductions if required

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table SIV.2: Exposure of special populations included or not in clinical trial development programmes

Type of special population	**Exposure**
Pregnant women	not included in the clinical development program
Breastfeeding women	
Patients with relevant comorbidities: • Patients with cardiovascular impairment • Immunocompromised patients with a disease severity different from inclusion criteria in clinical trials	not included in the clinical development program (outside of the development indications of WHIM and chronic neutropenia)

<table>
<tr><td>• Patients with hepatic impairment</td><td>Mavorixafor has not been studied in patients with mild, moderate, or severe hepatic impairment. A hepatic impairment study is ongoing.</td></tr>
<tr><td>• Patients with renal impairment</td><td>A preliminary population PK analysis of data from studies X4P-001-RCCA and X4P-001-MKKA studies showed no correlation between the estimated baseline creatinine clearance (CRCL) and plasma clearance of mavorixafor (n=60, CRCL range: 43 to 191 mL/min, including 23 patients with CRCL of 60 to 89 mL/min and 15 patients with CRCL of 30 to 59 mL/min), suggesting that mild to moderate renal impairment did not have a significant effect on the clearance of mavorixafor. Patients with severe renal impairment or end-stage renal disease have been excluded from clinical studies and will be restricted from using mavorixafor in the product label.</td></tr>
<tr><td>Population with relevant different ethnic origin</td><td>All participants in the Phase 2 and Phase 3 WHIM syndrome studies with mavorixafor were White, except 2 participants (1 Other, Arab and 1 Other, Asian); both participants received mavorixafor in Study X4P-001-103.</td></tr>
<tr><td>Subpopulations carrying relevant genetic polymorphisms</td><td>All patients included in the WHIM phase 3 study, X4P-001-103 had a genotype-confirmed variant of CXCR4 consistent with WHIM syndrome (n=31):

<table><tr><th>Mutation</th><th>n</th><th>%</th></tr><tr><td>Arg334</td><td>22</td><td>71.0</td></tr><tr><td>c.1013C>G p.Ser338*</td><td>3</td><td>9.7</td></tr><tr><td>c.950_953del p.Leu317Profs*3</td><td>2</td><td>6.5</td></tr><tr><td>c.959_960del p.Val320Glufs*23</td><td>2</td><td>6.5</td></tr><tr><td>c.976dup p.Leu326Profs*18</td><td>1</td><td>3.2</td></tr><tr><td>c.977_978del p.Leu326Glnfs*17</td><td>1</td><td>3.2</td></tr></table></td></tr>
<tr><td>Other</td><td>not included in the clinical development program</td></tr>
</table>

Part II: Module SV – Post-authorisation experience

Mavorixafor was approved by the US FDA in April 2024. Limited data are available and are summarised below.

SV.1 Post-authorisation exposure

SV.1.1 Method used to calculate exposure

As of 6 September 2024, 10 patients had received commercial mavorixafor. As of the 6 September 2024, all patients had received mavorixafor for less than 6 months.

SV.1.2 Exposure

Table SV.1: Exposure table by indication, gender, age group and dose

Indication	Sex		Age (years)			Dose		
	Male	*Female*	*12 to ≤18*	*>18 to 65*	*>65*	*unknown*	*400 mg*	*300 mg*
WHIM Syndrome	5	5	2	6	2	0	8	2

Part II: Module SVI – Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Not applicable

Part II: Module SVII – Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

- Headache
- Dizziness
- Syncope
- Nausea
- Diarrhoea
- Dyspepsia
- Abdominal pain
- Vomiting
- Epistaxis
- Rash
- Dry skin
- Psoriasiform dermatitis
- QT prolongation

- DDIs

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):

The following have been identified as adverse reactions of treatment with mavorixafor. However, all are considered non-important identified risks as these have minimal clinical impact on the patient safety given the features of WHIM syndrome and severity of these non-serious identified risks:

- Headache
- Dizziness
- Syncope
- Nausea
- Diarrhoea
- Dyspepsia
- Abdominal pain
- Vomiting
- Epistaxis
- Rash
- Dry skin
- Psoriasiform dermatitis

The above-mentioned non-important identified risks require no further characterisation.

- QT prolongation (Torsade de pointes): An effect on QT was identified in the QT study at supratherapeutic doses of mavorixafor. The potential risk and the need to monitor in the event of co-administration with medicines that may increase exposure to mavorixafor is included in the SmPC. Provisions in the case of potential risk of QT prolongation are recognised by prescribing physicians and the risk is therefore considered to be appropriately mitigated. The risk of "QT prolongation" will also be included as a safety concern in PSURs.
- DDIs: potential DDIs including with CYP2D6 inhibitors and substrates; CYP3A4 inhibitors, inducers and substrates; p-gp substrates and inhibitors and OCT2/MATE1 substrates have been identified and appropriately labelled. Prescribers are aware of the need to adhere to guidance on DDIs and therefore the risk is considered appropriately mitigated.

These non-important identified risks are followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorised).

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risks:

There are no important identified risks with mavorixafor.

Important Potential Risks:

Embryo-foetal toxicity

Risk-benefit impact:

Based on the mechanism of action of mavorixafor, embryo-foetal toxicity is anticipated with a CXCR4 antagonist as CXCR4 is critical during embryonic, foetal, and neonatal development (Ma et al., 1998; Zou et al., 1998) and wherein inhibition of the pathway may result in significant developmental toxicity in the hematopoietic, cardiovascular, and nervous systems (Ma et al., 1998; Zou et al., 1998; Escot et al., 2016).

In the SmPC, mavorixafor is contraindicated during pregnancy, and it is recommended that women of reproductive potential should use effective contraception during treatment and for three weeks after the final dose. Furthermore, it is recommended that male patients with female partners of childbearing potential should use condoms during treatment and for 3 weeks after the final dose. It is not known whether mavorixafor is excreted in human milk. Because many drugs are excreted in human milk, subjects should not breastfeed during treatment, and for 3 weeks after the final dose of mavorixafor. A decision must be made whether to discontinue breastfeeding during treatment and for three weeks after the final dose, or to discontinue mavorixafor therapy, considering the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Given the potential for malformations on the foetus to occur in the event of pregnancy or passing mavorixafor in the milk, this is a potential significant impact on the benefit risk of mavorixafor in women of childbearing potential (WOCBP).

Testicular toxicity

Risk-benefit impact:

The significance to humans of the testicular toxicity findings in animal studies is unclear. The relevant safety data and testicular assessments in the clinical studies to date, do not show evidence of testicular toxicity associated with mavorixafor treatment. However, should the potential risk be confirmed, this would have an impact on male fertility which would impact the benefit risk of the product.

Hepatotoxicity

Risk-benefit impact:

Evidence of potential hepatoxicity was identified in non-clinical studies with mavorixafor. There is insufficient evidence of mavorixafor related hepatic injury in patients, including in patients with WHIM syndrome. However, the number of patients and duration of exposure are limited and in the event that a causal link with mavorixafor was established, this would impact the benefit risk of the product.

Retinal degeneration and atrophy

Risk-benefit impact:

Non-clinical studies identified retinal effects of degeneration and atrophy. No relevant retinal findings were identified across all WHIM syndrome and non-WHIM syndrome studies. Across all studies, the most common PTs for eye-related TEAEs were dry eye and ocular/conjunctival hyperaemia. However, the incidence of these TEAEs was very low in the WHIM syndrome studies, and almost all events were reported in studies of oncology patients and healthy volunteers. However, in the event that findings are confirmed in patients, this would impact the benefit risk of the product.

Missing information

Long-term safety including risk of malignancy

Risk-benefit impact:

The safety profile of mavorixafor is relatively well understood given the rarity of the disease and patients have been treated for up to 5 years in clinical trials. However, given the necessarily small size of the clinical trials it has not been possible to identify rare events that may occur with long-term treatment of mavorixafor that may potentially have an impact on the overall benefit-risk.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Important Potential Risk: Embryo-foetal toxicity

Potential mechanisms:

Potential inhibition of the pathway by mavorixafor is anticipated to result in significant embryo-foetal toxicity. In mice, CXCR4−/− knockout is embryo lethal and causes multiple developmental toxicities, most notably in the hematopoietic, cardiovascular and nervous systems (Ma et al., 1998, Zou et al., 1998). CXCR4 deficient mice have severely reduced lymphopoiesis, reduced myelopoiesis in foetal liver, and a virtual absence of myelopoiesis in bone marrow. The cerebellum develops abnormally with an irregular external granule cell layer, ectopically located Purkinje cells, and numerous chromophilic cell clumps of abnormally migrated granule cells within the cerebellar anlage (Ma et al., 1998). DiGeorge syndrome, is the most common human genetic deletion syndrome (22q11.2 deletion), resulting in mental disorders, craniofacial dysmorphogenesis, thymus hypoplasia, and congenital heart defects caused by cardiac outflow anomalies. The phenotype of an SDF-1 (CXCR4 ligand)/CXCR4 knock-out mouse is comparable to that of a mouse exhibiting DiGeorge syndrome, with defects in heart development and mental retardation (Escot et al., 2016). Additionally, CXCR4−/− mice display impaired vascularization in various organs, including the intestines, stomach, and heart. The latter is a ventricular septal defect that occurs during embryogenesis (Tachibana et al., 1998). Furthermore, the approved CXCR4 antagonist Mozobil® (plerixafor) has known effects on foetal development in animal models. According to the product information, plerixafor is teratogenic in animals and may cause foetal harm when administered to a pregnant woman. In contrast to mice with targeted deletion of CXCL12 or CXCR4, which die between embryonic days 15 and 18 of gestation, CXCR4+/1013 (heterozygous knockout) mice are viable and their development appears normal. Histologic analyses of CXCR4+/1013 mice showed no apparent morphologic abnormality in the myocardium architecture, cerebellum organization, Peyer patches architecture and distribution, and Malpighi's glomerulus structure in the kidney. Together with the fact that CXCR4+/1013 mice display no alterations in weight and growth rate, these data indicate that the gain of CXCR4 function has no deleterious developmental effect (Balabanian et al., 2012).

Evidence source(s) and strength of evidence:

The non-clinical data of other products with a similar mechanism of action suggest a strong potential for embryo-foetal toxicity if mavorixafor is used during pregnancy. Evidence is also based on the

available literature and experience with other products with a similar mechanism of action. Pregnant women were excluded from clinical trials with mavorixafor and no pregnancies occurred during clinical trials.

Characterisation of the risk:

There are no data on use of mavorixafor during pregnancy.

Risk factors and risk groups:

This risk is applicable to pregnant women, WOCBP and to male partners of WOCBP.

Preventability:

Mavorixafor is contraindicated during pregnancy. Female patients of childbearing potential, and male patients with female partners of childbearing potential should be advised to use highly effective form of contraception during treatment with mavorixafor and for 3 weeks after the last dose. This is further described in Part V.1, Routine Risk Minimisation Measures.

Impact on the risk-benefit balance of the product:

In the event that an impact on embryofoetal development is confirmed, this would have an impact on the benefit risk of mavorixafor, particularly for WOCBP.

Public health impact:

It is unknown at what rate developmental abnormalities would occur in the event of pregnancies occurring during treatment with mavorixafor. It should be noted that WHIM syndrome is very rare disease and therefore overall impact to public health is anticipated to be minimal.

Important Potential Risk: Testicular toxicity

Potential mechanisms:

Testicular changes were observed in the 39-week dog study. The mechanism by which mavorixafor may exert this effect is unknown.

Evidence source(s) and strength of evidence:

Evidence comes from a 39-week study in dogs; similar changes were not observed in a 13-week dog study or a 26-week dog study in juvenile dogs covering the period of reaching sexual maturity. There are no findings to date in clinical studies, although numbers are limited. The strength of the data is therefore limited at this time.

Characterisation of the risk:

Evidence comes from non-clinical studies with the 39-week study of mavorixafor in dogs. The NOAEL was 11.4 mg/kg/day in males due to the seminiferous tubule degeneration/atrophy in the testes of males at this dose. No testicular changes were observed in the 13-week study in dogs (Study X4P-001-TOX-018) at the 70 mg/kg/day given as twice daily 35 mg/kg doses with exposures of 3430 ng/mL (C_{max}) and 28075 ng*h/mL (AUC_{0-24}). Considering spermatogonial stem cells within the seminiferous tubule were still present after 39-weeks of dosing, recovery of the degeneration/atrophy can be expected. In the 13-week study, the dogs were 7 to 8 months old at the start of dosing, however dogs used in the 39-week toxicology study of mavorixafor were not sexually mature at time of study initiation (approximately 5 to 6 months of age). It is important to note that, as established in the literature, testicular observations are more commonly observed in young male dogs which have not yet reached sexual maturity (Goedken 2008).

A 26-week study in dogs aged 9 weeks at study start was conducted and the treatment period continued until an age of ~8.5 months. This is considered an appropriate age to study the potential for an impact on spermatogenesis during development as male dogs reach sexual maturity at ~ 5 to 8 months of age (ICH S11, Table A3). The data from this study did not recapitulate the findings from the 39-week study in dogs prepubertal at study start.

The anatomic pathology review of testis did not identify any treatment-related macroscopic or microscopic findings across all dose levels. There were also no findings following the 6-week recovery phase. The highest dose level in this study exceeded the exposures at the doses where findings were observed in the 39-week study. With this study in male dogs covering the period of reaching sexual maturity not showing any evidence for testicular toxicity at similar and higher exposure levels, and the difference of a background of excessive CXCR4 activity seen in humans with WHIM syndrome vs healthy animals in toxicology studies setting a different context, the translation to similar findings in humans is uncertain.

Following a request from Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM), X4 Pharmaceuticals voluntarily instituted a population-based signal detection for testicular toxicity in at -risk individuals in the Phase 3 WHIM syndrome study, X4P-001-103. Testicular assessments were not conducted in the Phase 2 WHIM syndrome study, X4P-001-MKKA.

In Study X4P-001-103, testicular ultrasounds were normal throughout the duration of the study and local testicular evaluation showed generally similar results between treatment groups. There were no TEAEs of testicular toxicity reported in any patient treated with mavorixafor in either Study X4P-001-103 or Study X4P-001-MKKA.

Across all non-WHIM syndrome studies, six male patients reported at least one TEAE under SOC reproductive system and breast disorders. The TEAEs were reported in the oncology studies, X4P-001-RCCA and X4P-001-204. The AEs all occurred during combination treatment of mavorixafor with another agent and the majority were Grade 1 in severity and all were deemed unrelated or unlikely related to mavorixafor treatment. In all other non-WHIM syndrome studies, no testicular -related TEAEs were reported.

Similarly, post-marketing data and laboratory data in 8 male patients in the OLE of the X4P-001-103 study have not shown any evidence of testicular toxicity.

The significance to humans of the testicular toxicity findings in animal studies is unclear. The safety data and testicular assessments in the clinical studies to date, do not show evidence of testicular toxicity associated with mavorixafor treatment.

<u>Risk factors and risk groups:</u>

This risk is applicable to male patients regardless of age or ethnicity.

<u>Preventability:</u>

The current SmPC includes that the effect on human fertility in males of reproductive potential is not known and summarises the non-clinical data, but no other mitigations are considered necessary. At this time there is no known mechanism by which to prevent this potential risk although, in the event that the risk is confirmed, additional monitoring could be implemented as risk mitigation.

<u>Impact on the risk-benefit balance of the product:</u>

In the event that an impact on male fertility is established, there would be an impact to the benefit risk for male patients prescribed mavorixafor.

Public health impact

WHIM syndrome is very rare disease and therefore overall impact to public health is anticipated to be minimal.

Important Potential Risk: Hepatotoxicity

Potential mechanisms:

CXCR4 and its ligand are functionally and mechanistically involved in the progression of liver fibrosis. During chronic liver injury, activation of CXCR4 on liver sinusoid endothelial cells triggers a profibrotic response. However, blocking the profibrotic CXCR4 axis has shown contradictory results on liver fibrosis in vivo; inhibition of CXCR4 does not ameliorate fibrogenesis (Wang et al., 2021).

Evidence source(s) and strength of evidence:

The potential risk of hepatotoxicity was identified in non-clinical studies. Patients were carefully monitored and at this time there is insufficient evidence of mavorixafor related hepatic injury, including in patients with WHIM syndrome. However, the number of patients and duration of exposure are limited. The strength of the data is therefore limited at this time.

Characterisation of the risk:

Potential hepatotoxicity of mavorixafor in humans was identified in a 13 -week toxicology study in beagle dogs. This study with mavorixafor (free-base) showed mild ALT elevations (1.4×ULN to 2.4×ULN) without increased bilirubin. Microscopic liver findings included multifocal necrosis (single cell) in 4 of the 12 animals dosed at 34 or 70 mg/kg/day. In contrast, the 9-month repeat dose study in dogs showed no adverse mavorixafor -related liver injuries. However, considering these findings, safety monitoring for potential liver toxicity was assessed in a number of mavorixafor clinical studies, including studies X4P 001-MKKA and X4P-001-103 by measurement of liver enzymes. Additionally, TEAEs were evaluated using the FDA Medical Queries (FMQs) for hepatic failure and hepatic injury.

The available data do not indicate that mavorixafor treatment is associated with hepatotoxicity.

No patient in either of the two WHIM syndrome studies experienced clinically significant abnormalities in ALT, AST, or ALP enzyme levels. Additionally, no incidences of drug-induced liver injury in patients with WHIM syndrome or chronic neutropenia have been reported.

There was no evidence of mavorixafor related liver injury in oncology studies involving mavorixafor (RCCB, RCCA, MELA, WM studies). Findings consistent with drug induced hepatic injury have not been observed in studies conducted in healthy human subjects.

In conclusion, there is insufficient evidence of mavorixafor related hepatic injury, including in patients with WHIM syndrome. However, the number of patients and duration of exposure are limited. The strength of the data is therefore limited at this time.

Risk factors and risk groups:

This risk is applicable to all patients but may be particularly applicable to patients with hepatic impairment.

Preventability:

The current SmPC summarises the non-clinical data, but no other mitigations are considered necessary. At this time there is no known mechanism by which to prevent this potential risk.

Impact on the risk-benefit balance of the product:

In the event that an impact on hepatoxicity is established, there would be an impact to the benefit risk for patients prescribed mavorixafor, particularly those with hepatic impairment. This could reasonably be managed through standard monitoring of liver enzymes and appropriate mitigations in the SmPC.

Public health impact

WHIM syndrome is very rare disease and therefore overall impact to public health is anticipated to be minimal.

Important Potential Risk: Retinal degeneration and atrophy

Potential mechanisms:

Retinal changes were identified in non-clinical studies however the exact mechanism by which this effect may occur is not known.

Evidence source(s) and strength of evidence:

The potential risk of retinal degeneration and atrophy was identified in non-clinical studies. Patients were carefully monitored and at this time there is no evidence of mavorixafor related retinal related changes, including in patients with WHIM syndrome. The number of patients and duration of exposure are limited. The strength of the data is therefore limited at this time.

Characterisation of the risk:

Retinal degeneration was identified in the 26-week rat study of AMD11070PHB, conducted with the PHB salt form of mavorixafor, with dose-related increases in both incidence and severity; a single male rat had this change at the low dose (40 mg/kg/day FBE). Related findings reported as "retinal atrophy" were described only in the high-dose group (200 mg/kg/day FBE). Overall, retinal changes appeared to decrease among animals in the 4-week recovery group. These studies used albino rats, which are known to have increased sensitivity to ambient light-induced retinopathy; consequently, the clinical implications of these findings are uncertain. No retinal findings were observed in rats given AMD11070PHB for 13 weeks, in rats given X4P-001 (freebase) for 4 weeks, or in dogs given either drug form for up to 13 weeks. Dogs administered mavorixafor for 39 weeks exhibited retinal changes. These included an accumulation of finely granular tan to basophilic pigment consistent with lipofuscin present bilaterally in the retinal pigmented epithelium of the central aspect of the retina (predominantly affected), including regions overlying the tapetum. A concomitant diffuse increase in the size of tapetal cells was present, but none of these eye findings were concluded as adverse (Study X4P-001-TOX-017).

As a consequence, close monitoring for eye toxicities and regularly scheduled ophthalmologic examinations were included in the clinical studies with mavorixafor. An extensive review of ophthalmologic adverse event reports (WHIM syndrome studies) and retinal photographs (for all applicable studies) by an independent central review and an external ocular expert has been conducted.

The clinical studies have not shown evidence of retinal degeneration and atrophy.

The most commonly occurring eye-related TEAEs across all mavorixafor studies were dry eye and ocular/conjunctival hyperaemia. These events were reported more frequently in the oncology studies and healthy volunteer studies compared to studies in patients with WHIM syndrome. Several systemic medications are associated with these adverse effects (Fraunfelder et al., 2012; Miguel et al., 2014).

The clinical studies indicate that mavorixafor treatment is associated with mild and generally short-lived dry eye and ocular/conjunctival hyperaemia in healthy subjects.

In contrast, there were infrequent reports of dry eye and ocular/conjunctival hyperaemia in patients with WHIM syndrome.

Risk factors and risk groups:

This risk is applicable to all patients.

Preventability:

The current SmPC summarises the non-clinical data but no other mitigations are considered necessary. Should an effect on retinal degeneration and atrophy be confirmed, this could be mitigated through eye examinations and is reflected in the SmPC.

Impact on the risk-benefit balance of the product:

In the event that an impact on retinal degeneration and atrophy is established, there would be an impact to the benefit risk for patients prescribed mavorixafor. This could reasonably be managed through monitoring of eyes and appropriate mitigations in the SmPC.

Public health impact

WHIM syndrome is very rare disease and therefore overall impact to public health is anticipated to be minimal.

SVII.3.2. Presentation of the missing information

Long-term safety including risk of malignancy

Evidence source:

Thirty-eight patients have been treated with mavorixafor in the proposed indication. In addition, a larger number of healthy volunteers or patients with oncology diseases were exposed to mavorixafor (n=370).

Acknowledging that WHIM syndrome is a rare disease, the relevant safety database although limited in size, provides a reasonable amount of data to evaluate common safety aspects. No new safety signals were identified over long-term mavorixafor treatment in patients with WHIM syndrome, including in patients enrolled in the OLE who have been receiving mavorixafor for treatment for four to five years.

Given mavorixafor's intended use as a long-term therapy for WHIM syndrome, there remains uncertainty regarding its long-term safety profile especially with respect to ocular and testicular findings as based on the non-clinical safety studies, in the context of a limited safety database. Close monitoring in clinical trials, including ocular and testicular examinations, has not identified clinical sequalae of potential risks identified in the non-clinical programme, however it is accepted that, given the small number of participants exposed to date it is difficult to rule this out.

Anticipated risk/consequence of the missing information:

The current safety database, although limited in size, provides a reasonable amount of data to evaluate common safety aspects. Uncertainty on rarer safety aspects and impact on the long-term safety profile remain. Therefore, further characterization of the long-term safety of mavorixafor is planned in a post-authorisation study leveraging data from existing registries to continue to evaluate the long-term safety profile of mavorixafor.

Part II: Module SVIII – Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	Embryo-foetal toxicity Testicular toxicity Hepatotoxicity Retinal degeneration and atrophy
Missing information	Long-term safety including risk of malignancy

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires:

Not applicable.

Other forms of routine pharmacovigilance activities for safety concerns:

Not applicable

III.2 Additional pharmacovigilance activities

The MaH proposes specific pharmacovigilance activities to address the important potential risks identified from the non-clinical program.

The MaH proposes to conduct a Post-Authorisation Registry study in order to further characterise the long-term safety and efficacy of mavorixafor in patients with WHIM syndrome.

Post-Authorisation Registry study summary

Study short name and title:

Registry-based study to evaluate long-term safety and efficacy of mavorixafor in patients with WHIM syndrome.

Rationale and study objectives:

Given the rarity of WHIM syndrome and the resulting challenges to provide comprehensive safety and efficacy data, a post-authorisation registry study is proposed to continue assessing the long-term safety and efficacy of mavorixafor in the WHIM population post-marketing, leveraging existing registries. The objectives are to assess the long-term safety (primary objective) and efficacy

(secondary objective) of mavorixafor in patients with WHIM syndrome; more specific objectives to be established through generation of the protocol.

Study design:

The exact study design will be determined following a full feasibility assessment of data that can be leveraged from existing European Societies of immunodeficiencies (ESID) registry and the protocol will be agreed with the PRAC prior to implementation in accordance with the proposed milestones as outlined below.

Data will be collected on an annual basis using a defined Clinical report form (CRF) incorporating the important potential risks and missing information. Efficacy and laboratory parameters will include: general medical history; number, severity, and type of infections; number, location and severity of warts; malignancies; complete blood count; serum chemistry (including hepatic, renal markers, and pregnancy test in females of childbearing potential only). A secondary objective will be to assess the effectiveness of additional risk minimisation measures. The Applicant commits to determining the duration of the PASS in consultation with PRAC during the development and review of the full protocol, ensuring that the overall follow-up period is adequate to address the study objectives. Specifically, the initial protocol will include 10 years of follow-up with pre-defined interim analyses to allow the duration to be revisited as needed based on actual accrual, emerging data and the anticipated incremental value of extended follow-up over a period of 10 years and routine pharmacovigilance.

Study population:

Eligible patients for safety follow-up would include those with a confirmed diagnosis of WHIM syndrome and treated with mavorixafor in real-world settings.

Milestones:

The Post-Authorisation Registry study protocol and feasibility assessment for PRAC review will be provided within 6 months of approval of mavorixafor. Interim reports will be submitted within the annual reassessment procedure.

III.3 Summary Table of additional Pharmacovigilance activities

Table Part III.1: On-going and planned additional pharmacovigilance activities

Study / Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Registry-based study to evaluate long-term safety and efficacy of mavorixafor in patients with WHIM syndrome. Planned	To assess the long-term safety (primary objective) and efficacy (secondary objective) of mavorixafor in patients with WHIM syndrome.	Long-term safety including risk of malignancy Embryo-foetal toxicity Testicular toxicity Hepatotoxicity Retinal degeneration and atrophy	Protocol Feasibility report Interim results	Within 6 months of approval Within 6 months of approval Within the annual reassessment procedure Further milestones to be agreed with CHMP and PRAC.
Submission of yearly updates on any new information concerning the safety and efficacy of mavorixafor	Monitoring of safety and efficacy of mavorixafor in the treatment of 12 years of age and older for the treatment of WHIM syndrome to increase the number of circulating mature neutrophils and lymphocytes	Long-term safety including risk of malignancy Embryo-foetal toxicity Testicular toxicity Hepatotoxicity Retinal degeneration and atrophy	Annual report	Annual reassessment
Category 3 – Required additional pharmacovigilance activities				

Part IV: Plans for post-authorisation efficacy studies

Not applicable

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table Part V.1: Description of routine risk minimisation measures by safety concern

Safety concern	**Routine risk minimisation activities**
Important Potential Risk: Embryo-foetal toxicity	Routine risk communication: SmPC Sections 4.3, 4.4, 4.6 and 5.3 PIL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: Contraindication during pregnancy and guidance on contraception included in SmPC Sections 4.3, 4.4 and 4.6 and PIL Section 2. Other routine risk minimisation measures beyond the Product Information: NA
Important Potential Risk: Testicular toxicity	Routine risk communication: SmPC Sections 4.6 and 5.3 PIL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: NA Other routine risk minimisation measures beyond the Product Information: NA
Important Potential Risk: Hepatotoxicity	Routine risk communication: SmPC Sections 4.2 and 5.3 Routine risk minimisation activities recommending specific clinical measures to address the risk: NA Other routine risk minimisation measures beyond the Product Information: NA
Important Potential Risk: Retinal degeneration and atrophy	Routine risk communication: SmPC Section 5.3 Routine risk minimisation activities recommending specific clinical measures to address the risk: NA Other routine risk minimisation measures beyond the Product Information: NA

Missing Information: Long-term safety including risk of malignancy	Routine risk communication: NA Routine risk minimisation activities recommending specific clinical measures to address the risk: NA Other routine risk minimisation measures beyond the Product Information: NA

V.2. Additional Risk Minimisation Measures

Additional risk minimisation 1: Important potential risk: Embryo-foetal toxicity

Healthcare Professional Guide

Objectives:

To provide healthcare professionals (HCPs) with safety information to minimise the important potential risk of embryo-foetal toxicity.

Rationale for the additional risk minimisation activity:

Due to the potential of embryo-foetal harm additional educational material in the form of an HCP guide are required to ensure appropriate risk awareness and contraceptive use.

Target audience and planned distribution path:

The HCP guide will be distributed to the HCPs who are experienced in the treatment of WHIM syndrome and will prescribe appropriate products including Xolremdi. The distribution of the HCP guide will include electronic and/or hardcopy dissemination as per National Competent Authority requirements.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Effectiveness will be measured by outcome and process/knowledge indicators.

Outcome Indicators: All reports received describing exposure to Xolremdi during pregnancy and/or embryo-foetal toxicity will be assessed through the MAH's routine pharmacovigilance system. This information will be presented in each scheduled PSUR.

Process/ Knowledge Indicator: The proposed CRF to be implemented in the post-authorisation safety and efficacy registry study will request the HCP to confirm whether they had access to the educational material which discusses the potential risk of embryo-foetal toxicity and the need for contraception. The analysis of this will be provided as per the post authorisation study reporting commitments and in the PSUR.

Patient Card

Objectives:

To provide patients with safety information to minimise the important potential risk of embryo-foetal toxicity.

Rationale for the additional risk minimisation activity:

Due to the potential of embryo-foetal harm additional educational material in the form of a patient card are required to ensure appropriate risk awareness and contraceptive use.

Target audience and planned distribution path:

A patient card will be provided in the product package.

Plans to evaluate the effectiveness of the interventions and criteria for success:

Effectiveness will be measured by outcome indicator.

Outcome Indicators: All reports received describing exposure to Xolremdi during pregnancy and/or embryo-foetal toxicity will be assessed through the MAH's routine pharmacovigilance system. This information will be presented in each scheduled PSUR.

V.3 Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Potential Risk: Embryo-foetal toxicity	Routine risk minimisation measures: SmPC Sections 4.3, 4.4, 4.6 and 5.3 and PIL Section 2 including contraindication during pregnancy and guidance on contraception. Additional risk minimisation measures: Healthcare Professional guide Patient card	Additional pharmacovigilance activities: Post-authorisation safety and efficacy registry study
Important Potential Risk: Testicular toxicity	Routine risk minimisation measures: SmPC Sections 4.6 and 5.3 and PIL Section 2 No additional risk minimisation measures.	Additional pharmacovigilance activities: Post-authorisation safety and efficacy registry study
Important Potential Risk: Hepatotoxicity	Routine risk minimisation measures: SmPC Sections 4.2 and 5.3 No additional risk minimisation measures.	Additional pharmacovigilance activities: Post-authorisation safety and efficacy registry study
Important Potential Risk: Retinal	Routine risk minimisation measures: SmPC Section 5.3	Additional pharmacovigilance activities: Post-authorisation safety and efficacy registry study

Safety concern	Risk minimisation measures	Pharmacovigilance activities
degeneration and atrophy	No additional risk minimisation measures.	
Missing Information: Long-term safety including risk of malignancy	Routine risk minimisation measures: NA No additional risk minimisation measures.	Additional pharmacovigilance activities: Post-authorisation safety and efficacy registry study

Part VI: Summary of the risk management plan

Summary of risk management plan for Xolremdi (mavorixafor)

This is a summary of the risk management plan (RMP) for Xolremdi. The RMP details important risks of Xolremdi, how these risks can be minimised, and how more information will be obtained about Xolremdi's risks and uncertainties (missing information).

Xolremdi's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Xolremdi should be used.

This summary of the RMP for Xolremdi should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Xolremdi's RMP.

I. The medicine and what it is used for

Xolremdi is authorised for the treatment of Warts, Hypogammaglobulinemia, Infections and Myelokathexis (WHIM) syndrome in adult and adolescent patients 12 years of age and older (see SmPC for the full indication). It contains mavorixafor as the active substance and it is given by 100 mg hard capsules.

Further information about the evaluation of Xolremdi's benefits can be found in Xolremdi's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage (Xolremdi EPAR).

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Xolremdi, together with measures to minimise such risks and the proposed studies for learning more about Xolremdi's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Xolremdi, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Xolremdi is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Xolremdi are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Xolremdi. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	None
Important potential risks	Embryo-foetal toxicity Testicular toxicity Hepatotoxicity Retinal degeneration and atrophy
Missing information	Long-term safety including risk of malignancy

II.B Summary of important risks

Important Potential Risk: Embryo-foetal toxicity	
Evidence for linking the risk to the medicine	Non-clinical data of other products with a similar mechanism of action suggest a strong potential for embryo-foetal toxicity if mavorixafor is used during pregnancy. Evidence is also based on the available literature and experience with other products with a similar mechanism of action. Pregnant women were excluded from clinical trials with mavorixafor and no pregnancies occurred during clinical trials.
Risk factors and risk groups	This risk is applicable to pregnant women, WOCBP and to male partners of WOCBP.
Risk minimisation measures	Routine risk minimisation measures: SmPC Sections 4.3, 4.4 and 4.6 and PIL section 2 including contraindication during pregnancy and guidance on contraception. Additional risk minimisation measures: Healthcare Professional guide Patient card
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Post-authorisation safety and efficacy registry study See section II.C of this summary for an overview of the post-authorisation development plan.

Important Potential Risk: Testicular toxicity	
Evidence for linking the risk to the medicine	Evidence comes from a 39-week study in dogs; similar changes were not observed in a 13-week dog study or a 26-week dog study in dogs covering the period or reaching sexual maturity. There are no findings to date in clinical studies, although numbers are limited. The strength of the data is therefore limited at this time.
Risk factors and risk groups	This risk is applicable to male patients regardless of age or ethnicity.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.6 and 5.3 PIL section 2 No additional risk minimisation measures.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Post-authorisation safety and efficacy registry study See section II.C of this summary for an overview of the post-authorisation development plan.

Important Potential Risk: Hepatotoxicity	
Evidence for linking the risk to the medicine	The potential risk of hepatotoxicity was identified in non-clinical studies. Patients were carefully monitored and at this time there is no evidence of mavorixafor related hepatic injury, including in patients with WHIM syndrome. However, the number of patients and duration of exposure are limited. The strength of the data is therefore limited at this time.
Risk factors and risk groups	This risk is applicable to all patients but may be particularly applicable to patients with hepatic impairment.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 4.2 and 5.3 No additional risk minimisation measures.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Post-authorisation safety and efficacy registry study See section II.C of this summary for an overview of the post-authorisation development plan.

Important Potential Risk: Retinal degeneration and atrophy	
Evidence for linking the risk to the medicine	The potential risk of retinal degeneration and atrophy was identified in non-clinical studies. Patients were carefully monitored and at this time there is no evidence of mavorixafor related eye related

	changes, including in patients with WHIM syndrome. However, the number of patients and duration of exposure are limited. The strength of the data is therefore limited at this time.
Risk factors and risk groups	This risk is applicable to all patients.
Risk minimisation measures	Routine risk minimisation measures: SmPC Section 5.3 No additional risk minimisation measures.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Post-authorisation safety and efficacy registry study See section II.C of this summary for an overview of the post-authorisation development plan.

Missing Information: Long-term safety including risk of malignancy	
Risk minimisation measures	No Routine risk minimisation measures: No additional risk minimisation measures.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Post-authorisation safety and efficacy registry study See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

The following studies are conditions of the marketing authorisation:

Registry-based study to evaluate long-term safety and efficacy of mavorixafor in patients with WHIM syndrome.

Purpose of the study:

Given the rarity of WHIM syndrome and the resulting challenges to provide comprehensive safety and efficacy data, a post-authorisation registry study is proposed to continue assessing the long-term safety of mavorixafor in the WHIM population post-marketing, leveraging existing registries. The high-level objective will be to assess the long-term safety and efficacy of mavorixafor in patients with WHIM syndrome with more specific objectives to be established through generation of the protocol. A secondary objective will be to assess the effectiveness of additional risk minimisation measures.

II.C.2 Other studies in post-authorisation development plan

Not applicable

Part VII: Annexes

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Annex 4 – Specific adverse drug reaction follow-up forms

Not applicable

Annex 6 – Details of proposed additional risk minimisation activities (if applicable)

Draft key messages of the additional risk minimisation measures

Prior to the launch of Xolremdi in each Member State, the MAH must agree about the content and format of the educational programme, including communication media, distribution modalities and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at reducing the potential risk of embryo-foetal toxicity associated with Xolremdi.

The MAH shall ensure that in each member state where Xolremdi is marketed, all healthcare professionals who are expected to prescribe Xolremdi have access to/are provided with the following educational package:

- Physician educational materials

The MAH shall ensure that in each Member State where Xolremdi is marketed, all patients/carers who are expected to use Xolremdi are provided with the following educational package:

- Patient card

Physician educational material:

- Summary of Product Characteristics
- Guide for healthcare professionals

- **Guide for Healthcare Professionals**
    - Xolremdi may cause embryo-foetal harm when administered to a pregnant woman.
    - Xolremdi is contraindicated in pregnant women.
    - The pregnancy status of female patients of childbearing potential who are engaging in activities of reproductive potential should be verified prior to starting Xolremdi.
    - Female patients of childbearing potential must avoid becoming pregnant by using an effective method of contraception (e.g. double-barrier contraception) during treatment with Xolremdi and for three weeks after the final dose.

- Male patients with female partners of childbearing potential should use condoms during sexual intercourse while taking Xolremdi and for at least three weeks after stopping treatment.
- Treatment with Xolremdi should be discontinued if a patient is planning to become pregnant or has become pregnant.
- A patient card is included in the product package and the healthcare professional should inform each female patient of childbearing potential, and each male patient with female partners of child bearing potential, prior to initiation of treatment, about the purpose and importance of the card.
- Appropriate actions should be taken if a pregnancy is detected and the patient should receive appropriate counselling on possible actions by a specialist.

The patient information pack:

- Package leaflet
- Patient card

- **Patient card**:
  - Warning not to take Xolremdi if pregnant. Xolremdi poses a potential risk to your unborn child.
  - Instruction to use highly effective contraception methods (e.g. double-barrier contraception) for women of childbearing potential during treatment with Xolremdi and for three weeks after the last dose.
  - Instruction for male patients to use effective contraception when having sexual intercourse with a female partner of childbearing potential during treatment with Xolremdi and for three weeks after the last dose.
  - Instruction to contact relevant healthcare professional immediately if pregnancy is suspected.
  - Instruction to read the package leaflet for further information and guidance.