Amsterdam, 26 February 2026
EMADOC-1829012207-16377
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Xolremdi

International non-proprietary name: Mavorixafor

Procedure No. EMEA/H/C/006496/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation	Definition
%CV	Percent coefficient of variation
AC	Adjudication Committee
ADME	absorption, distribution, metabolism and excretion
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	area under the curve
AUC_{0-24}	area under the curve from dosing time to 24 hours post dose
AUC_{0-last}	area under the curve till last quantifiable concentration
BCS	Biopharmaceutics Classification System
BUN	Blood urea nitrogen
CEP	Certificate of Suitability of the EP
CD	Cluster of differentiation
CGI-C	Clinical global impression of change score
CGI-S	Clinical global impression of severity score
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
C_{max}	maximum observed concentration
COPD	chronic obstructive pulmonary disease
CNS	central nervous system
CPCA	Carcinogenic potential categorisation approach
CQA	Critical Quality Attribute
CSR	Clinical study report
CTCAE	Common terminology criteria for adverse events
CXCL12	C-X-C chemokine ligand 12
CXCR4	C-X-C chemokine receptor 4
CYP	cytochrome P450
DDI	drug-drug interactions
DRF	dose range-finding
DSUR	Development Safety Update Report
DV	Dependent variable
EC	European Commission
EC_{50}	concentration at which the target mRNA expression level is half of the difference between the baseline and the maximum target mRNA expression level
ECG	Electrocardiogram
EFD	embryo-fetal development
ESID	European Societies of immunodeficiencies
EU	European Union

Abbreviation	Definition
FT-IR	Fourrier transform infrared spectroscopy
G-CSF	granulocyte-colony stimulating factor
GC	Gas chromatography
GCP	Good clinical practice
GGT	Gamma-glutamyltransferase
GIT	gastrointestinal tract
GLP	Good laboratory practice
GMP	Good manufacturing practice
GOF	Goodness of fit
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HCP	Healthcare professional
HDPE	High density polyethylene
hERG	human ether-à-go-go-related gene
HI	Hepatic impairment
HLM	human liver microsomes
HPLC	high performance liquid chromatography
HPV	Human papilloma virus
HV	Healthy volunteers
IC_{50}	concentration causing 50% inhibition
ICE	Intercurrent events
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry
INDs	Investigational New Drugs
ITT	Intent to treat
IV	Intravenous
IVIG	Intravenous immunoglobulin G
KF	Karl Fischer titration
KLH	keyhole limpet hemocyanin
LCMS/MS	Liquid chromatography mass spectrometry/mass spectrometry
LDPE	Low density polyethylene
LOAEL	lowest observed adverse effect level
LS	Least square
MAA	Marketing authorisation application
MAH	Marketing authorisation holder
MATE	multidrug and toxic extrusion protein
MEC	molar extinction coefficient
MMRM	Mixed-model repeated measures
MRHD	Maximum human recommended dose
MTD	maximum tolerated dose
NADPH	Nicotinamide-adenine dinucleotide phosphate, reduced form
NF	National formulary
NMR	Nuclear magnetic resonance
NOAEL	no observed adverse effect level
OAT	organic anion transporter

Abbreviation	Definition
OATP	organic anion transport polypeptide
OCT	organic cation transporter
OLE	Open-label extension period
PASS	Post-authorisation safety study
Pc-VPC	Prediction-corrected visual predictive checks
PD	Pharmacodynamics
PDE	Permitted daily exposure
PED	Patient experience data
P-gp	permeability-glycoprotein
Ph.Eur.	European Pharmacopoeia
PHB	Para-hydroxy benzoate
PID	primary immunodeficiency syndromes
PK	Pharmacokinetics
PND	postnatal day
PO	Per os
PP	Per protocol
PPB	plasma protein binding
ppm	Parts per million
PRAC	Pharmacovigilance Risk Assessment Committee
QD	Once daily
QP	Qualified person
QTc	Corrected QT interval
QTPP	Quality target product profile
QWBA	quantitative whole body autoradiography
RCP	Randomised controlled period
RH	Relative humidity
RMP	Risk management plan
SAD	Single ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SCC	Squamous cell carcinoma
SD	Standard deviation
SDF-1	stromal-cell-derived factor 1
SE	Standard error
SmPC	Summary of product characteristics
SOB	Specific obligation
SOC	System organ class
$T_{1/2}$	elimination half-life
TAMC	Total aerobic microbial count
TAT	Time above threshold
TEAE	Treatment emergent adverse event
TK	Toxicokinetics
t_{max}	time to reach peak concentration
TQT	Thorough QT
TSE	Transmissible spongiform encephalopathy

Abbreviation	Definition
TCYM	Total combined yeasts/moulds count
ULN	Upper limit of normal
US FDA	Food and Drug Administration
USP	United States Pharmacopoeia
UV	Ultraviolet
V_d	volume of distribution
V_{max}	maximum rate of depolarization of the action potential upstroke
V_{ss}	volume of distribution at steady state
WBC	white blood cell
WHIM	warts, hypogammaglobulinemia, infections, and myelokathexis
WT	Wild type
XRPD	X-ray powder diffraction

1. Administrative/regulatory information and recommendations on the procedure

1.1. *Information on the product*

Product data	
Product name	Xolremdi
Active substance	Mavorixafor
INN or common name	Mavorixafor
Applicant	X4 Pharmaceuticals (Austria) GmbH Hoehenstaufengasse, 9/DG, Inner Stadt, 1010 Vienna, Austria
EMA Product Number	EMEA/H/C/006496
ATC code and Pharmacotherapeutic group	L03AX24
Pharmaceutical form(s) and strength (s)	Capsule, hard 100 mg
Packaging	bottle (HDPE)
Package size(s)	120 capsules, 60 capsules and 90 capsules
Route of administration	Oral use
Device or diagnostic	Not applicable
Orphan designation	Yes (EU/3/19/2183)
Orphan indication status confirmed	Pending
PRIME scheme	Not applied for
Type of marketing authorisation granted at opinion	Exceptional circumstances
Legal basis	Article 8.3 of Directive 2001/83/EC
Final indication	Xolremdi is indicated in patients 12 years of age and older for the treatment of WHIM syndrome (warts, hypogammaglobulinemia, infections and myelokathexis) to increase the number of circulating mature neutrophils and lymphocytes.
New active substance status	Granted

1.2. *Protocol assistance*

Table 1: Scientific advice and protocol assistance

Date	*Topic (quality/ non-clinical/ clinical)*	*Reference number / Coordinator(s)*	*Brief summary of the advice*
16	Non-	EMEA/H/SA/3433/1/2016/SME/III	The Protocol assistance

December 2016	clinical and clinical	Dr Caroline Auriche and Mr Thomas Lang	pertained to the following non-clinical, and clinical aspects: • Adequacy of the non-clinical studies to support the proposed phase 2/3 study and MAA • Starting dose • Design of the X4P-001-MKKA study • Overall clinical development plan to support a MAA
27 June 2019	Non-clinical and clinical	EMEA/H/SA/3433/1/FU/1/2019/SME/III Dr Ewa Balkowiec-Iskra and Dr Caroline Auriche	The Protocol assistance pertained to the following non-clinical and clinical aspects: • Non-clinical studies to support 12-month clinical program • Primary and secondary endpoints, randomisation, inclusion criteria
11 November 2021	Quality and non-clinical	EMA/SA/0000067085 Mario Miguel Coelho da Silva Rosa, Walter Janssens and Hrefna Gudmundsdottir	The Protocol assistance pertained to the following quality, non-clinical aspects: • Starting materials; control strategy for the active substance manufacturing; process validation of the drug substance and the drug product. • Juvenile non-clinical study to support paediatric clinical trials, embryofoetal developmental and carcinogenicity studies
21 March 2024	Non-clinical	EMA/SA/0000163154 Larissa Higgins and Valentina Conti	The Protocol assistance pertained to the following non-clinical aspects: • Timing of the non-clinical carcinogenicity study

CHMP scientific advice in relation to this marketing authorisation application (MAA) concerning clinical issues were obtained in November 2016 (ref. EMEA/H/SA/3433/1/2016/SME/III) and a follow–up Scientific Advice (EMEA/H/SA/3433/1/FU/1/2019/SME/III) in June 2019. These advices contained the following aspects for the pivotal phase III study:

Patient population: Agreement was reached on eligibility criteria including, but not limited to, genetic confirmation of a CXCR4 gain-of-function mutation, inclusion of patients ≥12 years of age and baseline neutrophils ≤400/µL.

Study design: Agreement was reached in terms of the duration of the double blinded treatment period of 52 weeks with a subsequent open-label period, 1:1 randomisation, stratification by prophylactic IG therapy, sample size of 28 planned patients.

Comparator: A comparison with placebo and with change from baseline was agreed on.

Primary and secondary endpoints: The principle of a primary haematological intermediate endpoint to reach statistical significance in combination with clinically meaningful but not necessarily fully powered secondary endpoints was accepted. Time in hours above the absolute neutrophil count threshold of 500 neutrophils /µl (TATANC), assessed four times through the study as primary endpoint with rates of infections and warts as key secondary endpoints was proposed. While this was approach was in principle endorsed, the applicant was alerted that the 500 neutrophils /µl threshold is rather unambitious, and results could be considered insufficient in case the infection rates do not show an improvement.

1.3. *Eligibility to the centralised procedure*

The applicant X4 Pharmaceuticals (Austria) GmbH submitted on 20 December 2024 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Xolremdi (mavorixafor), through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 January 2024.

The applicant applied for the following indication: Xolremdi is indicated in adult and adolescent patients 12 years of age and older for the treatment of WHIM syndrome (warts, hypogammaglobulinemia, infections and myelokathexis).

1.4. *Legal basis and dossier content*

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies.

1.5. *Information on paediatrics*

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0185/2024 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0185/2024 was not yet completed as some measures were deferred.

1.6. *Information on orphan market exclusivity*

Xolremdi was designated as an orphan medicinal product EU/3/19/2183 on 25 July 2019 in the following condition: Treatment of WHIM syndrome.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Xolremdi as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website:
https://www.ema.europa.eu/en/medicines/human/EPAR/Xolremdi

1.6.1. Similarity with authorised orphan medicinal products

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products from the start of the procedure because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.7. *Applicant's request(s) for consideration*

1.7.1. Marketing authorisation under exceptional circumstances

The applicant requested consideration of its application for a Marketing Authorisation under exceptional circumstances in accordance with Article 14(8) of Regulation (EC) No 726/2004. See section 9.6.3.1. of this document.

1.7.2. New active substance status

The applicant requested the active substance mavorixafor contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.7.2.1. CHMP recommendation on new active substance status

Based on the review of available data on the active substance, the CHMP considers that mavorixafor is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

1.8. *Patient experience data*

Table 2: Patient experience data relevant to the application

Patient experience data submitted with this application				*Section where discussed (if applicable)*
X	Patient experience data submitted by the applicant:			
	X	Clinical outcome assessments (COAs) such as		
		X	Patient-reported outcomes (PRO)	Section 5.3.2. .
		X	Other	Section 5.3.2.

Patient experience data submitted with this application			Section where discussed (if applicable)
	☐	Patient preference studies	
	☐	Observational studies/RWD designed to capture patient experience data	
	☐	Qualitative information or studies (e.g. summaries/analysis from patient engagement activities such as individual patient/caregiver interviews, focus group interviews, expert interviews, etc)	
	☐	Other (please specify)	
X	Other patient experience data not submitted by the applicant but considered in this evaluation:		
	☐	Input informed from participation in meetings or public hearings with patient stakeholders	
	X	CHMP early dialogue with patient organisations	Sections 5.3.8.
	☐	Third party interventions from patients and patient groups	
	☐	Other (such as medical literature, summaries/analysis from patient engagement activities - please specify)	

1.9. *Steps taken for the assessment of the product*

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur:	Martin Mengel
Co-Rapporteur:	Jayne Crowe, appointed at the start of the procedure. During the procedure, a new co-Rapporteur Finbarr Leacy was appointed.

The Rapporteur and Co-Rapporteur appointed by the PRAC were:

PRAC Rapporteur:	Karin Erneholm
PRAC Co-Rapporteur:	Martin Huber

The application was received by the EMA on	20 December 2024
The procedure started on	23 January 2025
The CHMP Rapporteur's first Assessment Report was received on	14 April 2025
The CHMP Co-Rapporteur's first Assessment Report was added to the Rapporteur's report on	16 April 2025
The PRAC Rapporteur's first Assessment Report was added to the Rapporteurs' report and circulated to all PRAC and CHMP members on	29 April 2025
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	22 May 2025
The applicant submitted the responses to the CHMP consolidated List of	9 October 2025

Questions on	
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP and PRAC members on	18 November 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	27 November 2025
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	11 December 2025
The applicant submitted the responses to the CHMP List of Outstanding Issues on	26 January 2026
The CHMP Rapporteur circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP and PRAC members on	11 February 2026
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Xolremdi on	26 February 2026
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	26 February 2026

1.10. *CHMP outcome*

1.10.1. Considerations related to paediatrics

The requirements for the submitted dossier in relation to paediatrics are described in section 1.5. of this report.

The CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0185/2024 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet. Relevant paediatric statement in Section 5.1 of the SmPC if the EMA has deferred a paediatric development have also been included.

1.10.2. Considerations related to orphan market exclusivity

The requirements of the submitted dossier in relation to orphan market exclusivity are described in section 1.6. of this report.

1.10.3. Opinion

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Xolremdi is favourable in the following indication(s):

Xolremdi is indicated in patients 12 years of age and older for the treatment of WHIM syndrome (warts, hypogammaglobulinemia, infections and myelokathexis) to increase the number of circulating mature neutrophils and lymphocytes.

The CHMP, therefore, recommends the granting of the marketing authorisation under exceptional circumstances subject to the conditions described in the following sections.

1.10.4. Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

1.10.5. Other conditions and requirements of the marketing authorisation

1.10.5.1. Periodic safety update reports (PSURs)

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

1.10.6. Conditions or restrictions with regard to the safe and effective use of the medicinal product

1.10.6.1. Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

1.10.6.2. 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 childbearing 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.

1.10.7. Specific obligation to complete post-authorisation measures for the marketing authorisation under exceptional circumstances

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	*Due date*
Non-interventional post-authorisation safety study (PASS): In order to investigate the long-term safety and efficacy of mavorixafor in the treatment of WHIM syndrome (warts, hypogammaglobulinemia, infections and myelokathexis) to increase the number of circulating mature neutrophils and lymphocytes in patients 12 years of age and older, the MAH shall conduct and submit the results of a non-interventional study based on a registry in patients collecting both safety and efficacy endpoints.	Annually (within annual reassessment)
In order to ensure adequate monitoring of safety and efficacy of mavorixafor in patients 12 years of age and older for the treatment of WHIM syndrome (warts, hypogammaglobulinemia, infections and myelokathexis) to increase the number of circulating mature neutrophils and lymphocytes, the MAH shall provide yearly updates on any new information concerning the safety and efficacy of mavorixafor.	Annually (within annual reassessment)

1.10.8. Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

1.10.9. Proposed list of recommendations

Table 3: Proposed list of recommendations

Description of Recommendation(s)
The applicant should continue stability studies including testing for X192, investigate the root cause for X192 formation, implement process changes to reduce levels of X192 as appropriate, and alert the competent authorities to any issues identified.
Complete the in-use drug product stability studies for the aged drug product batches and report any issues to the Competent Authorities.
Provide results from the Tg.rasH2 mouse carcinogenicity study once available.
Conduct and submit the data from a dedicated hepatic impairment study once available.
Perform a clinical characterisation of drug drug interaction (DDI) between mavorixafor as a DDI object and a CYP2D6 precipitant PI and provide the final Clinical Study Report (CSR) once available.

2. Introduction

2.1. *Therapeutic Context*

Disease setting:

WHIM syndrome (acronym for warts, hypogammaglobulinemia, infections, myelokathexis) is an ultra-rare autosomal dominant combined immunodeficiency disorder in which a mutant CXCR4 chemokine receptor causes abnormal apoptosis and lack of migratory function, with retention of mature white

blood cells (WBCs) in the bone marrow. Clinical features vary and may include neutropenia, lymphopenia, hypogammaglobulinemia and warts due to human papillomavirus infection (Uptodate).

CXC Chemokine Receptor 4 (CXCR4) is a G-protein coupled receptor with specificity for the chemokine stromal-cell-derived factor 1 (SDF-1, also known as CXCL12), activation leads to G-protein mediated and G-protein independent signalling followed by a desensitisation mediated by β-arrestin binding and endocytosis of the receptor, regulating WBC bone marrow homing and trafficking into the circulation and to sites of inflammation. The CXCR4 receptor is known to be involved in endothelial and epithelial development and has broad expression by haematopoietic stem and progenitor cells and mature leukocytes.

Gain of function mutations (hyperactivity with failure to downregulate) in the chemokine receptor CXCR4 can prevent the release of WBC from the bone marrow into the peripheral blood, with neutropenia and lymphopenia as the cause of repeated bacterial and viral infections (Beaussant Cohen 2012[1]). Heterozygous C-terminus deletional mutations result in partial truncation of the intracellular carboxy terminus of the chemokine receptor.

The inherited immunodeficiency disorder characterised by severe neutropenia, defective bone marrow release mechanism and hypogammaglobulinemia was finally codified and scientifically recognised as WHIM syndrome in 1990 (Wetzler M.D. et al; 1990) and accepted into the Online Mendelian Inheritance in Man[2] catalogue. In 2003, the genetic cause of the disease was elucidated when truncating mutations of the CXCR4 receptor on chromosome 2q21 were found in pedigrees of affected families (Hernandez et al.; 2003[3]).

The incidence of the disease is estimated to be 1 per 5 million, with approximately 105 identified cases described in the recent literature (Heusinkveld et al.; 2019[4]). Forty-five percent of these cases were *de novo* with no family history and 3% lacked CXCR4 mutations.

In terms of diagnosis, although research has identified molecular and phenotypic patterns, there is still a diagnostic grey area as not every clinical feature is necessary or sufficient for diagnosis, as only 38% of WHIM syndrome patients in the literature presented with all four clinical features plus pathognomic CXCR4-mutation. Patients usually present with recurrent severe bacterial infections, often of the upper or lower respiratory tract and skin warts in combination with severe neutropenia, mostly in combination with lymphopenia and hypogammaglobulinemia in childhood, while the diagnosis is often delayed for many years (Dotta et al.; 2019[5]).

Patients with WHIM syndrome usually do well between infectious events (Dotta et al.; 2019[5]). However, complications of recurrent bacterial lung infections, such as bronchiectasis or chronic obstructive pulmonary disease (COPD), with further respiratory failure have been described in the literature. Recurrent ear infections can lead to hearing loss, and recurrent periodontal infections can lead to tooth loss.

Chronic viral infections and its sequelae are the other major burden of disease. Human papillomavirus (HPV)-associated warts appeared in a recent cohort of 18 patients in 61 % of patients with a median age at onset of 10 years (Beaussant Cohen 2012[1]), with a high rate of treatment refractoriness and

[1] Beaussant-Cohen S, Fenneteau O, Plouvier E, Rohrlich PS, Daltroff G, Plantier I, et al. Description and outcome of a cohort of 8 patients with WHIM syndrome from the French Severe Chronic Neutropenia Registry. Orphanet J Rare Dis. 2012; 7:71.
[2] Online Mendelian Inheritance in Man, OMIM. Johns Hopkins University, Baltimore, MD. MIM Number: 193670: 2021 October 26: https://www.omim.org/entry/162643#editHistory. Last accessed 07 July 2023.
[3] Hernandez PA, Gorlin RJ, Lukens JN, et al. Mutations in the chemokine receptor gene CXCR4 are associated with WHIM syndrome, a combined immunodeficiency disease. Nat Genet. 2003; 34(1):70-4.
[4] Heusinkveld LE, Majumdar S, Gao JL, McDermott DH, and Murphy PM. WHIM Syndrome: from Pathogenesis Towards Personalized Medicine and Cure. J Clin Immunol. 2019; 39(6):532-56.
[5] Dotta L, Notarangelo LD, Moratto D, Kumar R, Porta F, Soresina A, et al. Long-term outcome of WHIM syndrome in 18 patients: high risk of lung disease and HPV-related malignancies. J Allergy Clin Immunol Pract. 2019; 7(5):1568-77. doi: 10.1016/j.jaip.2019.01.045.

extensive growth. Approximately 20 to 25% of patients had genital-anal condyloma acuminata in a recent review (Beaussant Cohen 2012[1]). Malignant anogenital squamous cell carcinoma (SCC) or head and neck was affecting up to 16% of patients with WHIM syndrome (Dotta et al.; 2019[5]), the overall cancer risk has been estimated to some sources to be 30% by the age of 40 (Beaussant Cohen 2012[1]). However, the natural course of disease is highly heterogenous, with patients described being more than 75 years of age with appropriate physical functions.

Treatment approach

There is no approved treatment specifically for WHIM syndrome in the European Union. The optimal therapy for WHIM syndrome has not been defined yet and treatment has been with supportive care using intravenous immunoglobulin (IVIG) and granulocyte colony stimulating factor (G-CSF). IVIG treatment aims to correct the humoral deficit of the immune system to treat or prevent infections with some evidence to reduce the risk of bronchiectasis (Beaussant Cohen 2012[1]). G-CSF selectively increases the neutrophil count, but the evidence for its role in preventing infections remains unclear. Potentially serious safety issues of G-CSF include acute respiratory distress syndrome, glomerulonephritis, splenomegaly and splenic rupture, capillary leak syndrome, malignant cell growth, autoimmune events including aortitis and immunogenicity.

Antibiotics and antivirals are commonly used in the treatment of infections. They are not established or recommended for long term therapy, with known adverse events and development of pathogen resistance. However, prophylactic antibiotic use affects up 50% of patients in an international cohort of 18 patients (Dotta et al.; 2019[1]). Quadrivalent HPV vaccination could be less effective in patients with WHIM syndrome (Handisurya et al.; 2010[6]). Allogenic stem cell transplantation is a therapeutic option; however, it is reserved for patients with very high levels of infections due to its own high morbidity.

In summary, the current standard of care for patients with WHIM syndrome aims to improve frequency, intensity and duration of infections. There is therefore an unmet medical need for effective therapies in the treatment of WHIM syndrome.

2.2. *Aspects of development*

The clinical development programme of mavorixafor includes 13 clinical studies and an Expanded Access Programme in which individual patients have continued with mavorixafor treatment under single patient Investigational New Drugs (INDs) upon completion of clinical studies.

The Phase 3 and Phase 2 WHIM syndrome studies provide the main evidence of safety and efficacy of mavorixafor for the target indication. The chronic neutropenia, healthy participant, and oncology studies provide supportive evidence of safety.

2.3. *Description of the product*

Mavorixafor is an orally bioavailable CXCR4 antagonist that blocks the binding of the CXCR4 ligand, SDF-1α/CXC Chemokine Ligand 12 (CXCL12). SDF-1/CXCR4 plays a role in trafficking and homing of leukocytes to and from the bone marrow compartment.

Gain of function mutations in the CXCR4 receptor gene that occur in patients with WHIM syndrome lead to increased responsiveness to CXCL12 and retention of leukocytes in the bone marrow. Mavorixafor inhibits the response to CXCL12 in both wild-type and mutated CXCR4 variants associated with WHIM syndrome. Treatment with mavorixafor results in increased mobilization of leukocytes including neutrophils, lymphocytes and monocytes, from the bone marrow into peripheral circulation.

[6] Handisurya, Alessandra, et al. "A quadrivalent HPV vaccine induces humoral and cellular immune responses in WHIM immunodeficiency syndrome." *Vaccine* 28.30 (2010): 4837-4841.

The initially proposed indication of mavorixafor was:

"Adult and adolescent patients 12 years of age and older for the treatment of WHIM syndrome (Warts, Hypogammaglobulinemia, Infections and Myelokathexis)."

The proposed posology of mavorixafor for all adult and adolescent patients aged 12 years and older weighing over 50 kg was 400 mg (four 100 mg capsules) once daily, administered orally. The proposed dose for all patients weighing ≤50 kg was 300 mg (three 100 mg capsules) once daily, administered orally.

Mavorixafor was approved in the United States of America in April 2024 for: *"patients 12 years of age and older with WHIM syndrome (warts, hypogammaglobulinemia, infections and myelokathexis) to increase the number of circulating mature neutrophils and lymphocytes."*

2.4. *Inspection issues*

2.4.1. GMP inspection(s)

No inspection required.

2.4.2. GLP inspection(s)

No inspection required.

2.4.3. GCP inspection(s)

No inspection required.

3. Quality aspects

3.1. *Introduction*

Mavorixafor drug product is presented as size 1 hard capsules containing 100 mg mavorixafor as active substance.

Other ingredients are:

Capsule content: silica, colloidal anhydrous (E551), croscarmellose sodium (E468), calcium hydrogen phosphate dihydrate (E3431(ii)), cellulose, microcrystalline (E460(i)), sodium laurilsulfate and sodium stearyl fumarate;

Capsule shell: indigotine (E132), gelatine (E441) and titanium dioxide (E171);

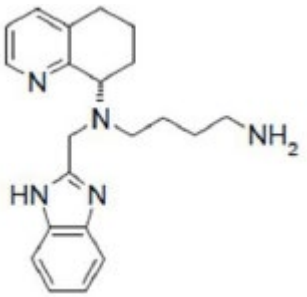
Printing ink: ammonia solution, concentrated (E527), black iron oxide (E172), isopropyl alcohol, n-butyl alcohol, propylene glycol (E1520) and shellac glaze in ethanol (E904);

The product is available in high density polyethylene round white bottles with 38 mm child-resistant screw caps with label. Each bottle contains one desiccant positioned between the rayon coil and cap as described in section 6.5 of the SmPC.

3.2. *Active substance*

3.2.1. General information

The chemical name of mavorixafor is *N*1-(1*H*-benzimidazol-2-ylmethyl)-*N*1-[(8*S*)-5,6,7,8-tetrahydroquinolin-8-yl]butane-1,4-diamine corresponding to the molecular formula $C_{21}H_{27}N_5$. It has a relative molecular mass of 349.48 and the following structure:



The chemical structure of mavorixafor was elucidated by a combination of elemental analysis, UV spectroscopy, FT-IR spectroscopy, NMR spectroscopy, mass spectrometry and single crystal x-ray diffraction. The solid-state properties of the active substance were measured by x-ray powder diffraction and gravimetric vapour sorption. The active substance is classified as BCS Class III (high solubility and low permeability).

The active substance is a white to pale yellow to light brown solid. The active substance has one chiral centre originating in one of the starting materials resulting in possible *R* and *S* configurations. The manufacturing process produces the *S* configuration which is controlled in the active substance specification. Mavorixafor exhibits pH-dependent solubility, being soluble in acidic media with solubility decreasing above pH 5.5.

3.2.2. Manufacture, characterisation, and process controls

The active substance is manufactured at a site for which evidence of GMP compliance has been provided in the QP declaration.

The manufacturing process of mavorixafor active substance consists of four main steps well defined starting materials with acceptable specifications. Adequate information on the source, impurity profiles and routes of synthesis of the starting materials was provided.

Adequate in-process controls are applied during the synthesis. Critical process parameters of the manufacturing process of mavorixafor have been identified and in-process controls with appropriate acceptance criteria for all steps have been set.

The specifications and control methods for intermediate products, starting materials and reagents have been presented, justified based on impurity fate and purge studies. The applied analyitical methods have been adequately described and batch data provided.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised. Mutagenic impurities were assessed and controlled according to ICH M7. A risk assessment indicated no risk of nitrosamine impurities.

Residual solvents are controlled according to ICH Q3C. Control of elemental impurities for Class 1 and Class 2A elements is based on ICH Q3D, Option 2a. The control strategy for tin and zinc, used during the process, is acceptable.

The active substance is packaged in double wrapped low-density polyethylene (LDPE) bags, each bag closed with a cable tie, which complies with Commission Regulation (EU) 10/2011, as amended. The bags are placed inside a foil/polythene bag containing silica desiccant sachets (4 x 100 g) and heat sealed. The heat-sealed bag is then placed inside a high-density-polyethylene (HDPE) keg with a screw cap closure.

3.2.3. Specification

The active substance specification includes tests for appearance (visual), identity (FT-IR, HPLC), physical form (XRPD), assay (HPLC), chiral purify (chrial HPLC), related substances (HPLC), residual solvents (GC), water content (KF), residue on ignition/sulfated ash (Ph. Eur.), elemental impurities (ICP-MS), residual benzene (GC-HS), and microbial limits (Ph. Eur.).

An impurity present at a higher level than the qualification threshold according to ICH Q3A was qualified by toxicological and clinical studies and an appropriate specification limit has been set.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards has been presented.

Batch analysis data from 8 batches of the active substance were provided. The results were within the specifications and consistent from batch to batch.

3.2.4. Stability

Stability data from 4 pilot to production scale batches of active substance from the proposed manufacturer stored in a container closure system representative of that intended for the market for up to 24 months under long term conditions (–20 °C ± 5 °C), for up to 24 months under intermediate conditions (5 °C ± 3 °C for 24 months) and for up to 6 months under accelerated conditions (25 °C ± 2 °C/60% RH ± 5% RH) according to the ICH guidelines were provided.

The parameters tested are the same as for release with the omission of tests for identity, residual solvents (including benzene), residue on ignition and elemental impurities.

Forced degradation and photostability studies were carried out. demonstrating the stability indicating nature of the analytical methods and that mavorixafor is photostable and this requires no protection from light.

All results comply with the specification set and no significant changes or trends were observed.

Based on the presented results and justification, the proposed re-test period of 24 months when stored at -20 °C ± 5 °C is acceptable.

3.3. *Finished medicinal product*

3.3.1. Description of the product and pharmaceutical development

The finished product is an immediate release solid oral dosage form in size 1 hard gelatine capsules. The Mavorixafor 100 mg capsules shells are comprised of a white opaque body and a light blue opaque

cap. Each capsule is printed with "MX4 100 mg" marking. The qualitative and quantitative composition of the finished product, gelatine capsules and printing ink were provided.

The development goal for the finished product was to deliver a robust formulation and manufacturing process with an appropriate control strategy that meets all aspects of the Quality Target Product Profile (QTPP, Table 4).

Table 4: finished product QTPP

QTPP Element	Target	Justification
Route of Administration	Oral	Patient compliance
Dosage Strength	100 mg	Enables patient daily doses of 200 mg or 400 mg
Drug Product Quality Attributes	Complies or exceeds regulatory or compendial requirements	Ensures patient safety and efficacy of delivered drug
Container Closure System	Container closure system qualified as suitable for product	Needed to achieve desired shelf-life and ensure product quality and integrity during storage and shipping
Stability/Shelf-Life	Minimum 24 months at 2°C to 8°C	Needed for management of global supply chain
Route of Administration	Oral	Patient compliance

In accordance with ICH Q8 Pharmaceutical Development and based on Quality Target Product Profile the critical quality attributes of the drug product were identified (Table 5).

Table 5: finished product CQAs

Drug Product Quality Attribute	Is this a CQA?	Justification
Appearance	Yes	Differentiation from other products
Identification	Yes	Ensures administration of the intended drug substance
Assay	Yes	Variability effects safety and efficacy
Related Substances	Yes	Impact on safety
Content Uniformity	Yes	Variability effects safety and efficacy
Dissolution	Yes	Impact on bioavailability
Water content	Yes	Potential to impact stability and potency Prevent microbial growth
Microbial limits	Yes	Impact on safety

Key physico-chemical properties of the active substance have been discussed. Mavorixafor has high aqueous solubility below pH 8.0 and is classified as a BCS Class III drug. The particle size distribution of the active substance is therefore not expected to have an impact on the performance of the drug product.

Compatibility of the active substance with the excipients has been confirmed through compatibility studies. The functionality related characteristics as specified in the Ph. Eur. monographs for excipients have not been discussed. However, relevant tests are included in specifications. All excipients are well known pharmaceutical ingredients. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Formulation development was described in detail. Three formulations of three dose strengths (10 mg, 25 mg and 100 mg) were developed and used in early clinical trials. The 100 mg capsule with an optimised composition was used in phase 2 and 3 clinical studies. The commercial formulation has a different coloured capsule shell, which does not impact the quality or stability of the drug product.

The dissolution method was changed during the development. The CHMP considered that the discriminatory power of the method had not been adequately discussed and that the proposed

specification limit was too wide resulting in 2 major objections. In response, the applicant provided the results of experiments investigating discriminatory power for "bad batches" manufactured with low levels of disintegrant, without the SLS wetting agent, or with a higher tamping force. None of these changes impacted dissolution rate. Considering the high solubility of the active substance, it was agreed that the investigation of discriminatory power is acceptable. The applicant tightened the release specification as requested. The choice of dissolution method and specification are justified, and both major objections are considered resolved. A bridging study between the new and old dissolution methods was performed and the new method validated.

The manufacturing process development has been described in detail including optimisation of the different unit operations. The quality of the finished product has remained constant throughout development, and all drug product lots that have been used in clinical and primary stability studies are representative of the proposed commercial product.

The primary packaging is high density polyethylene round white bottles with 38 mm child-resistant screw caps with label. Each bottle contains one desiccant positioned between the rayon coil and cap as described in section 6.5 of the SmPC. The materials comply with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

3.3.2. Manufacture of the product and process controls

For all sites involved in the manufacture, control and batch release of the finished product sufficient evidence of GMP compliance has been provided.

The manufacturing process is considered standard and consists of sifting, blending, encapsulation, weight sorting/metal check and packaging.

Blending was identified as critical step and appropriate in-process controls have been applied. The holding time of filling capsules before weight sorting has been justified.

An acceptable process validation protocol for the commercial batch size has been provided. Validation of the finished product manufacturing process will be conducted at the commercial site. The in-process controls are adequate for this type of manufacturing process.

3.3.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form including appearance (visual), identification (HPLC, UV), assay (HPLC), impurities (HPLC), uniformity of dosage units (Ph. Eur.), dissolution (Ph. Eur.), water content (KF), microbial contamination (Ph. Eur.) and nitrosamine impurity X192 (LCMS/MS). The specification limits are the same for release and during shelf life. The finished product specifications generally cover appropriate parameters for a capsule dosage form.

The limit for a specified impurity is above the qualification threshold but has been qualified toxicologically. Limits for unspecified and total impurities are set based on batch data and ICH guidance.

A risk assessment on the potential presence of elemental impurities in the finished product was provided and complies with ICH Q3D. The results of the risk assessment show that none of the evaluated elemental impurities exceed the established PDEs

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product was performed considering all suspected and actual root causes in line with the "Questions and

answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). The applicant concluded that there is no risk. However, considering the presence of secondary amine and amine-containing solvent impurities in the active substance, and the use of excipients known to contain nitrite in the finished product formulation, the CHMP raised a major objection requesting confirmatory testing. The applicant provided the requested data, showing that 3 potential impurities were not detected but that one impurity is present at levels up to the accpetable intake, derived using the CPCA approach. As such, the applicant added a routine test to the release and shelf-life specifications. Furthermore, considering the limited data available on stability batches and the potential for an increase of the impurity over time, the CHMP considered that extrapolation of shelf-life to 36 months was not justified. The applicant therefore tightened the shelf-life to 24 months and committed to continue the on-going stability studies and to report any issue to the competent authorities. Factors affecting the formation of this impurity are not fully understood. Therefore, the CHMP recommended conducting further root cause analysis and implementing process changes to reduce levels as appropriate. Furthermore, the applicant should complete in-use drug product stability studies for the aged drug product batches and report any issues to the Competent Authorities.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards has been presented.

Batch analysis results are provided for 13 pilot to production scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

3.3.4. Stability of the Product

Stability data from 3 production scale batches of finished product stored for up to 36 months under long term conditions (5 °C ± 3 °C) and for up to 6 months under accelerated conditions (25 °C/60% RH) according to the ICH guidelines were provided. Three batches of each proposed pack size (60, 90, 120 capsules) were conducted. The batches are representative of those proposed for marketing and were packed in the primary packaging proposed for marketing.

For the majority of tested parameters, no significant changes or trends were observed. However, impurities increased under accelerated conditions and were out of specification after 6 months.

Forced degradation and photostability studies have been performed during validation of the analytical method for identification, assay, uniformity of dosage units and related substances. The methods are stability indicating. The finished product is photostable.

The initially proposed shelf-life of 36 months is not acceptable considering the potential increase in one impurity over time. Based on the data available, a shelf-life 24 months and storage refrigerated at 5 °C ± 3 °C in the proposed container closure system and the in-use shelf-life of 45 days are considered acceptable. The shelf-life is granted with a commitment to continue the on-going stability studies and to report any issue to the competent authorities.

3.3.5. Adventitious agents

Gelatine obtained from bovine sources is used in the product. Valid TSE CEP from the suppliers of the gelatine used in the manufacture is provided.

3.4. *Discussion on chemical, pharmaceutical and biological aspects*

Information on the development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. Three major objections were raised during the procedure: the first two related to the dissolution method and were resolved by provision of further discussion on the investigation of discriminatory power and tightening of the specification limit. The nitrosamines major objection was resolved by addition a specification limit to the release and shelf-life specifications, shortening the shelf-life, and commitments to continue stability studies, investigate the root cause, implement process changes to reduce levels of as appropriate, complete the in-use drug product stability studies for the aged drug product batches and report any issues to the competent authorities. These points are put forward and agreed as recommendations for future quality development.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

3.5. *Conclusions on the chemical, pharmaceutical and biological aspects*

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

3.6. *Recommendations for future quality development*

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- The applicant should continue stability studies including testing for a nitrosamine impurity, investigate the root cause for formation, implement process changes to reduce levels as appropriate, and alert the competent authorities to any issues identified.
- The applicant should complete the in-use drug product stability studies for the aged drug product batches and report any issues to the competent authorities.

4. Non-clinical aspects

4.1. *Introduction*

The nonclinical testing programme of mavorixafor was designed in accordance with the International Council for Harmonization (ICH) M3(R2) guideline on "Non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals".

Pharmacology studies conducted with mavorixafor include *in vitro* assays measuring its inhibitory potency on CXCR4-mediated CXCL12 ligand binding and calcium mobilisation, off-target screening assays (radioligand binding), in vitro safety pharmacology studies for human ether-à-go-go-related gene (hERG) channel inhibition and effects on action potential in isolated dog Purkinje fibres. A battery of *in vivo*, Good Laboratory Practice (GLP)-compliant safety pharmacology studies to assess effects on vital organ systems were performed. Safety pharmacology studies were conducted based on recommendations in ICH S7A and S7B guidelines.

The assessment of the ADME (absorption, distribution, metabolism and excretion) characteristics of mavorixafor included the *in vivo* characterisation of the oral bioavailability and plasma pharmacokinetics (PK) following single-dose oral and intravenous (IV) administration to mice, rats, rabbits, and dogs; the effect of food on the absorption of mavorixafor; and the characterisation of plasma toxicokinetics (TK) following repeat oral doses in rats and dogs in the toxicology studies. Exposure in female rabbits was also assessed after repeated administration in a tolerability study. In addition, TK was evaluated in a preliminary embryo-foetal development (EFD) toxicity study in rats and juvenile toxicity studies in rats and dogs. *In vitro* studies were conducted to compare the plasma protein binding (PPB) and metabolite profiles (in liver microsomes) among non-clinical species and humans. Reaction phenotyping was performed using human liver microsomes (HLM) to identify the human cytochrome P450 (CYP) enzymes responsible for the metabolism of mavorixafor. Potential drug-drug interactions (DDI) liabilities were assessed using *in vitro* assays for CYP induction potential (in human hepatocytes), CYP inhibition potential (in HLM or using recombinant human CYPs), and ability of X4P-001 to act as an inhibitor or a substrate of the human transporters (using Caco-2, MDCKII and HEK293 cells). An *in vivo* quantitative whole-body autoradiography (QWBA) study was conducted in male rats to examine the ADME of mavorixafor following a single oral dose of [^{14}C]mavorixafor. Tissue distribution was also evaluated in mice by the cold method after single oral and IV administration. Repeat-dose TK studies were conducted either using mavorixafor, the free-base formulation used in clinical studies, or using the para-hydroxy benzoate (PHB) salt form (AMD11070PHB), which was never used in clinical studies and is not intended for marketing. The analytical methods used in pivotal repeat-dose toxicity studies in rats and dogs were validated in compliance with GLP standards, current FDA Guidance for Industry, Bioanalytical Method Validation and ICH M10.

For the evaluation of the toxicity of mavorixafor, the rat and dog were chosen as the rodent and nonrodent animal species to be used in single- and multiple-dose studies. Studies of up to 28 days in rats and 39 weeks in dogs were performed with mavorixafor free base. As no chronic rat toxicity studies were conducted with the free base of mavorixafor, the 26-weeks rat study conducted with the PHB salt form of mavorixafor, referred to as AMD11070PHB, provided only supportive data for the chronic toxicity of mavorixafor in rats. The X4P-001 test material used in non-clinical studies was representative of the material used in clinical studies and planned for commercial production. A carcinogenicity study was not yet conducted. An integrated weight of evidence assessment to assess the carcinogenic potential of mavorixafor was conducted. Fertility studies were not performed with mavorixafor but effects on reproductive organs were assessed in repeat-dose toxicity studies in rats and dogs. Non-GLP tolerability in rabbits (once daily dosing) and preliminary EFD studies in rats (twice-daily dosing), were conducted. Due to the poor tolerability observed at sub-clinical exposures in preliminary EFD studies in animals and in consideration of the known reproductive toxicity due to CXCR4 inhibition during early development, a weight of evidence assessment was conducted to evaluate the risk of mavorixafor administration on pregnancy and embryo-foetal development. A non-GLP dose range-finding (DRF) study was conducted in juvenile rats with once-daily administration from postnatal day (PND) 28 to 41. A follow-up non-GLP study in juvenile rats was conducted to evaluate changes if any in juvenile toxicity when dosing was initiated on PND 28 or PND 35. A definitive GLP-compliant 26-week juvenile toxicity study in dogs (Study X4P-001-TOX-033) including male fertility endpoints was completed and results provided during the procedure.

4.2. *Analytical methods*

The bioanalytical methods for determination of mavorixafor in rat and dog plasma were developed and successfully validated. In both matrices, carryover did not meet the acceptance criteria.

4.3. *Pharmacology*

4.3.1. Pharmacodynamics

4.3.1.1. Primary pharmacodynamics

Mavorixafor is a potent allosteric CXCR4 antagonist that binds to the receptor and prevents its interaction with CXCL12 thereby reducing ligand-induced downstream signalling. The compound inhibited CXCL12 binding to CXCR4 with an IC_{50} of 6.1 nM in K562 lymphoblast cells stably overexpressing wild type (WT) CXCR4 and IC_{50} ranging between 3.2 and 11 nM in cells overexpressing different WHIM mutant variants. In Jurkat cells endogenously expressing CXCR4, the IC_{50} values were 1.9 nM in the WT receptor cell line and 1.6-2.4 nM in the mutant counterparts. Downstream signalling (assessed as inhibition of Ca^{2+} mobilisation) was reduced with an IC_{50} of 5.1 nM in K562 cells featuring a WT receptor and 3.6-35.9 nM in WHIM mutant cell lines. K562 cells harbouring pathogenic mutations identified in patients in clinical studies NCT03005327 and NCT03995108 (including the most common mutations in WHIM syndrome, S338X and R334X, as reported by Rodriguez-Frade et al. 2024[7]) were also evaluated: CXCL12 binding was reduced with IC_{50} values between 3.4 and 8 nM, Ca^{2+} mobilisation was inhibited with IC_{50} of 6.1-17 nM.

Mavorixafor did not inhibit calcium flux of cells expressing CXCR3, CCR1, CCR2b, CCR4, CCR5 or CCR7, or ligand binding to CXCR7 and BLT1, indicating that mavorixafor has no activity against these chemokine receptors while also demonstrating selectivity for the CXCR4 chemokine receptor. No data was provided demonstrating inhibition of ligand-induced calcium flux and/or ligand binding for CXCR1, CXCR2, CCR3, CCR6 and CCR9 (Mosi et al. 2012[8]).

No studies in WHIM syndrome animal models were conducted with mavorixafor. Intraperitoneal administration of a selective and competitive CXCR4 antagonist plerixafor or a CXCL12-neutraliser chalcone 4 increased the absolute numbers of total leukocytes including neutrophils, B and T cells both in the blood of mice carrying WT CXCR4 and in blood of *Cxcr4$^{+/1013}$* mice. The accompanying decrease in leukocyte count in bone marrow was not significant in WT mice and not observed in mutant mice (the latter being a disease model). No effect on leukocytes in *Cxcr4$^{+/1013}$* mice was attributed to the relatively short half-life (0.9 hour) of plerixafor in rodents together with the gain of CXCR4 function in mutants, which may have forced the homing of peripheral leukocytes to the bone marrow (Balabanian et al. 2012[12]).

4.3.1.2. Secondary pharmacodynamics

At the concentration of 10 µM in a radioligand-binding assay, mavorixafor inhibited 15 of 173 targets studied to the extent of ≥50%. The IC_{50} values for these targets ranged from 0.52 to 16.2 µM corresponding to 0.79 – 24.5-fold of the unbound clinical Cmax of 661.85 nM as shown below.

Target	**Safety margin**
Adrenergic α2A	16.8
Calcium Channel L-Type, Benzothiazepine	10.4
Calcium Channel L-Type, Phenylalkylamine	2.6
Glutamate, NMDA, Phencyclidine	11.2

[7] Rodríguez-Frade, José Miguel, et al. "The complex nature of CXCR4 mutations in WHIM syndrome." *Frontiers in immunology* 15 (2024): 1406532.
[8] Mosi, Renee, et al. " The molecular pharmacology of AMD11070: an orally bioavailable CXCR4 HIV entry inhibitor." *Biochemical Pharmacology* 83.4 (2012): 472-479.

Histamine H1	7.45
Muscarinic, Oxotremorine M	12.6
Opiate κ (OP2, KOP)	4.6
Opiate μ (OP3, MOP)	3.6
Potassium Channel hERG	5.48
Sodium Channel, Site 2	2.81
Somatostatin sst1	5.82
Somatostatin sst4	4.06
Somatostatin sst5	24.5
Transporter, Norepinephrine (NET)	15.6
Urotensin II	0.79

4.3.1.3. Safety pharmacology

Mavorixafor inhibited hERG channel activity by 32% (-2.1-77.3%) at 13.28 μM and by 66% (13.3-88.8%) at 29.48 μM. The IC_{50} value was not determined.

In conscious telemetered Beagle dogs in a GLP study, single oral administration of mavorixafor at doses of 50, 150 and 400 mg/kg significantly increased heart rate in a dose-dependent fashion (by 49, 61 and 67% up to actual mean heart rates of 105, 127 and 132 beats per minute) accompanied by minor increase in diastolic arterial pressure. The maximum increase was considered within the range of expected animal variability. The mean total dog plasma Cmax at 50, 150 and 400 mg/kg was 6551, 7283 and 8508 ng/mL. No corrected QT interval (QTc) prolongation was observed in dogs up to 400 mg/kg. In isolated dog Purkinje fibres, mavorixafor significantly shortened action potential duration at 10 and 100 μM.

In a GLP-compliant safety pharmacology study evaluating central nervous system (CNS) effects of mavorixafor following oral dosing to Sprague-Dawley rats, a significant decrease in body temperature was noted in the 1000 mg/kg group at 40 min. and 24 h (but not at 90 min.) post-dose, with the absolute values being still in normal range. No test-item related mortalities, clinical signs or neurobehavioural effects were observed. The no observed adverse effect level (NOAEL) was set at 1000 mg/kg.

Oral administration of mavorixafor to Sprague-Dawley rats in a GLP respiratory study caused a statistically significant reduction in respiration rate at 1000 mg/kg 24 h post-dose but the values were within the expected range. Salivation was noted at 250 and 1000 mg/kg. The NOAEL was set at 1000 mg/kg.

4.3.1.4. Pharmacodynamic drug interactions

No PD drug interaction studies have been conducted.

4.3.2. Pharmacokinetics

4.3.2.1. Absorption

Following intravenous dosing to animals, mavorixafor was eliminated in a bi-exponential manner with $T_{1/2}$ ranging between 8.9 and 24.7 h. After oral dosing, mavorixafor exposure increased less than dose-proportionally in rats, slightly more than dose-proportionally in dogs and a lot more than dose-proportionally in rabbits. In mice, a saturation of absorption was seen at 300 mg/kg. Bioavailability was low in rats and rabbits and high in mice and dogs. The exposure was reduced in dogs in the fed state indicating potential food interference with absorption.

4.3.2.2. Distribution

Ultrafiltration analysis and equilibrium dialysis were utilised to determine protein binding of mavorixafor in human and animal plasma. The ultrafiltration method revealed the bound fraction of 66-93% in rat plasma, 87-95% in dog plasma, and 84-97% in human plasma. The percentage of protein-bound mavorixafor was determined by equilibrium dialysis as 93.6-95.2% in monkey, 90.4-94.0% in human, 56.5-73.1% in rat, 67.4-81.0% in mouse, and 62.7-92.7% in dog plasma.

The kinetics of tissue distribution was investigated with LC-MS/MS in Balb/c mice following IV administration at 5 mg/kg and oral administration at 100 and 300 mg/kg. Mavorixafor quickly distributed into tissues with liver, kidney, spleen and bone marrow having the highest drug levels (67-, 58-, 18- and 17-fold of the plasma AUC after 100 mg/kg PO, 21-, 90-, 32- and 26-fold of the plasma AUC following 5 mg/kg IV, respectively). Whereas concentrations in other tissues gradually declined, there was no apparent clearance from brain.

Tissue distribution in partially pigmented and non-pigmented rats was assessed using QWBA after oral dosing of 50 mg/kg [^{14}C]-mavorixafor. In non-pigmented animals, the highest levels of radioactivity at 1 h post-dose were seen in the stomach, small intestine and urinary bladder with notable concentrations found in the liver, kidney and adrenal gland. At 24 h post-dose, radioactivity was observed mainly in the gastrointestinal tract (GIT) with notable amounts in elimination organs and glandular tissues. Tissue concentrations gradually declined up to 168 h, though not in choroid plexus having higher radioactivity levels at later (rather than earlier) time points. In partially pigmented rats, highest concentrations of radioactivity were seen in the GIT, with notable amounts also measured in the uveal tract, tissues associated with elimination (liver, kidney, urinary bladder) and several glandular tissues such as the pituitary, thyroid and salivary glands. There was no accumulation in choroid plexus in partially pigmented rats. Radioactivity in uveal tract was still noted 840 h post-dose but slowly declined indicating that association of mavorixafor with melanin is reversible.

4.3.2.3. Metabolism

In liver microsomes, metabolism of mavorixafor was moderate in rodents and low in dog and human. Hydroxylation was the major biotransformation pathway in all species. No unique metabolites were detected in human liver microsomes. CYP3A4 and CYP2D6 were the major enzymes responsible for the biotransformation as demonstrated using specific CYP inhibitors and rhCYP.

In vivo, metabolism was investigated after a single oral administration of [^{14}C]-mavorixafor to Sprague-Dawley rats. The plasma, urine, faeces and bile had 17, 12, 4 and 10 radioactive components corresponding to more than 2% of the total sample radioactivity, respectively. Structural identification of the metabolites was performed only for those accounting for more than 10% of circulating radioactivity in plasma and more than 10% of the dose in faeces. Rat plasma had 27% unchanged

mavorixafor and 11% (1H-benzo[d]imidazol-2-yl) methanol, also referred to as M148. The parent drug accounted for 49% of the total administered radioactivity in rat faeces.

In human, parent mavorixafor accounted for 24.97% of the total radioactivity in plasma, for 26.43% in urine and 29.85% in faeces. No radioactive metabolite accounted for more than 10% of either the circulating radioactivity (plasma) or the total administered dose (excreta). Most metabolites identified in microsomes were also observed in human samples.

4.3.2.4. Excretion

Following oral dosing of [^{14}C]-mavorixafor, radioactivity was mainly excreted in faeces of normal male rats (85.1%), with renal excretion representing a minor elimination pathway (6.32%). In bile-duct cannulated male rats, 67.5% were excreted in faeces, 13.9% in bile and 8.46% in urine.

4.3.2.5. Pharmacokinetic drug interactions

Several studies were performed to assess inhibitory potential of mavorixafor towards CYP enzymes, one with CYP2B6 and CYP2C8 supersomes, an older study in human liver microsomes evaluating CYP1A2, CYP2C9, CYP2C19 and CYP3A4 and a more recent study in human liver microsomes, which covered all guideline-relevant CYPs and included time- and mechanism-based inhibition. In the latter study, mavorixafor inhibited CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A with IC_{50} values of 53.4, 15.8, 62.4, 55.5, 47.6, 1.26, and 15.4 μM, respectively. CYP3A was the only enzyme, which was also inhibited in time- and mechanism-based (NADPH-dependent) fashion.

Two studies have been carried out to evaluate mavorixafor potential to induce CYP enzymes, one with fresh human hepatocytes from one liver donor focused solely on enzyme activity and a guideline-conform study with cryopreserved hepatocytes from three different donors. Mavorixafor induced CYP1A2 mRNA in a concentration-dependent manner at ≥10 μM and CYP1A2 activity in a concentration-dependent manner at ≥15 μM. Mavorixafor did not induce CYP2B6 mRNA up to 30 μM, CYP2C8, CYP2C9 and CYP3A4 mRNA and CYP2C19 activity up to 25 μM. A slight reduction in CYP2C9 and CYP3A4 activity was seen in fresh human hepatocytes.

Mavorixafor is metabolised by CYP3A4 and CYP2D6.

Mavorixafor was found to inhibit P-gp, OAT1, OCT2, and MATE1 with IC_{50} values of 121, 25.6, 0.589, and 1.02 μM. Mavorixafor was not a substrate of OATP1B1, OATP1B3, OCT2, OAT1, OAT3, MATE1 and MATE2-K. The results of studies on P-gp and BCRP were inconclusive. In Caco-2 cells, the efflux ratio was above 2 at concentrations ≥1 μM. The efflux ratio was not reduced by P-gp inhibitors at 1 μM but it was reduced >50% at 10 μM. In a membrane vesicle assay, mavorixafor was found to be not a substrate of P-gp. In MDCKII/BCRP cells, efflux ratio was over 2 but comparable to control cells, which also had an efflux ratio higher than 2. The efflux ratio was reduced >50% by lopinavir and <50% by Ko143 (BCRP inhibitor). In membrane vesicles, mavorixafor was found to be not a substrate of BCRP.

4.4. *Toxicology*

4.4.1. Single-dose toxicity

Single dose toxicity studies were conducted in rats and dogs (1 study each). Animals were orally administered with up to 1500 mg/kg/day (gavage, formulated in sterile water) (rats) or up to 600 mg/kg/day (capsule) (dogs). Mortality occurred in rats at the mid- and high-dose accompanied with changes in clinical signs (fur staining on muzzle, jaw, hindlimbs and/or urogenital areas, dehydration, salivation), clinical pathology (increase in blood urea nitrogen (BUN), total bilirubin, alanine aminotransferase (AST), aspartate aminotransferase (ALT), cholesterol and triglycerides) and

microscopic changes (in stomach, cecum, liver, spleen, mandibular and mesenteric lymph nodes, stomach, bone marrow and thymus).

Non-rodent acute toxicity was further tested with escalating doses of mavorixafor in dogs. In the tested animals (1M+1F dog in each group) the severity of adverse effects increased with dose and included GIT toxicity (vomiting and abnormal faeces), decreased body weight and food consumption and changes in clinical pathology in the escalating group.

4.4.2. Repeat-dose toxicity

The toxicity of X4P-001 (mavorixafor free base) was determined following repeat administration of twice-daily oral doses for 28 days in rats and for 10, 28 days and 13 weeks in dogs, while the 39-week toxicity study in dogs was conducted with once-daily capsule administration.

Non-pivotal studies included one maximum tolerated dose (MTD) dose finding study in dogs, two bridging studies with X4P-001 (mavorixafor free base) and AMD11070PHB (salt form of mavorixafor) in rats and dogs (one study each; non-GLP), four long-term studies with the salt form in rats and dogs (2 studies each) and five pivotal studies in rats and dogs (one rat study and four dog studies).

Evaluation of repeat dose administration of mavorixafor to dogs treated twice daily (capsule or gavage) for 10 days resulted in early termination of the high dose group animals (≥400 mg/kg/day). Increased WBCs were attributed to the pharmacological activity of X4P-001 and clinical signs of GIT (vomiting and abnormal faeces) were present in all dose groups. Prominent changes were further inflammation and necrosis in the liver accompanied with increases in ALT, AST and decreases in alkaline phosphatase (ALP). Within this study, animals were dosed either with a capsule or by gavage. In general, there was no difference in toxicity between capsule and gavage formulation.

The toxicity of the salt-form (AMD11070PHB) was evaluated in 7-day (rat) and 14-day (dog) bridging studies (non-GLP) with equimolar doses of X4P-001. Observed changes (notably increase in WBCs) are attributable to the pharmacological activity of X4P-001. Groups treated with the salt form of X4P-001 exhibited more effects compared groups treated with X4P-001 free base. In general, there were no significant differences between toxicity at equimolar doses of X4P-001 and AMD11070PHB-treated groups. The toxicity of the salt-form was further evaluated in long-term studies. However, since severe toxicity occurred in the dogs including deaths, the study protocols were modified: the 39-week dog study was reduced to a three-month period, and the planned 13-week dog study was reduced to a one-month period. In addition, both studies were completed without a recovery period. In rats, the planned study duration of 13- and 26 weeks plus a 4-week recovery period could be performed as planned demonstrating that dogs were more sensitive to the mavorixafor salt form compared to rats. It was, however, not demonstrated which entity was responsible for toxicity. Deaths occurred not only in the dog studies but also in the rat studies at the highest dose tested. Adverse effects in rats and dogs comprised changes in liver, kidney, bone marrow, spleen, thymus. In addition, retinal degeneration/atrophy was noted in rats. Non-reversible liver changes observed with the PHB salt form included vacuolation and histopathology changes (mononuclear cell infiltration, multifocal vacuolation, multifocal bile duct hyperplasia) in the 6-month study. In the 3-month dog study, histopathology changes indicative of liver and renal toxicity was noted. In dogs, liver toxicities were observed after administration of the PHB-salt form of mavorixafor (minimal to moderate multifocal hepatocellular single cell necrosis) in the one- and three-month study; reversibility was not assessed due to early abortion of the studies.

The pivotal studies comprised a twice-daily dosing for 28 days in rats and a duration of 10, 28 days and 13 weeks in dogs, while the 39-week toxicity study in dogs was conducted with once-daily capsule

administration. Results of the repeat-dose toxicity studies in rats (28-day) and dogs (28-day, 13 weeks, and 39 weeks with interim necropsis) are provided in Table 6.

Table 6: Repeat-dose toxicity studies in rats (28-day) and dogs (28-day, 13 weeks, and 39 weeks with interim necropsis)

Study details Species Duration + recovery (weeks) Route GLP status (Study ID)	**No:Sex/ Group** <text>	**Dose** (mg/kg/ day)	**Exposure**		**Major findings & NOAEL**
			Cmax ng/ml	$AUC_{0\text{-}tlast}$ ng*h/ml	
Repeat-dose toxicity studies (NOAELs highlighted)					
RAT (Sprague Dawley) 28 + 14 d PO, gavage GLP X4P-001-TOX-009	Main: 15M/15F Recovery: 4F/4M TK Vehicle: Treated: 21F/21M	0	-	-	**Mortalities**: two female animals at 250 mg/kg/day died due to gavage injury **≥30 mg/kg:** see all doses **≥62.5 mg/kg:** see all doses **≥125 mg/kg**: Gastrointestinal findings included dilation of cecum with increased incidence (1/10 in males and 2/10 females), ↑ALT (33%) **≥250 mg/kg**: ↓body weight gain in males compared to control. Gastrointestinal findings included dilation of cecum with increased (3/10 males and 6/10 females), ↑ALT (74%), ↓reticulocytes, • Bone marrow: hypocellularity (minimal) in male and female rats. **All doses:** ↑WBC including neutrophils, monocytes, basophils and large unstained cells at ≥30 mg/kg/day, decrease in lymphocytes and eosinophils, ↓thymus weights in all mavorixafor treated groups with marked decrease (↓up to 39%) at 125 and 250 mg/kg/day. **Recovery**: ↓body weight gain in males at 250 mg/kg/day (↓ 11%) compared to control **NOAEL 125 mg/kg (0.2x at Maximum Recommended Human Dose (MRHD))**
		30	ND	ND	
		62.5	198/329	711/1345	
		125	383/497	2247/3008	
		250	1973/1201	9572/13147	

DOG (Beagle) 4 w + 14 d PO, capsule GLP X4P-001- TOX-010	Main: 5M/5F at 0+100mg/kg/day 3M/3F at 10+30 mg/kg/d Recovery: 2F/2M at 0+50 mg/kg/d TK: 3F/3M 10+30 mg/kg/d 5F/5M 100 mg/kg/d	0	-	-	**Mortality**: None **≥10 mg/kg**: •thymus and lymph node: lymphoid atrophy **≥30 mg/kg**: •Lymph node: erythrocytosis/haemorrhage **≥100 mg/kg**: Gastrointestinal toxicity (emesis and abnormal faeces) ↓body weight gain in males and females (↓15%) and lower food consumption compared to control, decreases in reticulocytes, ↓ALP, total protein, and albumin, •Bone marrow: hypocellularity, •Liver: pigment deposits, •thymus and lymph node: lymphoid atrophy, •Ileum: GALT atrophy (females), •Spleen: lymphoid atrophy **All doses:** ↑WBC including neutrophil, lymphocyte, and monocyte counts, ↓thymus weights, ↑mesenteric lymph node, erythrocytosis/haemorrhage **Recovery**: 100 mg/kg/day: ↓body weight gain, histopathology findings in bone marrow, liver, and mesenteric lymph node were present **NOAEL 30 mg/kg (0.4x at MRHD)**
		10	482/563	1619/1949	
		30	2136/1116	6677/5054	
		100	2167/3207	133534/ 18725	
DOG (Beagle) 13w PO, capsule GLP X4P-001- TOX-018	Main: 3M/3F Recovery: No TK satellites: 3F/3M	0	-	-	**Mortality**: None **≥10 mg/kg**: •Liver: focal/multifocal hepatocellular loss/necrosis in one male dog **≥20 mg/kg**: see all doses **≥35 mg/kg**: moderate lower food consumption, ↓ total protein and albumin likely related to body weight changes, •Bone marrow: (slight) hypocellularity, •Liver: focal/multifocal hepatocellular loss/necrosis in 3/3 male dogs **≥70 mg/kg**: ↓ body weights (>10%) in males and moderate lower food consumption, ↓ total protein and albumin likely related to body weight changes, increases in ALT (1.3x) and ALP,
		10	1487/1493	10648/9272	
		20	3270/2183	18452/ 16614	
		35	3170/3933	21561/ 28994	
		70	3430/5940	28075/ 46412	

					•Bone marrow: (slight) hypocellularity, •Necrosis of individual hepatocytes (single cell necrosis) 2/3 female dogs **All doses:** Gastrointestinal toxicity (emesis and abnormal faeces) at all doses, ↑WBC neutrophils, and lymphocytes, Dose-dependent ↓spleen weights (up to 53%) in males, •Liver: pigment •Kidney: accumulation of golden-brown granular pigment in the epithelial cells of the proximal tubules **Recovery**: no recovery period included **LD: 10 mg/kg** **NOAEL could not determine due to the presence of pigment at all doses**
DOG (Beagle) 39w PO, capsule GLP X4P-001-TOX-017	Main: 9M/9F Interim necropsy of 3 animals/ sex/group after 3 and 6 months of dosing	0	-	-	**Findings for animals at 3-, 6-, 9-month study duration** **≥3.8 mg/kg**: ↓body weights (>10%) in males at 3-month, ↓food consumption **≥11.4 mg/kg**: pigment in salivary glands (females) **≥34.1 mg/kg**: minimal decreases (↓7%) in red cell parameters (erythrocytes, haemoglobin, haematocrit, and red cell width distribution), decreases (↓7%) in red cell parameters (erythrocytes, haemoglobin, haematocrit, and red cell distribution width), lower ALP and ASP, and higher (2-3-fold) GLDH activity (males), Brown or green discoloration in •kidneys (correlated with tubular cell pigmentation in males), •Liver (correlated with hepatocellular and Kupffer cell pigmentation in males), and •salivary glands (correlated with acinar cell pigmentation) **All doses:** incidence of emesis, soft, watery, mucoid, and/or discoloured faeces, Lower food consumption was noted at Week 26 (↓18 to ↓34%) and Week 39 (↓6 to↓31%) of dosing in males and females, ↑WBCs (↑42% neutrophils ↑55%, and monocytes
		3.8	1220/1660	3490/4410	
		11.4	2750/3680	9110/14000	
		34.1	6390/8470	33900/ 45600	

					↑71%), decrease in testes and epididymis with correlating degeneration/atrophy, decrease in ovary **Recovery**: no recovery period included **NOAEL (females) 3.8 mg/kg/day (0.3x MRHD);** **NOAEL (males): could not be determined due to seminiferous tubule degeneration/atrophy of the testes at all dose levels**

Additional findings at interim necropsy
3-month:
3.8: short QTc (females), **11.4:** longer QRS (males), **34.1:** longer QRS (males+females)
6-month:
34.1: Eyes: pigmentation+increased size of tapetal cells
9-month:
3.8: neurological dysfunction (1 dog)
11.4 + 34.1: fascial nerve disfunction (female)

Histopathology:
Dose-dependent minimal to mild accumulation of pigment was observed in liver hepatocytes and Kupffer cells, gallbladder, kidneys, thyroid, stomach, salivary gland, and eyes in males and females. The pigment was consistent with lipofuscin in multiple organs at 3.8 mg/kg/day and above. Increased incidence of minimal to mild hypertrophy/hyperplasia of the gallbladder epithelium was observed at 11.4 mg/kg/day and 34.1 mg/kg/day characterized by a diffuse increase in mucosal thickness and epithelial cell size/height. Minimal to marked bilateral seminiferous tubule degeneration/atrophy at all doses characterized by variable hypospermatogenesis, cytoplasmic vacuolation within tubules, swollen spermatocytes, multinucleate giant cells, degenerate/necrotic germ cells, and/or luminal cellular debris. The findings were dose-dependent with increased incidence and severity. One male in control also displayed minimal findings. Minimal to severe oligospermia/ germ cell debris minimal to severe was observed at 11.4 mg/kg/day and 34.1 mg/kg/day, and minimal necrosis at 34.1 mg/kg/day was observed at terminal necropsy. Reversibility of these findings were not assessed.

4.4.3. Genotoxicity

Mavorixafor was tested in a standard Ames test, an *in vitro* chromosome aberration assay and an oral *in vivo* Micronucleus test in rats. All tests were in line with ICH S2(R1) and according to GLP. There were no indications of genotoxic effects of mavorixafor in none of the test systems. Based on this, mavorixafor can be considered as non-genotoxic.

4.4.4. Carcinogenicity

No carcinogenicity study has been performed with mavorixafor. The applicant received a Scientific Advice in 2024 by CHMP (EMA/SA/0000163154) where it was concluded that the integrated weight of evidence assessment provided supports that mavorixafor has low carcinogenic potential, and that the results of the planned 6-month Tg.rasH2 mouse carcinogenicity study can be provided as a commitment following approval of the MAA.

A weight of evidence was submitted based on the following:

- Mavorixafor is not genotoxic.

- The target biology of mavorixafor is relatively well characterized with no known class effects with regards to risk of carcinogenicity and there is no evidence that its inhibition by CXCR4 antagonists lead to cancer initiation or promotion in humans or in test species. In addition, various preclinical models demonstrated efficacy of CXCR4 antagonism in various cancers.
- There were no relevant inhibitions of other receptors in off-target screens at clinically relevant concentrations.
- There was no relevant indication of hormonal perturbation in non-clinical toxicity studies.
- Mavorixafor stimulates the immune system by mobilizing sequestered leukocytes to the periphery, it is not immunotoxic and is not an immunosuppressant that would give rise to concern of a carcinogenic risk.

According to the applicant, the weight of evidence does not give rise to an increased carcinogenic risk for patients.

4.4.5. Developmental and reproductive toxicity

A reduced programme of developmental and reproductive toxicity studies has been performed with mavorixafor. No definitive Developmental and Reproductive Toxicology (DART) studies have been performed with mavorixafor. The studies in respect to DART of mavorixafor included a preliminary EFD study in rats and a dose range finding study in non-pregnant rabbits. Furthermore, two juvenile dose-ranging and tolerability studies were conducted in rats.

Fertility and early embryonic development

No studies on fertility and early embryonic development have been performed with mavorixafor. This is in line with ICH M3 (R2) as repeat-dose studies of sufficient therapeutic duration included a histopathological evaluation of male and female reproductive organs. In rats, no adverse effects on male and female reproductive organs were observed, but in male dogs at all tested doses in a 39-week study with mavorixafor, adverse effects on the testes were found, expressed in minimal to moderate bilateral seminiferous tubule degeneration/atrophy. The changes in males were considered test article-related by the applicant at ≥11.4 mg/kg/day due to the bilateral distribution, overall severity of the changes, and that all males at these dose levels were affected but were considered adverse only at 34.1 mg/kg/day.

Moreover, literature data (not provided by the applicant) suggest a role of CXCL12/CXCR4 system on early placenta development and implantation suggesting a potential risk for adverse effects on early pregnancy (Koo et al., 2021[31]; Ashley et al., 2011[32]; Kumar et al., 2004[33]; McIntosh et al., 2021[34]; Bao et al., 2016[35]; Sun et al., 2022[36]).

Embro-foetal development

A preliminary non-GLP study in rats was conducted to determine the initial embryo-foetal toxicities of mavorixafor after administration by oral gavage with daily doses of 50, 100 or 200 mg/kg during gestation days 6 through 17. No embryolethal or teratogenic effects were observed. However, the treatment was poorly tolerated by the Fo dams and 50 mg/kg/day was identified as NOAEL based on abnormal breathing in maternal animals and reduced foetal weights at higher doses. The maternal exposures at the NOAEL provided safety margin of 0.1 for AUC0-last for the 400 mg once daily dose in humans based on total (i.e., uncorrected for plasma protein binding) mavorixafor, and the corresponding safety margins based on the free (unbound) drug in plasma is 0.4.

Similarly, a non-pivotal tolerability study in non-pregnant rabbits treated with oral doses of 100 and 300 mg/kg/day of mavorixafor showed poor tolerability.

Given the inability to conduct meaningful EFD studies in rats and rabbits, a weight of the evidence assessment was conducted by the applicant. Submitted literature data revealed that CXCR4 is critical during normal embryonic, foetal, and postnatal development. Potential inhibition of the pathway by mavorixafor is anticipated to result in significant developmental toxicity. In mice, CXCR4-/- knockout is embryolethal and causes multiple developmental toxicities, most notably in the hematopoietic, cardiovascular and nervous systems (Ma 1998[9]; Zou 1998[10]; Tachibana 1998[11]; Escot 2016[12]). Furthermore, the approved CXCR4 antagonist plerixafor has known effects on foetal development in animal models. Given the known risk based on the mechanism of action, EFD-testing at doses in animals which would result in exposures below the human clinical exposure was not performed.

Pre- and postnatal development

No prenatal and postnatal development toxicity studies were conducted with mavorixafor. Based on results from CXCR4/SDF-1 knock out mice which showed high peri-postnatal lethality and adverse effects on developmental, mavorixafor as an CXCR4 antagonist has the potential to affect pre-postnatal development.

There are no data on the excretion of mavorixafor in animal or human milk and its effects on milk production and lactation.

Juvenile animals

Data from age-relevant repeat-dose studies with mavorixafor in rat and dog provide supporting information on tolerability and possible adverse effects.

To make a therapy with mavorixafor also available to younger paediatric patients in the future two juvenile DRF and tolerability studies in rats and one juvenile DRF study using dogs were performed at initial application. During the procedure, results a 26-Week Oral Gavage Toxicity and Toxicokinetic Study with X4P-001 in Juvenile Dogs with a 6-Week Recovery Phase (Study X4P-001-TOX-033) were submitted.

Dose range findings studies

All three DRF studies included TK data but were non-GLP compliant. First a DFR study was carried out on rats at doses of 75, 150, and 300/225 mg/kg/day of mavorixafor administered via oral gavage on postnatal day (PND) 28 through 41 (comparative human age ~ 8-12 years). In a follow-up tolerability study, juvenile rats were treated with 200 or 300 mg/kg/day of mavorixafor by oral gavage over shorter durations starting on PND 28 through 34 (Cohort 1) or starting on PND 35 through 41 (Cohort 2). In both studies, the treatment was not tolerated, indicated by laboured breathing and a high rate of morbidity and mortality at exposures at LOAEL/NOAEL that were below the exposure at the clinical dose of 400 mg once daily in humans. Histologic examination showed acute inflammation of laryngeal tissues, and it was hypothesised that this local toxicity was caused by gavage or reflux injury and results in laryngospasms and death by asphyxiation. Mechanisms that initiated the reflux response were uncertain. But since nasal reflux is only a local toxic effect and rats are obligate nasal breathers, these observations in juvenile rats were not considered relevant to humans and a definitive juvenile toxicity study in rats was not considered appropriate. Based on weight of evidence assessment and the potential risk of CXCR4 inhibition for brain development, an additional juvenile dog study was

[9] Ma Q, Jones D, Borghesani PR, Segal RA, Nagasawa T, et al. Impaired B-lymphopoiesis, myelopoiesis, and derailed cerebellar neuron migration in CXCR4- and SDF-1-deficient mice. Proc Natl Acad Sci USA. 1998; 95:9448-53.
[10] Zou YR, Kottmann AH, Kuroda M, Taniuchi I, and Littman DR. Function of the chemokine receptor CXCR4 in haematopoiesis and in cerebellar development. Nature. 1998; 393:595-9.
[11] Tachibana K, Hirota S, Iizasa H, Yoshida H, Kawabata K, Kataoka Y, Kitamura Y, Matsushima K, Yoshida N, Nishikawa S. et al. 1998. The chemokine receptor CXCR4 is essential for vascularization of the gastrointestinal tract. Nature 393: 591-594.
[12] Escot S, Blavet C, Faure E, Zaffran S, Duband JL and Fournier-Thibault C. Disruption of CXCR4 signaling in pharyngeal neural crest cells causes DiGeorge syndrome-like malformations. Development. 2016; 143:582-8.

considered necessary to predict safety for paediatric patients with the youngest intended age of 2 years. First, a juvenile DRF study was conducted in dogs aged 10 to 11 weeks. In the first phase, escalating doses of 3, 10, 30, and 100 mg/kg mavorixafor were administered via oral gavage, followed by a 7 day-repeat-dose phase at fixed doses of 3, 10, 60, or 125 mg/kg mavorixafor once daily via oral gavage. Test-item-related adverse effects were only observed in Phase II at 125 mg/kg and included vomitus, decreased general activity, and whole-body tremors at approximately 2 hours post the first dose, body weight loss, decreased cumulative body weight gains as well as haematology effects. No mortality occurred. Safety margins at the NOAEL (60 mg/kg) were ~1.7 and 1.2 for male and females, respectively.

26-Week Oral Gavage Toxicity and Toxicokinetic Study with X4P-001 in Juvenile Dogs with a 6-Week Recovery Phase (Study X4P-001-TOX-033)

In this study, male and female juvenile dogs aged 9 weeks old at start of treatment (corresponding to an age of approximately 2 to 3 years of age in humans) were administered vehicle control or 10, 25, or 60 mg/kg/day mavorixafor once daily via oral gavage for 26 weeks followed by a 6-week recovery phase (2 dogs each for control and high-dose group).

Mavorixafor-related clinical observations were noted in dogs administered ≥25 mg/kg/day including decreases in body weight gains and in 60 mg/kg/day also included thin appearance, decreased activity, and excessive salivation (≥25 mg/kg/day food supplementation necessary in several animals).

Mavorixafor-related clinical pathology and clinical chemistry findings were suggestive of hepatocellular and/or hepatobiliary perturbation and comparable to findings in adult animal studies. Mavorixafor-related effects in hematology were noted in animals administered ≥10 mg/kg/day. Following the 6-week recovery phase, all liver findings in females had completely reversed; moderate pigment was noted in the liver of the recovery male administered 60 mg/kg/day. Microscopic liver findings in males and females administered ≥25 mg/kg/day and body weight loss with correlated clinical pathology findings suggestive of hepatocellular/hepatobiliary perturbation for individual animals administered ≥25 mg/kg/day requiring dosing holiday were considered adverse.

This study should support development in children ≥2 years, but it is also considered relevant for the intended juvenile patients of ≥12 years since the treatment period continued up to 35 weeks of age (~8.5 months), thus covering the period of prepubertal and pubertal development in dogs up to reaching sexual maturity (~5 to 8 months of age for male dogs).

4.4.6. Toxicokinetics and exposure margins

Toxicokinetic data has been collected in nearly all repeat-dose toxicity studies, with the free base as well as with the PHB salt form. Exposure multiples were calculated based on AUC_{0-24} values, both, for total and unbound exposure of the parent.

During the assessment, the CHMP considered the followings to define the safety margins:

- exposure margins were calculated for the NOAELs in the pivotal repeat-dose toxicity studies compared to projected human clinical exposure considering the recommended human dose of mavorixafor at 400 mg once daily (mean AUC_{0-24}: 13970 ng*h/mL).
- regarding safety margins based on the free mavorixafor concentrations, concentration dependency of plasma protein binding in the dog was considered (for males with Cmax of 7.8 µM f_u of 20.7% obtained at 10 µM from study X4P-ADME-0005 was used, for females with Cmax of 24.2 µM a mean f_u value was derived from 20.7% obtained at 10 µM and 37.3% obtained at 30 µM). For the rat, f_u of 26.9% measured at 1 µM was applied.

Based on the total AUC_{0-24}, the exposures at the NOAEL in the 28-day study in females and males was 0.2-fold, compared to the exposure at the recommended human dose of mavorixafor at 400 mg once daily. Based on unbound drug in plasma, considering the differential protein binding properties of mavorixafor in rat (56.5% to 73.1%) which was concentration-dependent vs. human plasma (90.4 to 94.0%), the free-fraction AUC_{0-24} exposures at the NOAEL in the 28-day study in females and males were 0.8-fold and 0.6-fold, respectively, compared to the exposure at the recommended human dose of mavorixafor at 400 mg once daily.

Based on the total AUC_{0-24}, the exposures at the NOAEL in the 39-week study in females (34.1 mg/kg) and males (11.4 mg/kg) 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. Based on unbound drug in plasma, considering the differential protein binding properties of mavorixafor in dog (62.7% to 92.7%) which was concentration-dependent vs. human plasma, the free-fraction AUC_{0-24} exposures at the NOAEL in the 39-week study in females and males were 13.5 fold and 1.9-fold, respectively, compared to the exposure at the recommended human dose of mavorixafor at 400 mg once daily.

A preliminary embryofetal study was conducted in pregnant rats with mavorixafor at 50, 100 or 200 mg/kg/day following twice daily oral administration from GD 6 to 17 (Study X4P-001-TOX-023). In this study, a mavorixafor dose of 50 mg/kg/day was identified as NOAEL based on abnormal breathing in maternal animals and reduced fetal weights at higher doses (i.e., 100 or 200 mg/kg/day) which were not tolerated. The C_{max} and AUC_{0-last} at the 50 mg/kg/day dose on GD 12 were 408 ng/mL and 1400 ng*h/mL, respectively. The safety margin for pregnant rats at the NOAEL-based total AUC_{0-24} of 1400 ng*h/ml was 0.1. Hence, safety margins based on the unbound was 0.4.

4.4.7. Local tolerance

No dedicated local tolerance studies were conducted with mavorixafor. Effects suggestive of gastrointestinal toxicity was observed in the pivotal 28-day rat and dog study.

4.4.8. Other toxicity studies

Mavorixafor did not inhibit primary antibody to keyhole limpet hemocyanin (KLH) and was not cytotoxic to granulocyte-macrophage, erythroid, or multipotential progenitor cells up to a concentration of 10 µM. In cellular cytotoxicity studies, concentrations of mavorixafor required to inhibit cell growth were 100x higher than those that produced pharmacologic effects in vivo in animals. No phototoxicity risks are expected for humans based on mavorixafor MEC of less than 1000 L mol^{-1} cm^{-1} at any wavelength between 290 and 700 nm.

Studies on impurities

The applicant provided a comprehensive assessment of potential mutagenic and non-mutagenic impurities, which evolve in the mavorixafor drug substance manufacturing process. Impurity classification was performed according to ICH M7(R2) applying validated in silico QSAR models or available Ames test data. In case publicly available literature (e.g. ECHA registration dossiers) was available, this information was used to classify impurities as mutagenic or non-mutagenic.

4.4.9. Ecotoxicity/environmental risk assessment

Table 7: Summary of main study results: Phase I

Substance (INN/Invented Name):	Mavorixafor
CAS-number (if available):	558447-26-0

PBT/vPvB screening			
Study type	**Test protocol**	**Result**	**Conclusion**
Bioaccumulation potential- log Kow	OECD 107	Log K_{OW} = 3.62 $logD_{OW}$ = -1.18 at pH 6 $logD_{OW}$ = 0.32 at pH 7 $logD_{OW}$ = 1.98 at pH 8.8	Potential PBT/vPvB: N

Phase I			
Parameter	**Value**	**Unit**	**Conclusion**
$PEC_{sw,}$ refined with prevalence: 0.0001%)	0.002	µg/L	≥ 0.01 threshold: N
Other concerns (e.g. chemical class)			N

PECsurfacewater for mavorixafor is below the action limit of 0.01. Consequently, a Phase II risk assessment is not required.

A bioaccumulation potential is not indicated based on the log K_{OW} < 4.5. A definitive PBT/vPvB assessment is not required.

4.5. *Overall discussion and conclusions on non-clinical aspects*

4.5.1. Discussion

The WHIM syndrome is a clinical condition caused by gain-of-function mutations in *CXCR4* gene, which interfere with CXCR4 receptor internalisation and desensitisation (inactivation) resulting in prolonged CXCR4 signalling upon ligand (CXCL12) stimulation. This impairs the release of neutrophils and other leukocytes from bone marrow into bloodstream leading to pancytopenia and increased susceptibility to infections.

Mavorixafor is a potent allosteric CXCR4 antagonist that binds to the receptor and prevents its interaction with CXCL12 thereby reducing ligand-induced downstream signalling. *In vitro* pharmacological activity of mavorixafor was demonstrated at concentrations far below the expected unbound clinical Cmax of 661.85 nM (231 ng/mL) as calculated based on total Cmax of 9.455 µM (3304 ng/mL) and the free fraction of 7%.

The CHMP noted that mavorixafor is active not only on mutant variants of CXCR4, which represent the underlying cause of the WHIM syndrome, but also on the WT receptor. However, the literature reports indicate that WT and mutant alleles are likely co-expressed (Milanesi et al. 2020[13]) and that aberrant CXCL12/CXCR4 responses are also observed in leukocytes from the minority of patients, who carry a WT CXCR4 (Balabanian et al. 2012[14]).

No studies in WHIM syndrome animal models were conducted with mavorixafor. Intraperitoneal administration of a selective and competitive CXCR4 antagonist plerixafor or a CXCL12-neutraliser chalcone 4 was reported to increase the absolute numbers of total leukocytes including neutrophils, B and T cells both in the blood of mice carrying WT CXCR4 and in blood of *Cxcr4*$^{+/1013}$ mice. However, the

[13] Milanesi, Samantha, Massimo Locati, and Elena Monica Borroni. "Aberrant CXCR4 signaling at crossroad of WHIM syndrome and Waldenstrom's macroglobulinemia." *International Journal of Molecular Sciences* 21.16 (2020): 5696.
[14] Balabanian, Karl, et al. "Proper desensitization of CXCR4 is required for lymphocyte development and peripheral compartmentalization in mice." *Blood, The Journal of the American Society of Hematology* 119.24 (2012): 5722-5730.

accompanying decrease in leukocyte count in bone marrow was not significant in WT mice and not observed in mutant mice (the latter being a disease model). No effect on leukocytes in *Cxcr4$^{+/1013}$* mice was attributed to the relatively short half-life (0.9 hour) of plerixafor in rodents together with the gain of CXCR4 function in mutants, which may have forced the homing of peripheral leukocytes to the bone marrow (Balabanian et al. 2012[12]). While the former explanation is plausible, the latter remains speculative. Similar results were obtained in the *Cxcr4$^{+/1013}$* model with a CXCR4 antagonist X4-185, but this compound was able to mobilise functional neutrophils from bone marrow in contrast to plerixafor (Roland et al. 2012[15]). Nevertheless, considering the compounds used in these studies, the data provided did not demonstrate non-clinical efficacy of mavorixafor in the WHIM syndrome *in vivo*. No PK/PD correlation data in animal models to support clinical dose finding were presented either. Hence, conclusion in terms of efficacy were derived solely from clinical data discussed under Section 5.3.9.2.

It is acknowledged that WBC increase was noted in all toxicology studies as could be expected given the mechanism of action of mavorixafor. However, the activity of mavorixafor towards animal CXCR4 is not known and the effect on leukocytes cannot be with certainty attributed to the pharmacological action alone.

At the concentration of 10 µM in a radioligand-binding assay, mavorixafor inhibited 15 of 173 targets studied to the extent of ≥50%. The IC_{50} values for these targets ranged from 0.52 to 16.2 µM corresponding to 0.79 – 24.5-fold of the unbound clinical Cmax of 661.85 nM. Functional activity of mavorixafor on off-targets with >50% inhibition at 10 µM was evaluated (data not submitted for most of the targets). While for some targets agonistic or antagonistic effects were detected, all EC_{50} values were above the unbound clinical C_{max} of 0.66 µM. The lowest EC_{50} of 1.6704 µM was determined for agonistic activity on the urotensin II receptor and this is 2.5-fold higher than the clinical plasma level. Therefore, no clinically relevant off-target effects are expected.

Literature data (Mosi et al. 2012[16]) showed that mavorixafor did not inhibit calcium flux of cells expressing CXCR3, CCR1, CCR2b, CCR4, CCR5 or CCR7, or ligand binding to CXCR7 and BLT1, indicating that mavorixafor has no activity against these chemokine receptors while also demonstrating selectivity for the CXCR4 chemokine receptor. Although no data for CXCR1, CXCR2, CCR3, CCR6 or CCR9 are available, considering the lack of inhibition and/or binding for the targets covered by Mosi et al. 2012[16], and high specificity for CXCR4, no further studies were requested.

Mavorixafor demonstrated no relevant activity on the human Nav1.5 sodium channel and the calcium channel CaV1.2. These channels are thus not responsible for the clinically observed QT prolongation. Mavorixafor significantly inhibited hERG channel activity by 32% (-2.1-77.3%) at 13.28 µM and by 66% (13.3-88.8%) at 29.48 µM (both are experimentally measured concentrations). In the clinical QT study X4P-001-106 where modest QTc interval prolongation was observed, mean C_{max} was 6,170 ng/ml corresponding to the unbound clinical plasma concentration of 431.9 ng/ml or 1.24 µM (fu = 7%) and this is around 10 times lower than 13.28 µM. In the hERG inhibition assay, no effects were observed up to the measured concentration of 3.87 µM providing a safety margin of 3.1 that is relatively small. Therefore, QT prolongation in humans may be associated with hERG inhibition.

In conscious telemetered Beagle dogs in a GLP study, single oral administration of mavorixafor at doses of 50, 150 and 400 mg/kg significantly increased heart rate in a dose-dependent fashion accompanied by minor increase in diastolic arterial pressure. The maximum increase was within the range of expected animal variability. The mean total dog plasma C_{max} at 50, 150 and 400 mg/kg was 2-, 2.2- and 2.6-fold higher than mean total plasma C_{max} in patients of 3304 ng/mL. A safety margin of

[15] Roland, Lilian, et al. " CXCR4 antagonism ameliorates leukocyte abnormalities in a preclinical model of WHIM syndrome." *Frontiers in Immunology* 15 (2024): 1468823.
[16] Mosi, Renee, et al. " The molecular pharmacology of AMD11070: an orally bioavailable CXCR4 HIV entry inhibitor." *Biochemical Pharmacology* 83.4 (2012): 472-479.

2.7 to 13.7 was calculated considering the free fraction in dogs at 400 mg/kg and a protein binding range of 62.7-92.7%. No QTc prolongation was observed in dogs up to 400 mg/kg. In isolated dog Purkinje fibres, mavorixafor significantly shortened action potential duration at 10 and 100 µM, which similarly to the findings in dogs did not indicate a clinical risk of QTc prolongation.

In a GLP-compliant safety pharmacology study evaluating CNS effects of mavorixafor following oral dosing to rats, a significant decrease in body temperature was noted in the 1000 mg/kg group, with the absolute values being still in normal range. No test-item related mortalities, clinical signs or neurobehavioural effects were observed. The NOAEL was set at 1000 mg/kg, which corresponds to 28-fold MRHD based on boday surface area and human weight of 60 kg.

Oral administration of mavorixafor to Sprague-Dawley rats in a GLP respiratory study caused a statistically significant reduction in respiration rate at 1000 mg/kg but the values were within the expected range. Salivation was noted at 250 and 1000 mg/kg. The NOAEL was set at 1000 mg/kg that corresponds to 28-fold MRHD.

The bioanalytical methods for determination of mavorixafor in rat and dog plasma were developed and successfully validated. In both matrices, carryover did not meet the acceptance criteria. To minimise the potential carryover, blank samples were introduced into analytical runs. The measurements were repeated if carryover impact was identified. The approach was acceptable to the CHMP.

Following intravenous dosing to animals, mavorixafor was eliminated in a bi-exponential manner. After oral dosing, mavorixafor exposure increased less than dose-proportionally in rats, slightly more than dose-proportionally in dogs and a lot more than dose-proportionally in rabbits. In mice, a saturation of absorption was seen at 300 mg/kg. Bioavailability was low in rats and rabbits and high in mice and dogs. The exposure was reduced in dogs in the fed state indicating potential food interference with absorption.

It was noted that exclusively male animals were used in the PK studies. This was acceptable to the CHMP as gender differences were assessed in the TK studies.

Ultrafiltration analysis and equilibrium dialysis were utilised to determine protein binding of mavorixafor in human and animal plasma. The ultrafiltration method revealed the bound fraction of 66-93% in rat plasma, 87-95% in dog plasma, and 84-97% in human plasma. However, this study was performed with much lower mavorixafor concenrations than the clinically relevant. The percentage of protein-bound mavorixafor was determined by equilibrium dialysis as 93.6-95.2% in monkey, 90.4-94.0% in human, 56.5-73.1% in rat, 67.4-81.0% in mouse, and 62.7-92.7% in dog plasma. The large variability in the PPB data is due to concentration dependence of mavorixafor plasma protein binding across species. In the ultrafiltration study, the data were corrected for non-specific binding. This was not for the case in the equilibrium dialysis study.

The kinetics of tissue distribution was investigated in mice following IV administration at 5 mg/kg and oral administration at 100 and 300 mg/kg. The data of the 300 mg/kg PO were considered less relevant because the absorption was saturated at this dose. Mavorixafor quickly distributed into tissues with liver, kidney, spleen and bone marrow having the highest drug levels. Whereas concentrations in other tissues gradually declined, there was no apparent clearance from brain.

Tissue distribution in partially pigmented and non-pigmented rats was assessed after oral dosing of 50 mg/kg [^{14}C]-mavorixafor. In non-pigmented animals, the highest levels of radioactivity at 1 h post-dose were seen in the stomach, small intestine and urinary bladder with notable concentrations found in the liver, kidney and adrenal gland. At 24 h post-dose, radioactivity was observed mainly in the gastrointestinal tract with notable amounts in elimination organs and glandular tissues. Tissue concentrations gradually declined up to 168 h, though not in choroid plexus having higher radioactivity levels at later time points. This finding correlated with the absence of mavorixafor clearance from brain

and cerebrospinal fluid in the mouse tissue distribution study. In partially pigmented rats, highest concentrations of radioactivity were seen in the GIT, with notable amounts also measured in the uveal tract, tissues associated with elimination and several glandular tissues. There was no accumulation in choroid plexus in partially pigmented rats. Radioactivity in uveal tract was still noted at later timepoints but slowly declined indicating that association of mavorixafor with melanin is reversible.

It was concluded that mavorixafor crosses the blood-cerebrospinal fluid barrier (hence accumulation in choroid plexus) but not the blood-brain barrier. Although no apparent clearance from brain was observed in mice 24 h after administration, the overall concentration was low. Brain concentrations in rats were the lowest of all tissues. The applicant's claim that mavorixafor is not likely to cross the blood-brain barrier is further supported by the fact that mavorixafor is a P-gp substrate and is thus expected to be expelled from the brain by this transporter. Mavorixafor accumulation in the choroid plexus is attributed to lysosomal sequestration of the drug, which limits the free fraction and subsequently the toxic potential. This is corroborated by the absence of histopathological findings in the choroid plexus and neurobehavioural effects in animal studies and CNS-related adverse events in clinical studies.

In liver microsomes, metabolism of mavorixafor was moderate in rodents and low in dog and human. Hydroxylation was the major biotransformation pathway in all species. No unique metabolites were detected in human liver microsomes. CYP3A4 and CYP2D6 were the major enzymes responsible for the biotransformation as demonstrated using specific CYP inhibitors and rhCYP.

In vivo, metabolism was investigated after a single oral administration of [^{14}C] mavorixafor to rats. The plasma, urine, faeces and bile had 17, 12, 4 and 10 radioactive components corresponding to more than 2% of the total sample radioactivity, respectively. Structural identification of the metabolites was performed only for those accounting for more than 10% of circulating radioactivity in plasma and more than 10% of the dose in faeces. This was seen as a gap in non-clinical development, especially with only one animal species used to study biotransformation *in vivo*, but was not further pursued given the overall metabolic stability of mavorixafor in animals and humans. Rat plasma had 27% unchanged mavorixafor. The parent drug accounted for 49% of the total administered radioactivity in rat faeces.

In human, parent mavorixafor accounted for about 25% of the total radioactivity in plasma, 26% in urine and 30% in faeces. No radioactive metabolite accounted for more than 10% of either the circulating radioactivity (plasma) or the total administered dose (excreta). Toxicological evaluation of metabolites was thus not warranted. Most metabolites identified in microsomes were also observed in human samples.

Following oral dosing of [^{14}C]-mavorixafor, radioactivity was mainly excreted in faeces of normal rats, with renal excretion representing a minor elimination pathway (6.32%). In bile-duct cannulated rats, radioactivity was mainly excreted in faeces, and to a lesser extent in bile and in urine. No assessment of gender differences was possible as only male animals were used. This was acceptable as no great differences in TK were noted between sexes.

Several studies were performed to assess inhibitory potential of mavorixafor towards CYP enzymes, one with CYP2B6 and CYP2C8 supersomes, an older study in human liver microsomes evaluating CYP1A2, CYP2C9, CYP2C19 and CYP3A4 and a more recent study in human liver microsomes, which covered all guideline-relevant CYPs and included time- and mechanism-based inhibition. The latter study was methodologically sound, more comprehensive and yielded lower IC_{50} values, thus considered the worst-case scenario. Therefore, this recent study (X4P-001-DMPK-007) was used to estimate the need of DDI clinical evaluation (conservative approach). For CYP2D6, the applicant calculated Ki values using different equations but this was not further considered as the calculations were not in line with ICH M12 guideline. In human liver microsomes, mavorixafor inhibited CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A with IC_{50} values of 53.4, 15.8, 62.4, 55.5, 47.6, 1.26, and 15.4

μM, respectively. CYP3A was the only enzyme, which was also inhibited in time- and mechanism-based (NADPH-dependent) fashion. Of these interactions, inhibition of CYP2B6, CYP2D6 and CYP3A warrant further clinical investigation. Clinical studies with a CYP2D6 and a CYP3A4 substrate have been conducted. Physiologically based pharmacokinetic modelling and simulation showed almost no change in bupropion plasma PK exposure (Cmax and AUC ratios) with and without mavorixafor, hence, it is considered that mavorixafor does not inhibit CY2B6.

Two studies have been carried out to evaluate mavorixafor potential to induce CYP enzymes, one with fresh human hepatocytes from one liver donor focused solely on enzyme activity and a guideline-conform study with cryopreserved hepatocytes from three different donors. Mavorixafor induced CYP1A2 mRNA in a concentration-dependent manner at ≥10 μM and CYP1A2 activity in a concentration-dependent manner at ≥15 μM. This warranted clinical evaluation as done by the applicant.

Mavorixafor did not induce CYP2B6 mRNA up to 30 μM, CYP2C8, CYP2C9 and CYP3A4 mRNA and CYP2C19 activity up to 25 μM. A slight reduction in CYP2C9 and CYP3A4 activity was seen in fresh human hepatocytes but it may have been due to cytotoxicity.

Mavorixafor is metabolised by CYP3A4 and CYP2D6 warranting clinical DDI studies with mavorixafor as victim of CYP3A4 and CYP2D6 inhibitors, only CYP3A4 was investigated. This is further discussed in Clincal Pharmacology Section 5.2.6.1.

Mavorixafor was found to inhibit P-gp, OAT1, OCT2, and MATE1. These inhibitions were considered clinically relevant; hence, they were further investigated accordingly.

Mavorixafor was not a substrate of OATP1B1, OATP1B3, OCT2, OAT1, OAT3, MATE1 and MATE2-K. The results of studies on P-gp and BCRP were inconclusive. In Caco-2 cells, the efflux ratio was above 2 at concentrations ≥1 μM. The efflux ratio was not reduced by P-gp inhibitors at 1 μM but it was reduced >50% at 10 μM, which comprises ca. 15-fold clinical unbound plasma concentrations. In a membrane vesicle assay, mavorixafor was found to be not a substrate of P-gp. In MDCKII/BCRP cells, efflux ratio was over 2 but comparable to control cells, which also had an efflux ratio higher than 2. The efflux ratio was reduced >50% by lopinavir and <50% by Ko143 (BCRP inhibitor). In membrane vesicles, mavorixafor was found to be not a substrate of BCRP. These data indicated that mavorixafor is a substrate of P-gp but not BCRP.

The toxicological programme of mavorixafor was assessed according to ICH M3. The oral route of exposure was selected as it is the intended clinical route of administration. Repeat-dose toxicology studies with mavorixafor were conducted in rats and dogs as relevant species. Rats were about 6-7 weeks of age and dogs about 5 to 8 months of age corresponding to 12 to 16 years of human age. Since the intended indication is for adult and adolescent patients 12 years of age and older, this was acceptable.

Results of only four pivotal studies (one rat study and three dog studies) with the free base substance of mavorixafor, which is the clinically relevant form, were available to characterise the toxicological profile of mavorixafor. Supportive information was available from the long-term studies with the salt (PHB) form of mavorixafor where severe toxicity was observed including deaths of the animals. Given the intended life-long treatment together with the fact that the studies were performed with a limited number of animals (e.g. 3 animals/sex/dose in the long-term dog studies) and the absence of margins of exposure, the presented database was considered rather scarce.

Single dose toxicity

Information on acute toxicity was derived from studies in rats and dogs. Animals were orally administered with up to 1500 mg/kg/day (gavage) (rats) or up to 600 mg/kg/day (capsule) (dogs).

Mortality occurred in rats at the mid- and high-dose accompanied with changes in clinical signs (fur staining on muzzle, jaw, hindlimbs and/or urogenital areas, dehydration, salivation), clinical pathology (increase in BUN, total bilirubin, AST, ALT, cholesterol and triglycerides) and microscopic changes (in stomach, cecum, liver, spleen, mandibular and mesenteric lymph nodes, stomach, bone marrow and thymus).

Non-rodent acute toxicity was further tested with escalating doses of mavorixafor in dogs. In the tested animals, the severity of adverse effects increased with dose and included GIT toxicity (vomiting and abnormal faeces), decreased body weight and food consumption and changes in clinical pathology in the escalating group.

Repeat dose toxicity

Mavorixafor (free base) was tested in repeat-dose toxicity studies up to 28 days in rats and up to 39-weeks in dogs. While mavorixafor (free base) was ultimately developed for marketing, a PHB salt form of mavorixafor, was tested in nonclinical studies to support clinical development of mavorixafor. In 7-day rat and 14-day dog studies designed to compare data from the PHB salt form to studies with the free base form of mavorixafor, there were no significant differences in exposure or toxicity profile between the PHB salt form and mavorixafor free base at equimolar doses. Based on these data, longer term, GLP nonclinical toxicology studies with the PHB salt form were initiated in rats and dogs. However, in the GLP-compliant general toxicology studies, the PHB salt form was associated with significant toxicities including deaths, hepatic, and/or retinal toxicities in dogs and rats. In addition, retinal toxicities were noted in rats in the 26-week study at 0.2-fold the recommended clinical dose (based on AUC) and liver toxicities were observed in dogs in one-month (0.2-fold the recommended clinical dose based on AUC) and 3-month studies (at 1.8-fold the recommended clinical dose based on AUC). The CHMP considered that, in the absence of major differences in toxicity of the salt form versus the free base form, it could not be fully ruled out that the toxicities observed with the PHB salt form were not related to mavorixafor and were considered for the assessment of liver and eye toxicities below. Finally, the CHMP acknowledged that the study results obtained with the salt form were not intended for use in clinical trials and were only supportive.

Mortality

Severe toxicity resulting in mortality was observed in the rat single dose study at doses ≥1500 mg/kg/day, in all studies with the salt form, and in the pivotal repeat-dose toxicity study in rats. The cause of deaths observed in the repeat-dose toxicity studies was considered treatment-related because of micro- and macroscopic findings in the lung of the animals. No toxicity leading to death was seen in the three dog pivotal studies administered the free base form assuming that the PHB was responsible for the severe toxicity. Since the free-base form is the clinically relevant form, further evaluation of the mortalities in response to the PHB salt is not considered necessary.

Gastrointestinal toxicity

In the 28-day pivotal studies in rats and dogs, gastrointestinal toxicity was characterized by vomiting and diarrhoea without accompanying histopathology findings. However, the CHMP noted that animals at the high dose lost weight ≥10%, thus it remained questionable whether sufficient drug substance was available for histopathological evaluation at the end of the studies. The issue on the non-clinical aspect was not pursued since gastrointestinal toxicity was also observed in patients and is adequately addressed under section 4.8 of the SmPC.

Liver

In rats, non-reversible liver changes observed with the PHB salt form included vacuolation and histopathology changes (mononuclear cell infiltration, multifocal vacuolation, multifocal bile duct

hyperplasia) in the 6-month study. Administration of the free base resulted in increases in ALT values but without microscopic correlates in the liver.

In dogs, liver toxicities were observed after administration of the PHB-salt form of mavorixafor (minimal to moderate multifocal hepatocellular single cell necrosis) in the one- and three-month study; reversibility was not assessed due to early abortion of the studies. In contrast to the salt form, administration of the free base did not result in severe liver toxicities but in non-reversible liver pigments in the 28-day dog study at 100 mg/kg/day. Further, focal liver necrosis was seen in the 13-week dog study and benign lipofuscin accumulation was seen in the 39-week study. The latter at exposures up to 2.8-fold the MRHD based on AUC. Since the long-term dog studies were performed without a recovery period, a possible liver toxicity for patients cannot be ruled out assuming a life-long treatment of mavorixafor. Liver toxicity was also noted in a 26-week juvenile toxicity study in dogs at exposures below the expected clinical exposure. The liver findings were reversible in females and partially reversible in male dogs following the 6-week recovery period. Further clinical investigation with respect to possible hepatic impairment is ongoing and the applicant has committed to submit the results upon completion (clinical study report expected end of May 2026). Hepatotoxicity is included as an important potential risk in the RMP and the adverse reaction of hepatotoxicity observed in animals is included in section 5.3 of the SmPC.

Eye

Non-reversible adverse effects in the eyes were observed in rats and dogs (rats - with the PHB salt form: retinal degeneration and atrophy; dogs – with the free base form: pigmentation and increased size of tapetal cells). The applicant argued that the CXCR4 receptor is widely expressed on many cell types including retinal epithelial cells. As such, the observed ocular findings could have been expected after administration of mavorixafor. Effects on the retina were observed only in the long-term rat study (with the PHB salt) and dog study (free base) with partial recovery in the rat study. The fact that no full recovery was observed might be due to the use of albino rats and the fact that recovery of retinal damages can take long periods to recover as pointed out by the applicant. The latter is, however, speculative. The impact of the PHB entity on the ocular findings could not be determined. Nevertheless, retinal degeneration and atrophy is an important potential risk in the RMP and these adverse effects on the retina are included in section 5.3 of the SmPC.

Reproductive organs

In the 39-week dog toxicology study, dose-dependent seminiferous tubule degeneration/atrophy in testes and oligospermia in epididymis were observed. The findings were characterised by variable hypospermatogenesis, cytoplasmic vacuolation within tubules, swollen spermatocytes, multinucleate giant cells, degenerate/necrotic germ cells, and/or luminal cellular debris and occurred at nearly similar exposures (0.7x) the recommended human dose of 400 mg/kg/day (based on AUC). No information about reversibility was included. Toxicity on reproductive organs is further discussed below under Developmental and reproductive toxicity.

Other

Decreased thymus weights were observed in rats and dogs at the lowest doses tested with exposures similar or below the exposures seen in patients. The applicant argued that this finding could be attributed to the pharmacological activity of mavorixafor since T cell progenitors were not affected and CXCR4 deficient thymocytes were able to differentiate from immature CD41yCD81 cells to mature positive cells. The applicant's arugmentation was followed and the issue was not further pursued.

Mild/moderate haemorrhage in lymph nodes was observed in the 28-day study in dogs at exposures below clinical exposures. This was considered a common finding in the mesenteric lymph nodes of dogs and not treatment-related.

Pigment deposition (lipofuscin) in the kidney, liver and/or gallbladder were observed in the dog studies with exposures at or slightly above clinical exposures. Lipofuscin is a pigmented, heterogenous byproduct of failed intracellular catabolism conventionally found within lysosomes or the cytosol of aging postmitotic cells and can exist in almost any tissue. However, the exact details of lipofuscin's effect on the cell are not completely characterized but more hypothetical. Thus, it is difficult to exclude potential negative effects in the clinical setting. The role of the PHB salt in the accumulation is unknown. From the provided results and existing literature data, it was considered that the lipofuscin accumulation is negligible for patients except for accumulation in eyes. This further supported the inclusion of retinal degeneration and atrophy as an important potential risk in the RMP.

Genotoxicity and carcinogenicity

Mavorixafor was tested in a standard Ames test, an *in vitro* chromosome aberration assay and an oral *in vivo* Micronucleus test in rats. All tests were in line with ICH S2(R1) and according to GLP. There were no indications of genotoxic effects of mavorixafor in none of the test systems. Based on this, the CHMP agreed that mavorixafor can be considered as non-genotoxic.

No carcinogenicity study was performed with mavorixafor. The weight of evidence did not give rise to an increased carcinogenic risk for patients. Therefore, the conduct of a 6-month Tg.rasH2 mouse carcinogenicity post approval was acceptable. The Tg.rasH2 mouse carcinogenicity study is expected to be completed by Q4 2026. Considering the low carcinogenic potential, the CHMP considered that a 2-year rat carcinogenicity study was not required, particularly with respect to the 3Rs principles of animal use.

Developmental and reproductive toxicity

Fertility and early embryonic development

No dedicated fertility and early embryonic developmental studies have been conducted with mavorixafor. In repeat-dose toxicity studies in rats with mavorixafor, no histopathological evidence of toxicity to male and female reproductive organs was observed. In male dogs in a 39-week study with mavorixafor, adverse effects on the testes were observed in all dose groups. In this study, the testes of affected male animals had minimal to moderate bilateral seminiferous tubule degeneration/atrophy while only 1 male control at Day 274 had similar findings of minimal magnitude. Seminiferous tubule degeneration/atrophy was characterized by variable hypospermatogenesis (absence of some or all of the germ cells within individual tubules), cytoplasmic vacuolation within tubules, swollen spermatocytes, multinucleate giant cells, degenerate/necrotic germ cells, and/or luminal cellular debris).

As discussed by the applicant, there is no evidence for testicular effects nor any reproductive tissue effects in mice engineered to be deficient for the CXCR4 gene. Hence, a testicular effect based upon pharmacologic inhibition of the CXCR4 receptor appeared unlikely (Escot et al., 2016[17] ; Ma et al., 1998[18]; Odemis et al., 2005[19]). The applicant concluded that the mechanism by which mavorixafor may exert this effect is unknown. However, the CHMP considered that the lack of testicular effects in

[17] Escot S, Blavet C, Faure E, Zaffran S, Duband JL and Fournier-Thibault C. Disruption of CXCR4 signaling in pharyngeal neural crest cells causes DiGeorge syndrome-like malformations. Development. 2016; 143:582-8.
[18] Ma Q, Jones D, Borghesani PR, et al. Impaired B-lymphopoiesis, myelopoiesis, and derailed cerebellar neuron migration in CXCR4- and SDF-1-deficient mice. Proc Natl Acad Sci U S A. 1998;95(16):9448-9453.
[19] Odemis V, Lamp E, Pezeshki G, et al. Mice deficient in the chemokine receptor CXCR4 exhibit impaired limb innervation and myogenesis. *Mol Cell Neurosci*. 2005;30(4):494-505.

these studies may be due to the inability to detect potential testicular effects by the methods and endpoints used.

In contrast, an association between treatment with the CXCR4 antagonist AMD3100 (plerixafor) and impairment of spermatogenesis was reported in the literature. It was shown that treatment of adult mice with AMD3100 for 7 days resulted in loss of spermatogonial stem cells (SSC) (Yang et al., 2012[20]). Similar effects were also seen in pre-pubertal boar SSC cultures *in vitro* (Park et al., 2018[21]) where inhibition of the CXCR4 receptor signalling pathway by AMD3100 significantly decreased the colony formation of SSCs in a dose-dependent manner (0, 0.1, 1, 10 µg/mL). In addition, in a recent study (Wang et al., 2025[22]) prospermatogonia (ProSGs) obtained from the testes of 7-day-old pigs treated for 7 days with AMD3100 at 6 µg/ml may predispose ProSGs towards differentiation. Also, a recent study in dogs with acquired infertility due to chronic asymptomatic orchitis, a condition with histopathology findings similar to those observed in the 39-week dog study, showed an increased expression of CXCL12 in tested samples of dogs with chronic asymptomatic orchitis (Rehder et al., 2025[23]).

The CXCL12–CXCR4 axis plays an important role for maintenance of the spermatogonial stem cell niche. Postnatally, the CXCL12/CXCR4 signalling regulates SSC migration and ensures they settle in specific locations within the seminiferous tubules to maintain their stem cell properties (Liu et al., 2024[24]). Gilbert et al. showed that CXCL12 and CXCR4 are expressed in adult human testis at comparable levels to tissues where physiological effects are documented (Gilbert et al., 2009[25]). Therefore, the likelihood that the CXCR4 antagonistic properties of mavorixafor contribute to the testicular findings in the 39-week dog study or may worsening the common background finding in the dogs (Goedken et al., 2008[26]) cannot be excluded. The applicant considered that the testicular observations in male dogs were adverse and test-article related in the High Dose Group (34.1 mg/kg), hence, considered that the 11.4 mg/kg dose was the NOAEL for testicular toxicity. However, the CHMP considered that this effect should be regarded as adverse already in the 3.4 mg/kg/day dose group. Although these findings occurred with a lower incidence of 2/3 animals at 3 months and 1/3 animals at 6-and 9 months, respectively and the incidence lay within those reported by Goedken et al., 2008 and showed a trend to decline in older animals, an increase of severity of the findings was observed at 9-months showing marked effects, which points out to a treatment-related effect already in the lowest dose group. Thus, the CHMP concluded that no NOAEL for this effect exists.

Mavorixafor is a substrate for the P-gp efflux pump which is also expressed in the blood-testis barrier and indeed in tissue distribution studies in rats mavorixafor-related radioactivity was not detected in the testis. Hence, it was agreed that this would protect relevant exposure to the testis. However, the blood-testis barrier is developed during the puberty at around the age of 11-12 years (Voigt et al.

[20] Yang QE, Kim D, Kaucher A, Oatley MJ, Oatley JM. CXCL12-CXCR4 signaling is required for the maintenance of mouse spermatogonial stem cells. J Cell Sci. 2013 Feb 15;126(Pt 4):1009-20. doi: 10.1242/jcs.119826. Epub 2012 Dec 13. PMID: 23239029; PMCID: PMC4074255

[21] Park HJ, Lee WY, Kim JH, Park C, Song H. Expression patterns and role of SDF-1/CXCR4 axis in boar spermatogonial stem cells. Theriogenology. 2018 Jun;113:221-228. doi: 10.1016/j.theriogenology.2018.03.008. Epub 2018 Mar 15. PMID: 29573661

[22] Wang X, Wen J, Tian H, Li X, Xie W, Zou K. SDF-1/CXCR4 axis maintains porcine prospermatogonia undifferentiated state through regulation of transcription suppressor PLZF. Theriogenology. 2025 Mar 1;234:198-207. doi: 10.1016/j.theriogenology.2024.12.018. Epub 2024 Dec 20. PMID: 39721337

[23] Rehder P, Packeiser EM, Körber H, Goericke-Pesch S. Altered Sertoli Cell Function Contributes to Spermatogenic Arrest in Dogs with Chronic Asymptomatic Orchitis. Int J Mol Sci. 2025 Jan 27;26(3):1108. doi: 10.3390/ijms26031108. PMID: 39940876; PMCID: PMC11817828

[24] Liu W, Du L, Li J, He Y, Tang M. Microenvironment of spermatogonial stem cells: a key factor in the regulation of spermatogenesis. Stem Cell Res Ther. 2024 Sep 11;15(1):294. doi: 10.1186/s13287-024-03893-z. PMID: 39256786; PMCID: PMC11389459.

[25] Gilbert DC, Chandler I, McIntyre A, Goddard NC, Gabe R, Huddart RA, Shipley J. Clinical and biological significance of CXCL12 and CXCR4 expression in adult testes and germ cell tumours of adults and adolescents. J Pathol. 2009 Jan;217(1):94-102. doi: 10.1002/path.2436. PMID: 18839394.

[26] Goedken MJ, Kerlin RL, Morton D. Spontaneous and age-related testicular findings in beagle dogs. Toxicol Pathol 2008, 36:465-471.

2023[27]). As discussed by Voigt et al., spermatogonial stem cells are experiencing two distinct environments before and after puberty. This leads to the assumption that the currently intended youngest patient population may be more sensitive to potential testicular effects of mavorixafor.

In repeated dose toxicity studies with mavorixafor, effects on the seminiferous tubules of the testes were only observed in the 39-week study initiated in young peripubertal dogs, but not in the 13-week study initiated in sexually mature dogs and in the 26-week juvenile study in prepubertal dogs (completed during the evaluation procedure) as well as in the rat studies. However, in the 12-week repeated dose toxicity study starting treatment in peripubertal dogs with the PHB salt of mavorixafor at doses of 0, 8, 20 and 50 mg/kg/day of mavorixafor as the free base, 1 of 3 and 5 dogs, respectively, in the low dose and high dose group of this study, showed effects on the testis (Low dose: degeneration, atrophy, tubular, slight, bilateral; High dose: small, atrophy, severe, unilateral) and epididymides (High dose: oligospermia, severe, unilateral). The severe findings in testis and epididymides at the high dose group may indicate a potential treatment-related effect.

This supports the hypothesis that effects seen in the 39-week dog study could be an enhancement of pre-existing/spontaneous seminiferous tubule findings as reported by Goedken et al., 2008[26] for dogs of the age used in the 39-week study at start of treatment. As the blood-testis barrier is not yet established in juvenile animals, the absence of findings in the juvenile toxicology study does not support the blood-testis barrier formation as the primary rationale for the difference noted between earlier studies.

In the 39-week study in dogs, no recovery phase was included. The applicant discussed that based upon the nature of the histopathologic finding (testicular atrophy), considering the preservation of Sertoli (support cells) and germ cells, spermatogenesis would be expected to fully recover. Further, since there is no complete loss of spermatogonial stem cells in the testis, the applicant considered that full recovery of the testicular degeneration/atrophy observed for the 39-week dog study could be expected. However, this view was not followed since a study in mice with busulfan-induced SSC depletion suggested that there is a threshold of SSC numbers that allows the restoration of fertility (Zohni, K. et al., 2012[28]). Hence, testicular findings observed in the 39-week study in young prepubertal dogs at exposure levels equivalent to the human exposure at MRHD but not observed in a 13-week dog study in sexually mature male dogs and in a 26-week dog study in juvenile dogs covering the period of puberty are included in SmPC Section 5.3. It is further stated in SmPC Section 4.6 that the relevance of these findings for male patients is not known.

Apart from the role of the CXCL12/CXCR4 system on the maintenance of the spermatogonial stem cell niche, several further functions of this system on male and female fertility have been found in the literature. CXCR4 was expressed in the head of human spermatozoa after capacitation and CXCL12 is localized to the oocytes, follicle fluid and endometrium in the female genital tract and its action is involved in the regulation of sperm chemotaxis and motility and CXCL12/CXCR4 signalling plays a vital role in manipulating human fertilization (Dai et al., 2024[29]; Wang et al., 2019[30]). Literature data also suggest a role of CXCL12/CXCR4 system on early placenta development and implantation (Koo et al.,

[27] Voigt AL, de Lima E Martins Lara N, Dobrinski I. Comparing the adult and pre-pubertal testis: Metabolic transitions and the change in the spermatogonial stem cell metabolic microenvironment. Andrology. 2023 Sep;11(6):1132-1146. doi: 10.1111/andr.13397. Epub 2023 Feb 3. PMID: 36690000; PMCID: PMC10363251
[28] Zohni, K.; Zhang, X.; Tan, S.L.; Chan, P.; Nagano, M.C. The Efficiency of Male Fertility Restoration Is Dependent on the Recovery Kinetics of Spermatogonial Stem Cells after Cytotoxic Treatment with Busulfan in Mice. Hum. Reprod. Oxf. Engl. 2012, 27, 44–53

[29] Dai P, Chen C, Yu J, Ma C, Zhang X. New insights into sperm physiology regulation: Enlightenment from G-protein-coupled receptors. Andrology. 2024 Sep;12(6):1253-1271. doi: 10.1111/andr.13593. Epub 2024 Jan 15. PMID: 38225815.
[30] Wang C., Huang J., Ding L., Huang R., Dai L., Zhou W. Effects of CXCL12/CXCR4/CXCR7 axis on human sperm motility and chemotaxis. 2019; doi: 10.1101/831065

2021[31]; Ashley et al., 2011[32]; Kumar et al., 2004[33]; McIntosh et al., 2021[34]; Bao et al., 2016[35], Sun et al., 2022[36]). Considering the advice given in the SmPC of Xolremdi to verify the pregnancy status before initiation of treatment in women of childbearing potential and to use an effective method of contraception for female patients and condoms for male patients with female partners of childbearimg potential during treatment with Xolremdi and for 3 weeks after the final dose, the risk of adverse effects on early pregnancy is adequately addressed in the SmPC.

Embryo-foetal development

The applicant did not conduct definitive EFD toxicity studies. This was agreed in the scientific advice (EMA/SA/0000067085).

Albeit no embryolethal or teratogenic effects were observed in the preliminary EFD study with mavorixafor in rats, the exposures in the animals at the NOAEL were far below the human exposure at the maximum recommended human dose (approximately 0.1-fold) and embryolethal and/or teratogenic effects maybe occurred at higher doses, which were not considered possible to test in animals studies due to the maternal toxicity of mavorixafor. Therefore, currently no embryolethal or teratogenic effect has been demonstrated for mavorixafor.

However, a weight of evidence assessment was performed by the applicant based on literature data from CXCR4 knock out mice and findings from the approved CXCR4 inhibitor plerixafor. These data showed that CXCL12/CXCR4 is essential for embryo/foetal development and that potential inhibition of the pathway by mavorixafor is anticipated to result in significant developmental toxicity.

There are many phenotypes that have been observed to be associated with deletion of the SDF-1/CXCR4 genes. These include deficits in β lymphopoiesis and myelopoiesis, cardiogenesis, angiogenesis, neurogenesis and germ cell migration and development by (reviewed by Miller et al., 2008[37]). In addition, a recent study (Lyu et al., 2023[38]) which investigated the effect on embryonic development when only the CXCR4 gene was deleted in the maternal female mice found increased pregnancy resorptions and decreased litter size which assumes that not only the direct embryo/foetal effect of CXCR4 depletion but also maternal depletion of CXCR4 and its effects on immune cell function results in adverse effects on embryo/foetal development via impairment of placenta development and pregnancy maintenance.

[31] Koo HS, Yoon MJ, Hong SH, Ahn J, Cha H, Lee D, Ko JE, Kwon H, Choi DH, Lee KA, Ko JJ, Kang YJ. CXCL12 enhances pregnancy outcome via improvement of endometrial receptivity in mice. Sci Rep. 2021 Apr 1;11(1):7397. doi: 10.1038/s41598-021-86956-y. PMID: 33795831; PMCID: PMC8016928.
[32] Ashley RL, Antoniazzi AQ, Anthony RV, Hansen TR. The chemokine receptor CXCR4 and its ligand CXCL12 are activated during implantation and placentation in sheep. Reprod Biol Endocrinol. 2011 Nov 3;9:148. doi: 10.1186/1477-7827-9-148. PMID: 22053725; PMCID: PMC3217910.
[33] Kumar A, Kumar S, Dinda AK, Luthra K. Differential expression of CXCR4 receptor in early and term human placenta. Placenta. 2004 Apr;25(4):347-51. doi: 10.1016/j.placenta.2003.10.003. PMID: 15028427.
[34] McIntosh SZ, Maestas MM, Dobson JR, Quinn KE, Runyan CL, Ashley RL. CXCR4 signaling at the fetal-maternal interface may drive inflammation and syncytia formation during ovine pregnancy†. Biol Reprod. 2021 Feb 11;104(2):468-478. doi: 10.1093/biolre/ioaa203. PMID: 33141178.
[35] Bao S, Li T, Long X, Zhang J, Zhao H, Ren Y, Zhao Y, Li R, Tan T, Yu Y, Qiao J. Chemokine Receptor Type 4 Regulates Migration and Invasion of Trophectoderm Cell in the Human Blastocyst. Biol Reprod. 2016 Jul;95(1):21. doi: 10.1095/biolreprod.116.138826. Epub 2016 May 4. PMID: 27146031.
[36] Sun XL, Zhao J, Leng Z, Lin H, Huang Y. Low Expression Levels of CXCL12, CXCR4, and CXCR 7 in Peripheral Blood and Decidual Tissues are Associated with Miscarriage in Women. Immunol Invest. 2022 Oct;51(7):2053-2065. doi: 10.1080/08820139.2022.2106871. Epub 2022 Aug 1. PMID: 35912820.
[37] Miller RJ, Banisadr G, Bhattacharyya BJ. CXCR4 signaling in the regulation of stem cell migration and development. J Neuroimmunol. 2008 Jul 31;198(1-2):31-8. doi: 10.1016/j.jneuroim.2008.04.008. Epub 2008 May 27. PMID: 18508132; PMCID: PMC4448969
[38] Lyu F, Burzynski C, Fang YY, Tal A, Chen AY, Kisa J, Agrawal K, Kluger Y, Taylor HS, Tal R. Maternal CXCR4 deletion results in placental defects and pregnancy loss mediated by immune dysregulation. JCI Insight. 2023 Nov 8;8(21):e172216. doi: 10.1172/jci.insight.172216. PMID: 37815869; PMCID: PMC10721256.

WHIM syndrome is an autosomal dominant inheritance (congenital) immune deficiency attributable to heterozygous mutations in *CXCR4* and the risk of passing the gene variant from affected parent to child is reported to be 50% for each pregnancy, regardless of the sex of the resulting child.

Very limited data suggest that the WHIM syndrome–associated CXCR4 truncating mutation might increase the risk of congenital heart defects (Beaussant-Cohen et al., 2012[39]; Geier et al., 2022[40]; Badolato et al., 2012[41]; Khojah et al., 2023[42]). A study in by Cronshaw et al., 2010 in which mutant mice with a ''knock-in'' approach addressing the region of the CXCR4 gene which showed truncation in WHIM-syndrome patients indicates that, although the overall impact on animal development is relatively mild, the ΔT mutation imposes almost identical effects as the CXCR4-null mutation on the development of neural, vascular and hematopoietic systems. Furthermore, in patients with primary immunodeficiency disease (PID), pregnancy is more complicated because not only the child can inherit the disease but also the mothers are at risk because of defects in the immune systems (Mallart et al., 2023[43]; Sheikhbahaei et al., 2018[44]).

Although the defects of the immune system associated with the WHIM syndrome can have negative effects on the course of pregnancy and pregnancy outcome which can be mitigated by treatment with the CXCR4 antagonist mavorixafor, mavorixafor is no curable therapy. Therefore, the risk of passing the gene variant to the child and the associated risk of congenital anomalies in the heart cannot be reduced by treatment with mavorixafor. Instead, the mechanism of action of mavorixafor (CXCR4 antagonism) itself has been shown to induce teratogenic effects, including heart malformations.

Hence, weighting up all aspects relevant for benefit-risk assessment for use during pregnancy as are (a) potential embryo/foetal lethal and teratogenic effects of mavorixafor due to CXCR4 inhibition, (b) adverse effect on the WHIM syndrome associated immune defects on pregnancy, (c) WHIM associated risk for development of congenital heart disease and 50% risk of passing gene variant from affected parent to child, (d) treatment with mavorixafor is no curable therapy, (e) no experience with mavorixafor during pregnancy and (f) availability of alternative therapeutic options with more experience during pregnancy, the risk for potential adverse effects on embryo-foetal and postnatal development associated with mavorixafor treatment during pregnancy is considered higher than the therapeutic benefit for the pregnant women. Therefore, in consideration of the Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling (EMEA/CHMP/203927/2005), the use of mavorixafor is contraindicated during pregnancy. Women of childbearing potential must use an effective method of contraception during treatment and for 3 weeks after the final dose. The pregnancy status of female patients of childbearing potential who are engaging in activities of reproductive potential should be verified prior to starting mavorixafor. Furthermore, as mavorixafor is considered a potent teratogen, male patients with female partners of childbearing potential should use condoms during treatment and for at least 3 weeks after stopping

[39] Beaussant Cohen S, Fenneteau O, Plouvier E, et al. Description and outcome of a cohort of 8 patients with WHIM syndrome from the French Severe Chronic Neutropenia Registry. Orphanet J Rare Dis. 2012;7:71.
[40] Geier CB, Ellison M, Cruz R, Pawar S, Leiss Piller A, Zmajkovicoa K, et al. Disease progression of WHIM syndrome in an international cohort of 66 pediatric and adult patients. J Clin Immunol. 2022; 42(8):1748 65. doi: 10.1007/s10875 022 01312 7.
[41] Badolato R, Dotta L, Tassone L, Amendola G, Porta F, Locatelli F, Notarangelo LD, Bertrand Y, Bachelerie F, Donadieu J. Tetralogy of fallot is an uncommon manifestation of warts, hypogammaglobulinemia, infections, and myelokathexis syndrome. J Pediatr. 2012 Oct;161(4):763-5. doi: 10.1016/j.jpeds.2012.05.058. Epub 2012 Jun 27. PMID: 22748845; PMCID: PMC3458406.
[42] Khojah A, Alshareef H, Alzahrani L, Binhussein M, Bukhari A, Khojah I. Warts, hypogammaglobulinemia, infections, and myelokathexis (WHIM) syndrome and tetralogy of fallot; Case report and literature review. J Clin Exp Hematol. 2023;2(1):1-5.
[43] Mallart E, Françoise U, Driessen M, Blanche S, Lortholary O, Lefort A, Caseris M, Fischer A, Mahlaoui N, Charlier C; PREPI study group. Pregnancy in primary immunodeficiency diseases: The PREPI study. J Allergy Clin Immunol. 2023 Sep;152(3):760-770. doi: 10.1016/j.jaci.2023.05.006. Epub 2023 May 18. PMID: 37210041.
[44] Sheikhbahaei S, Sherkat R, Camacho-Ordonez N, Khoshnevisan R, Kalantari A, Salehi M, Nazemian SS, Nasr-Esfahani MH, Klein C. Pregnancy, child bearing and prevention of giving birth to the affected children in patients with primary immunodeficiency disease; a case-series. BMC Pregnancy Childbirth. 2018 Jul 11;18(1):299. doi: 10.1186/s12884-018-1927-6. PMID: 29996795; PMCID: PMC6042236.

treatment.

Pre- and postnatal development

No prenatal and postnatal development (PPND) toxicity studies were conducted with mavorixafor. However, given the difficulties to perform animal reproduction toxicity studies with human relevant exposure and based on the results from CXCR4/SDF-1 knock out mice which showed high peri-postnatal lethality and adverse effects on developmental, this was acceptable to the CHMP.

There are no data on the excretion of mavorixafor in animal or human milk and its effects on milk production and lactation. Literature studies in mice suggest a role of the CXCL12/CXCR4 axis on adult mammopoiesis (Shiah et al., 2015[45]) and on maternal immune system enhancement during lactation (Medeiros et al., 2025[46]). The section 4.6 of the SmPC indicates that it is unknown whether mavorixafor/metabolites are excreted in human and animal milk. Further, in line with the guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling (EMEA/CHMP/203927/2005), SmPC Section 4.6 indicates that a decision must be made whether to discontinue breast-feeding 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 Xolremdi therapy for the woman.

Juvenile animals

In two DRF and tolerability studies in juvenile rats, treatment with mavorixafor (PND 28-41 or PND 28-34 or PND 35-41) was not tolerated, indicated by laboured breathing and a high rate of morbidity and mortality. Histologic examination showed acute inflammation of laryngeal tissues, and it was hypothesised that this local toxicity was not treatment related but was caused by gavage or reflux injury and results in laryngospasms and death by asphyxiation. Mechanisms that initiated the reflux response were uncertain and this substantial toxicity and morbidity was not observed in older rats (~6 weeks old) in the 4-weeks repeat-dose toxicity study (X4P-001-TOX-009). Mavorixafor is only indicated for adult and adolescent patients 12 years of age and older, therefore the intended patient population is considered to be not at risk.

It was agreed that a definitive juvenile toxicity study in rats is not feasible due to poor tolerance of mavorixafor at low exposures in juvenile rats.

Results of a definitive GLP-compliant 26-week toxicity study including a 6-week recovery phase in juvenile dogs (Study X4P-001-TOX-033) covering the period of puberty were submitted during the procedure. In this study, male and female juvenile dogs aged 9 weeks old at start of treatment (corresponding to an age of approximately 2 to 3 years of age in humans) were administered vehicle control or 10, 25, or 60 mg/kg/day mavorixafor once daily via oral gavage.

At terminal necropsy, no macroscopic abnormalities were revealed in relation to the fertility-related male organs evaluated, specifically the epididymis and testes. Unfortunately, no analysis of sperm was included in the study protocol. These results suggested that there were no macroscopic or histopathological signs that would indicate treatment-related effects on male reproductive tissues. Testicular findings of the 39-week study were not recapitulated in the 26-week study (as discussed above in the section on fertility).

Mavorixafor-related clinical pathology and clinical chemistry findings were suggestive of

[45] Shiah YJ, Tharmapalan P, Casey AE, Joshi PA, McKee TD, Jackson HW, Beristain AG, Chan-Seng-Yue MA, Bader GD, Lydon JP, Waterhouse PD, Boutros PC, Khokha R. A Progesterone-CXCR4 Axis Controls Mammary Progenitor Cell Fate in the Adult Gland. Stem Cell Reports. 2015 Mar 10;4(3):313-322. doi: 10.1016/j.stemcr.2015.01.011. Epub 2015 Feb 19. PMID: 28447939; PMCID: PMC4376056.

[46] Medeiros NC, Santos Filho END, Ayres DAS, Cancio BHMA, Smaniotto S, Reis MDDS, Lins MP. Involvement of CXCL12/CXCR4 pair in migration of thymocytes from lactating mice. J Reprod Immunol. 2025 Mar;168:104444. doi: 10.1016/j.jri.2025.104444. Epub 2025 Jan 29. PMID: 39904071.

hepatocellular and/or hepatobiliary perturbation and comparable to findings in adult animal studies. Mavorixafor-related effects in hematology were noted in animals administered ≥10 mg/kg/day. Following the 6-week recovery phase, all liver findings in females had completely reversed; moderate pigment was noted in the liver of the recovery male administered 60 mg/kg/day. Microscopic liver findings in males and females administered ≥25 mg/kg/day and body weight loss with correlated clinical pathology findings suggestive of hepatocellular/hepatobiliary perturbation for individual animals administered ≥25 mg/kg/day requiring dosing holiday were considered adverse.

Therefore, the overall NOAEL and the fertility NOAEL were determined to be 10 mg/kg/day and 60 mg/kg/day, respectively, for males and females corresponding to exposures below or in range of the exposure at the intended clinical dose of 400 mg once daily in humans.

Including the results available from rat repeat-dose toxicity studies of mavorixafor nonclinical data were considered sufficient to support treatment of paediatric patients aged 12 years and above.

Toxicokinetics and interspecies comparison

A substantial amount of toxicokinetic data was collected in the non-pivotal and pivotal animal studies (rats and dogs). Exposure multiples were calculated based on AUC_{0-24} values, both for total and unbound exposure of the parent drug compared to human exposure at the recommended dose.

In the pivotal rat study, the exposure multiple was 0.2 for males and females. In addition, the safety margin for pregnant rats at the NOAEL-based AUC_{0-24} of 1400 ng*h/ml was 0.1.

In the pivotal dog repeat-dose studies, exposure multiples were around 1 for total exposure. For unbound exposure, the margins of exposure were a little higher. An exception were the female dogs in the 39-week study with an exposure multiple of 13.5. For the 3-month dog study, no NOAEL could be observed due to adverse events at the lowest dose tested. As such, the values were based on 2 dog studies achieved with a limited number of animals (3 animals/sex/dose).

The CHMP concluded that, for the most parts, there were no margins from the NOAELs to clinical exposure.

Local tolerance

No dedicated local tolerance studies were conducted with mavorixafor. This was agreed by the CHMP since mavorixafor is administered orally.

Other toxicity studies

Mavorixafor did not inhibit primary antibody to KLH and was not cytotoxic to granulocyte-macrophage, erythroid, or multipotential progenitor cells up to a concentration of 10 µM. In cellular cytotoxicity studies, concentrations of mavorixafor required to inhibit cell growth were 100x higher than those that produced pharmacologic effects *in vivo* in animals. No phototoxicity risks are expected for humans based on mavorixafor MEC of less than 1000 L mol^{-1} cm^{-1} at any wavelength between 290 and 700 nm.

Studies on impurities

The applicant provided a comprehensive assessment of potential mutagenic and non-mutagenic impurities, which evolve in the mavorixafor drug substance manufacturing process. Overall, the classification of impurities was in line with ICH M7(R2) and considered acceptable to the CHMP from a toxicological point of view.

Environmental risk assessment

$PEC_{surfacewater}$ for mavorixafor is below the action limit of 0.01 µg/L. Consequently, a Phase II_risk assessment is not required.

A bioaccumulation potential is not indicated based on the log K_{OW} < 4.5. A definitive PBT/vPvB assessment is not required.

4.5.2. Conclusions

Mavorixafor is a potent allosteric CXCR4 antagonist that decreases ligand-induced CXCR4 downstream signalling. No proof of non-clinical efficacy in animal models has been presented, which is acceptable in view of the clinical data available. Mavorixafor demonstrated secondary activity at 15 off-targets at concentrations around and up to 24-fold the unbound clinical Cmax.

The pharmacokinetics of mavorixafor has been well characterised. Accumulation of mavorixafor in the choroid plexus of rodents is not considered clinically relevant.

The toxicological programme of mavorixafor is based on results with the free base form as the clinically relevant one and with supportive data generated with a PHB salt form. The provided data base is rather scarce since only four pivotal studies with a limited number of animals (e.g. 3 animals/sex/dose in the long-term dog studies) were performed and within these studies no margin of exposure could be achieved.

Overall, based on the findings from the non-clinical data with mavorixafor and the literature, embryo-foetal toxicity, testicular toxicity, hepatotoxicity and retinal degeneration and atrophy have been identified as important potential risks for mavorixafor in the RMP and will be further characterised in the registry-based study (SOB).

As mavorixafor is considered a potent teratogen, the use of mavorixafor is contraindicated during pregnancy, women of childbearing potential must avoid becoming pregnant by using an effective method of contraception during treatment and for 3 weeks after the final dose and male patients with female partners of childbearing potential should use condoms during treatment and for at least 3 weeks after stopping treatment. In order to further mitigate this risk, an HCP guide and patient card were implemented.

There is no unacceptable risk for the environment by using Xolremdi according to the ERA.

The following measures necessary are considered necessary to address the issues related to non-clinical aspects:

- Provide results from the Tg.rasH2 mouse carcinogenicity study once available.

5. Clinical aspects

5.1. *Introduction*

5.1.1. GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Based on the review of clinical data, CHMP did not identify the need for a GCP inspection of the clinical trials included in this dossier (see section 2.4.3.).

5.1.2. Tabular overview of clinical trials

Table 8: Description of Clinical Efficacy Studies in Patients with WHIM Syndrome

Study and study status	Patient population	Actual sample size (Plan)	Design and study objective(s)	Mavorixafor dose and regimen (all oral)	Duration
X4P-001-MKKA Completed	Adult patients (≥18 years of age) with WHIM syndrome	8 (up to 15)	Phase 2, dose finding, safety, tolerability, PK/PD	Mavorixafor 50 mg QD 100 mg QD 150 mg QD 200 mg QD 300 mg QD 400 mg QD	24 weeks of dose escalation, followed by an extension phase. Five patients completed the extension phase. Of the 5 patients who completed the extension phase, 3 patients transitioned to single patient INDs.
X4P-001-103 RCP completed OLE ongoing	Patients with WHIM syndrome 12 years of age and above	31 (18 to 28) in total: Placebo: 17 (14) Mavorixafor: 14 (14)	Phase 3, double-blind, placebo-controlled, randomised RCP: to demonstrate efficacy and safety OLE: to demonstrate long-term efficacy and safety	Mavorixafor 400 mg QD or placebo for 52 weeks followed by open label mavorixafor 400 mg QD (200 mg QD for patients 12 to <18 years weighing <50 kg).	52-week RCP followed by OLE (total 30 patients treated with mavorixafor).

CSR=clinical study report; IND=investigational new drug application; OLE= Open-label extension period; PD=pharmacodynamics; PK=pharmacokinetics; QD=once daily; RCP= Randomized placebo-controlled period; WHIM=Warts, Hypogammaglobulinemia, Infections, and Myelokathexis.

a. In total, 31 patients were enrolled onto Study X4P-001-103. One patient enrolled into the placebo group during the randomized-controlled period did not proceed into the open-label extension and therefore 30 patients in total were exposed to mavorixafor during the study.

5.2. *Clinical pharmacology*

5.2.1. Methods

Two LC/MS/MS methods were validated for the determination of mavorixafor in human plasma: a method that was used in the Phase 2, Phase 3 and most of the Phase 1 clinical studies, and a method that was used in the mass balance study. In addition, a method for the determination of mavorixafor in human urine was validated; as well as methods for the determination of radio-labelled mavorixafor in human biomaterials and S-mavorixafor with its chiral enantiomer R-mavorixafor. The other methods were developed and validated for the quantification of drugs co-administered with mavorixafor in drug-drug interaction studies. All methods were suitable for the intended use and demonstrated reliable performance.

In the Phase 3 study X4P-001-103, ALC, AMC, ANC, and WBC counts were determined by standard methods. Whole blood samples were sent to a central laboratory selected by the Sponsor. All individual values and the calculated TAT and AUCs for ALC, AMC, ANC, and WBC count were reported to either the Investigator or the Sponsor until the RCP was unblinded. For the Phase 2 dose finding study X4P-001-MKKA, whole blood samples were sent to a central laboratory selected by the Sponsor, and WBC, ANC, ALC, and AMC were determined by standard methods.

Results for laboratory test related to immunogenicity have not been provided.

5.2.2. Pharmacokinetics

5.2.2.1. Introduction

Mavorixafor (ATC-code L03AX24 (WHO), also referred to as AMD11070, AMD070, X4-135, and X4P-001 during (early) development) is an orally bioavailable, small-molecule, antagonist of the CXCR4 receptor that acts by binding to the receptor.

Mavorixafor is supplied as oral immediate release 100 mg solid capsules.

The same 100 mg capsule formulation was used across the clinical development programme, which is also the intended commercial formulation.

Studies in healthy volunteers

Five Phase 1 studies in healthy volunteers (HV) evaluated the ADME, potential QT effect, food effect, and DDI of mavorixafor.

Study X4P-001-105 was an open-label mass balance study to investigate the absorption, metabolism, and excretion of 14C-mavorixafor. Following administration of a single oral dose of 14C-mavorixafor at a nominal specific activity of 400 mg /5 µCi to 6 male HV, total radioactivity was determined in plasma, whole blood, urine, and faeces and percent of dose recovered was determine in excreta.

Study X4P-001-106 was a Phase 1, single centre, 2-part study comprising:

- Part 1: a single ascending dose study to assess the safety and tolerability of mavorixafor at supratherapeutic doses in adult HV, and to evaluate the PK profile of mavorixafor following oral administration of single ascending doses.
- Part 2: a randomised, partially-blinded, placebo- and moxifloxacin-controlled, 3-period crossover thorough QT study to evaluate the effect of a supratherapeutic mavorixafor dose on 12-lead ECG parameters, and the relationship between mavorixafor plasma concentration and QTc.

Study X4P-001-107 was a Phase 1, randomised, open-label, single-centre, single dose, 6-period, 6-sequence crossover study to assess the PK, safety, and tolerability of mavorixafor in HV under fasted and fed states.

Study X4P-001-108 was a Phase 1, open-label, single-centre, sequential-design drug interaction study to evaluate the effect of mavorixafor (following 12 doses) on the PK of a single dose of COC (EE and NET) in female HV, and to evaluate the PK and safety of mavorixafor following COC administration.

Study X4P-001-109 was a Phase 1, open-label, single-centre, three-part study to evaluate the DDI potential of orally administered mavorixafor with CYP probe substrates (caffeine, losartan, omeprazole, dextromethorphan, and midazolam), drug transporter probe substrates (digoxin, furosemide, and metformin), or itraconazole (a strong CYP3A inhibitor and P-gp inhibitor) in HV.

Studies in patients with WHIM syndrome

The PK, PD, and exposure-response relationships of mavorixafor were evaluated in 2 studies in patients with WHIM syndrome.

Study X4P-001-MKKA was a Phase 2 study in 8 patients with WHIM syndrome, designed to evaluate the safety and tolerability of single-agent mavorixafor, and to determine the dose required to achieve a consistent increase in circulating neutrophils and lymphocytes, as well as evaluating efficacy (in terms of TAT of ANC, ALC, and AMC), PK, and PD (exposure-efficacy relationships and biomarkers including subpopulations of PBMCs).

Study X4P-001-103 was a Phase 3, two-period study, with an initial 12-month, randomised, double-blind, placebo-controlled period (RCP) followed by an open-label extension (OLE). The primary objective of the RCP was to assess the efficacy of mavorixafor on absolute levels of circulating neutrophils in blood compared with placebo and relative to a clinically meaningful threshold (ANC ≥500 cells/µL over a 24-hour period). Key secondary endpoints were to evaluate TAT_{ALC} as well as effects on warts and infections. Other objectives included evaluation of the safety and tolerability of mavorixafor,

and mavorixafor PK. The primary objective in the OLE was the assessment of long-term safety and tolerability while efficacy was a secondary objective.

5.2.2.2. Evaluation and qualification of models

5.2.2.2.1. Population Pharmacokinetics

See pop PKPD analysis in section 5.2.4.

5.2.2.2.2. Physiology based pharmacokinetic model

N/A

5.2.2.3. Absorption

Healthy Volunteers

X4P-001-105 (ADME)

Following a single oral dose of 400 mg/5 µCi ^{14}C-mavorixafor, plasma concentrations reached a peak by approximately 1.25 h (median) and thereafter declined with a mean terminal t1/2 of 82.14 h. The arithmetic mean (SD) Cmax of mavorixafor was 2090 (938) ng/mL, mean (SD) AUC0-last was 6810 (2350) h*ng/mL, and mean (SD) AUC0-inf was 6950 (2380) h*ng/mL. The mean (SD) clearance (CL/F) of mavorixafor was approximately 65700 (27900) mL/h and a mean (SD) volume of distribution (Vz/F) was 7210000 (2040000) mL. Mean (SD) Tmax of plasma mavorixafor in these healthy, male adult subjects was 1.09 (0.48) h and mean (SD) t1/2 was 82.14 (28.06) h. The mean (SD) λz was 0.00905 (0.00219).

Table 9: X4P-001-105 Pharmacokinetic Parameters of Plasma Mavorixafor and Plasma and Whole Blood Radioactivity – PK Population

		Mavorixafor	Radioactivity	
PK Parameter (Units)		**Plasma**		**Whole Blood**
C_{max} (mavorixafor: ng/mL; radioactivity: ngEq/mL)	Geometric mean (n; %CV)	1880 (6;58.9)	2620 (6;59.7)	1850(6;55.9)
T_{max} (h)	Median (n; range)	1.25 (6;0.5-1.5)	1.5 (6;0.53-2.0)	1.25 (6;0.53-2.00)
T_{last} (h)	Median (n; range)	240.2 (6;192.0-503.0)	587.0 (6;336.0-671.0)	288.0 (6;144.0-503.0)
AUC_{last} (mavorixafor: h*ng/mL; radioactivity: h*ngEq/mL)	Geometric mean (n; %CV)	6430 (6;40.3)	24700 (6;26.5)	16300 (6;38.1)
AUC_{0-inf} (mavorixafor: h*ng/mL; radioactivity: h*ngEq/mL)	Geometric mean (n; %CV)	6570 (6;39.7)	–	16100 (4;41.8)
$t_{½}$ (h)	Arithmetic mean (n; %CV)	82.14 (6;34.2)	367.17 (2;15.7)	191.86 (6;59.6)
CL/F (L/h)	Geometric mean (n; %CV)	61.5 (6;39.7)	–	25.0 (4;41.7)
V_Z/F (L)	Geometric mean (n; %CV)	7010 (6;25.9)	–	4080 (4;39.8)

n = number of subjects with event.
Except for subject 011033, AUC0-inf may not be reliable since AUC%extrap >20.0% or R^2 adjusted was lower than 0.80.

Based on geometric means and not arithmetic means

Patients with WHIM Syndrome

X4P-001-MKKA (Phase II study)

Table 10: Summary of Plasma Mavorixafor Pharmacokinetic Parameters at Steady State by Dose Level

	Dose Level					
	50 mg (N=2)	100 mg (N=4)	150 mg (N=3)	200 mg (N=4)	300 mg (N=7)	400 mg (N=5)
Number of patients	2	4	2	3	7	3
C_{max}, arithmetic mean (SD), (ng/mL)	117 (44.3)	564 (233.2)	633 (511.2)	953 (338.0)	2290 (1358)	2230 (870.5)
Dose Normalized C_{max}, arithmetic mean (SD), (ng/mL/mg)	2.3 (0.9)	5.6 (2.3)	4.2 (3.4)	4.8 (1.7)	7.7 (4.5)	5.6 (2.2)
AUC_{0-24}, arithmetic mean (SD), (h*ng/mL)	255 (129.8)	1470 (1313)	1630 (1491)	3120 (1030)	8460 (5109)	8140 (1176)
Dose Normalized AUC_{0-24}, arithmetic mean (SD), (h*ng/mL/mg)	5.1 (2.6)	14.7 (13.1)	10.9 (9.940)	15.6 (5.2)	28.2 (17.0)	20.4 (2.9)
Tmax, median (range) (h)	1.25 (0.5-2.0)	1.25 (1.0-2.0)	1.75 (1.5-2.0)	1.50 (1.0-2.0)	2.00 (0.5-3.0)	2.00 (1.5-2.0)

As some subjects provided multiple values for the same dose level, median values were taken at the same dose level for each subject, the median values were then used in the analysis.

X4P-001-103 (Phase III study)

Table 11: Summary of PK Parameters of X4P-001 Following 400 mg Mavorixafor QD – Randomized Placebo-Controlled Period – Pharmacokinetic Population

Dose	**Statistics**	**AUC_{0-24h}** (h*ng/mL)	**$AUC_{0-tlast}$** (h*ng/mL)	**C_{Max}** (ng/mL)	**C_{Min}** (ng/mL)	**T_{max}** (h)	**T_{Last}** (h)
400	n	12	12	12	12	12	12
	Mean (SD)	15,980 (8741.20)	15,970 (8742.80)	3714.60 (1736.44)	157.84 (97.52)	2.81 (0.66)	23.92 (0.09)
	CV%	54.70	54.70	46.75	61.78	23.41	0.36
	Median	13,560	13,540	3565.00	117.55	2.80	23.91
	Min; max	6120; 33,700	6110; 33,700	935; 7580	54.10; 315.50	1.88; 4.00	23.75; 24.01
	GeoMean (Geo CV%)	13,970 (58.44)	13,960 (58.49)	3304.40 (58.57)	132.17 (69.10)	2.74 (23.08)	23.91 (0.36)

Abbreviations: AUC0-24h = area under the plasma concentration curve over dosing interval; AUCtlast = area under the plasma concentration curve from time of dosing to time of last quantifiable concentration; Cmax = maximum concentration; Cmin = minimum concentration; CV = coefficient of variation; Geo = geometric; GeoMean = geometric mean; max = maximum; min = minimum; PK = pharmacokinetic; QD = once daily; SD = standard deviation; Tlast = time of last quantifiable concentration; Tmax = time of maximum concentration.
Note: Median values for each participant/parameter combination are taken, and summary statistics are then calculated.
Note: One participant had dose modifications on Week 26, 39, and 52. As a result, this participant is included in both the 200-mg Dose Group and the 400-mg Dose Group based on the dose level of the drug at the time of PK measurement

The 200-mg dose level had only 2 participants and included 1 participant from the < 18 and 1 participant from the ≥ 18 age group, in which one participant had dose modifications at Weeks 26, 39, and 52, which was expected to result in lower exposure. One participant received 200 mg QD based on age and weight criteria (age < 18 and weight < 50 kg). Therefore, the results for the 2 participants dosed at the 200-mg dose level were listed only (no statistical evaluation, data not shown).

Influence of food

Table 12: Study X4P-001-107: Percentage Ratios of Bioavailability Parameters of Various Fed Conditions Versus Fasted Conditions in Healthy Versus Fasted Conditions in Healthy Adults

Conditions Compared	% Ratio (90% CI)		
	C_{max} (ng/mL)	$AUC_{0\text{-}inf}$ (h*ng/mL)	$AUC_{0\text{-}last}$ (h*ng/mL)
Fed (B) vs. Fasted (A)	33.8 (27.05, 42.23)	44.7 (38.99, 51.19)	45.2 (39.33, 51.93)
Fed (C) vs. Fasted (A)	45.3 (36.07, 56.77)	48.9 (42.71, 55.90)	48.1 (41.72, 55.40)
Fed (D) vs. Fasted (A)	114.1 (90.67, 143.65)	82.1 (71.54, 94.31)	83.3 (72.13, 96.15)
Fed (E) vs. Fasted (A)	41.1 (32.83, 51.42)	63.4 (55.35, 72.73)	61.4 (53.38, 70.69)
Afternoon Fasted (F) vs. Overnight Fasted (A)	56.5 (45.19, 70.68)	76.1 (66.61, 86.84)	76.5 (66.51, 88.00)

Conditions were as follows:
(A)=overnight fasted (≥10 hours) until 4 hours post-dose,
(B)=overnight fasted (≥10 hours) with high-fat meal within 30 minutes before dosing,
(C)=overnight fasted (≥10 hours) with low-fat meal within 30 minutes before dosing,
(D)=overnight fasted (≥10 hours) and low-fat meal 30 minutes post-dose,
(E)=afternoon fasted (≥4 hours) with high-fat meal 2 hours prior to dosing, and
(F)=afternoon fasted (≥4 hours) until 4 hours post-dose.

In all conditions, food or drink (except water), that was additional to the planned meal or fast, was not permitted until 4 hours post-dose. Water intake was allowed up to 1 hour before dosing and from 1 hour after dosing.

5.2.2.4. Distribution

According to the applicant's conclusions, given that the mean C_{max} concentration following multiple dosing in the Phase 3 study in patients with WHIM syndrome (X4P-001-103) was 3304.4 ng/mL (9.455 µM), protein binding would be expected to be approximately 93%.

Following a single dose of 400 mg/5 µCi ^{14}C mavorixafor, the mean (percent coefficient of variation [%CV]) AUC whole blood to plasma total radioactivity ratio was 65.4% (17.4), indicating minimal partitioning to red blood cells.

The mean (%CV) plasma mavorixafor to total radioactivity AUC ratio was 25.6% (21.2).
The half-life of plasma radioactivity (parent with radio-labelled metabolites) was approximately 4.47-fold longer than the half-life of plasma mavorixafor, which was discussed to maybe reflect lower clearance rates or larger apparent volumes of distribution of the unidentified (minor) circulating metabolites.

The mavorixafor geometric mean Vz/F was between 2420 L and 7010 L in studies in healthy subjects. As discussed by the Applicant, this is significantly greater than total body water (42 L) and indicates that mavorixafor is extensively distributed to peripheral tissues.

The population PK analysis determined that the inclusion of a peripheral compartment in the final model was necessary to accurately reflect mavorixafor. The final population PK model was a two-compartment disposition model. The parameter estimate for *Apparent Central Volume of Distribution* (Vc/F) was 64.6 (7.6) (%RSE) and the *Apparent Peripheral Volume of Distribution* (Vp/F, L) was 703 (13.8) L (%RSE).

5.2.2.5. Metabolism

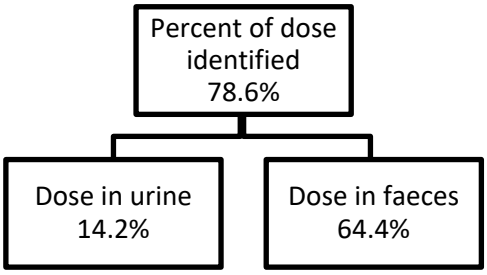
In vitro studies suggest that the primary enzymes responsible for mavorixafor metabolism in humans are CYP3A4 and to a lesser extent CYP2D6.

A mass balance study of ^{14}C-mavorixafor in healthy subjects performed metabolite identification on pooled samples using accurate mass positive ion full scan and product ion analyses (X4P-001-105). The samples (plasma, urine, and faeces extract) were screened for the presence of mavorixafor and its potential metabolite. They were also screened for the presence of metabolites previously observed in microsomes as well as additional potential metabolites seen in non-clinical studies. Except for the unchanged parent mavorixafor in plasma and faeces, no single, radioactive component accounted for more than 10% of the circulating radioactivity (plasma) or the total administered dose (urine and faeces) and therefore no metabolite identification was performed. However, the different analyses performed in this study consistently pointed to the presence of multiple, undefined metabolites. LC-UV analysis identified 2 regions of interest each accounting for >5% of total radioactivity in urine and 6 in faeces. Similarly, exposure of total radioactivity in plasma was 3.73-fold higher than that of mavorixafor and cumulative recovery of total radioactivity in urine was 4.75-fold higher than that of mavorixafor. Further, the 4.47-fold longer t1/2 of plasma radiolabel compared with plasma mavorixafor suggests that these metabolites may have lower clearance rates or larger apparent volumes of distribution than parent drug.

5.2.2.6. Elimination

After single oral administration of ^{14}C-mavorixafor in humans in study X4P-001-105, a mean (SD) of 61.0% (5.21) of administered radioactivity was recovered in faeces and 13.2% (3.57) was recovered in the urine over the 240-hour collection period.

Figure 1: Mass balance studies (recovery over 816 hours)



Unchanged parent mavorixafor was the major radioactive component in all sample types, 24.97% of total radioactivity in the 0 – 336 h plasma pool and 26.43% and 29.85% in the 1 – 192 h urine and faeces extract pools, respectively.

Following a single administration of mavorixafor in humans, observed half-life ranged between mean (SD) 11.24 (4.43) hours in X4P-001-108 to 82.14 (28.06) hours in X4P-001-105 (Table 13).

Table 13: Summary of Mavorixafor PK Parameters in Healthy Subjects Following Administration of a Single Oral Dose

Study number	Mavorixafor Dose/ Fasting conditions/ Duration of sampling period	N/n	Tmax (h)	t½ (h)	CL/F (mL/h)	Vz/F (L)
			Median (range)	Arithmetic mean (SD)	Geometric mean (%CV)	
X4P-001-105 [a]	^{14}C-mavorixafor 400 mg /5 µCi Overnight fasted (≥8 h) until 4 hours postdose 29-day sampling period	6/6	1.25 (0.5-1.5)	82.14 (28.06)	61500 (39.7)	7010 (25.9)

Study number	Mavorixafor Dose/ Fasting conditions/ Duration of sampling period	N/n	Tmax (h)	t½ (h)	CL/F (mL/h)	Vz/F (L)
			Median (range)	Arithmetic mean (SD)	Geometric mean (%CV)	
X4P-001-107 [b]	Mavorixafor 400 mg Overnight fasted (≥10 h) until 4 hours postdose 96-hour sampling period	24/20	1.54 (0.50-4.01)	42.31 (11.290)	40840 (45.3)	2420 (54.7)
	Mavorixafor 400 mg Overnight fasted (≥10 h), low-fat meal 30 min postdose 96-hour sampling period	24/20	1.03 (0.96-6.00)	41.49 (7.544)	51470 (49.1)	3032 (53.1)
X4P-001-108	Mavorixafor 400 mg Overnight fasted (≥10 h) until 4 hours post-dose 24-hour sampling period	19/18	1.99 (0.48-4.02)	11.24 (4.426)	NR	NR
X4P-001-109	Cohort 3: mavorixafor 400 mg, Overnight fasted (≥10 h) until 4 hours postdose 24-hour sampling period	16/16	1.32 (0.5-3.02)	27.0 (6.73) [c]	NR	NR

NR = not reported.
a In X4P-001-105, a different bioanalytical method was used for the assay of mavorixafor plasma concentrations .
b In X4P-001-107, there was a washout period of at least 7 days between each single administration of mavorixafor under different fasting conditions.
c Only 3 subjects were evaluable for AUC0-inf and half-life in Cohort 3 of X4P-001-109.
Geometric mean (geometric %CV) is shown for all PK parameters except median (range) for Tmax and arithmetic mean (±Std Dev) for half-life

5.2.2.7. Dose proportionality and time dependency

Dose proportionality was assessed in study X4P-001-MKKA (see "Absorption" section above) over a dose range of 50 to 400 mg.

Additionally, a mixed linear analysis of ln-transformed steady-state Cmax and AUC0-24 and dose, also known as a power model, was used. AUC0-24 increased more than proportionally with dose in the range of 50 mg to 400 mg QD with a slope estimate of 1.67 (95% CI 1.26-2.07) (Table 14).

Table 14: X4P-001-MKKA: Dose Proportionality Assessment Over a Dose Range of 50 to 400 mg of a Single Oral Dose

Parameter (Steady-state)	Estimate	95% CI
C_{max}	1.33	0.937-1.72
AUC_{0-24}	1.67	1.26-2.07

Following QD dosing in healthy subjects (studies X4P-001-108 and X4P-001-109), mavorixafor concentrations reached steady-state after approximately 9 to 12 days.

In patients with WHIM syndrome in study X4P-001-103, Cmax and AUC_{0-24} at Week 52 (2975.0 ng/mL and 14440 h*ng/mL, respectively) were comparable to the values at Week 13 (3264.1 ng/mL and 13850 h*ng/mL).

5.2.2.8. Pharmacokinetics in the target population

See above

5.2.2.9. Special populations

Potential effect of intrinsic factors like hepatic impairment, renal impairment or ethnic factor have not been investigated in dedicated clinical studies.

5.2.2.10. Pharmacokinetic interaction studies

X4P-001-108 (DDIs with COC containing EE and NET)

Table 15: Statistical Analysis to Assess Drug-Drug Interaction of Mavorixafor on Plasma Pharmacokinetic Parameters of EE/NET (Days 1 and 14) Excluding Participants with %AUCex Higher than 20% (COC Pharmacokinetic Analysis Set)

Study Drug	Parameter (Unit)	Geometric Least-Squares Mean (90% CI)				% Ratio (90% CI) (Day 14/Day 1)
		n	Day 1	n	Day 14	
Ethinyl Estradiol	C_{max} (pg/mL)	18	69.78 (58.98, 82.56)	18	64.84 (54.81, 76.71)	92.92 (86.35, 99.98)
	AUC_{0-inf} (h*pg/mL)	12	756.83 (661.88, 865.41)	12	879.09 (768.80, 1005.21)	116.15 (101.79, **132.54**)
	AUC_{0-48} (h*pg/mL)	18	650.01 (558.08, 757.08)	18	720.76 (618.82, 839.48)	110.88 (103.76, 118.50)
Norethindrone	C_{max} (pg/mL)	18	7852.09 (6763.42, 9115.99)	18	7285.52 (6275.40, 8458.23)	92.78 (82.13, 104.82)
	AUC_{0-inf} (h*pg/mL)	18	55185.59 (46478.21, 65524.24)	17	64517.11 (54283.58, 76679.85)	116.91 (107.00, **127.74**)
	AUC_{0-48} (h*pg/mL)	18	52078.09 (44159.42, 61416.74)	18	61665.11 (52288.69, 72722.91)	118.41 (109.04, **128.58**)

CI = confidence interval; COC = combined oral contraceptive; EE = ethinyl estradiol; n = number of observations; NET = norethindrone.

Result based on a mixed-effect model of log transformed PK parameter of Day 1 and Day 14 with treatment (mavorixafor + EE and NET versus EE and NET alone) as fixed effect and participant as random effect.
Geometric least-squares mean and corresponding 90% CI were back-transformed (exponentially) to obtain estimated geometric mean ratio and corresponding 90% CI for each primary PK parameter.
Equivalence limit of the ratio of means was 80% to 125%.
Participants with %AUCex>20% were excluded from the analysis of AUC0-inf.

Colours to indicate if confidence interval (CI) is within BE-limits (green), CI is not contained within BE-limits (yellow), or point estimate is not contained within BE-Limits ("reddish") were added by the Assessor

X4P-001-109 (DDI cocktail study CYP enzymes and transporter)

The PK results for CYP probe substrates exposure (Cmax, AUC_{0-t} and AUC_{0-inf}) following single dose administration of the Inje cocktail (caffeine, losartan, omeprazolam, dextromethorphan and midazolam), in the presence and absence of steady-state concentrations of mavorixafor, are tabulated below:

Table 16: Statistical Analysis to Assess the Effect Mavorixafor on Plasma Pharmacokinetic Parameters of the Inje Cocktail (Day 1 and 11) – Cohort 1 (Pharmacokinetic Analysis Set by CYP Substrate)

Study Intervention	Enzyme	Parameter (unit)	Least-Squares Mean				% Ratio (90% CI) (Day 11 / Day 1)
			N	Day 1	n	Day 11	
Caffeine	CYP1A2	C_{max} (ng/mL)	24	2114.794	24	2104.010	99.490 (92.89, 106.56)
		AUC_{0-inf} (h*ng/mL)	22	16835.192	22	15970.019	94.861 (88.40, 101.80)
		AUC_{0-t} (h*ng/mL)	24	15888.245	24	15341.329	96.558 (90.87, 102.60)

Losartan	CYP2C9	C_{max} (ng/mL)	22*	96.797	24	80.093	82.73 (**70.39**, 97.27)
		AUC_{0-inf} (h*ng/mL)	22	320.201	22	273.903	85.541 (**77.61**, 94.28)
		AUC_{0-t} (h*ng/mL)	22	313.410	24	263.276	84.004 (**76.32**, 92.46)
Omeprazole	CYP2C19	C_{max} (ng/mL)	24	348.264	24	360.312	103.460 (83.12, **128.78**)
		AUC_{0-inf} (h*ng/mL)	19	869.905	20	1005.302	115.698 (95.43, **140.27**)
		AUC_{0-t} (h*ng/mL)	24	743.380	24	870.810	117.142 (98.79, **138.90**)
Dextromethorphan	CYP2D6	C_{max} (ng/mL)	24	1.835	24	11.937	**650.695 (511.03, 828.53)**
		AUC_{0-inf} (h*ng/mL)	17	13.185	21	118.258	**896.974 (653.68, 1230.74)**
		AUC_{0-t} (h*ng/mL)	24	13.804	24	103.386	**748.967 (587.31, 955.08)**
Midazolam	CYP3A	C_{max} (ng/mL)	24	7.977	24	9.805	113.888 (100.45, **129.13**)
		AUC_{0-inf} (h*ng/mL)	13	20.325	16	34.961	**172.007 (143.60, 206.03)**
		AUC_{0-t} (h*ng/mL)	24	18.386	24	30.286	**164.722 (145.90, 185.97)**

*Some losartan samples were not available for bioanalysis.

Colours to indicate if confidence interval (CI) is within BE-limits (green), CI is not contained within BE-limits (yellow), or point estimate is not contained within BE-Limits ("reddish") were added by the Assessor

The PK results for transporter probe exposures (Cmax, AUC_{0-t} and AUC_{0-inf}) following single dose administration of the transporter cocktail (digoxin, furosemide and metformin), in the presence and absence of steady-state concentrations of mavorixafor, are tabulated below:

Table 17: Statistical Analysis to Assess the Effect of Mavorixafor on Plasma Pharmacokinetic Parameters of Transporter Substrates Cocktail (Day 1 and 14) – Cohort 2 (Pharmacokinetic Analysis Set by Transporters Substrate)

Study Intervention	Transporter	Parameter (unit)	Least Square Mean				% Ratio (90% CI) (Day 14 / Day 1)
			N	Day 1	n	Day 14	
Digoxin	P-gp	C_{max} (ng/mL)	14	1.047	13	1.612	**153.956 (131.94, 179.60)**
		AUC_{0-96} (h*ng/mL)	13	10.919	13	17.956	**164.453 (142.81, 189.38)**
Furosemide	OAT1	C_{max} (ng/mL)	13	34.006	13	27.264	80.175 (**65.86**, 97.60)

		AUC_{0-96} (h*ng/mL)	13	66.591	13	53.282	80.015 (**69.74**, 91.80)
		AUC_{0-inf} (h*ng/mL)	12	66.366	12	54.581	82.241 (**70.25**, 96.28)
Metformin	OCT2/MATE1	C_{max} (ng/mL)	14	41.047	13	26.742	**65.151** (**50.96**, 83.29)
		AUC_{0-96} (h*ng/mL)	13	217.629	12	318.766	**60.064 (49.81, 72.43)**
		AUC_{0-inf} (h*ng/mL)	13	212.782	12	138.766	**65.215** (**52.88**, 80.42)

Colours to indicate if confidence interval (CI) is within BE-limits (green), CI is not contained within BE-limits (yellow), or point estimate is not contained within BE-Limits ("reddish") were added by the Assessor

The PK results for a single dose of 400 mg mavorixafor given alone on Day 1 compared to a single dose of 200 mg mavorixafor (half the dose compared to Day 1) following 5 days of itraconazole, are tabulated below:

Table 18: Statistical Analysis to Assess Effect of Itraconazole on Plasma Pharmacokinetic Parameters of Mavorixafor (Day 1 and 10) – Cohort 3 (Itraconazole Pharmacokinetic Analysis Set)

Study Intervention	Parameter (unit)	Least Square Mean				% Ratio (90% CI) (Day 10 / Day 1)
		n	Day 1 (400 mg)	n	Day 10 (200 mg)	
Mavorixafor	C_{max} (ng/mL)	16	3222.248	15	3232.420	100.316 (91.24, 110.30)*
	AUC_{0-72} (h*ng/mL)	16	11561.535	15	12148.060	105.073 (99.02, 111.50)*
	AUC_{0-inf} (ng/mL)	3	15791.972	2	12788.627	80.982*(52.07, 125.95)

* Calculated % Ratio (90% CI) comparing different doses (400 mg vs. 200 mg)!

5.2.3. Pharmacodynamics

5.2.3.1. Mechanism of action

Mavorixafor is an orally bioavailable CXCR4 antagonist that blocks the binding of the CXCR4 ligand, SDF -1 α/ CXCL12. SDF-1/CXCR4 plays a role in trafficking and homing of leukocytes to and from the bone marrow compartment. Gain of function mutations in the CXCR4 receptor gene that occur in patients with WHIM syndrome lead to increased responsiveness to CXCL12 and retention of leukocytes in the bone marrow. Mavorixafor inhibits the response to CXCL 12 in both wild-type and mutated CXCR4 variants associated with WHIM syndrome. Treatment with mavorixafor results in increased mobilisation of neutrophils and lymphocytes and monocytes from the bone marrow into peripheral circulation as indicated in Section Clinical Efficacy 5.3. of this report.

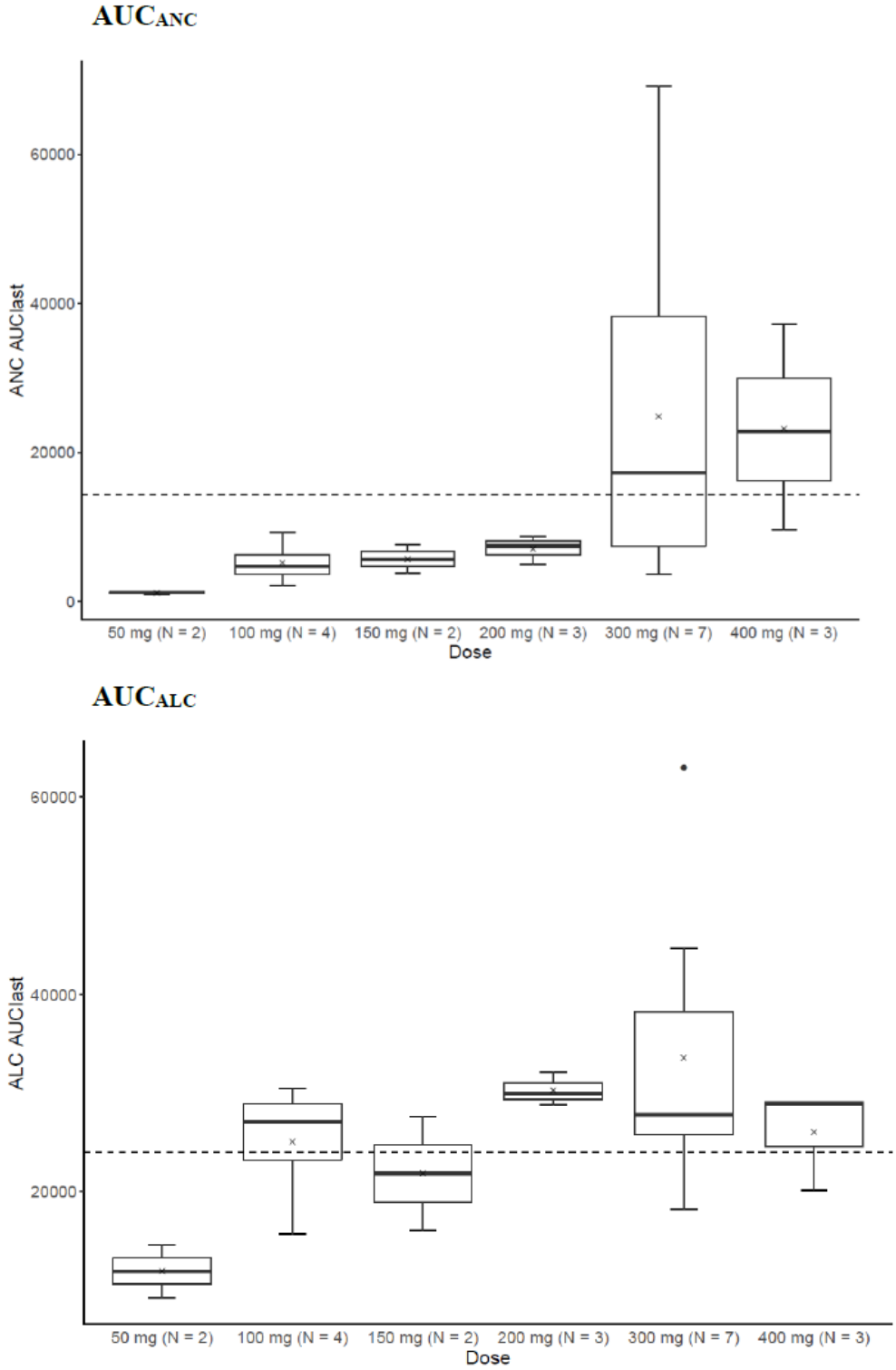
5.2.3.2. Primary and secondary pharmacology

Primary pharmacology

X4P-001-MKKA evaluated the PD of mavorixafor over the dose range 50 to 400 mg PO QD.

Doses at 300/400 mg were needed to achieve sustained increases in ANC ≥600 cells/μL and ALC ≥1000 cells/μL. At lower doses, AUC_{ANC} was below the threshold adjusted level at all visits (Figure 2).

Figure 2: (X4P-001-MKKA) Box Plots of AUCANC and AUCALC by Dose (Dotted line marks the AUC corresponding to values being above the thresholds (ANC ≥600 cells/μL and ALC ≥1000 cells/μL), see legend)

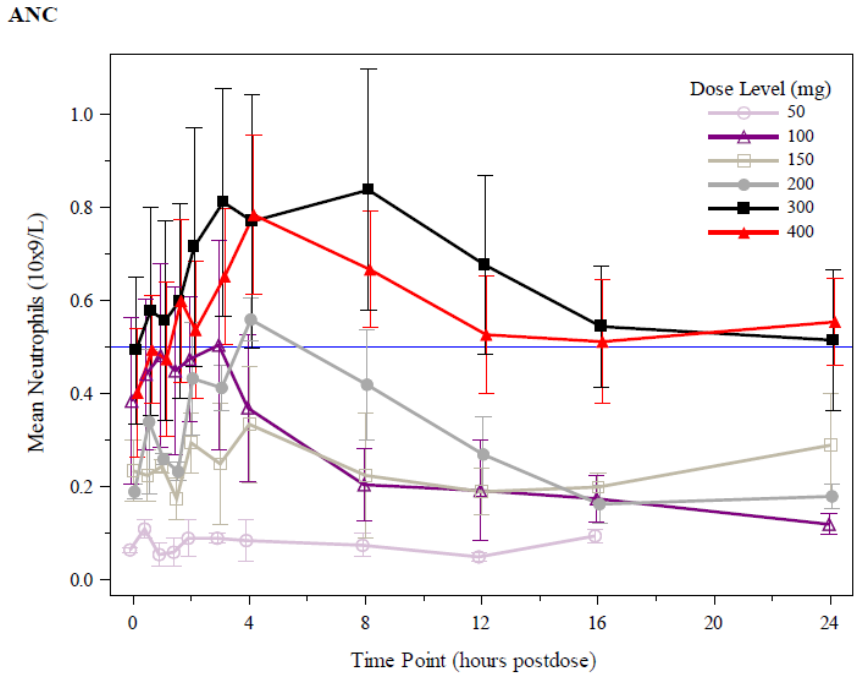


Relative to a threshold of 600 cells/μL for AUC_{ANC} and 1000 cells/μL for AUC_{ALC}.
Dotted line marks the AUC corresponding to values being above the threshold during the entire 24-hour period:
14400 h*cells/*L for AUCANC and 24000 h*cells/μL for AUC_{ALC}..

Absolute neutrophil count (ANC)

As illustrated in Figure 3, over the course of the 24-hour ANC sampling period, mean ANC levels were maintained above the pre-dose level only at 300/400 mg doses.

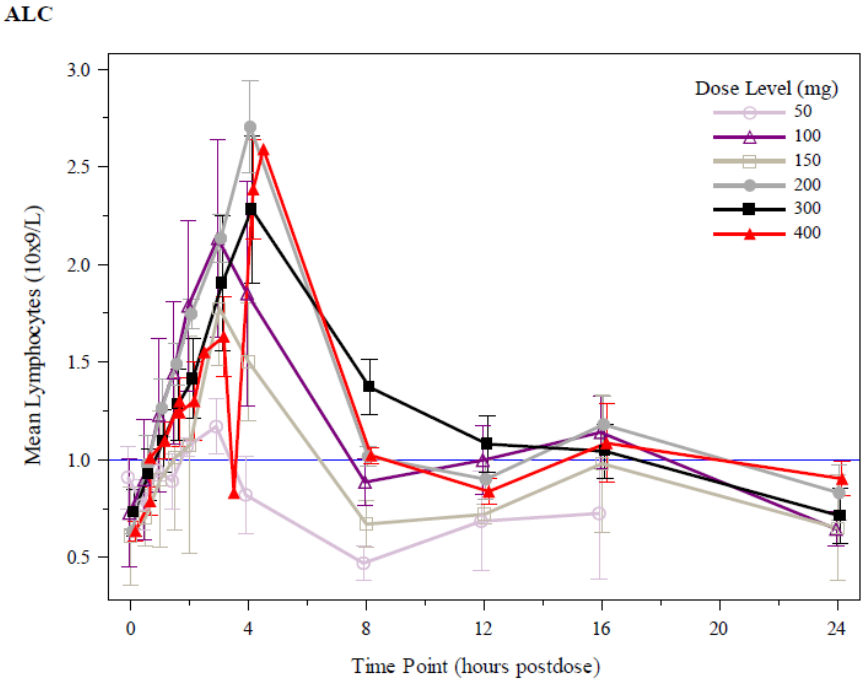
Figure 3: (X4P-001-MKKA) Mean (±SE) Dose Response of ANC-TimeProfile)



Absolute lymphocyte count (ALC)

For ALC, a dose of 100 mg was sufficient to induce levels above the 1000 cells/µL threshold by approximately 2 to 4 hours post-dose. However, at doses below 300 mg, ALC levels rapidly fell back below the threshold, while ALC levels were maintained longer for 300 mg and 400 mg (Figure 4).

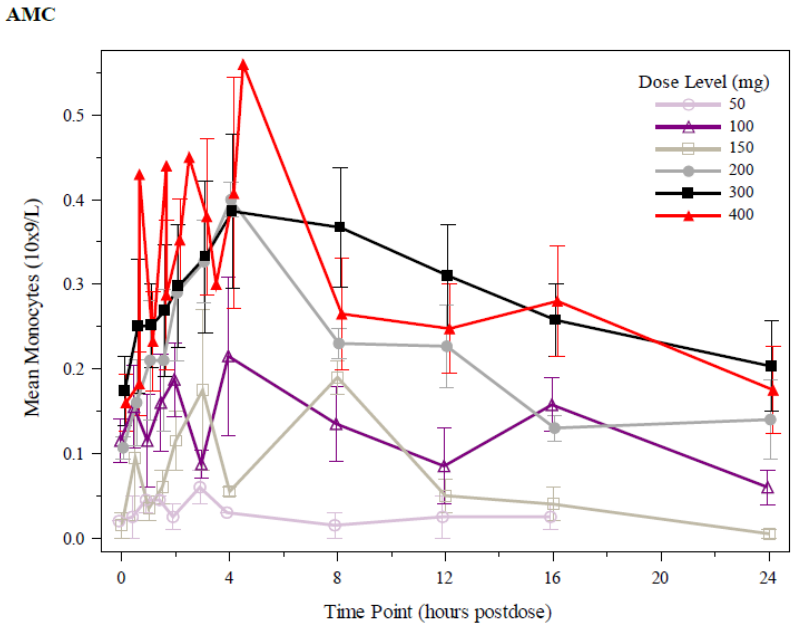
Figure 4: (X4P-001-MKKA) Mean (±SE) Dose Response of ALC-Time Profile)



Absolute monocyte count (AMC)

For AMC, a 200 mg dose was sufficient to induce transient elevations. The 300 and 400 mg dose resulted in sustained elevations, until 24 hours post-dose, Figure 5:

Figure 5: (X4P-001-MKKA) Mean (±SE) Dose Response of AMC -Time Profile



Secondary pharmacology

Clinical Study X4P-001-106 was a "Phase 1, Single Centre, Two-part, Randomized, Partially-blind, Placebo and Moxifloxacin-controlled, Three-period Crossover Thorough QT Study to Evaluate the Effect

of Mavorixafor on 12-lead Electrocardiogram Parameters in Healthy Adult Subjects, following a Single Ascending Dose Study to Assess the Safety and Tolerability of Mavorixafor at Supratherapeutic Doses".

Part 1 of the study was single ascending dose (SAD) to identify a supratherapeutic dose of mavorixafor in healthy adult participants for use in Part 2 of the study based on safety and pharmacokinetic (PK) profile. Part 2 was a TQT study with the primary objective, 'to evaluate the effect of mavorixafor on the corrected QT interval (QTc).

Part 1

Following single dose administration of mavorixafor 800 mg and 1000 mg, mavorixafor was rapidly absorbed to systemic circulation with peak plasma concentrations observed at a median Tmax of 2 to 3.5 hours post dose and geometric mean (CV%) Cmax values of 5260 ng/mL (52.0%) and 6170 ng/mL (48.0%), respectively. Mavorixafor concentrations were quantifiable up to 72 hours post dose. No summary statistics were performed for single dose administration of mavorixafor 1200 mg due to insufficient data (4/6 participants experienced emesis [reported as an AE of vomiting]). The plasma profiles for the 800 mg and 1000 mg dose levels declined in parallel in a biphasic manner.

Part 2

Following single dose administration of mavorixafor 800 mg (a supratherapeutic dose), peak plasma concentrations occurred with median Tmax of 2.07 hours and were quantifiable up to 72 hours post-dose in all participants.

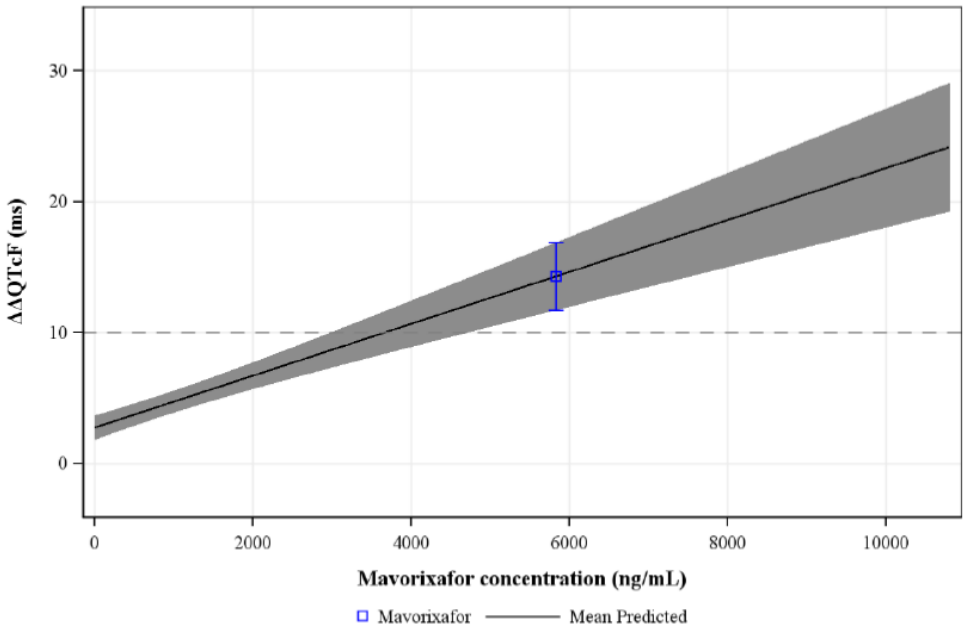
Following single dose administration of mavorixafor 800 mg, no participant had clinically significant ECG morphology findings. A mild effect on heart rate (HR) and QRS duration was observed, and a small but not clinically relevant effect on the PR interval was also observed.

The cardiodynamic results were summarised, as follows:

- An increase in least squares (LS) mean change from baseline placebo-corrected HR (ΔΔHR) was observed from 1.5 to 12 hours post-dose, reaching 11.1 and 10.3 bpm at 4 and 6 hours post-dose, respectively. Across all post-dose time points, LS mean ΔΔHR ranged from 0.7 bpm at 0.5 hours post-dose to 11.1 bpm at 4 hours post-dose.
- There was also a clear increase in LS mean change from baseline QRS (ΔQRS) compared with placebo during the first 12 hours post-dose, reaching a maximum of 5.0 ms at 4 hours post-dose. Across all post-dose time points, LS mean placebo-corrected ΔQRS (ΔΔQRS) ranged from -0.9 ms at 72 hours post-dose to 4.6 and 4.5 ms at 3 and 4 hours post-dose, respectively.
- LS mean placebo-corrected ΔPR (ΔΔPR) varied between -4.0 ms at 1 hour post-dose and 7.7 ms at 3 and 4 hours post-dose.
- In the by-time point analysis, LS mean change from baseline placebo-corrected QTcF (ΔΔQTcF) exceeded 10 ms between 1.5 and 4 hours post-dose, varying from 11.6 ms (90% CI: 9.05 to 14.19) at 1.5 hours post-dose to 15.6 ms (90% CI: 11.35 to 19.84) at 4 hours post-dose. Across all post-dose time points, LS mean ΔΔQTcF ranged from -0.7 ms at 72 hours post-dose to 15.6 ms at 4 hours post-dose. As a reminder, the highest plasma concentration of mavorixafor was observed at 2.5 hours post-dose.
- The estimated slope of the mavorixafor concentrations in the concentration-QTc relationship was positive and statistically significant: 0.0020 ms per ng/mL (90% CI: 0.00150 to 0.00247; P <0.0001]) with a statistically significant treatment effect-specific intercept of 2.70 ms.

The model predicted effect on ΔΔQTcF at the geometric mean Cmax of mavorixafor 800 mg (5837.0 ng/mL) was 14.28 ms (90% CI: 11.69 to 16.87).

Figure 6: (Study X4P-001-106) Model-predicted ΔΔQTcF (mean and 90% CI) interval at geometric mean peak mavorixafor concentrations (PK/QTc population)



The solid black line with grey shaded area denotes the model-predicted mean ΔΔQTcF with 90% CI, which is calculated from the equation ΔΔQTcF (ms) = 2.7 (ms) + 0.002 (ms per ng/mL) × mavorixafor plasma concentration (ng/mL). The non-grey whiskers denote the estimated mean (90% CI) ΔΔQTcF at the geometric mean Cmax of mavorixafor.

Based on this concentration-QTc analysis, a QTc effect (i.e., ΔΔQTcF) exceeding 10 ms can be excluded up to the mavorixafor plasma concentrations of ~2992 ng/mL.

Due to the effect of mavorixafor on HR, additional correction methods were evaluated, including the HR corrected QT interval (QTcS) and optimized HR corrected QT interval (QTcI).
Based on the concentration-QTc analysis for QTcS, an effect on ΔΔQTcS exceeding 10 ms can be excluded up to the mavorixafor plasma concentrations of approximately ~2773 ng/mL, which is slightly lower than that from QTcF concentration-QTc analysis (~2992 ng/mL).

Assay sensitivity was demonstrated using moxifloxacin which is well characterized in terms of effects on the QTcF interval.

5.2.3.3. Pharmacodynamic interactions with other medicinal products or substances

Pharmacodynamic interactions with other medicinal products or substances are presented in section 5.2.3.2.

5.2.3.4. Genetic differences in PD response

A genetic difference in PD response was not reported.

5.2.4. Pharmacokinetics/pharmacodynamics (PK/PD)

Population PKPD modelling report of mavorixafor (X4P-001) in adults and adolescent patients with WHIM syndrome.

The general objective of this analysis was to develop a PKPD model of mavorixafor based on data from the X4P-001-103 clinical trial in adults and adolescents with WHIM syndrome. These data included 480 PK observations and 394 PD observations from 14 adult and adolescent patients.

The relationship between patient specific covariates and PK or PD parameters was evaluated using a forward addition and backward elimination approach. Covariates tested included weight, age, sex, race and at baseline: BALT (alanine aminotransferase), BAST (aspartate aminotransferase), albumin (BALB), total bilirubin (BTBILI), creatinine clearance (BCRCL), baseline count of lymphocytes (BALC) and baseline count of neutrophils (BANC).

The model-predicted concentration versus time course of mavorixafor for each individual was used as the driver for the effect measured as neutrophils and lymphocytes levels over time. The PD component of the model consisted of an indirect response model stimulating the production of the response, compatible with the mechanism of action of mavorixafor, i.e., stimulating neutrophils and lymphocytes release into blood stream.

Parameter estimates of the final model for ANC as PD dependent variable (DV) are provided in Table 19. The analogous model but using ALC as PD DV is presented in Table 20.

Table 19: Mavorixafor PKPD model parameter estimates (for ANC as PD DV).

Parameter	Estimate	RSE (%)	Parameter	Estimate	RSE (%)
KA (1/h)	0.938	FIX	ωBOVKA	0.213	37.9
BIO	1.00	FIX	ωBOVBIO	0.658	26.7
V2 (L)	31.6	24.3	ωV2 (L)	0.611	43.2
CL (L/h)	14.5	10.6	ωCL (L/h)	0.109	53.9
-	-	-	ωCL ~ V2	0.213	44.3
Q (L/h)	4.54	9.2	-	-	-
V3 (L)	143	26.2	-	-	-
LWTCL	0.75	FIX	-	-	-
σ_PK	0.229	8.3			
EMAX (cells/uL)	1.00	FIX	-	-	-
EC50 (ng/mL)	11.7	2.5	-	-	-
BASE (cells/uL)	6.07	9.8	-	-	-
KOUT (1/h)	0.281	37.0	ωKOUT	0.0154	57.1
GAM	4.12	FIX	-	-	-
σ_PD	0.238	8.6	-	-	-

Table 20: Mavorixafor PKPD model parameter estimates (for ALC as PD DV).

Parameter	Estimate	RSE (%)	Parameter	Estimate	RSE (%)
KA (1/h)	0.938	FIX	ωBOVKA	0.213	37.9
BIO	1.00	FIX	ωBOVBIO	0.658	26.7
V2 (L)	31.6	24.3	ωV2 (L)	0.611	43.2
CL (L/h)	14.5	10.6	ωCL (L/h)	0.109	53.9
-	-	-	ωCL ~ V2	0.213	44.3
Q (L/h)	4.54	9.2	-	-	-
V3 (L)	143	26.2	-	-	-
LWTCL	0.75	FIX	-	-	-
σ_PK	0.229	8.3			
EMAX (cells/uL)	1.00	FIX	-	-	-
EC50 (ng/mL)	11.6	1.9	-	-	-
BASE (cells/uL)	6.63	1.5	-	-	-
KOUT (1/h)	0.667	8.0	ωKOUT	0.0018	71.3
GAM	3.44	5.5	-	-	-
σ_PD	0.071	6.2	-	-	-

Goodness of fit (GOF) plots are presented in Figure 7 for the PK model Figure 8 and Figure 9 for the PD model (neutrophiles and lymphocytes, respectively).

Figure 7: Mavorixafor PK model GOF plots.

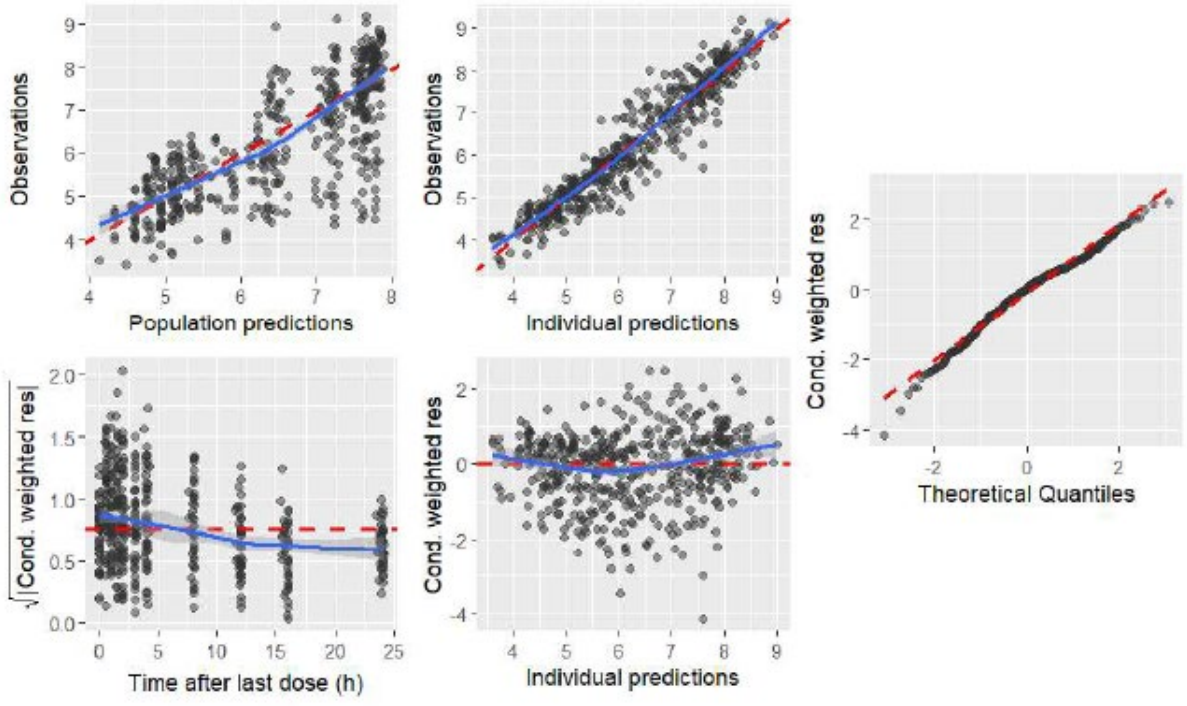


Figure 8: Mavorixafor PD model GOF plots (ANC as PD DV)

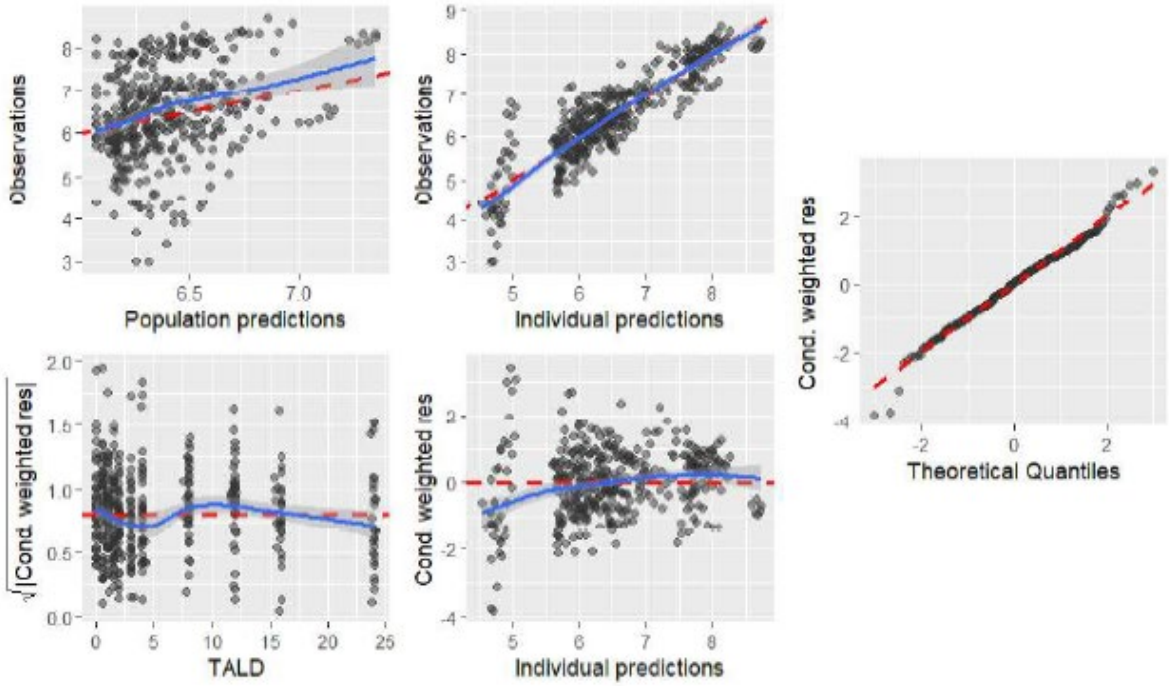
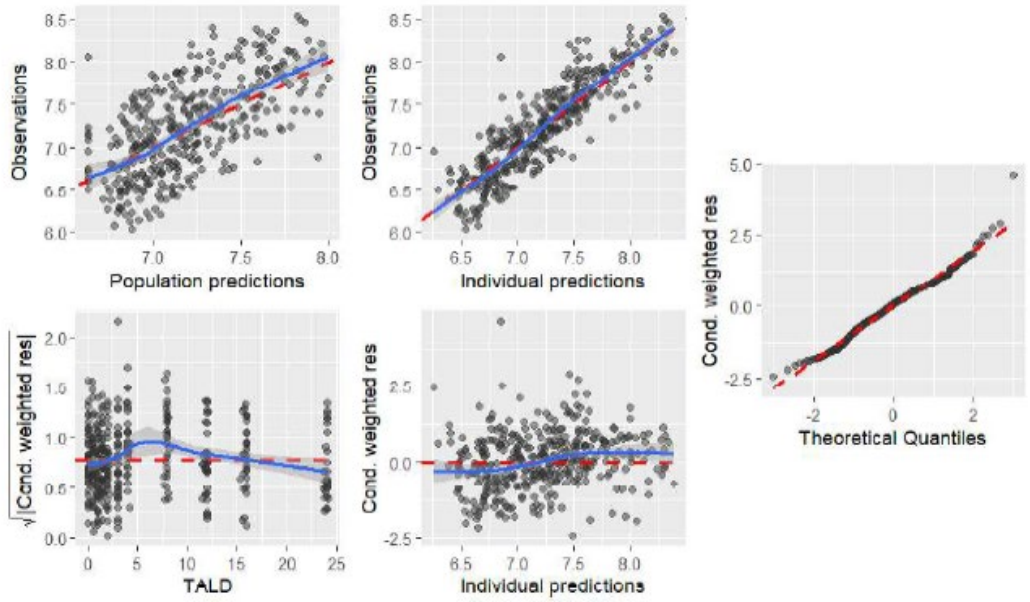


Figure 9: Mavorixafor PD model GOF plots (ALC as PD DV)



The results of the prediction-corrected visual predictive checks (pc-VPC) are shown in Figure 10 for PK, in Figure 11 for the neutrophils and Figure 12 for the lymphocytes.

Figure 10: pc-VPC from N=500 simulated data from the original dataset. DV = mavorixafor plasma concentration with log-transformation (percentiles and 95% CI). TIME= time after dose

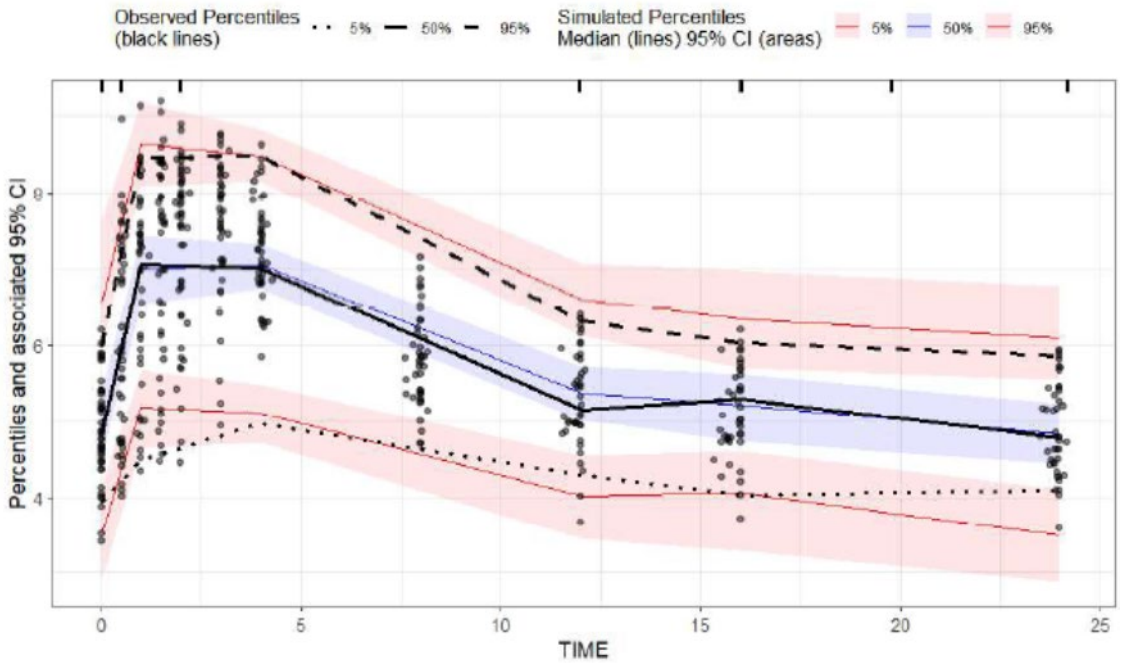


Figure 11: pc-VPC from N=500 simulated data from the original dataset. DV = ANC (cells/uL) with log-transformation (percentiles and 95% CI). TIME= time after dose

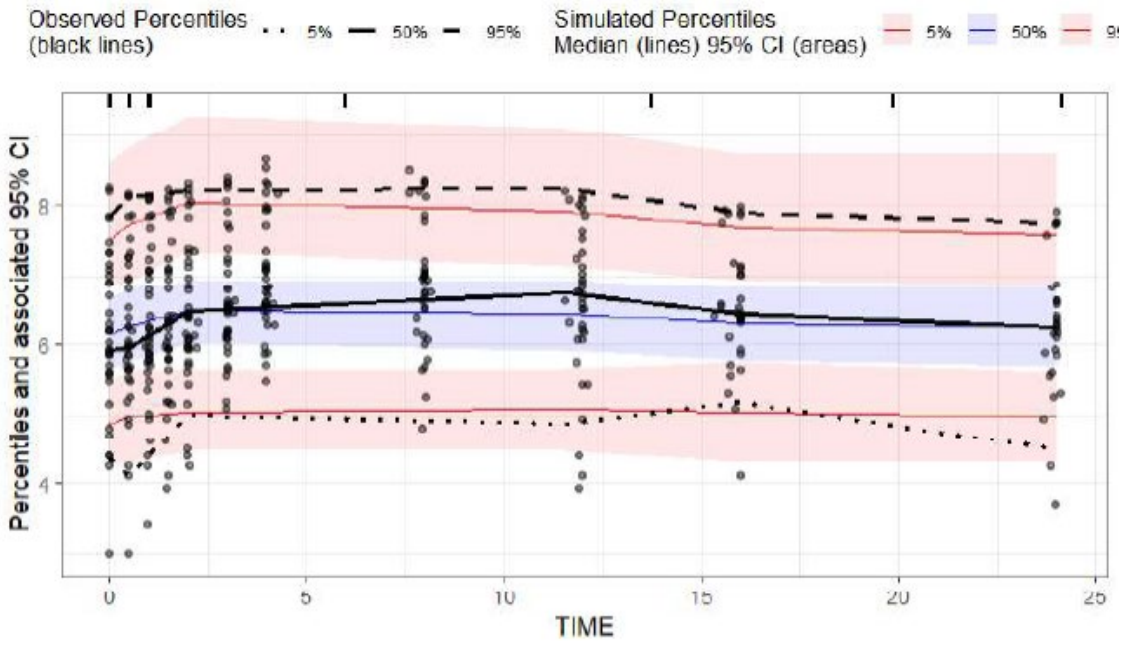
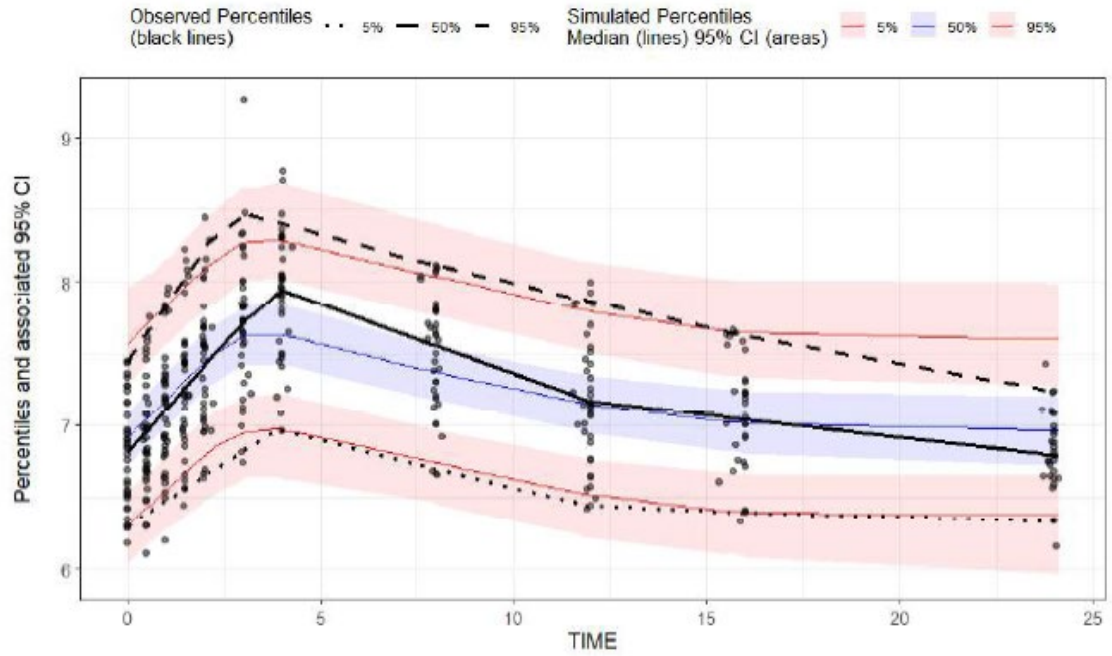


Figure 12: pc-VPC from N=500 simulated data from the original dataset. DV = ALC (cells/uL) withlog-transformation (percentiles and 95% CI). TIME= time after dose



Simulations

Simulations based on the final PKPD model were performed to find the dose in adolescents weighing ≤50 kg that would lead to similar exposure and effect to that of adults with the 400 mg dose. For adolescents with a body weight ≤50 kg, two different doses were simulated: 200 mg or 300 mg. For the adults and adolescents weighing >50 kg, a 400mg dose was used.

Model results are cited in the section on dose selection below.

Exposure-Efficacy Relationship

Exposure-response was evaluated in patients with WHIM syndrome in study X4P-001-MKKA. The study design is provided in Section 5.2.2.3. Absorption and Clinical efficacy Section 5.3.5.

PD results are included in Section 5.2.3.2.

Population PK Analysis of Exposure-Response

TAT_{ANC} and TAT_{ALC} were the primary and key secondary efficacy endpoints in the Phase 3 study.

The exposure-response analysis dataset comprised 151 values each of TAT_{ANC} and TAT_{ALC} from 19 patients who received mavorixafor (X4P-001-MKKA: 5 patients, X4P-001-103: 14 patients) and 17 who received placebo in X4P-001-103. All values of TAT_{ALC} and TAT_{ANC} were paired with the corresponding model-derived exposure metrics by date.

The relationship between model-predicted exposure and dose were stated to be consistent with expectations from the graphical analysis and population PK model, which observed and accommodated nonlinearity in the PK. It was highlighted that over half of the exposures were derived from the 400 mg dose.

For all assessed relationships, TAT_{ANC} and TAT_{ALC} were consistently longer at higher levels of exposure of mavorixafor. Moreover, for both TAT_{ANC} and TAT_{ALC}, all exposure metrics appeared to exhibit strong exposure-response signals, with the majority of TAT_{ANC} and TAT_{ALC} values at the higher exposures being higher than the mean TAT. Additionally, there were notable overlaps in the distributions of model-predicted $C_{max,ss}$, $C_{trough,ss}$, and $AUC_{0-24,ss}$ at 200, 300, and 400 mg for both TAT_{ANC} and TAT_{ALC}.

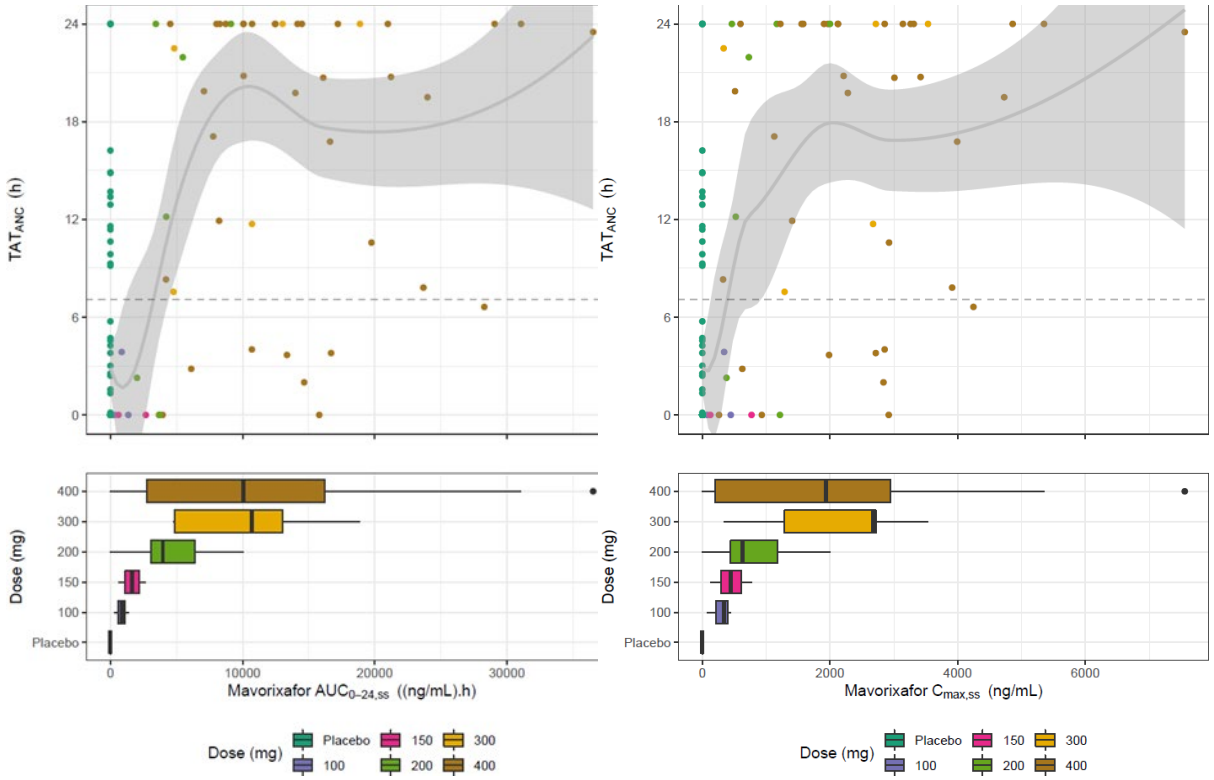
Model-predicted $C_{max,ss}$ and $AUC_{0-24,ss}$ versus TAT_{ANC} are shown in Figure 13, as an example for the relationships cited above:

Additional population PK/PD modelling in adults and adolescents was also conducted as a commitment in the mavorixafor PIP to support dose recommendations for paediatric patients.

Exposure-Safety Relationship

No formal exposure-safety analyses have been undertaken.

Figure 13: Model-predicted $C_{max,ss}$ and $AUC_{0-24,ss}$ Versus TAT_{ANC}



Scatter plots: Each data point (circle) is a date-matched pair of model-predicted exposure metric and observed efficacy endpoint, the solid line indicates fits from a LOESS smoother, the shaded region displays the 95% CI for the smoother, and the dotted horizontal line is the mean time-above-threshold.
Boxplots: The thick horizontal lines (middle of the boxes) represent the median of the data, the hinges (left and right of the boxes) represent the 25th and 75th percentiles, the left and right whiskers extend to the smallest and the largest values that are within 1.5 * IQR of the hinges, respectively. Outlier was indicated (circle). The colors for the scatter plots correspond to the colors of the boxplots.
Note the exposure metrics of 0 represent placebo or patients assigned to active treatment at baseline (i.e., prior to drug administration).

5.2.5. Dose selection and therapeutic window

Dosing Recommendations in adolescent patients

Based on available data, the PK profile of mavorixafor in adolescents >50 kg treated with 400 mg QD doses in the pivotal phase 3 study has been observed to be similar to that of adults treated with 400 mg QD doses.

The pivotal phase 3 study included a dose of 200 mg for adolescents weighing less than or equal to 50 kg. However, only 1 adolescent subject with weight ≤50 kg was enrolled in X4P-001-103 and initiated mavorixafor treatment at 200 mg.

Following additional modelling, the applicant proposed a dose of 300 mg for adult and adolescent patients weighing ≤50 kg in the SmPC section 4.2. This amended dose was further justified as follows:

Adults with Low Body Weight (≤ 50 kg)

The SmPC recommendation for adults with Low Body Weight (≤50 kg) which is different to the dose used in the pivotal 3 study was justified based on exposures simulations as follows:

For the purposes of the Phase 3 study, only adolescent patients weighing ≤50 kg were to receive a lower dose. However, popPK/PD analyses revealed that body weight was the key covariate impacting mavorixafor exposure. As such, the need to also consider a lower dose in adult patients ≤50 kg was investigated. This further analysis revealed that the proposed dose of 400 mg daily in adults with low body weight (i.e., ≤50 kg) is predicted to result in 34% higher median AUC_{0-24}, 20% higher median

Cmax, and 36% higher median Ctrough compared to 400 mg daily in adults with average body weight (i.e., 50 to <85 kg) at Week 13 (Table 21):

Table 21: Summary of Model-Predicted Week 13 Exposure in Adult Patients Following 400 mg Daily Mavorixafor

	AUC_{0-24} (ng*h/mL)			**C_{max} (ng/mL)**			**C_{trough} (ng/mL)**		
STATISTIC	**<50 kg**	**50 kg to <85 kg**	**85 kg and greater**	**<50 kg**	**50 kg to <85 kg**	**85 kg and greater**	**<50 kg**	**50 kg to <85 kg**	**85 kg and greater**
N	215	2277	508	215	2277	508	215	2277	508
Geometric mean	17797	12713	8747	2559	1995	1517	221	149	95
Geo CV%	93%	78%	76%	83%	83%	88%	132%	101%	97%
Median	16300	12200	8545	2507	2094	1633	187	138	89
5^{th} to 95^{th}percentile	6973 to 54460	4608 to 37940	2938 to 25245	851 to 8134	537 to 5819	374 to 4740	77 to 892	47 to 596	28 to 353

Table 22: Summary of Model-Predicted Week 13 Median Exposure in Low Body Weight Adults Compared to Reference

Exposure	**Statistic**	**Reference (400 mg QD in 50 to <85 kg adults)**	**200 mg daily in <50 kg adults**	**300 mg daily in <50 kg adults**	**400 mg daily in <50 kg adults**
Week 13 $_{AUC0-24}$ (ng*h/mL)	Median	12200	56% lower	19% lower	34% higher
Week 13 C_{max} (ng/mL)	Median	2094	53% lower	19% lower	20% higher
Week 13 C_{trough} (ng/mL)	Median	138	60% lower	23% lower	36% higher

Based on amended exposure simulations, 300 mg daily in adults with low body weight is expected to reduce the C_{max} and thereby reduce the safety risk but maintain adequate exposure to give appropriate efficacy. As a result, the dose for adult patients weighing under 50 kg applied in the SmPC Section 4.2 was 300 mg.

Adults and Adolescent patients weighing ≤ 50 kg

Additional analyses showed that the proposed dose of 200 mg daily in adolescents with low body weight is predicted to result in >50% lower median AUC_{0-24}, C_{max}, and C_{trough} compared to 400 mg daily in adolescents with average body weight.

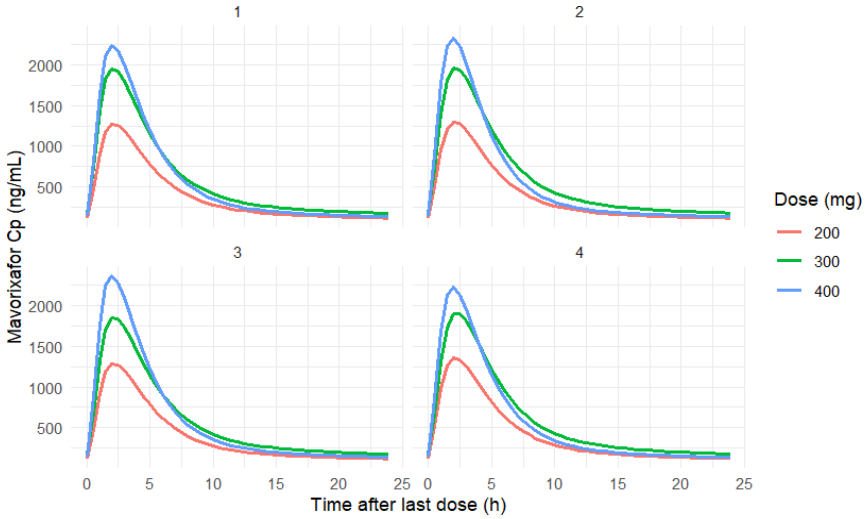
The decrease in exposure may result in lower efficacy compared to adults with average body weight who receive 400 mg daily, and clinical data are insufficient to support efficacy of the originally proposed 200 mg daily dose in adult patients weighing ≤50 kg.

According to the exposure simulations, exposure is slightly lower following 300 mg daily in adolescents with low body weight compared to 400 mg daily in adults with average body weight. However, the exposure is expected to provide similar TAT_{ALC} and TAT_{ANC} responses to adults.

In addition, a further popPK/PD model was developed for mavorixafor in adults and adolescents with WHIM syndrome in an integrated manner based on the data from the clinical efficacy and safety study, Study X4P-001-103, as a commitment in the mavorixafor PIP.

Within this, a population of N=500 patients with WHIM was generated of which 250 patients correspond to adolescents with a body weight ≤50 kg and 250 correspond to adults and adolescents with a body weight greater than 50 kg. For the first group, 2 different doses were used: 200 mg or 300 mg; for the adults and adolescents weighting >50 kg a 400 mg of mavorixafor orally was used. The same 4 occasions (OCC) than those analysed during the clinical study corresponding to the following weeks were used in the analysis: 13 (OCC=1), 26 (OCC=2), 39 (OCC=3) and 52 (OCC=4). The purpose of the simulation was to find the dose in adolescents weighing ≤50 kg that would lead to similar exposure and effect to that of adults with the 400 mg dose. The mean pharmacokinetic profiles are shown in Figure 14:

Figure 14: Simulated Pharmacokinetic Profiles Separated by Occasion (1,2,3 and 4) and Coloured by Administered Dose of Mavorixafor



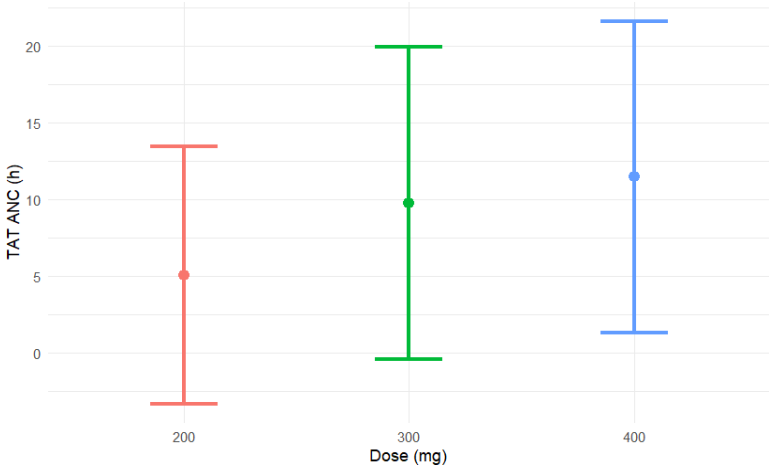
The following PK metrics were determined based on the simulated pharmacokinetic profiles: area under the curve from zero to infinity (AUC) and maximum observed concentration (C_{max}). These results are presented in Table 23:

Table 23: Simulated AUC and C_{max} per Population Group and Mavorixafor Dose (mg)

Dose (mg)	N	Population	AUC (SD), ng.h/mL	C_{max} (SD), ng/mL
200	500	Adolescents ≤50 kg	9569.06 (4193.81)	1445.57 (967.69)
300	500	Adolescents ≤50 kg	14272.85 (6608.24)	2121.05 (1385.22)
400	500	Adults and Adolescents >50 kg	14157.42 (6901.00)	2520.89 (1709.08)

Based on presented simulations, the administration of 300 mg of mavorixafor in the age group of adolescents weighing ≤50 kg led to exposures similar to that of 400 mg in adults. In addition, the model was used to predict the neutrophils counts over time and calculate the TAT_{ANC} in the same population (Figure 15):

Figure 15: Simulated TAT_{ANC} after 400 mg (blue) of Mavorixafor in Adults and Adolescents Weighing >50 kg and 200 mg (red) and 300 mg (green) Dose in Adolescents Weighing ≤50 kg.



The results of the simulation are summarized in Table 24.

Table 24: Comparison of the Simulated TAT_{ANC} in Adults and Adolescents by Weight and Dose of a Single Oral Dose

Dose (mg)	N	Population	TAT_{ANC} (SD), h
200	500	Adolescents ≤50 kg	5.05 (8.37)
300	500	Adolescents ≤50 kg	9.75 (10.18)
400	500	Adults and Adolescents >50 kg	11.48 (10.15)

The applicant concluded that PD simulations also support the recommendation of 300 mg dose of mavorixafor in the adolescents' groups weighting ≤50 kg considering the similar TAT that in adults with the 400 mg dose.

It was emphasised that the PK/PD model offered a powerful means of leveraging the existing data from the Phase 3 trial X4P-001-103 and incorporating weight as a key covariate to generate insights and guide dose decision-making in the entire population based on the weight bands.

According to the simulations carried out with the developed model, the applicant proposed in the SmPC section 4.2 a dose of 300 mg of mavorixafor for the group of adolescents with a body weight ≤50. The administration of 300 mg of mavorixafor in the age group of adolescents (≤50 kg) led to exposures and TAT_{ANC} similar to that of 400 mg in adults. Although not an objective of this study, the applicant concluded that this analysis supported also the choice of the 300 mg dose for adults ≤50 kg according to the effect of body weight as a covariate on the pharmacokinetics of mavorixafor.

5.2.6. Overall discussion and conclusions on clinical pharmacology

5.2.6.1. Discussion

Bioanalytics

All bioanalytical methods used in the clinical studies were validated, suitable for the intended use and they demonstrated reliable in-study performance. The main method for the determination of mavorixafor in human plasma was the LC/MS/MS method BAC-XK-L001 developed and validated by Charles River Laboratories, Inc. This method was linear, selective, sensitive and reliable.

For the Phase 2 dose finding study X4P-001-MKKA and the Phase 3 study X4P-001-103, the ALC, AMC, ANC and WBC were determined by a standard method in a central laboratory. The WBC, ANC, ALC, and AMC counts were performed by flow cytometry using validated and standardised methods. No manual counts were performed. Sample shipment conditions were clearly described. No special circumstances or deviations in the analysis method were noted by the central laboratory.

Pharmacokinetics

General Aspects

Mavorixafor is supplied as oral immediate release 100 mg solid capsules. According to the applicant, the same 100 mg capsule formulation was used across the clinical development programme, which is also the intended commercial formulation. Therefore, it was agreed that no bridging was needed between different formulation during development.

Mavorixafor was concluded to be a BCS Class III drug based on its highly solubility and low permeability.

Five Phase 1 studies in HV were completed with mavorixafor:
Study X4P-001-105 (ADME), Study X4P-001-106 (QT), Study X4P-001-107 (food effect), as well as Study XP-001-108 and Study X4P-001-109 (both DDIs). Two studies in patients with WHIM Syndrome contributed to clinical pharmacology results in patients, Phase 2 study X4P-001-MKKA and the pivotal Phase 3 study X4P-001-103.

Absorption

Pharmacokinetic data from study X4P-001-105 (ADME) in HV showed that mavorixafor is readily absorbed after administration as oral solution, with a median T_{max} value of 1.25 hours.
In subjects with WHIM Syndrome in Phase 2 study X4P-001-MKKA, after doses of 50 mg to 400 mg, median T_{max} values at steady-state ranged between 1.25- and 2.00-hours post-dose.
Dose proportionality was assessed and, based on the geometric means and dose normalized values, Cmax increased approximately proportionally for doses in the range 100 mg to 400 mg QD, but not for 50 mg to 100 mg QD; AUC increased more than proportionally with dose in the range of 50 mg to 400 mg QD. The conclusions on dose proportionality should be interpreted with caution due to the very limited sample size and the high variability of the PK results, especially in the 300 mg dose group.

Mavorixafor is both a substrate and a weak inhibitor of CYP3A4/5 and demonstrated time- and NADPH-dependent CYP3A inhibition *in vitro* which was discussed to potentially contribute to the observed non-

linear increase in total exposure of mavorixafor at steady state. In the pivotal phase III study, notably, Cmax and AUC0-24 at Week 52 (2975.0 ng/mL and 14440 h*ng/mL, respectively) were comparable to the values at Week 13 (3264.1 ng/mL and 13850 h*ng/mL) in patients with WHIM syndrome, indicating that there were no time-dependent changes in PK beyond Week 13. In the PK Population of this study, the mean mavorixafor steady state C_{max} was 3.304 (58.6%) ng/mL and the AUC from 0 to 24 hours (AUC_{0-24h}) was 13970 (58.4%) ng×h/mL following 400 mg once daily.

Following QD dosing in healthy subjects, mavorixafor concentrations reached steady state after approximately 9 to 12 days.

Food effects were investigated in a randomised, phase I, open-label, single-centre, single dose, 6-period, 6-sequence crossover study to assess the pharmacokinetics, safety, and tolerability of mavorixafor in healthy participants under fasted and fed state. Administration of mavorixafor after food (from 0 to 4 hours after food administration), regardless of meal fat content, decreased mavorixafor bioavailability by approximately 40% compared to when mavorixafor was administered after an overnight fast of 10 hours. The exact mechanism of this observation is not known, but the reduced bioavailability could be due to reduced dissolution of mavorixafor at the expected higher gastric pH following feeding. These results supported the recommendation to take mavorixafor on an empty stomach after an overnight fast (SmPC Section 4.2). After overnight fasted, the possibility to eat after the administration of mavorixafor (i.e. low-fat meal 30 minutes post-dose) was also investigated and compared to fasted administration (i.e. fasted 4 hours post-dose). A moderate impact of food administration 30 minutes after dosing was observed. Hence, acknowledging that administration of mavorixafor at least 30 minutes before food would be less burdensome to patients than maintaining the fasted conditions for 2 hours post dose as done in the pivotal study Study X4P-001-103, mavorixafor is recommended to be given at least 30 minutes before food (SmPC Section 4.2).

Distribution

Based on Study X4P-001-105, the mean apparent volume of distribution was 7210 L. For a 60 kg adult, this would correspond to a volume of distribution of 120 L/kg.

Elimination

The results of mass balance study X4P-001-105 indicate that faecal excretion is the major route of elimination, while urinary excretion is the minor elimination pathway. The mean (SD) cumulative recovery over the initial collection period (0-240 h) was 74.2% (3.49), with 13.2% (3.57) being excreted in urine and 61.0% (5.21) in faeces. By 816 h post-dose, mean recovery was 78.6% in total and 64.4% in faeces. No concern was raised. Nevertheless, the CHMP noted that a longer sampling should have been considered to reach the recovery amounts recommended in the Guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2*) "*Preferably total recovery of radioactivity in urine and faeces should exceed 90% of the dose and more than 80% of the recovered radioactivity be identified*".
Terminal half-life was 82 h with an apparent clearance of 62 L/h following single-dose administration of mavorixafor in clinical Study X4P-001-105. Mavorixafor exhibits at least partial nonlinear apparent clearance; however, this is not clinically significant at the approved recommended dosage. Statements in the SmPC in section 5.2 on elimination are based on these results in HV and acceptable to the CHMP.

Metabolism

Results from *in vitro* studies suggest that the primary enzymes responsible for mavorixafor metabolism in humans are CYP3A4 and CYP2D6. Results of non-clinical drug metabolism studies revealed that no unique human metabolites were identified, as all the metabolites identified in humans were also

formed in at least one of the toxicology species. *In vitro* metabolite identification showed formation of 8 metabolites with hydroxylation accounting for the primary metabolites in human, rat, dog and monkey liver microsomes.

In clinical ADME study X4P-001-105, except for the unchanged parent mavorixafor in plasma and faeces, no single, radioactive component accounted for more than 10% of the circulating radioactivity (plasma) or the total administered dose (urine and faeces) and therefore no metabolite identification was performed, which was acceptable to the CHMP.

Special populations

Potential effect of intrinsic factors like hepatic impairment, renal impairment or ethnic factor have not been investigated in dedicated clinical studies. However, a dedicated hepatic impairment (HI) study is ongoing (final report expected in May 2026), and, upon completion, the applicant committed to submit the results of this study for regulatory assessment. As mavorixafor is mainly metabolised by the liver, it is agreed to inform the treating physician that mavorixafor is not recommended for use in patients with moderate to severe hepatic impairment, until results of the HI study are available.

Renal clearance is a minor excretion pathway for mavorixafor. No dose adjustment is recommended in patients with creatinine clearance ≥ 30 mL/min, including in patients with mild to moderate renal impairment. The safety and efficacy of Xolremdi have not been established in patients with severe renal impairment (creatinine clearance 15 to less than 30 mL/min) or end-stage renal disease (creatinine clearance less than 15 mL/min). It is therefore not recommended to administer Xolremdi to patients with severe renal impairment or end-stage renal disease.

Clinical DDI Study X4P-001-109 (study design described in section "Pharmacokinetic interaction studies" below) included a sensitivity analysis for the impact of specific genotypes on the statistical analysis of compounds within the Inje cocktail and transporter cocktail. The Applicant did not identify an impact of possible genetic polymorphism on PK.

In the clinical studies included in this submission, mavorixafor has not been evaluated in older or elderly subjects (maximum age was ≤58 years) or non-Caucasian patients (93.5% of patients in X4P-001-103 and 100% of patients in X4P-001-MKKA were reported to be of white race).

DDIs

DDIs were discussed based on the provided results of *in vitro* non-clinical studies using human biomaterial and *in vivo* clinical DDI studies in healthy volunteers. Potential DDIs with mavorixafor as a victim or perpetrator have been overall adequately investigated.

- Effect of mavorixafor on other medicinal products

The use of mavorixafor with medicinal products highly dependent on CYP2D6 for clearance (e.g. dextromethorphan, codeine, tramadol) is contraindicated. A washout period of approximately 30 days (corresponding to 9 half-lives) should be considered prior to initiating treatment with medicinal products highly dependent on CYP2D6 for clearance. Further, the interactions of mavorixafor with medicinal products dependent on CYP3A4 substrates, P-gp substrates and OCT2/MATE1 substrates are adequately described in the SmPC Section 4.5 including recommendations in case of concomitant administration.

- Effect of other medicinal products on mavorixafor

Concomitant use with strong CYP3A4 inducers is not recommended as it is expected to decrease the concentration of mavorixafor, which may reduce the therapeutic effect. Further, the interactions of mavorixafor with strong or moderate CYP3A4 inhibitors and P-gp inhibitors are adequately described in the SmPC Section 4.5 including recommendations in case of concomitant administration.

Recommendations for dose modifications of mavorixafor in case of concomitant use with strong or moderate CYP3A4 inhibitors and P-gp inhibitors are addressed in SmPC Sections 4.2 and 4.5.

- Food

Since grapefruit is a strong CYP3A4 inhibitor, patients should avoid eating or drinking products with grapefruit, as it may increase the risk of adverse reactions from mavorixafor.

The applicant stated that the contribution of CYP3A4 to mavorixafor metabolism is greater compared to CYP2D6. While this is agreed, CYP2D6-mediated biotransformation cannot be ignored: in one HLM study, mavorixafor metabolism was reduced by quinidine (CYP2D6 inhibitor) by 17.1%, in another HLM study metabolism inhibition by 42.1% in the presence of paroxetine (another CYP2D6 inhibitor) was observed. It was highlighted that the second study (X4P-001-DMPK-004) is more scientifically sound as it included positive and negative controls in contrast to the first study (X4P-001-DMPK-015). Mavorixafor elimination rate was higher with rhCYP2D6 than with rhCYP3A4. The correlation analysis study X4P-001-DMPK-016 had no added value as the correlation is strongly impacted by the inhibitory potential of mavorixafor towards CYP2D6. According to ICH M12, an enzyme contributing ≥25% to total elimination normally needs clinical characterisation as is the case with CYP2D6. As requested, the applicant commited to perform a clinical characterisation of DDI between mavorixafor as a DDI object and a CYP2D6 precipitant PI. The final Clinical Study Report (CSR) is anticipated to be available for assessment by September 2028.

Pharmacodynamics

Pharmacodynamic aspects are closely linked to the Efficacy assessment and in some respects also to Safety assessment (e.g. QT effects) and results of the Phase III clinical study (and partly Phase 2 dose finding study) are discussed as part of the assessment of respective sections below.

Mechanism of action

Mavorixafor is an orally bioavailable CXCR4 antagonist that blocks the binding of the CXCR4 ligand, stromal-derived factor-1α (SDF-1α)/CXC Chemokine Ligand 12 (CXCL12). SDF-1/CXCR4 plays a role in trafficking and homing of leukocytes to and from the bone marrow compartment. Gain of function mutations in the CXCR4 receptor gene that occur in patients with WHIM syndrome lead to increased responsiveness to CXCL12 and retention of leukocytes in the bone marrow. Mavorixafor inhibits the response to CXCL12 in both wild type and mutated CXCR4 variants associated with WHIM syndrome.

The mechanism of action has been mainly investigated in non-clinical studies. Increased mobilisation of neutrophils and lymphocytes and monocytes from the bone marrow into peripheral circulation has been seen in clinical trials.

Primary pharmacology

The PD of mavorixafor in patients with WHIM syndrome was evaluated in clinical Phase 2 study X4P-001-MKKA over the dose range 50 to 400 mg PO QD and Clinical Phase 3 study X4P-001-103.
Doses at 300/400 mg were needed to achieve sustained increases in ANC ≥600 cells/μL and ALC ≥1000 cells/μL. At lower doses, AUC_{ANC} was below the threshold adjusted level at all visits.
For ALC, a dose of 100 mg was sufficient to induce levels above the 1000 cells/μL threshold by approximately 2 to 4 hours post-dose. However, at doses below 300 mg, ALC levels rapidly fell back below the threshold, while ALC levels were maintained longer for 300 mg and 400 mg. For AMC, a 200 mg dose was sufficient to induce transient elevations. The 300 and 400 mg dose resulted in sustained elevations, until 24 hours post-dose.

The design of the Phase 3 study is illustrated and discussed in the "Efficacy" section below where also the results on PD parameters are discussed in detail. Dose finding is summarised in the Exposure-response subsection further below.

Secondary pharmacology

Clinical Study X4P-001-106 was a Phase 1, Single Centre, Two-part, Randomized, Partially-blind, Placebo and Moxifloxacin-controlled, Three-period Crossover Thorough QT (TQT) Study to Evaluate the Effect of Mavorixafor on 12-lead Electrocardiogram Parameters in Healthy Adult Subjects, following a Single Ascending Dose Study to Assess the Safety and Tolerability of Mavorixafor at Supratherapeutic Doses. Following single dose administration of mavorixafor 800 mg, peak plasma concentrations occurred with median Tmax of 2.07 hours and were quantifiable up to 72 hours post-dose in all participants. In this TQT study, the maximum mean increase in the QTc interval was 15.6 ms (upper bound of the 90% confidence interval = 19.8 ms) after administration of Xolremdi 800 mg (2 times the maximum recommended dose) in healthy volunteers. Results of this study are included in SmPC Section 5.1. Precautions for use of mavorixafor in patients with risk factors for QTc prolongation and/or when used concomitantly with medicinal products with a known potential to prolong the QTc interval are included in SmPCs Section 4.4 and 4.5 and recommendations for dose modification including reduction or discontinuation of mavorixafor in SmPC Section 4.2.

Population PKPD analysis

A popPK/PD model was developed for mavorixafor in adults and adolescents with WHIM syndrome based on data from the clinical efficacy and safety study X4P-001-103. The methods used for model development and evaluation were acceptable to the CHMP. In the covariate analysis, the only significant covariate was body weight on mavorixafor clearance. After accounting for body weight, no further differences were found between adults and adolescents.

The final model was shown to adequately describe the PK and PD of mavorixafor after repeated oral administration. Model parameters were estimated with good precision. The GOF plots did not reveal any model misspecification and the pcVPCs showed that the model was able to predict the central trend and variability of the observed PK and PD (neutrophils and lymphocytes) data. Overall, there were no notable issues with this analysis and the population PKPD model was deemed fit for performing dosing simulations of mavorixafor.
Simulations based on the final PKPD model indicated that a 300 mg dose of mavorixafor in adolescents weighing ≤50 kg results in exposures and time above threshold ANC comparable to adults and adolescents >50 kg receiving 400 mg. Dose justification is further discussed below.

Exposure-response analyses following treatment with mavorixafor

Exposure-response was evaluated in patients with WHIM syndrome in X4P-001-MKKA. No formal exposure-safety analyses have been undertaken. The exposure-response analysis dataset comprised 151 values each of TAT_{ANC} and TAT_{ALC} from 19 patients who received mavorixafor (X4P-001-MKKA: 5 patients, X4P-001-103: 14 patients) and 17 who received placebo in X4P-001-103. All values of TAT_{ALC} and TAT_{ANC} were paired with the corresponding model-derived exposure metrics by date. The relationship between model-predicted exposure and dose were stated to be consistent with expectations from the graphical analysis and population PK model, which observed and accommodated nonlinearity in the PK. It was highlighted that over half of the exposures were derived from the 400 mg dose. For all assessed relationships, TAT_{ANC} and TAT_{ALC} were consistently longer at higher levels of exposure of mavorixafor. Moreover, for both TAT_{ANC} and TAT_{ALC}, all exposure metrics appeared to exhibit strong exposure-response signals, with the majority of TAT_{ANC} and TAT_{ALC} values at the higher exposures being higher than the mean TAT. Additionally, there were notable overlaps in the

distributions of model-predicted $C_{max,ss}$, $C_{trough,ss}$, and $AUC_{0-24,ss}$ at 200, 300, and 400 mg for both TAT_{ANC} and TAT_{ALC}.

Dose justification

Based on the results of study X4P-001-MKKA and population PK simulations, the 400 mg QD dose was chosen for further evaluation in pivotal phase 3 study X4P-001-103, for all adults and adolescents weighing > 50 kg. In this study, no clear trends for systematic differences at the Week 13, 26, 39, and 52 visits between patients above or below 18 years of age could be seen for the 400 mg QD dose, as at some time points, the AUC0-24 was higher in subjects ≥ 18 years and at others, in subjects below 18 years. The small groups (especially at later time points) and the high variability (see geometric %CV) need to be acknowledged.

In the pivotal study X4P-001-103, a dose of 200 mg was foreseen for adolescents weighing ≤50 kg. Notably, nearly all patients were treated with mavorixafor 400 mg QD and only 2 patients received a dose of 200 mg (only one received an initial dose of 200 mg based on weight ≤50 kg, the other patient had a dose reduction to 200 mg). It was agreed with the applicant that the effect of low weight on mavorixafor PK cannot be adequately evaluated based on only 1 adolescent subject with weight ≤50 kg that was enrolled in the pivotal study and initiated mavorixafor treatment at 200 mg.

Exposure simulations were performed and indicated that the administration of 300 mg of mavorixafor in the age group of adolescents weighing ≤50 kg led to exposures similar to that of 400 mg in adults. Simulated TAT_{ANC} was also similar to that of 400 mg in adults.

Further, PopPK/PD analyses revealed that body weight was the key covariate impacting mavorixafor exposure. Hence, a lower dose in adult patients ≤50 kg was investigated and indicated that the proposed dose of 400 mg daily in adults with low body weight (i.e., ≤50 kg) is predicted to result in 34% higher median AUC_{0-24}, 20% higher median Cmax, and 36% higher median Ctrough compared to 400 mg daily in adults with average body weight (i.e., 50 to <85 kg) at Week 13. Based on amended exposure simulations, 300 mg daily in adults with low body weight (≤50 kg) is expected to reduce the Cmax and thereby reduce the safety risk but maintain adequate exposure to give appropriate efficacy.

Therefore, the CHMP agreed with the proposed posology based on patient weight i.e. 400 mg once daily for patients weighing more than 50 kg and of 300 mg once daily for patients weighing less than or equal to 50 kg.

5.2.6.2. Conclusions

Pharmacokinetic and pharmacodynamic properties of mavorixafor have been overall adequately described.

Since mavorixafor causes concentration-dependent QTc prolongation, adequate precautions for use of mavorixafor in patients with risk factors for QTc prolongation and/or when used concomitantly with medicinal products with a known potential to prolong the QTc interval are implemented in the SmPC.

Mavorixafor is primarily metabolised by CYP3A4 and, to a lesser extent, CYP2D6.
Information on medicinal products interacting with mavorixafor are implemented in SmPC Sections 4.2, 4.3 and 4.5 and include the contraindication for the use of mavorixafor with medicinal products highly dependent on CYP2D6 for clearance.

The CHMP agreed that the available data support the following posology of mavorixafor for the treatment of patients with WHIM syndrome:

- 400 mg once daily for patients weighing more than 50 kg.
- 300 mg once daily for patients weighing less than or equal to 50 kg.

Mavorixafor should be taken orally once daily on an empty stomach after an overnight fast, and at least 30 minutes before food.

The following post-authorisation measures (RECs) are considered necessary to address remaining issues related to pharmacology:

- Perform a clinical characterisation of drug drug interaction (DDI) between mavorixafor as a DDI object and a CYP2D6 precipitant PI and provide the final Clinical Study Report (CSR) once available.
- Conduct and submit the data from a dedicated hepatic impairment study once available.

5.3. *Clinical efficacy*

5.3.1. Dose response study

Completed uncontrolled phase II study X4P-001-MKKA is an open-label, dose-escalation study with a 24-week treatment period and an extension phase in patients older than the age of 18 with WHIM syndrome.

For more detailed information, see sections 5.2.5. and 5.3.5.

5.3.2. Main study X4P-001-103

5.3.2.1. Study title

A phase 3, randomized, double-blind, placebo-controlled, multicenter study of mavorixafor in participants with whim syndrome with open-label extension

5.3.2.2. Study design

The phase 3 study X4P-001-103 is a multicentre, 1:1 randomised, double-blind, placebo-controlled, two period trial comparing mavorixafor monotherapy to placebo in patients ≥ 12 years of age with genetically confirmed WHIM-syndrome with efficacy as a primary objective.

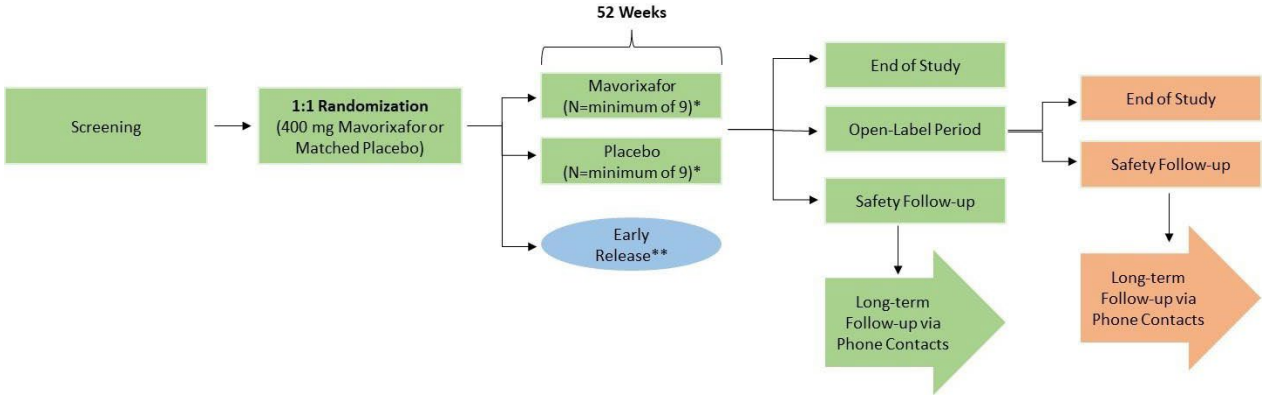
The primary endpoint was the duration of an absolute neutrophil count above a threshold of ≥500 cells/µL over 24 hours (TAT_{ANC} in hours), assessed four times during the study (every 13 weeks for one year).

Key secondary endpoints in order of the predefined statistical testing hierarchy were:

- the duration of an absolute lymphocyte count above a threshold of ≥1000 cells/µL in the peripheral blood over 24 hours, assessed four times throughout the study
- a composite clinical efficacy endpoint based on total infection score and total wart change score
- total wart change score based on blinded independent review
- total infection score assessed by a blinded, independent adjudication committee.

Stratification was done by the use of immunoglobulin-therapy in the previous 5 months (y/n).

Figure 16: Design of study X4P-001-103



Treatment

Mavorixafor was administered orally at 400 mg QD for all adults and adolescents > 50 kg, and 200 mg qd for adolescents with a body weight ≤50 kg.

Randomisation

Randomisation was performed with a IXRS system at a 1:1 allocation to mavorixafor or placebo and stratified by treatment of any immunoglobulin treatment within five months prior to the signing of the informed consent form (yes/no) with a cap at 30% for patients with immunoglobulin substitution. In a subsequent amendment, the cap was removed.

Blinding

The sponsor, the study team and the investigator were blinded to the treatment allocation, laboratory assessments and PK data from randomisation on. Breaking the blind should only occur in exceptional circumstances on the investigator's discretion. This could be medical necessities to manage severe AE appropriately. Prompt communication with the medical monitor and avoidance of disclosing treatment assignment to site personnel and the sponsor is requested in that case. Once the blind is broken, the patients may not continue the randomised treatment but may roll over to the open- label – period.

Patient population

Key inclusion criteria:

Patients with the clinical diagnosis of WHIM syndrome must have met all the following key eligibility criteria:

1) Were at least 12 years of age
2) Had a genotype-confirmed mutation of *CXCR4* consistent with WHIM phenotype 4

   Note: Genotyping was performed centrally by Sanger sequencing, either as a primary test for patient selection or as a confirmation test for a local test from a (CLIA- certified) laboratory.
3) Had a confirmed ANC ≤ 400 cells/µL during screening, obtained while participant had no clinical evidence of infection. Local laboratory could be used if the central laboratory was not available.
   a) If the ANC was below the lower limit of detection for the laboratory and the total WBC count was ≤ 400 cells/µL, the participant was considered eligible for the study.

b) If the ANC was > 400 cells/µL in the context of a recent infection or inflammation prior to screening, it was acceptable to redraw a blood sample and confirm that the ANC meets inclusion criteria (≤ 400 cells/µL) once the infection or inflammatory episode was resolved.

c) If the participant experienced an infection or inflammatory episode between screening and baseline that may have impacted the ANC, or received G-CSF between screening and baseline, the baseline visit could be postponed for up to 4 weeks until the ANC was confirmed to be ≤ 400 cells/µL.

4) Agreed to use a highly effective form of contraception.

Inclusion criteria for the open label period:

1. Completion of the RCP
2. Granted Early Release from the RCP
3. Blind broken in exceptional circumstances

Key exclusion criteria:

Patients with any of the following were excluded from participation:

1. Had, at screening, safety laboratory tests that met one or more of the following criteria:
    a. Haemoglobin < 8.0 g/dL
    b. Platelets < 75,000 cells/µL
    c. Estimated glomerular filtration rate based on the Modification of Diet in Renal Disease of ≤ 29 mL/min/1.73 m2 (Stage 4 or 5 chronic kidney disease)
    d. Serum aspartate aminotransferase (AST) > 2.5 × upper limit of normal (ULN) − serum alanine aminotransferase (ALT) > 2.5 × ULN
    e. 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)
2. Had, at screening, laboratory tests meeting 1 or more of the following criteria:
    a. A positive hepatitis C virus antibody with confirmation by hepatitis C virus ribonucleic acid polymerase chain reaction reflex testing.
    b. A positive hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb).

If a participant tested negative for HBsAg but positive for HBcAb, the participant was considered eligible if the participant tested positive for hepatitis B surface antibody (also referred to as anti-HBsAg) on reflex testing.

3. Had a known history of positive serology or viral load for human immunodeficiency virus (HIV) or a known history of Acquired Immunodeficiency Syndrome (AIDS).
4. Received any of the following treatments:
    a. Plerixafor within 6 months prior to day 1 of treatment.
    b. Chronic or prophylactic use of antibiotics (systemic or inhaled) within 4 weeks prior to day 1.
    c. Chronic or prophylactic use of G-CSF or granulocyte-macrophage colony stimulating factor within 2 weeks of day 1.

d. Chronic or prophylactic use of systemic glucocorticoid (> 5 mg prednisone equivalent per day) within 2 weeks prior to day 1.

e. Any investigational therapy within 5 half-lives or 2 weeks prior to day 1, whichever is longer. Prior use of any investigational therapies must be discussed with the Medical Monitor.

f. Was taking or had, within 2 weeks prior to Day 1, received any medication that was prohibited based on potential for drug-drug interactions.

5. Had corrected QT interval using Fridericia's formula of > 450 ms.
6. Had, at the planned initiation of study drug, a clinically diagnosed active infection (excluding warts) that had the potential to raise the ANC counts.
7. Had a total splenectomy within 1 year.
8. Had a medical history of hematological malignancies.
9. Had surgery requiring general anesthesia within the 4 weeks prior to Day 1.
10. Had any other medical or personal condition that, in the opinion of the Investigator, potentially compromised the safety or compliance of the participant or may have precluded the participant's successful completion of the clinical study.
11. Was pregnant or breastfeeding.
12. Had known systemic hypersensitivity to the mavorixafor drug substance, its inactive ingredients, or the placebo.

5.3.2.3. Objectives and estimands

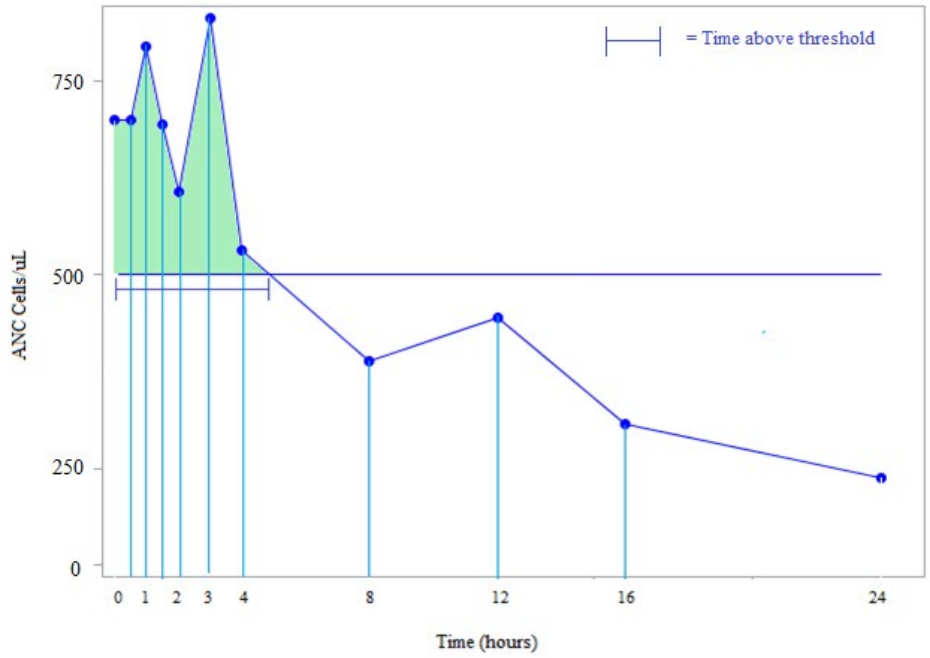
Primary objective

The primary objective of the randomised period was the time (in hours) above the ANC threshold of 500 cells/µl over a 24-hour period, assessed four times through the study (every three months).

For the primary endpoint, the difference between mavorixafor and placebo with respect to mean TAT_{ANC} threshold using mixed-model repeated measures (MMRM) analysis in the ITT population. For the primary analysis, TAT was calculated using a linear interpolation.

Eleven sequential peripheral blood samples were collected at pre-determined time points: pre-dose and 30 min, 60 min, 90 min, 2, 3, 4, 8, 12, 16 and 24 h post-dose at five time points in the study for in-residency evaluation: at baseline (day -1 to day 1), week 13, 26, 39 and week 52 (all ± 14 days) to determine a time – neutrophil count relationship and calculate the TAT_{ANC} subsequently (Figure 17).

Figure 17: Calculation of time above threshold for a hypothetical set of ANC Data



Clinical justification for the chosen threshold provided by the applicant:

Neutrophils normally comprise the majority of the circulating white blood cells and are critical in providing antimicrobial activity against bacteria and fungi. Neutropenia is a decrease in the number of circulating neutrophils in peripheral blood and generally refers to absolute neutrophil count (ANC) <1,500/mm3. The ANC in peripheral blood defines the presence and severity of neutropenia. An abnormally low ANC is <1,500/µL in children above 12 months of age and in adults, and <1,000/µL in younger children (Vlacha 2007). Fewer than 1,000 cells/µL is considered moderate neutropenia (Common Terminology Criteria for Adverse Events [CTCAE] Grade 3), and <500 cells/µL is severe neutropenia (CTCAE Grade 4) (CTCAE v5.0, 2017) (Table 25). Severe neutropenia is considered a well-established threshold for high risk of infection and therefore of high clinical significance (Cadavid 2021[47]). An inverse quantitative relationship between neutropenia and infection was first firmly established more than five decades ago in patients following acute leukaemia (Bodey 1966[48]) and is widely accepted today.

Table 25: Neutropenia Severity Grade: Excerpt from CTCAE – Investigations

CTCAE Term (Severity)	Grade 0	Grade 1	Grade 2 (Mild)	Grade 3 (Moderate)	Grade 4 (Severe)
Neutrophil count decreased	≥2000/µL	<2,000-1,500/µL	<1,500-1000/µL	<1,000-500/µL	<500/µL

Nearly all patients with WHIM syndrome suffer from severe chronic neutropenia (ANC <500/µL) and the majority also suffer from severe chronic lymphopenia (absolute lymphocyte count [ALC] <500/µL) and monocytopenia (<300/µL). Neutropenia and lymphopenia are believed to be the major contributors to the susceptibility to infections (Dale 2019[49]). Their pancytopenia puts patients with

[47] Cadavid D. TAT ANC as Surrogate of Clinical Benefit in WHIM Syndrome [White paper]. 2021; X4 Pharmaceuticals Inc.
[48] Bodey G, Buckley M, Sathe YS and Freireich EJ. Quantitative Relationships between Circulating Leukocytes and Infection in Patients with Acute Leukemia. Annals of Internal Medicine. 1966; 64:328-40.
[49] Dale D, Dick E, Kelley M, Makaryan V, Connelly J, Bolyard AA et al. Family studies of warts, hypogammaglobulinemia, immunodeficiency, myelokathexis syndrome Curr Opin Hematol. 2019, 26:000 000.

WHIM syndrome at risk of recurrent and/or severe infections including upper and lower respiratory (otitis, pneumonia) infections, cellulitis, and warts that could lead to malignancy (Dotta 2019[50]). The risk of infection in patients with cancer affected by neutropenia is substantially linked to the duration of severe neutropenia (Bodey 1966[48], Hsieh 2007[51]). The longer the duration, the higher the risk of infection. In the Bodey study in patients with leukaemia and very severe neutropenia (ANC <100/µL), active infections were present on 53% of the days studied (Bodey 1966[48]). The percentage of time suffering from active infections decreased sharply with increasing neutrophil levels, and the plateau was reached at ANC levels above l,000/µL (Cadavid 2021[47]). Another important development linking neutropenia to risk of infection came from studies of patients receiving chemotherapy that causes acute neutropenia (CDC 2022[52]). Equally relevant is the demonstration that the risk of infection in chemotherapy induced neutropenia is significantly reduced by treatments that reduce the duration of severe neutropenia, such as injection with the hematopoietic growth factors G-CSF or granulocyte-macrophage colony-stimulating factor (GM-CSF). NEUPOGEN (filgrastim G-CSF) injection, for subcutaneous or intravenous use, received initial United States (US) approval in 1991 to decrease the incidence of infection, as manifested by febrile neutropenia in patients with non-myeloid malignancies receiving myelosuppressive anticancer drugs associated with a significant incidence of severe febrile neutropenia (Neupogen USPI 2015).

The risk of infection in patients with cancer affected by neutropenia is substantially linked to the duration of severe neutropenia (Bodey 1966[48], Hsieh 2007[51]). The longer the duration, the higher the risk of infection. In the Bodey study in patients with leukaemia and very severe neutropenia (ANC <100/µL), active infections were present on 53% of the days studied (Bodey 1966[48]). The percentage of time suffering from active infections decreased sharply with increasing neutrophil levels, and the plateau was reached at ANC levels above l,000/µL (Cadavid 2021[47]). Another important development linking neutropenia to risk of infection came from studies of patients receiving chemotherapy that causes acute neutropenia (CDC 2022[52]). In patients with WHIM syndrome, in addition to achieving clinically meaningful thresholds of neutrophil and lymphocyte counts in peripheral blood (ANC and ALC, respectively), the length of time that these cells remain above the thresholds is also meaningful. The Time Above Threshold (TAT) for ANC and ALC (TATANC and TATALC, respectively) measure durability and consistency of increased cell counts to the clinically meaningful threshold, over a 24-hour period, and negatively correlate with infection risk and burden of infection (Dale 2020[49]). Mavorixafor has been shown to elevate both the peripheral blood count (ANC and ALC) and time in circulation (TAT_{ANC} and TAT_{ALC}) of neutrophils and lymphocytes in patients with WHIM syndrome. Consistent with these blood leukocyte elevations, mavorixafor has been shown to decrease the frequency, severity, and duration of infections, as well as reduce antibiotic use in patients with WHIM syndrome.

[50] Dotta L, Notarangelo LD, Moratto D, Kumar R, Porta F, Soresina A, et al. Long term outcome of WHIM syndrome in 18 patients: high risk of lung disease and HPV related malignancies. J Allergy Clin Immunol Pract. 2019; 7(5):1568 77. doi: 10.1016/j.jaip.2019.01.045.

[51] Hsieh M, Everhart JE, Byrd Holt DD, Tisdale JF, and Rodgers GP. Prevalence of Neutropenia in the U.S. Population: Age, Sex, Smoking Status, and Ethnic Differences. Ann Intern Med. 2007; 146(7):486 92. doi:10.7326/0003 4819 146 7 200704030 00004.

[52] Centers for Disease Control and Prevention. Neutropenia and Risk for Infection, 2022. Available At: Https://Www.Cdc.Gov/Cancer/Preventinfections/Neutropenia.Htm. Accessed 02 June 2023.

Estimands for the primary and secondary objective

Table 26: Estimands for primary objective

Primary Estimand	
Population	Adult and adolescent patients 12 years of age and older with WHIM syndrome (warts, hypogammaglobulinemia, infections and myelokathexis) through inclusion and exclusion criteria as stated in the protocol.
Treatment condition<s>	Assignment to investigational interventions, mavorixafor or placebo, regardless of treatment discontinuation and/or use of prohibited/rescue medications/therapies.
Endpoint (variable)	Time above threshold-absolute neutrophil count (TAT-ANC; in hours) of ≥500 cells/µL over a 24-hour period, assessed 4 times (every 3 months for 12 months) during the 52 weeks of randomised controlled period.
Population-level summary	Difference between mavorixafor and placebo with respect to the mean time above threshold of ANC (TAT_{ANC}).
Intercurrent events (ICE) and strategy to handle them	
ICEs: Treatment discontinuation and prohibited/rescue medication/therapies	The ICEs of treatment discontinuation and use of prohibited/rescue medication/therapies will be handled by treatment policy strategy, where all observed data will be used regardless of the occurrence of the ICEs

Table 27: Estimands for secondary objective

Key Secondary Estimands	
Population	Same as primary estimand.
Treatment condition<s>	Same as primary estimand.
Endpoint (variable)	Key secondary endpoints are: 1) Time above threshold-absolute lymphocyte count (TAT_{ALC}) of ≥1000 cells/µL over a 24-hour period. 2) Composite Clinical Efficacy Endpoint for mavorixafor, based on total infection score and total wart change score. 3) Total wart change score for mavorixafor, based on central, blinded, independent review of 3 target skin regions 4) Total infection score for mavorixafor based on number and severity of infections adjudicated by a blinded, independent Adjudication Committee (AC).
Population-level summary	For the four endpoints above, respectively: 1) Difference between mavorixafor and placebo with respect to the mean TATALC. 2) Difference between mavorixafor and placebo with respect to the mean composite rank from total infection score and total wart change score. 3) Difference between mavorixafor and placebo with respect to the mean total wart change score. 4) Difference between mavorixafor and placebo with respect to the mean total infection score.
Intercurrent events (ICE) and strategy to handle them	

Key Secondary Estimands	
ICEs: Treatment discontinuation and prohibited/rescue medication/therapies	Same as primary estimand.

Statistical methods for estimation and sensitivity analysis on primary estimands

The ITT Population (all randomized patients analyzed as randomised) was the primary population for the analyses of efficacy endpoints.
The primary endpoint analysis compared the difference between mavorixafor and placebo with respect to the mean time above ANC threshold averaged across all post baseline visit (overall effect) using a MMRM analysis in the ITT Population. TAT was calculated using a linear interpolation. For assessments where the ANC value crosses the threshold multiple times, the time above threshold was the sum of each occurrence.

The MMRM accounted for treatment, visit (Weeks 13, 26, 39 and 52), treatment*visit, Ig use (randomisation strata), and baseline time above threshold as covariates; and participant as the repeated random effect. The unstructured covariance matrix will be used to estimate model within-subject errors. The overall adjusted estimated mean difference between treatments (effect across all visits) will be calculated and the basis for inferential decision making.

For each visit, missing time points within dense sampling were handled using linear interpolation based on available values. Evaluation started at the fist available value and if the ANC at the 24-hour time point was missing, the time 0 value was used to impute the missing value.

Sensitivity analyses

- Jump to reference Multiple imputation (J2R MI) approach.
- A tipping point analysis using delta adjustment
- MMRM analysis using the PP Population and Completer's Population.
- MMRM on ITT population while setting the ANC assessment of a visit to missing, if there are more than 50% (6 or more) timepoints with data missing consecutively. If the ANC at the 0-hour time point is missing, the value of ANC from the safety hematology assessment collected at the same time will be used.
- A supportive analysis of time above threshold will be performed using an interval method for calculation, as opposed to linear interpolation.

Key secondary objectives

Table 28 presents the hierarchically ordered, alpha-error controlled key secondary endpoints following protocol version 3.1. The primary and key secondary endpoints were hierarchically tested at the 2-sided alpha level of 0.05 in the intent-to-treat population.

Table 28: Key secondary endpoints - defined by statistical analysis plan

Randomised controlled period	
Objectives	**Key secondary endpoints in the order of testing**
To demonstrate the efficacy of mavorixafor in patients with WHIM syndrome as assessed by increasing levels of circulating lymphocytes compared with placebo and relative to a clinically meaningful threshold.	1. Time above threshold-absolute lymphocyte count (TAT-ALC) of ≥ 1000 cells/μL over a 24-hour period assessed 4 times throughout the study (every 3 months for 12 months) in the ITT Population.
To demonstrate the clinical efficacy of mavorixafor in patients with WHIM syndrome as assessed by a composite endpoint of infections and warts.	2. Composite Clinical Efficacy Endpoint for mavorixafor based on total infection score and total wart change score in the ITT Population.
To demonstrate the efficacy of mavorixafor in patients with WHIM syndrome as assessed by improvement in warts.	3. Total wart change score for mavorixafor based on central blinded, independent review of 3 target skin regions in the ITT Population.
To demonstrate the efficacy of mavorixafor in patients with WHIM syndrome as assessed by reduction in infections.	4. Total infection score for mavorixafor based on number and severity of infections adjudicated by a blinded, independent Adjudication Committee (AC) in the ITT Population.

- to 1.: TAT_{ALC} was assessed in the same manner as $TAT_{ANC.}$ At baseline and every three months in the RCP samples of peripheral blood were obtained during an in-residency evaluation at eleven predefined timepoint of a 24h period.
- to 2: A composite clinical endpoint was chosen to improve the power of the test, based on an analysis of covariance (ANCOVA) of the rank sum of the total wart change score and total infection (both see below) score for each patient
- to 3.: local dermatologist selected three target regions in each patient for a central blinded, independent dermatological review to assess two scores, Clinical Global Impression of severity (CGI-S) and Clinical Global Impression of Change (CGI-C). The assessment of the severity of findings was performed by CGI-S score on a five-tier scale (1=no warts; 2=mild; 3=moderate; 4=severe; 5=very severe). The global change from screening to post-baseline visits of the target warts areas 1-3 is rated by CGI-C score on a revised four-point scale (-2=remission; -1=improved; 0=no change; 1=worsened). To calculate the total wart change score, the CGI-C of all 3 target regions were added, the total wart change score had to be between a minimum of –6/ and maximum of 3. The result was analysed using MMRM model.

Table 29: Total Wart Change Score Example

Examples	Regional Wart Change Score	Total Wart Change Score
Participant 1	Region 1: -1 Region 2: -1 Region 3: 0	-2
Participant 2	Region 1: -1 Region 2: -1 Region 3: 1	-1

- To 4: total infection score was calculated as the annualised infection rate weighted by event severity based on a adjudicated infection event data, summing up the number of infection events by severity and dividing by the total exposure time (in years; see Table 30 , Table 31).

Table 30: Weight of infection severity

Infection Severity Level	Weight
0 – no therapy	1
1 - OTC drugs	2
2- prescription medication	3
3 -i.v. medication	4
4- hospitalisation	5

Table 31: Total Infection Score - Calculation example

Examples	Exposure	Events and Severity	Total Infection Score
Participant 1	1.0 year	2 events with severity level 1, and 2 events with severity level 3	[(2*2) + (2*4)]/1 = 12
Participant 2	0.5 year	2 events with severity level 1, and 2 events with severity level 3	[(2*2) + (2*4)]/0.5 = 24

Estimands for the key secondary objectives

No estimand was specified in study protocol or SAP.

Statistical methods for estimation and sensitivity analysis on the secondary estimands

The first key secondary endpoint TAT_{ALC} is analysed like the primary endpoint.

The second key secondary composite clinical endpoint consisted of two individual components: total infection score and total wart change score. Total infection score over 52 weeks was calculated as the annualized event rate weighted by event severity based on the adjudicated infection event data. The weight for event severity was from 1 to 5, corresponding to the protocol-defined severity Level 0 to

Level 4, since 0 could not be used in the calculation. The total infection score was calculated by summing the number of infection events by severity and dividing by the total exposure time (in years). The effect of treatment on warts was assessed based on changes in warts at the 3 regions of interest (target regions, or lesions) assessed locally and again by blinded, independent, central review. The total wart change score was calculated using the central reviewed CGI-C at Week 52 for the 3 target regions (-2 (remission), -1 (improved), 0 (no change), 1 (worsened)). The total wart change score was calculated by summing the Regional Wart Change Scores from all 3 target regions (lesions).

The two-component composite score for each patient was calculated by summing up the ranks of the two individual components (total infection score and Week 52 total wart change score). The baseline rank sum was calculated as the sum of the ranks for infection history and baseline warts for each patient.

The comparison between mavorixafor and placebo was performed based on analysis of covariance (ANCOVA) of the rank sum with treatment group and prior Ig use as factors and covariates of the baseline rank sum, age, and gender.

The total infection score (see above) was analyzed using an ANCOVA model. Independent variables included treatment and prior Ig use (randomization strata). Infection rate of previous 12 months prior to first dosing, age, and gender were included as covariates.

The total wart change score (see above). The total wart change score was analyzed using MMRM model with factors of treatment, visit, treatment*visit, Ig use (randomization strata), and baseline CGI-S (sum in the 3 target areas), age, and gender as covariates. The missing total wart change score was imputed with the multiple imputation method (under missing at random assumption) using the SAS PROC MI procedure. Sensitivity analysis where the missing total wart change score was imputed with 0 was performed.

Post hoc Win Ratio analysis for composite score: The Win ratio analysis was a post-hoc analysis recommended by FDA to analyse the composite endpoint of warts and infections. Since frequent infection is the most significant clinical manifestation in patients with WHIM syndrome compared with warts (Geier 2022[53], Dotta 2019[54], Heusinkveld 2019[55], Kawai 2009[56]), the WIN ratio analysis was performed prioritizing total infection score first and total wart change score second.

a. Win Ratio Categories (Infection score first, then wart score)

b. Active had lower total infection score (winner)

c. Placebo had lower total infection score (loser)

d. Active had lower total warts change score (winner)

e. Placebo had lower total warts change score (loser)

f. None of the above

The assumption is that categories (a) and (b) take priority over (c) and (d).

Multiplicity is controlled across primary and key secondary endpoints by specification of a single

[53] Geier CB, Ellison M, Cruz R, Pawar S, Leiss-Piller A, Zmajkovicoa K, et al. Disease progression of WHIM syndrome in an international cohort of 66 pediatric and adult patients. J Clin Immunol. 2022; 42(8):1748-65.
[54] Dotta L, Notarangelo LD, Moratto D, Kumar R, Porta F, Soresina A, et al. Long term outcome of WHIM syndrome in 18 patients: high risk of lung disease and HPV related malignancies. J Allergy Clin Immunol Pract. 2019;7(5):1568 77. doi: 10.1016/j.jaip.2019.01.045.
[55] Heusinkveld LE, Majumdar S, Gao JL, McDermott DH, Murphy PM. WHIM Syndrome: from Pathogenesis Towards Personalized Medicine and Cure. J Clin Immunol. 2019; 39(6):532-556.
[56] Kawai T and Malech HL. WHIM syndrome: congenital immune deficiency disease. Curr Opin Hematol. 2009; 16(1):20 6.

primary endpoint and use of a hierarchical approach to the analysis of the key secondary endpoints. Each endpoint will be hierarchically tested at the 2-sided alpha level of 0.05, in the order below:

1. TAT ALC (≥1000 cells/μL) over 52 weeks
2. Composite endpoint based on total infection score and total wart change score
3. Total wart change score based on central review of 3 target regions
4. Total infection score based on infections adjudicated by a blinded, independent AC

Other secondary objectives

Randomized controlled period:

Other secondary objectives:

- To demonstrate the efficacy of mavorixafor in patients with WHIM syndrome including as assessed by patient reported outcomes.
- To evaluate the safety and tolerability of mavorixafor in patients with WHIM syndrome
- To evaluate PK of mavorixafor in patients with WHIM syndrome.

Other secondary endpoints:

- Time to Early Release as confirmed by blinded independent AC in the ITT Population
- TAT-ALC of ≥ 1000 cells/μL in patients with lymphopenia at baseline.
- Composite endpoint based on total infection score and total wart change score for patients with warts at baseline or patients with non-Ig use
- Total infection score based on infections adjudicated by a blinded, independent AC for patients with non-Ig use.
- Total wart change score (Clinical Global Impression of Change [CGI-C]) based on blinded central review of 3 target skin regions for patients with warts at baseline.
- Total wart change score (CGI-C) based on local dermatologist review of all regions for patients with warts at baseline.
- Patient Global Impression of Change (PGI- C) from baseline.
- Patient Global Impression of Severity (PGI- S) during treatment.
- Vaccine titer levels at Week 52 in the Randomized Placebo-Controlled Period in all patients vaccinated at Week 13 with tetanus, diphtheria, and pertussis (Tdap), including pertussis toxin and tetanus.
- Vaccine titer levels at Week 52 in the Randomized Placebo-Controlled Period for human papillomavirus (HPV) 16 and HPV 18 in all patients receiving vaccinations with HPV 9-valent vaccine, recombinant (Gardasil9) during the study.
- Change from baseline in wart severity based on local dermatological assessment (all regions) and central dermatological assessment (3 target skin regions) as determined by the Clinical Global Impression of Severity (CGI-S) for patients with warts at baseline and the ITT Population.

- Infection characteristics (eg, type of infection, duration of treatment, severity) by treatment group as adjudicated by an independent AC.
- Infection-free time by treatment group.
- Number of days lost from work/school by treatment group.
- Number of days lost from work/school by treatment group.
- Quality of life by treatment group as measured by the 36-Item Short Form Survey and EQ-5D-5L, Life Quality Index, for all patients.
- Quality of life by treatment group as measured by The Dermatology Life Quality Index.
- Quality of life by treatment group
- in adolescent patients as measured by the Pediatric Quality of Life Inventory.
- Change from baseline in anogenital (AG) warts, based on dermatologist CGI-C and AG wart severity assessment, in patients with AG evaluation.
- Frequency of events requiring rescue treatment due to infection.
- Incidence, frequency, and duration of hospitalizations due to infections.
- Incidence of newly developed warts.
- Area under the curve for absolute neutrophil count (AUC_{ANC}) over 24 hours, calculated using the trapezoidal method.
- Proportion of neutrophil responders, defined as patients with ANC ≥ 500 cells/μL threshold at least 50% of the time, as well as ANC above threshold for the entire 24-hour period.
- AUC_{ANC} over 24 hours, to be assessed by a within-group comparison with the clinically meaningful threshold of ≥ 500 cells/μL in the mavorixafor treatment group (where the 24-hour threshold area under curve is calculated as 500 × 24).
- AUC_{ALC} over 24 hours, calculated using the trapezoidal method.
- Proportion of lymphocyte responders, defined as patients with baseline ALC below the lower limit of normal who achieve on-treatment ALC ≥ 1000 cells/μL threshold at least 50% of the time, as well as ALC above threshold for the entire 24-hour period.
- Absolute and fold change from baseline for total ALC, absolute monocyte count (AMC), ANC, and white blood cell (WBC) count.

<u>Open label extension period</u>

Primary objective:

- To evaluate the long-term safety and tolerability of mavorixafor in patients with WHIM syndrome

Secondary objective:

- Proportion of neutrophil responders, defined as patients with ANC ≥ 500 cells/μL threshold.
- Proportion of lymphocyte responders, defined as patients with baseline ALC below the lower limit of normal who achieve on-treatment ALC ≥ 1000 cells/μL threshold.
- Absolute and fold change from baseline for total ALC, AMC, ANC, and WBC count.

- Vaccine titer levels during the Open-Label Period in all patients vaccinatedwith Tdap during the study, including pertussis toxin and tetanus.
- Vaccine titer levels during the Open-Label Period for HPV 16 and HPV 18 in all patients receiving vaccinations with HPV 9- valent vaccine, recombinant (Gardasil®9) during the study.
- Change from baseline in cutaneous warts, based on central review of CGI-C and CGI-S.
- Change from baseline in cutaneous warts, based on local dermatologist review of CGI-C and CGI-S.
- Change over time in PGI-S and PGI-C.
- Total infection score as adjudicated by an independent AC.

Estimand for other secondary objectives

No estimand was specified in study protocol or statistical analysis plan (SAP).

Statistical methods for estimation and sensitivity analysis of other secondary objectives

Other secondary efficacy endpoints were analysed to provide additional evidence of treatment effect. They were not included in the hierarchy for alpha control.

5.3.2.4. Results

Participant flow and numbers analysed

The first participant was enrolled in study X4P-001-103 in November 2019 and the last participant was enrolled in October 2022. Data-cut off for the primary analysis was on 11 November 2022, for the OLE on 31 August 2023.

A total of 35 participants were screened, 4 of which were deemed screen failures. Of the 31 participants eligible for randomization into the study, all (100%) participants were included the ITT population and Safety population (received at least 1 dose of study drug), 29 (93.5%) in the Per-Protocol population, 14 (45.2%) in the PK population, and 28 (90.3%) in the Completer's population. Twenty-eight (90.3%) participants overall completed the 52-week randomised-controlled period, 1 (3.2%) of which was eligible for early release, and 27 (87.1%) continued into the Open Label Period. Of the 31 participants who were randomized, 3 (9.7%) discontinued study treatment during the randomised-controlled period, primarily due to participant request (2 participants, 6.5%) followed by Early Release 1 (3.2%). As of the data cut-off date for primary analysis, 20 (64.5%) patients were in long-term follow-up.

There were 2 patients in the mavorixafor group who did not have sufficient dense samples to enable TAT calculation at Week 39 and one at Week 52, therefore they did not contribute to the TAT_{ANC} analysis at those specific visits. Sensitivity analyses using different missing assumptions confirm the significance and robustness of the primary analysis.

The mavorixafor (n=14) and placebo (n=17) groups were similar with respect to median duration of study drug exposure (359.0 vrs 364.0 days, respectively). Among the 14 patients treated with mavorixafor, one was randomized to 200 mg QD and 13 received 400 mg QD.

The treatment compliance, as measured by the relative dose intensity, was similar between the mavorixafor and placebo groups, with a mean (SD) of 97.8% (6.2) and 95.5% (7.8) respectively, and a median of 99.5% and 99.2% for the mavorixafor and placebo groups respectively.

Table 32: Participant Flow

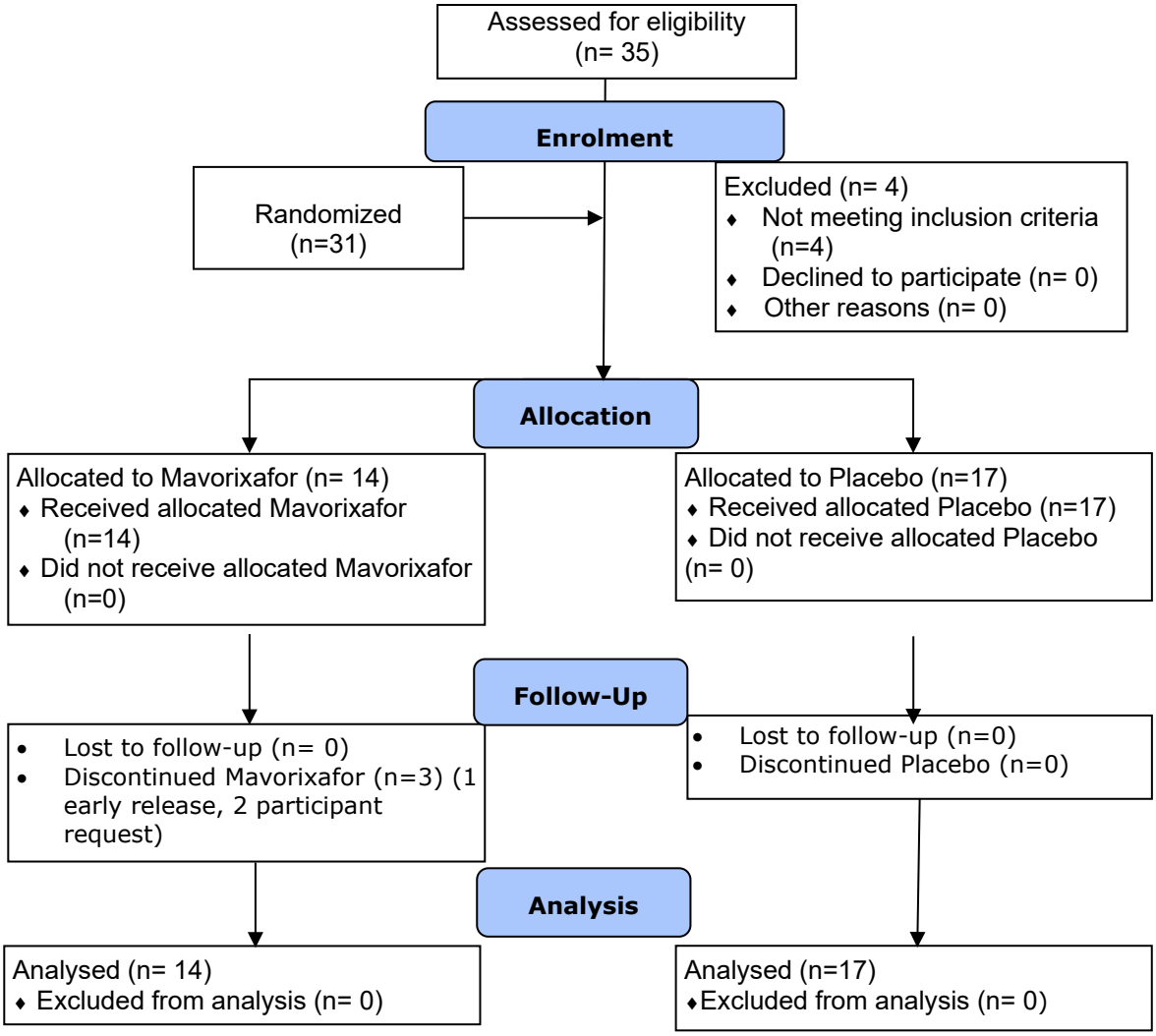


Table 33: Summary of Analysis Population and Patient Disposition – Randomized Placebo-Controlled Period – All Screened Patients

	Placebo (N=17) n (%)	Mavorixafor (N=14) n (%)	Total (N=31) n (%)
Patients screened	-	-	35
Screened failures[a]	-	-	4 (11.4)
Randomized into study	17 (100)	14 (100)	31 (100)
Safety population	17 (100)	14 (100)	31 (100)
ITT population	17 (100)	14 (100)	31 (100)
Per-Protocol population	16 (94.1)	13 (92.9)	29 (93.5)
PK population	0[b]	14 (100)	14 (45.2)
Completer's population	17 (100)	11 (78.6)	28 (90.3)
Completed treatment in the RCP	17 (100)	11 (78.6)	28 (90.3)
Eligible for early release	0	1 (7.1)	1 (3.2)
Continued onto Open-Label Period	16 (94.1)	11 (78.6)	27 (87.1)

Table 33: Summary of Analysis Population and Patient Disposition – Randomized Placebo-Controlled Period – All Screened Patients

	Placebo (N=17) n (%)	Mavorixafor (N=14) n (%)	Total (N=31) n (%)
Discontinued from treatment during RCP	0	3 (21.4)	3 (9.7)
Primary reason for discontinuation			
TLT event	0	0	0
AE, other than TLT	0	0	0
Patient request	0	2 (14.3)	2 (6.5)
Lost to follow-up	0	0	0
Study termination by the Sponsor	0	0	0
Early Release	0	1 (7.1)	1 (3.2)
Other	0	0	0

AE=adverse event; ITT=intent-to-treat; PD=pharmacodynamic; PK=pharmacokinetic; RCP=randomized placebo-controlled period; TLT=treatment-limiting toxicity.
Note: Unless otherwise specified, percentages are calculated based on the number of randomized patients in each analysis group.
[a] Percentage of screen failure is calculated based on the number of screened patients.
[b] Patients in the Placebo group were all below the level of quantification for PK analysis or had PD of dosing errors and were therefore excluded from the PK analysis by definition.

Deviations from study plan

According to protocol deviations, a total of 8 (25.8%) participants had major deviations related to protocol eligibility criteria, primarily surrounding the ICF (updated ICF not signed or signed late).

There were country specific protocol amendments for Germany, United Kingdom and Canada. Furthermore, there were two main amendments:

In protocol amendment 1 (20 May 2020), the requirement of having at least in the Tanner stage >=3 for adolescent patients aged 12 years or older was removed from the inclusion criteria. For patients 12-17 years of age and weighing <=50 kg the dose of mavorixafor was lowered to 200 mg QD. Time to early release as confirmed by blinded independent AC and wart severity based on dermatological assessment (CGI-S score) were both added as key secondary endpoints. In addition, the cap of 30% for patients receiving immunoglobulin treatment was removed. The timing of IG treatment was specified, with administration prohibited at the time of ANC assessments (+/- 4 days). Vaccination with Tdap and HP9 valent vaccine was made optional for patients stratified in the IG stratum, and revaccination for patients who had completed a full course of vaccination prior to the study.

In the amendment 2 (20 October 2021), following to the applicant, prior to any data analysis, the key secondary endpoints were changed to, in order of testing hierarchy, TAT_{ALC} of ≥1000 cells/μL over 24 hours, composite clinical efficacy endpoint based on total infection score (adjudicated data) and total wart change score (central review data), total wart change score, and total infection score.

In the first version of the protocol (dated 24 April 2019), the key secondary endpoints were defined as the following: 1) AUC_{ANC} over 24 hours; 2) Infection rate based on infections adjudicated by a blinded, independent AC; 3) Incidence of protective vaccine titers at Week 52 in patients vaccinated at Week 13; 4) change from baseline in cutaneous warts, based on CGI – C score.

Baseline data

Among the randomised patients, 17 of 31 (55%) had documented infections during the 12 months preceding study enrolment. With the exception of one patient receiving fluconazole prophylaxis for chronic recurrent vaginal candidiasis and another patient with gingivitis treated with azithromycin for more than 200 days, all anti-infective treatments were of therapeutic intent, primarily targeting airway and skin/soft tissue infections. One patient required hospitalisation for pneumonia, and another experienced a herpes zoster infection, which was treated with aciclovir for six days. No clinically meaningful imbalance between the treatment and placebo arms was observed.

Demographic and baseline characteristics are summarised in Table 34.

Table 34: Summary of Demographic and Baseline Characteristics – Randomized Placebo-Controlled Period – Safety Population

	Placebo (N=17) n (%)	Mavorixafor (N=14) n (%)	Total (N=31) n (%)
Age (years) [a]			
N	17	14	31
Mean (SD)	30.9 (21.25)	22.1 (12.20)	27.0 (18.03)
Median	23.0	17.5	18.0
Min, max	13, 72	12, 58	12, 72
Age group, n (%)	17	14	31
12 to <18 years old	8 (47.1)	7 (50.0)	15 (48.4)
≥18 years old	9 (52.9)	7 (50.0)	16 (51.6)
Sex, n (%)	17	14	31
Male	8 (47.1)	5 (35.7)	13 (41.9)
Female	9 (52.9)	9 (64.3)	18 (58.1)
Child-bearing potential			
Yes	6 (66.7)	7 (77.8)	13 (72.2)
No	3 (33.3)	2 (22.2)	5 (27.8)
Reason			
Premenarchal	1 (33.3)	0	1 (20.0)
Hysterectomy	1 (33.3)	2 (100)	3 (60.0)
Bilateral salpingectomy	0	0	0
Bilateral oophorectomy	0	0	0
Other	1 (33.3)	0	1 (20.0)
Race, n (%)	17	14	31
American Indian or Alaska Native	0	0	0
Asian	1 (5.9)	0	1 (3.2)
Black or African American	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0
White	16 (94.1)	13 (92.9)	29 (93.5)
Other	0	1 (7.1)	1 (3.2)
Ethnicity, n (%)	17	14	31
Hispanic or Latino	0	1 (7.1)	1 (3.2)
Not Hispanic or Latino	17 (100)	13 (92.9)	30 (96.8)
Baseline weight (kg)			
N	17	14	31
Mean (SD)	64.288 (17.9244)	61.989 (13.0059)	63.250 (15.6845)

	Placebo (N=17) n (%)	Mavorixafor (N=14) n (%)	Total (N=31) n (%)
Median	57.000	60.950	60.800
Min, max	45.40, 103.50	47.50, 94.00	45.40, 103.50
Baseline adolescent (12 to <18 years) weight (kg)			
N	8	7	15
Mean (SD)	51.075 (6.5436)	63.336 (15.5885)	56.797 (12.8701)
Median	47.450	61.100	54.500
Min, max	45.40, 62.40	47.50, 94.00	45.40, 94.00
Baseline adult (≥18 years) weight (kg)			
N	9	7	16
Mean (SD)	76.033 (16.5928)	60.643 (10.9211)	69.300 (16.0226)
Median	76.700	60.800	71.250
Min, max	51.00, 103.50	47.90, 78.00	47.90, 103.50
Region, n (%)	17	14	31
US	4 (23.5)	2 (14.3)	6 (19.4)
Non-US	13 (76.5)	12 (85.7)	25 (80.6)
Baseline Ig use, n (%)	17	14	31
Yes	8 (47.1)	6 (42.9)	14 (45.2)
No	9 (52.9)	8 (57.1)	17 (54.8)
Baseline Tanner Stage – pubic hair (12 to <18 years), n (%)	8	7	15
Stage 1	0	0	0
Stage 2	1 (12.5)	0	1 (6.7)
Stage 3	2 (25.0)	0	2 (13.3)
Stage 4	4 (50.0)	1 (14.3)	5 (33.3)
Stage 5	0	4 (57.1)	4 (26.7)
Not done	1 (12.5)	2 (28.6)	3 (20.0)
Screening absolute neutrophil count (10^9/L)			
N	17	14	31
Mean (SD)	0.194 (0.1231)	0.173 (0.1122)	0.185 (0.1169)
Median	0.200	0.150	0.170
Min, max	0.00, 0.40	0.04, 0.39	0.00, 0.40
Baseline mean absolute neutrophil count (10^9/L) [b]			
N	16	13	29
Mean (SD)	0.281 (0.2327)	0.155 (0.0938)	0.224 (0.1920)
Median	0.206	0.125	0.163
Min, max	0.08, 0.94	0.04, 0.33	0.04, 0.94
Baseline mean absolute lymphocyte count (10^9/L)[b]			
N	16	13	29
Mean (SD)	0.563 (0.1991)	0.501 (0.2048)	0.535 (0.2005)
Median	0.582	0.447	0.529
Min, Max	0.25, 1.14	0.28, 1.09	0.25, 1.14

	Placebo (N=17) n (%)	Mavorixafor (N=14) n (%)	Total (N=31) n (%)
Baseline mean absolute monocyte count (10^9/L)[b]			
N	13	9	22
Mean (SD)	0.112 (0.0308)	0.114 (0.0795)	0.113 (0.0543)
Median	0.121	0.093	0.101
Min, Max	0.06, 0.17	0.04, 0.32	0.04, 0.32
Baseline mean white blood cell count (10^9/L)[b]			
N	17	14	31
Mean (SD)	1.087 (0.5517)	0.810 (0.3708)	0.962 (0.4914)
Median	0.891	0.723	0.860
Min, max	0.54, 2.74	0.45, 1.61	0.45, 2.74
Time since WHIM syndrome symptoms (years)			
Mean (SD)	24.83 (18.988)	19.59 (13.674)	22.46 (16.743)
Median	16.57	13.46	14.80
Time since WHIM syndrome diagnosis (years)			
Mean (SD)	9.92 (6.931)	10.01 (8.252)	9.96 (7.425)
Median	8.51	8.32	8.51
Genetic mutation, n (%)	17	14	31
Arg334	12 (70.6)	10 (71.4)	22 (71.0)
Others	5 (29.4)	4 (28.6)	9 (29.0)
Participants with any infections over the past 12 months, n (%)	11 (64.7)	6 (42.9)	17 (54.8)
Number of infection events Mean (SD)	1.9 (0.83)	2.3 (1.03)	2.1 (0.90)
Duration of infections (days) Mean (SD)	1674.1 (3236.48)	570.3 (1165.22)	1284.5 (2695.68)
Subjects that used antibiotic, n (%)			
Yes	9 (52.9)	5 (35.7)	14 (45.2)
No	2 (11.8)	1 (7.1)	3 (9.7)
Number of subjects with prior infections that led to a hospitalization, n (%)	2 (11.8)	0	2 (6.5)
Number of Hospitalizations due to infections Mean (SD)	1.0 (0.00)	NA (NA)	1.0 (0.00)
Duration of hospitalization (days) Mean (SD)	5.5 (3.54)	NA (NA)	5.5 (3.54)
Type of infection, n (%)			
Aphthous ulcer	0	1 (7.1)	1 (3.2)
Bronchiectasis	1 (5.9)	0	1 (3.2)
COVID-19	1 (5.9)	0	1 (3.2)
Cellulitis	2 (11.8)	1 (7.1)	3 (9.7)
Conjunctivitis	0	1 (7.1)	1 (3.2)
Cough	0	1 (7.1)	1 (3.2)

	Placebo (N=17) n (%)	Mavorixafor (N=14) n (%)	Total (N=31) n (%)
Folliculitis	1 (5.9)	0	1 (3.2)
Gingivitis	1 (5.9)	1 (7.1)	2 (6.5)
Helicobacter infection	1 (5.9)	0	1 (3.2)
Herpes zoster	1 (5.9)	0	1 (3.2)
Impaired healing	0	1 (7.1)	1 (3.2)
Impetigo	2 (11.8)	0	2 (6.5)
Influenza	0	1 (7.1)	1 (3.2)
Lower respiratory tract infection	1 (5.9)	0	1 (3.2)
Lymphangitis	1 (5.9)	0	1 (3.2)
Papilloma viral infection	1 (5.9)	0	1 (3.2)
Pharyngitis	0	1 (7.1)	1 (3.2)
Pharyngotonsillitis	0	1 (7.1)	1 (3.2)
Pneumonia	1 (5.9)	0	1 (3.2)
Pyrexia	0	1 (7.1)	1 (3.2)
Rhinitis	1 (5.9)	1 (7.1)	2 (6.5)
Sinusitis	2 (11.8)	0	2 (6.5)
Skin infection	1 (5.9)	0	1 (3.2)
Tracheitis	0	1 (7.1)	1 (3.2)
Upper respiratory tract infection	1 (5.9)	0	1 (3.2)
Urinary tract infection	0	1 (7.1)	1 (3.2)
Vulvovaginal mycotic infection	1 (5.9)	1 (7.1)	2 (6.5)
Participants with any history of cutaneous or anogenital warts, n (%)	11 (64.7)	11 (78.6)	22 (71.0)
If yes - wart, n (%)			
Cutaneous	10 (58.8)	11 (78.6)	21 (67.7)
Anogenital	4 (23.5)	3 (21.4)	7 (22.6)
Duration of Wart History (years) Mean (SD)	16.355 (16.0923)	12.024 (14.9267)	14.087 (15.2593)
Number of Regions with Cutaneous Warts at Baseline Mean (SD)	3.7 (5.38)	3.4 (3.41)	3.6 (4.53)
Number of Regions with Anogenital Warts at Baseline Mean (SD)	0.2 (0.39)	0.0 (0.00)	0.1 (0.30)

Ig=immunoglobulin; SD=standard deviation.
Note: Percentages are calculated based on the number of patients in each characteristic as denominator.
[a] Age at baseline visit.
[b] Baseline is defined as mean of dense sample values.

Outcomes and estimation

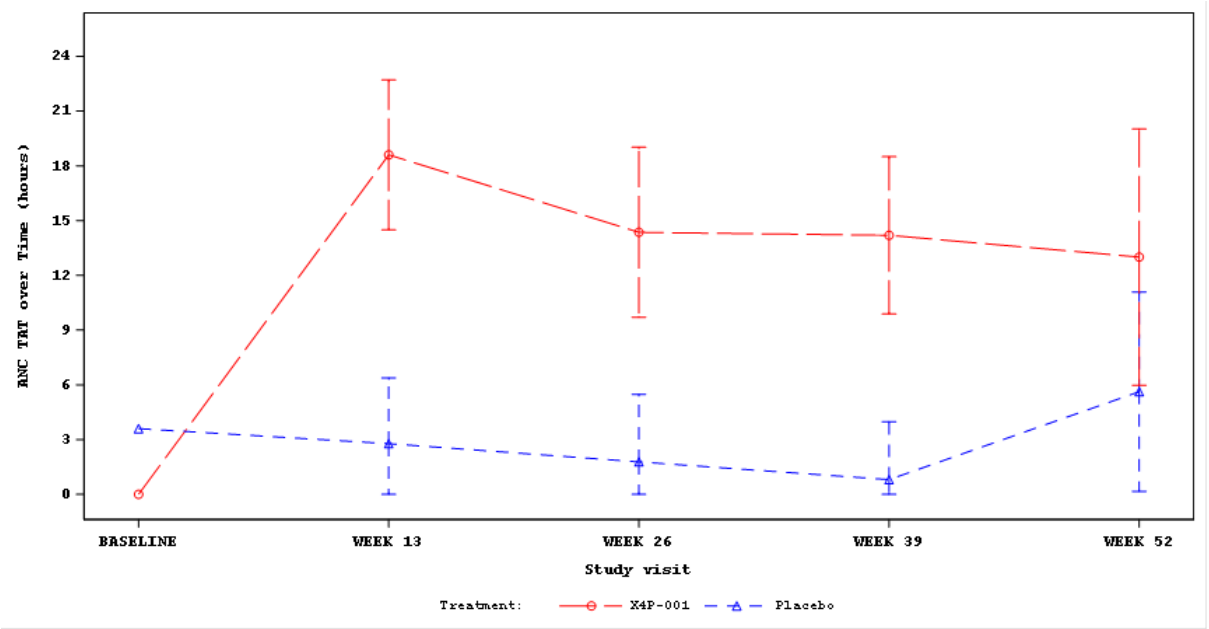
Primary Endpoint: Time above a threshold of ≥ 500 neutrophiles/µL (TAT_{ANC})

The pre-specified primary endpoint was the time (in hours) in which the neutrophil count is measured above a threshold of ≥500 cells/µL over a 24-hour period (see methods, Figure 18). TAT_{ANC} was assessed by in residency four times throughout the study (every 13 weeks) in the ITT population.

TAT_{ANC} was statistically longer for mavorixafor treated patients compared with placebo treated patients, with an TAT_{ANC} increase to 15.04 hours (SE 1.891; p <0.0001) with mavorixafor treatment from 2.75 hours (SE 1.518) with placebo during the 52 week RCP (Table 35). Furthermore, the TAT_{ANC} change

from neutrophil baseline levels (d0) was significantly higher in mavorixafor treated patients compared to placebo (p value <0.0001; Figure 18).

Figure 18: TAT_{ANC} Over Time (Hours) (LS Mean ±95% CI) by Treatment Group – Randomised Placebo-Controlled Period – ITT Population



	Baseline	Week 13	Week 26	Week 39	Week 52
X4P, N=14[a]	n=13	n=13	n=11	n=9	n=10
Pbo, N=17[a]	n=16	n=16	n=17	n=17	n=17

ANC=absolute neutrophil count; CI=confidence interval; ITT=Intent-to-Treat; LS least squares; Pbo=placebo; TAT=total time (hours) above threshold (500 cells/µL) in 24 hours; X4P=mavorixafor

Notes: Negative values of LS mean or lower bound of 95% CI produced from the model were mapped to 0.

a. TAT_{ANC} values were not obtained for some patients because of insufficient number of blood samples and/or some blood samples were not measurable.

Table 35: Summary and Analysis of TAT_{ANC} (in Hours) (≥500 cells/µL) by Visit – ITT Population (Study X4P-001-103 RCP)

		Placebo (N=17) n (%)		Mavorixafor (N=14) n (%)	
Visit	**Statistics**	**Actual**	**Change[a]**	**Actual**	**Change[a]**
Baseline	n	16	-	13	-
	Mean (SD)	3.60 (5.713)	-	0.00 (0.000)	-
Overall MMRM results	LS mean (SE)	2.75 (1.518)	0.49 (1.518)	15.04 (1.891)	12.78 (1.891)
	Difference from placebo:				
	LS mean difference (SE)	-	-	12.30 (2.494)	12.30 (2.494)
	P-value[b,c]	-	-	<0.0001*	<0.0001*

Table 35: Summary and Analysis of TAT_{ANC} (in Hours) (≥500 cells/µL) by Visit – ITT Population (Study X4P-001-103 RCP)

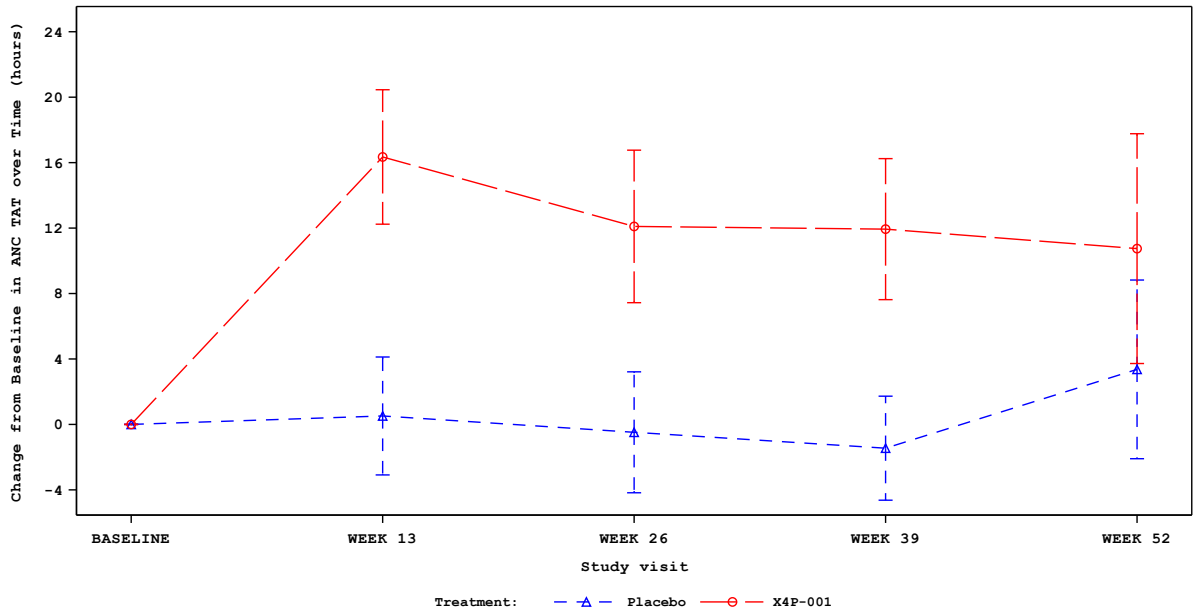
		Placebo (N=17) n (%)		Mavorixafor (N=14) n (%)	
Visit	**Statistics**	**Actual**	**Change[a]**	**Actual**	**Change[a]**

LS=least squares; MMRM=mixed-model repeated measures; SD=standard deviation; SE=standard error.
Note: "*" represents p-values ≤0.05.
Note: Baseline is based on the baseline visit values.
[a] Represents change from baseline.
[b] The results are based on an MMRM analysis with time above threshold as a dependent variable; treatment, visit (Weeks 13, 26, 39, and 52), treatment*visit, Ig use (randomization strata), and baseline time above threshold as covariates; and patient as the repeated random effect. The Kenward-Roger approximation for degrees of freedom is used. The UN covariance structure is employed. Negative values of LS mean or lower bound of 95% CI produced from the model for the actual values are mapped to 0.
[c] P-value for overall treatment comparison.

Sensitivity analysis TAT_{ANC} change from baseline

A longer change from baseline in TAT_{ANC} over time compared with placebo was demonstrated (p value <0.0001).

Figure 19: Change from Baseline in TAT_{ANC} Over Time (Hours) (LS Mean ±95% CI) by Treatment Group – Randomized Placebo-Controlled Period – ITT Population



	Baseline	Week 13	Week 26	Week 39	Week 52
X4P, N=14	n=13	n=12	n=10	n=8	n=9
Pbo, N=17	n=16	n=15	n=16	n=16	n=16

ANC=absolute neutrophil count; CI=confidence interval; ITT=Intent-to-Treat; LS least squares; Pbo=placebo; TAT=total time (hours) above threshold (500 cells/µL) in 24 hours; X4P=mavorixafor

a. TAT_{ANC} values were not obtained for some patients because of insufficient number of blood samples and/or some blood samples were not measurable.

Notes: Negative values of LS mean or lower bound of 95% CI produced from the model were mapped to 0.

Sensitivity analysis TAT_{ANC} by visit

Table 36 shows the summary and analysis of TAT_{ANC} by visit for patients in the ITT population of the randomised-controlled period.

Table 36: Summary and Analysis of TAT_{ANC} (in Hours) (≥500 cells/µL) by Visit – Randomised -Controlled Period – ITT Population

		Placebo (N=17) n (%)		Mavorixafor (N=14) n (%)	
Visit	**Statistics**	**Actual**	**Change[a]**	**Actual**	**Change[a]**
Baseline	N	16	-	13	-
	Mean (SD)	3.60 (5.713)	-	0.00 (0.000)	-
	Median	0.00	-	0.00	-
	Min, max	0.0, 16.2	-	0.0, 0.0	-
Week 13	N	16	15	13	12
	Mean (SD)	3.18 (6.746)	-0.45 (7.264)	18.48 (7.208)	18.02 (7.327)
	Median	0.00	0.00	20.81	20.34
	Min, max	0.0, 24.0	-13.7, 14.9	2.0, 24.0	2.0, 24.0
	LS mean (SE)	2.78 (1.753)	0.52 (1.753)	18.61 (1.998)	16.35 (1.998)
	LS mean 95% CI	(0.00, 6.38)	(-3.09, 4.12)	(14.50, 22.72)	(12.24, 20.46)
	Difference from placebo:				
	LS mean difference (SE)	-	-	15.83 (2.730)	15.83 (2.730)
	LS mean difference 95% CI	-	-	(10.23, 21.43)	(10.23, 21.43)
	P-value[b]	-	-	<0.0001*	<0.0001*
Week 26	N	17	16	11	10
	Mean (SD)	2.13 (4.042)	-1.34 (6.063)	15.35 (10.391)	14.48 (10.527)
	Median	0.00	0.00	20.70	20.23
	Min, max	0.0, 13.7	-12.0, 9.9	0.0, 24.0	0.0, 24.0
	LS mean (SE)	1.78 (1.790)	-0.48 (1.790)	14.36 (2.267)	12.10 (2.267)
	LS mean 95% CI	(0.00, 5.47)	(-4.18, 3.21)	(9.70, 19.02)	(7.44, 16.76)
	Difference from placebo:				
	LS mean difference (SE)	-	-	12.58 (2.944)	12.58 (2.944)
	LS mean difference 95% CI	-	-	(6.53, 18.64)	(6.53, 18.64)
	P-value[b]	-	-	0.0002*	0.0002*
Week 39	N	17	16	9	8
	Mean (SD)	2.09 (4.639)	-2.31 (4.624)	16.34 (8.537)	15.38 (8.594)
	Median	0.00	0.00	20.74	16.45
	Min, max	0.0, 14.8	-11.4, 4.7	3.7, 24.0	3.7, 24.0

		Placebo (N=17) n (%)		Mavorixafor (N=14) n (%)	
Visit	**Statistics**	**Actual**	**Change[a]**	**Actual**	**Change[a]**
	LS mean (SE)	0.81 (1.518)	-1.45 (1.518)	14.20 (2.081)	11.94 (2.081)
	LS mean 95% CI	(0.00, 3.99)	(-4.63, 1.73)	(9.89, 18.51)	(7.63, 16.25)
	Difference from placebo:				
	LS mean difference (SE)	-	-	13.39 (2.637)	13.39 (2.637)
	LS mean difference 95% CI	-	-	(7.92, 18.86)	(7.92, 18.86)
	P-value[b]	-	-	<0.0001*	<0.0001*
Week 52	N	17	16	10	9
	Mean (SD)	5.75 (9.556)	2.51 (9.116)	13.39 (10.718)	12.21 (10.659)
	Median	0.00	0.00	15.04	10.58
	Min, max	0.0, 24.0	-9.8, 24.0	0.0, 24.0	0.0, 24.0
	LS mean (SE)	5.62 (2.621)	3.36 (2.621)	13.00 (3.399)	10.74 (3.399)
	LS mean 95% CI	(0.16, 11.09)	(-2.10, 8.82)	(5.98, 20.03)	(3.72, 17.77)
	Difference from placebo:				
	LS mean difference (SE)	-	-	7.38 (4.331)	7.38 (4.331)
	LS mean difference 95% CI	-	-	(-1.58, 16.34)	(-1.58, 16.34)
	P-value[b]	-	-	0.1019	0.1019

ANC=absolute neutrophil count; CI=confidence interval; LS=least squares; Ig=immunoglobulin; max=maximum; min=minimum; MMRM=mixed-model repeated measures; SD=standard deviation; SE=standard error; TAT=time above threshold; UN=unstructured.
Note: "*" represents p-values ≤0.05.
Note: Baseline is based on the baseline visit values.
[a] Represents change from baseline.
[b] The results are based on an MMRM analysis with time above threshold as a dependent variable; treatment, visit (Weeks 13, 26, 39, and 52), treatment*visit, Ig use (randomization strata), and baseline time above threshold as covariates; and patient as the repeated random effect. The Kenward-Roger approximation for degrees of freedom is used. The UN covariance structure is employed. Negative values of LS mean or lower bound of 95% CI produced from the model for the actual values are mapped to 0.
[c] P-value for overall treatment comparison.

Subgroup analysis concerning the primary endpoint

Following the applicant, sensitivity analyses of the primary efficacy endpoint were performed. These included analyses to assess the analysis assumptions and impact of missing data, a tipping point analysis, and a repeat analysis of the primary endpoint using MMRM and the per-protocol-/ and completers populations. A post hoc nonparametric analysis (Wilcoxon rank sum test) was performed on the primary endpoint using the ITT population. Results of these sensitivity analyses are consistent with those of the primary analysis (MMRM) of the ITT population.

Subgroup analysis concerning the primary endpoint are provided in Table 37.

Table 37: Subgroup Analysis of the Primary Endpoint TAT_{ANC} – Randomized Placebo-Controlled Period (ITT Population), Study X4P-001-103

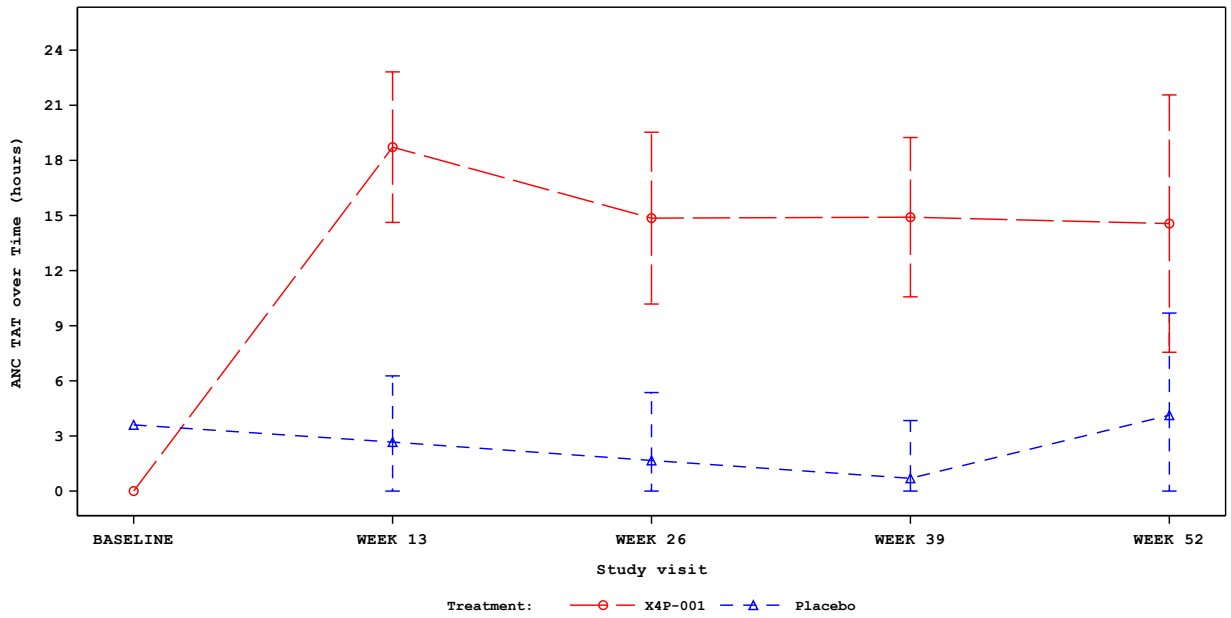
Subgroup Category	N in ITT (%)	$N_{placebo}$ / $N_{mavorixafor}$	Difference of Mavorixafor-Placebo (SE)	LS Mean 95% CI
All subjects in the ITT	31 (100)	17/14	12.30 (2.494)	(7.16, 17.43)
Age				
<18 years old	15 (48.4)	8/7	12.87 (3.281)	(6.13, 19.61)
≥18 years old	16 (51.6)	9/7	11.49 (3.596)	(4.14, 18.84)
Gender				
Female	18 (58.1)	9/9	11.83 (2.925)	(5.82, 17.83)
Male	13 (41.9)	8/5	11.99 (4.183)	(3.41, 20.56)
Baseline Ig use				
Yes	14 (45.2)	8/6	9.51 (3.480)	(2.41, 16.60)
No	17 (54.8)	9/8	14.34 (3.102)	(7.98, 20.70)
Geographic region				
US	6 (19.4)	4/2	11.05 (6.372)	(-2.14, 24.24)
Non-US	25 (80.6)	13/12	12.01 (2.771)	(6.31, 17.71)
Initial randomized dose				
200 mg	6 (19.4)	5/1	22.59 (5.404)	(11.40, 33.77)
400 mg	25 (80.6)	12/13	11.40 (2.785)	(5.69, 17.11)
Genetic				
mutation	22 (71.0)	12/10	12.81 (2.739)	(7.18, 18.45)
Arg334				
Other	9 (29.0)	5/4	9.77 (5.041)	(-0.62, 20.16)

Abbreviations: ANC, absolute neutrophil count; CI, confidence interval; Ig, immunoglobulin; ITT, intent-to-treat; LS, least squares; N, number of subjects with given characteristic; SE, standard error; TAT, time above threshold

Sensitivity per protocol analysis for the primary endpoint regarding medication error at week 52

At week 52, confidence intervals for the primary endpoint were overlapping. Three patients in the placebo arm were mistakenly dosed with mavorixafor because they were mistakenly given open-label period treatment at week 52 visit. One patient in the mavorixafor arm accidentally missed a dose of mavorixafor at week 52. A sensitivity analysis removing the compromised results of patients with incorrect treatment showed a significant result (p-value 0.0256; Figure 20).

Figure 20: TAT_{ANC} over Time (hours) (LS Mean ±95% CI) by Treatment Group (Sensitivity Analysis) - Randomized Placebo-Controlled Period – ITT Population



	Baseline	Week 13	Week 26	Week 39	Week 52
X4P, N=14[a]	n=13	n=13	n=11	n=9	n=10
Pbo, N=17[a]	n=16	n=16	n=17	n=17	n=17

ANC=absolute neutrophil count; CI=confidence interval; ITT=Intent-to-Treat; LS least squares; Pbo=placebo; TAT=total time (hours) above threshold (500 cells/µL) in 24 hours; X4P=mavorixafor

Notes: Negative values of LS mean or lower bound of 95% CI produced from the model were mapped to 0.

The Week 52 visit data were removed for the 3 placebo patients who took the active drug (X4P-001), and one Mavorixafor patient who did not take Mavorixafor at the Week 52 visit.

a. TAT_{ANC} values were not obtained for some patients because of insufficient number of blood samples and/or some blood samples were not measurable.

Sensitivity analysis of TAT_{ANC} (in hours) at different thresholds

An additional post-hoc sensitivity analysis conducted for the primary endpoint undertook a comparison between the mavorixafor-/ and placebo-arm for TAT_{ANC} (in hours) at different neutrophil thresholds up to 1 G/L (Table 38).

Table 38: Summary and Analysis of TAT_{ANC} (in Hours) by Different Thresholds – ITT Population (Study X4P-001-103 RCP)

ANC Threshold cutoff	TAT_{ANC} LS Mean Placebo	TAT_{ANC} LS Mean Mavorixafor	TAT_{ANC} LS Mean Difference Mavorixafor - Placebo	P-value from MMRM Analysis
500 cells/µL (primary endpoint)	2.75	15.04	12.30	<0.0001*
600 cells/µL	1.94	11.97	10.03	0.0004*
700 cells/µL	1.36	9.79	8.43	0.0007*
800 cells/µL	0.68	7.88	7.20	0.0024*
900 cells/µL	0.58	6.40	5.83	0.0119*
1000 cells/µL	0.45	5.24	4.79	0.0312*

LS=least squares; MMRM=mixed-model repeated measures
Note: "*" represents p-values ≤0.05.

First key secondary endpoint: Time above a threshold of ≥ 1000 lymphocytes/ µL (TATALC)

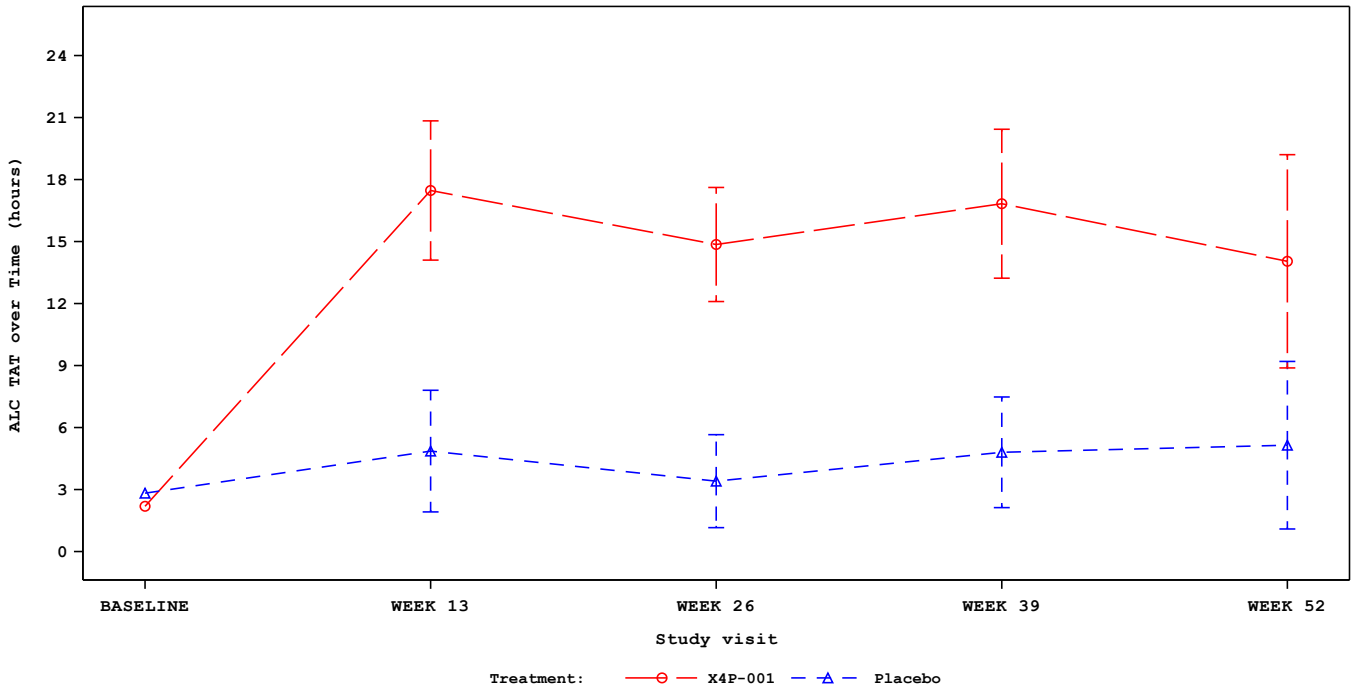
The first key secondary endpoint according to the testing hierarchy was met, TAT_{ALC} (hours) with ≥ 1000 lymphocytes/µL in the peripheral blood as the predefined threshold. Results of the analyses on TAT_{ALC} are provided in Table 39 and Figure 21.

Table 39: Summary and Analysis of TAT_{ALC} (in Hours) (1000 cells/µL) by Visit – ITT Population (Study X4P-001-103 RCP)

		Placebo (N=17) n (%)		Mavorixafor (N=14) n (%)	
Visit	**Statistics**	**Actual**	**Change[a]**	**Actual**	**Change[a]**
Baseline	n	16		13	
	Mean (SD)	2.82 (5.858)		2.19 (5.074)	
Overall MMRM results	LS mean (SE)	4.55 (1.148)	1.89 (1.148)	15.80 (1.385)	13.13 (1.385)
	Difference from placebo:				
	LS mean difference (SE)			11.25 (1.801)	11.25 (1.801)
	P-value[b,c]			<0.0001*	<0.0001*

LS=least squares; MMRM=mixed-model repeated measures; SD=standard deviation; SE=standard error.
Note: "*" represents p-values ≤0.05.
Note: Baseline is based on the baseline visit values.
[a] Represents change from baseline.
[b] The results are based on an MMRM analysis with time above threshold as a dependent variable; treatment, visit (Weeks 13, 26, 39, and 52), treatment*visit, Ig use (randomization strata), and baseline time above threshold as covariates; and patient as the repeated random effect. The Kenward-Roger approximation for degrees of freedom is used. The UN covariance structure is employed. Negative values of LS mean or lower bound of 95% CI produced from the model for the actual values are mapped to 0.
[c] P-value for overall treatment comparison.

Figure 21: TAT_{ALC} over time (hours) (LS Mean ±95% CI) by treatment group – ITT population (study X4P-001-103 RCP)



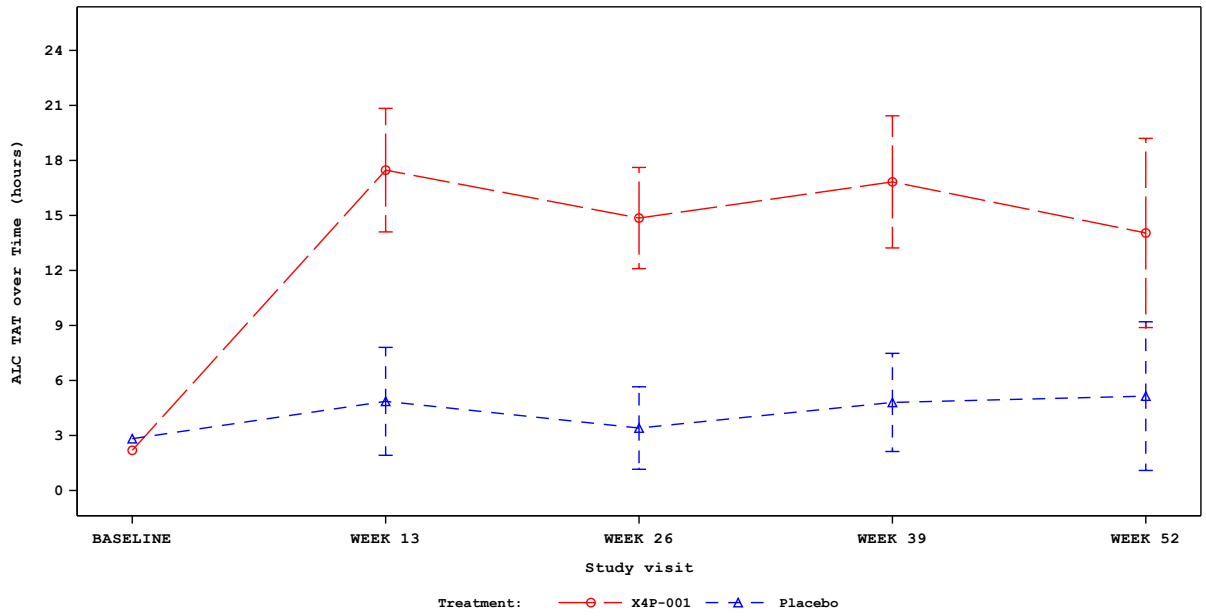
	Baseline	Week 13	Week 26	Week 39	Week 52
X4P, N=14[a]	n=13	n=13	n=11	n=9	n=10
Pbo, N=17[a]	n=16	n=16	n=17	n=17	n=17

ALC=absolute lymphocyte count; CI=confidence interval; ITT=Intent-to-Treat; LS least squares; Pbo=placebo; TAT=total time (hours) above threshold (500 cells/µL) in 24 hours; X4P=mavorixafor

a. TAT_{ALC} values were not obtained for some patients because of insufficient number of blood samples and/or some blood samples were not measurable.

Notes: Negative values of LS mean or lower bound of 95% CI produced from the model were mapped to 0.

Figure 22: Change from baseline in TAT_{ALC} over time (Hours) (LS Mean ±95% CI) by Treatment Group – ITT Population (Study X4P-001-103 RCP)



	Baseline	Week 13	Week 26	Week 39	Week 52
X4P, N=14[a]	n=13	n=12	n=10	n=8	n=9
Pbo, N=17[a]	n=16	n=15	n=16	n=16	n=16

ALC=absolute lymphocyte count; CI=confidence interval; ITT=Intent-to-Treat; LS least squares; Pbo=placebo; TAT=total time (hours) above threshold (500 cells/µL) in 24 hours; X4P=mavorixafor

a. TAT_{ALC} values were not obtained for some patients because of insufficient number of blood samples and/or some blood samples were not measurable.

Notes: Negative values of LS mean or lower bound of 95% CI produced from the model were mapped to 0.

Table 40: Summary and Analysis of TAT_{ALC} (in Hours) (1000 cells/µL) by Visit – Randomized Placebo-Controlled Period – ITT Population

		Placebo (N=17) n (%)		Mavorixafor (N=14) n (%)	
Visit	Statistics	Actual	Change[a]	Actual	Change[a]
Baseline	n	16		13	
	Mean (SD)	2.82 (5.858)		2.19 (5.074)	
	Median	0.00		0.00	
	Min, max	0.0, 21.9		0.0, 16.5	
Week 13	n	16	15	13	12
	Mean (SD)	6.04 (8.832)	2.24 (4.678)	17.97 (6.175)	15.10 (6.288)
	Median	0.00	0.00	18.38	13.58
	Min, max	0.0, 24.0	0.0, 13.9	8.5, 24.0	7.5, 24.0
	LS mean (SE)	4.86 (1.424)	2.19 (1.424)	17.47 (1.629)	14.80 (1.629)
	LS mean 95% CI	(1.92, 7.80)	(-0.75, 5.14)	(14.10, 20.84)	(11.44, 18.17)
	Difference from placebo:				

Visit	Statistics	Placebo (N=17) n (%) Actual	Change[a]	Mavorixafor (N=14) n (%) Actual	Change[a]
	LS mean difference (SE)			12.61 (2.165)	12.61 (2.165)
	LS mean difference 95% CI			(8.13, 17.09)	(8.13, 17.09)
	P-value[b]			<0.0001*	<0.0001*
Week 26	n	17	16	11	10
	Mean (SD)	4.72 (7.258)	0.70 (3.177)	16.17 (7.539)	12.77 (6.216)
	Median	0.00	0.00	15.15	10.59
	Min, max	0.0, 24.0	-4.2, 6.8	6.6, 24.0	6.6, 24.0
	LS mean (SE)	3.41 (1.087)	0.74 (1.087)	14.86 (1.340)	12.19 (1.340)
	LS mean 95% CI	(1.16, 5.65)	(-1.51, 2.99)	(12.10, 17.62)	(9.43, 14.95)
	Difference from placebo:				
	LS Mean Difference (SE)			11.45 (1.726)	11.45 (1.726)
	LS mean difference 95% CI			(7.89, 15.01)	(7.89, 15.01)
	P-value[b]			<0.0001*	<0.0001*
Week 39	n	17	16	9	8
	Mean (SD)	6.04 (8.573)	2.09 (4.318)	17.41 (6.884)	14.52 (7.547)
	Median	0.00	0.00	21.75	13.66
	Min, max	0.0, 24.0	0.0, 16.2	6.0, 24.0	5.2, 23.3
	LS mean (SE)	4.80 (1.294)	2.14 (1.294)	16.83 (1.755)	14.16 (1.755)
	LS mean 95% CI	(2.12, 7.48)	(-0.54, 4.81)	(13.23, 20.43)	(10.56, 17.77)
	Difference from placebo:				
	LS mean difference (SE)			12.03 (2.182)	12.03 (2.182)
	LS mean difference 95% CI			(7.54, 16.52)	(7.54, 16.52)
	P-value[b]			<0.0001*	<0.0001*
Week 52	n	17	16	10	9
	Mean (SD)	6.36 (8.349)	2.43 (7.471)	14.88 (10.034)	10.97 (8.565)
	Median	0.40	0.00	18.75	9.75
	Min, max	0.0, 24.0	-7.1, 23.4	0.0, 24.0	0.0, 23.6
	LS mean (SE)	5.14 (1.956)	2.48 (1.956)	14.04 (2.510)	11.38 (2.510)
	LS mean 95% CI	(1.09, 9.20)	(-1.57, 6.53)	(8.88, 19.20)	(6.22, 16.54)
	Difference from placebo:				
	LS mean difference (SE)			8.90 (3.183)	8.90 (3.183)

Visit	Statistics	Placebo (N=17) n (%) Actual	Change[a]	Mavorixafor (N=14) n (%) Actual	Change[a]
	LS mean difference 95% CI			(2.34, 15.46)	(2.34, 15.46)
	P-value[b]			0.0099*	0.0099*
Overall MMRM results	LS mean (SE)	4.55 (1.148)	1.89 (1.148)	15.80 (1.385)	13.13 (1.385)
	LS mean 95% CI	(2.18, 6.93)	(-0.49, 4.26)	(12.95, 18.65)	(10.28, 15.99)
	Difference from placebo:				
	LS mean difference (SE)			11.25 (1.801)	11.25 (1.801)
	LS mean Difference 95% CI			(7.53, 14.96)	(7.53, 14.96)
	P-value[b,c]			<0.0001*	<0.0001*
Overall P-Value	Baseline time above ANC threshold			0.0003*	0.1135
	Treatment			<0.0001*	<0.0001*
	Visit			0.1438	0.1438
	Ig use			0.1912	0.1912
	Treatment*visit			0.5869	0.5869

ALC=absolute lymphocyte count; CI=confidence interval; Ig=immunoglobulin; LS=least squares; max=maximum; min=minimum; MMRM=mixed-model repeated measures; SD=standard deviation; SE=standard error; TAT=time above threshold; UN=unstructured.
Note: "*" represents p-values ≤0.05.
Note: Baseline is based on the baseline visit values.
[a] Represents change from baseline.
[b] The results are based on an MMRM analysis with time above threshold as a dependent variable; treatment, visit (Weeks 13, 26, 39, and 52), treatment*visit, Ig use (randomization strata), and baseline time above threshold as covariates; and patient as the repeated random effect. The Kenward-Roger approximation for degrees of freedom is used. The UN covariance structure is employed. Negative values of LS mean or lower bound of 95% CI produced from the model for the actual values are mapped to 0.
[c] P-value for overall treatment comparison.

Effects on lymphocytic subpopulations

As predefined sensitivity analyses, lymphocytic subpopulations were analysed. Mavorixafor treatment resulted on average in a 4.6-fold increase in lymphocytes, 26.8-fold increase in B cells, 5.4-fold increase in CD4+ T cells, and 4.5-fold increase in CD8+ T cells. The CD4+/CD8+ T-cell ratio in patients participating in this study was higher than published reference ranges for healthy individuals. Analysis of the subsets of CD4+ and CD8+ T cells showed an increase in cell counts of each subset. B cell subsets also showed an increase in cell counts with a major increase in the naïve B cell counts. NK cell counts only were not significantly different in the mavorixafor group at any timepoint compared with the placebo group.

Second key secondary endpoint: composite endpoint of total infection score and total wart change score

Table 41 shows a summary and analysis of the composite clinical efficacy endpoint using multiple imputation methods for patients in the ITT population of the randomised-controlled period. The two contributing factors, total infection score and total wart change score will be discussed in detail in their *own role as subsequent key secondary endpoints according to the testing hierarchy.*

Table 41: Summary and Analysis of the Composite Endpoint Using Multiple Imputation Methods under Missing at Random Assumption – Randomized Placebo-Controlled Period – ITT Population

	Statistics	Placebo (N=17) n (%)	Mavorixafor (N=14) n (%)
Baseline rank sum[a]	n	17	13[d]
	Mean (SD)	30.97 (12.366)	31.04 (15.568)
	Median	32.50	27.50
	Min, max	12.5, 47.5	12.5, 56.0
Composite rank[b]	n	17	11
	Mean (SD)	31.29 (8.702)	25.45 (10.706)
	Median	31.50	25.00
	Min, max	15.5, 48.0	7.0, 41.0
	LS mean (SE)	33.37 (2.769)	26.72 (3.472)
	LS mean 95% CI	(27.94, 38.79)	(19.92, 33.53)
	Difference from placebo[c]		
	LS mean difference (SE)		-6.64 (4.527)
	LS mean difference 95% CI		(-15.52, 2.23)
	Model effect p-value:		
	Treatment		0.1422

CGI-S=Clinical Global Impression of Severity; CI=confidence interval; Ig=immunoglobulin; ITT=Intent-to-Treat; LS=least squares; max=maximum; min=minimum; SD=standard deviation; SE=standard error.

Note: Descriptive statistics are based on observed values, and inferential statistics are based on imputed values.

[a] Baseline rank sum is the sum of the ranks for infection history and baseline warts for each patient. Infection rates are based on patient's medical records from the 12 months preceding the drug treatment (including the screening period prior to first dose). Each patient's baseline wart burden is ranked based on the sum of baseline CGI-S for the 3 targets.

[b] Composite rank for each patient is calculated by summing up the ranks of the 2 individual components (total infection score and 52-week total wart change score). Note that a lower value for composite rank indicates a better result.

[c] From ANCOVA model comparing mavorixafor and placebo with composite score as the response and treatment group, Ig use, and treatment* Ig use as factors and covariates of the baseline rank sum, age, and sex. Missing Week 52 total wart scores are imputed using the multiple imputation method under missing at random assumption.

[d] No wart score was available post-baseline for one patient therefore this patient was not included in the composite endpoint analysis.

Post – hoc WIN ratio analysis of the key secondary composite endpoint

The study did not show statistical significance on the composite endpoint of total infection score and wart change score, using the pre-defined rank-sum analysis. The applicant conducted a post-hoc WIN analysis in which total infection score was prioritised first and total wart score second. Following the applicant, this was done as frequent infection is the most significant clinical manifestation compared to warts.

This WIN ratio analysis showed a statistically significant effect (p-value 0.0025 for stratified unmatched analysis and p-value 0.0003 for unstratified unmatched analysis) in favour of the mavorixafor arm on the composite endpoint (Table 42).

Table 42: Unmatched Win Ratio Analysis (Infection score first, then wart score)

Ig use: Yes	P (N = 8), M (N = 6)				P (N = 17), M (N = 14)				
Ig use: No	P (N = 9), M (N = 8)								
category	n				category	n			
a	83				a	174			
b	36				b	63			
c	0				c	0			
d	0				d	0			
e	1				e	1			
win ratio:	2.305556	95% CI:	1.34086	3.964312	win ratio:	2.761905	95% CI:	1.603011	4.75862
z score:	3.020661				z score:	3.660049			
two-sided p-value:	0.002522				two-sided p-value:	0.000252			

CI=confidence interval; Ig=immunoglobulin.
Note: P-placebo; M-mavorixafor; N-Number of subjects; n-number of winner or loser at each category for the mavorixafor group.
Note: the groups were as follows; a: active had lower total infection score (winner), b: placebo had lower total warts change score (loser), c: active had lower total infection score (winner), d: placebo had lower total infection score (loser), e: none of the above.

Third key secondary endpoint total wart change score

Total wart change score is calculated by the sum of all three regional wart change scores (CGI-C) by central blinded, independent review from three target lesions assessed at week 52 (+/-14d).

Results are descriptive following the testing strategy and provided in Table 43.

Table 43: Summary and Analysis of Total Wart Change Score Based on CGI-C From Central Review for the Target Regions – Randomized Placebo-Controlled Period – ITT Population

Visit	Statistics	Placebo (N=17) n (%)	Mavorixafor (N=14) n (%)
Baseline CGI-S	n	17	13
	Mean (SD)	4.9 (1.58)	5.7 (2.56)
	Median	5.0	6.0
	Min, Max	3, 8	3, 10
Week 26 total wart change score[a]	n	17	12
	Mean (SD)	-0.4 (1.50)	-0.2 (1.64)
	Median	0.0	0.0
	Min, max	-4, 2	-4, 3
	LS mean (SE)	-0.32 (0.376)	-0.71 (0.503)
	LS mean 95% CI	(-1.06, 0.41)	(-1.70, 0.28)
	Difference from placebo:		
	LS mean difference (SE)		-0.39 (0.643)
	LS mean difference 95% CI		(-1.65, 0.87)
	p-value[b]		0.5450
Week 52 total wart change score[a]	n	17	11
	Mean (SD)	-1.2 (1.91)	-0.6 (2.34)

Visit	Statistics	Placebo (N=17) n (%)	Mavorixafor (N=14) n (%)
	Median	0.0	0.0
	Min, max	-5, 1	-6, 3
	LS mean (SE)	-1.15 (0.545)	-1.08 (0.697)
	LS mean 95% CI	(-2.21, -0.08)	(-2.45, 0.29)
	Difference from placebo:		
	LS mean difference (SE)		0.07 (0.896)
	LS mean difference 95% CI		(-1.69, 1.82)
	p-value[b]		0.9408

CGI-C=Clinical Global Impression of Change; CGI-S=Clinical Global Impression of Severity; CI=confidence interval; Ig=immunoglobulin; LS=least squares; max=maximum; min=minimum; MMRM=mixed-model repeated measures; SD=standard deviation; SE=standard error; UN=unstructured.
Note: "*" represents p-values ≤0.05.
Note: The total wart change score is calculated by summing the Regional Wart Change Scores from all 3 target regions.
Note: For patients without warts at baseline and with no new wart developed during treatment, the CGI-C is considered as no change.
Note: The missing total wart change score is imputed with the multiple imputation method (under missing at random assumption) using the SAS PROC MI procedure.
Note: Descriptive statistics are based on observed values.
[a] Represents change from baseline.
[b] The results are based on an MMRM analysis with total wart change score as a dependent variable; treatment, visit (Weeks 26 and 52), treatment*visit, Ig use (randomization strata), baseline CGI-S (sum in the 3 target areas), age, and sex as covariates; and patient as the repeated random effect. The Kenward-Roger approximation for degrees of freedom is used. The UN covariance structure is employed. Note that a lower value for total wart change score indicates a better result.

Sensitivity analysis excluding patients without warts at baseline

For participants without warts at baseline and with no new wart developed during the treatment, the CGI-C was considered as no change. An additional pre-specified analysis excluding patients with no warts at baseline showed similar results to the ITT population analysis (Table 44).

Table 44: Total Wart Change Score based on CGI-C from Central Review for the Target Regions for Subjects with Warts at Baseline

Visit	Statistics	Placebo (N=12)	X4P-001 (N=10)
Baseline CGI-S	n	12	10
	Mean (SD)	5.7 (1.15)	6.5 (2.37)
	Median	6.0	6.5
	Min, Max	4, 8	3, 10
Week 26 Total Wart Change Score [1]	n	12	9
	Mean (SD)	-0.5 (1.78)	-0.2 (1.92)
	Median	-0.5	0.0
	Min, Max	-4, 2	-4, 3
	LS Mean (SE)	-0.30 (0.521)	-0.89 (0.653)
	LS Mean 95% CI	(-1.32, 0.72)	(-2.17, 0.40)
	Difference from Placebo:		
	LS Mean Difference (SE)		-0.59 (0.888)
	LS Mean Difference 95% CI		(-2.33, 1.15)
	P-Value [2]		0.5083

Visit	Statistics	Placebo (N=12)	X4P-001 (N=10)
Week 52 Total Wart Change Score [1]	n	12	8
	Mean (SD)	-1.7 (2.10)	-0.9 (2.75)
	Median	-1.5	0.0
	Min, Max	-5, 1	-6, 3
	LS Mean (SE)	-1.46 (0.763)	-1.36 (0.921)
	LS Mean 95% CI	(-2.96, 0.03)	(-3.17, 0.44)
	Difference from Placebo:		
	LS Mean Difference (SE)		0.10 (1.234)
	LS Mean Difference 95% CI		(-2.32, 2.52)
	P-Value [2]		0.9346

Another sensitivity analysis was conducted for the total wart change score based on CGI-C scores from central review of the target regions with missing total wart change score imputed with zero. The results are consistent with the results of the multiple imputation method (Table 45).

Table 45: Total Wart Change Score based on CGI-C from Central Review for the Target Regions with Missing Total Wart Change

Visit	Statistics	Placebo (N=17)	X4P-001 (N=14)
Baseline CGI-S	n	17	13
	Mean (SD)	4.9 (1.58)	5.7 (2.56)
	Median	5.0	6.0
	Min, Max	3, 8	3, 10
Week 26 Total Wart Change Score [1]	n	17	13
	Mean (SD)	-0.4 (1.50)	-0.2 (1.57)
	Median	0.0	0.0
	Min, Max	-4, 2	-4, 3
	LS Mean (SE)	-0.33 (0.370)	-0.66 (0.465)
	LS Mean 95% CI	(-1.09, 0.44)	(-1.62, 0.30)
	Difference from Placebo:		
	LS Mean Difference (SE)		-0.33 (0.606)
	LS Mean Difference 95% CI		(-1.58, 0.92)
	P-Value [2]		0.5900

Visit	Statistics	Placebo (N=17)	X4P-001 (N=14)
Week 52 Total Wart Change Score [1]	n	17	13
	Mean (SD)	-1.2 (1.91)	-0.5 (2.15)
	Median	0.0	0.0
	Min, Max	-5, 1	-6, 3
	LS Mean (SE)	-1.15 (0.528)	-1.04 (0.634)
	LS Mean 95% CI	(-2.24, -0.06)	(-2.34, 0.26)
	Difference from Placebo:		
	LS Mean Difference (SE)		0.11 (0.833)
	LS Mean Difference 95% CI		(-1.60, 1.82)
	P-Value [2]		0.8978

Note: "*" represents p-values that are <=0.05.
SD = standard deviation, min = minimum; max = maximum; LS = least squares; SE = standard error; CI = confidence interval.
Note: The total wart change score is calculated by summing the Regional Wart Change Scores from all 3 target regions.
Note: For participants without warts at baseline and with no new wart developed during treatment, the CGI-C is considered as no change.
Note: The missing total wart change score is imputed with zero.
Note: Descriptive statistics are based on observed values.
[1] Represents change from baseline
[2] The results are based on an MMRM analysis with total wart change score as a dependent variable; treatment, visit (Weeks 26 and 52), treatment*visit, Ig use (randomization strata), baseline CGI-S (sum in the three target areas), age, and sex as covariates; and participant as the repeated random effect. The Kenward-Roger approximation for degrees of freedom is used. The UN covariance structure is employed.
Cross-reference: Listing 16.2.6.4.1
Program: t_l4_2_3_3_2.sas Data cut-off date: 11NOV2022 Run Date: 21DEC2022 14:14

Local Dermatologist Review of Warts

Local dermatological review of warts was based on evaluation across all 23 body regions (in contrast to 3 targeted regions that were assessed in the central review). When evaluated locally, all 23 regions were assessed using the same scale as for the central reviews (i.e., CGI-C and CGI-S).

Analyses of total wart change acore based on CGI-C from local dermatological review are provided in Table 46.

Table 46: Summary and Analysis of Total Wart Change Score Based on CGI-C From Local Dermatologist Review of Warts for All Regions for Patients with Warts at Baseline – Randomized Placebo-Controlled Period – ITT Population

Visit	Statistics	Placebo (N=17) n (%)	Mavorixafor (N=14) n (%)
Baseline CGI-S	n	12	10
	Mean (SD)	30.79 (9.703)	30.50 (8.182)
	Median	26.75	27.00
	Min, Max	24.0, 57.0	24.0, 50.0
Number of regions with warts at baseline	Mean (SD)	5.33 (5.852)	4.40 (3.273)
Week 26 total wart change score[a]	n	12	9
	Mean (SD)	-1.46 (3.917)	0.89 (3.919)
	Median	-1.00	0.00
	Min, max	-11.0, 6.0	-4.0, 10.0
	LS mean (SE)	-1.02 (1.064)	0.39 (1.304)
	LS mean 95% CI	(-3.11, 1.06)	(-2.17, 2.94)
	Difference from placebo:		
	LS mean difference (SE)		1.41 (1.722)
	LS mean difference 95% CI		(-1.96, 4.79)
	p-value [b]		0.4126
Week 52 total wart change score[a]	n	12	8
	Mean (SD)	-0.67 (3.085)	-0.25 (4.132)
	Median	-1.00	-0.50
	Min, max	-6.0, 7.0	-5.0, 8.0
	LS mean (SE)	-0.23 (0.900)	-0.41 (1.191)
	LS mean 95% CI	(-2.00, 1.53)	(-2.74, 1.93)
	Difference from placebo:		
	LS mean difference (SE)		-0.17 (1.538)
	LS mean difference 95% CI		(-3.19, 2.84)
	p-value[b]		0.9097

CGI-C=Clinical Global Impression of Change; CGI-S=Clinical Global Impression of Severity; CI=confidence interval; Ig=immunoglobulin; ITT=Intent-to-Treat; MMRM=mixed-model repeated measures; LS=least squares; max=maximum; min=minimum; SD=standard deviation; SE=standard error; UN=unstructured.
Note: "*" represents p-values ≤0.05.
Note: The total wart change score is calculated by summing the Regional Wart Change Scores from all 3 target regions.
Note: For patients without warts at baseline and with no new wart developed during treatment, the CGI-C is considered as no change.
Note: The missing total wart change score is imputed with the multiple imputation method (under missing at random assumption) using the SAS PROC MI procedure.
Note: Descriptive statistics are based on observed values.
[a] Represents change from baseline.
[b] The results are based on an MMRM analysis with total wart change score as a dependent variable; treatment, visit (Weeks 26 and 52), treatment*visit, Ig use (randomization strata), baseline CGI-S (sum in the 3 target areas), age, and sex as covariates; and patient as the repeated random effect. The Kenward-Roger approximation for degrees of freedom is used. The UN covariance structure is employed.

Incidence of new warts

The development of new warts was assessed based on dermatological examination by the investigator (local review). At baseline, 10 (71.4%) patients in the mavorixafor arm and 12 (70.6%) patients in the placebo arm had warts.

In mavorixafor-treated patients who had warts at baseline, 5 (35.7%) patients developed warts at 13 new locations at any timepoint after baseline, and at both week 26 and week 52 of treatment, there

were 3 (21.4%) mavorixafor patients who developed warts at a new location. In the placebo group, 6 (35.3%) patients who had warts at baseline developed new warts at any timepoint after baseline. Among patients with warts at baseline, the incidence of new wart development was similar between treatment groups; however, proportionally fewer patients treated with mavorixafor developed warts at week 52 compared with placebo (21.4% versus 35.3%), as 6 patients in the placebo group developed new warts in 10 locations.

In patients without warts at baseline, no (0%) patients treated with mavorixafor developed new warts at any time during the study compared with 1 (5.9%) placebo-treated patient who developed new warts. New warts developed in the 52-week randomised-controlled period by 3 (21.4%) patients in the mavorixafor arm and 7 (41.2%) patients in the placebo arm.

Fourth key secondary endpoint total infection score

For each patient, a total infection score over 52 weeks was calculated by a blinded, independent adjudication committee, summing the number of infection events by severity and dividing by the total exposure time (in years). Results are descriptive following the testing strategy and provided in Table 47.

Table 47: Summary and Analysis of Total Infection Score- Randomized Placebo- Controlled Period - ITT Population

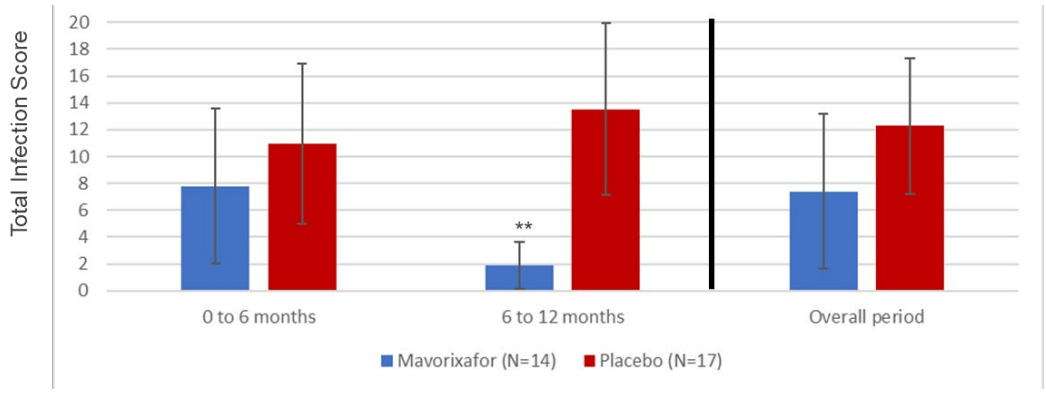
	Statistics	Placebo (N = 17) n (%)	X4P-001 (N = 14) n (%)
Previous 12 months infection rate	n	17	14
	Mean (SD)	1.24 (1.147)	1.00 (1.359)
	Median	1.00	0.00
	Min, max	0.0, 3.0	0.0, 4.0
Total infection score	n	17	14
	Mean (SD)	12.45 (11.510)	6.30 (9.053)
	Median	6.02	3.03
	Min, max	2.2, 36.6	0.0, 35.3
	LS mean (SE)	12.27 (2.443)	7.41 (2.805)
	LS mean 95% CI	(7.24, 17.30)	(1.64, 13.19)
	Difference from placebo:		
	LS mean difference(SE)		-4.85 (3.745)
	LS mean difference 95% CI		(-12.57, 2.86)
	Model effects p-value:		
	Treatment		0.2068
	Ig use		0.1193
	Infection rate of previous 12 months		0.0496

	Statistics	Placebo (N = 17) n (%)	X4P-001 (N = 14) n (%)
	Age		0.9266
	Sex		0.7605

Sensitivity analysis for different time intervals of the 52-week RCP

Analysis of the 6-month intervals demonstrated a greater reduction in the 6 to 12 month interval (~80%) in the mavorixafor arm (LS mean [SE] 2.67 [3.104]) compared with the placebo arm (13.34 [2.387]), p value 0.0122) (Figure 23).

Figure 23: Total Infection Score by 6 Month Interval and Overall Period



Important subgroup analysis for the fourth key secondary endpoint

For patients with concomitant immunoglobulin treatment, there is a numerical trend towards a lower total infection score for mavorixafor-arm compared to placebo. Furthermore, the same tendency towards a lower total infection score for treatment months 7-12 is observed.

Table 48: Total Infections Score by Subgroup and Treatment – Immunglobulin use strata

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Table 14.2.3.2.2
Summary and Analysis of Total Infections Score by Subgroup and Treatment - Randomized Placebo-Controlled Period
Intent-to-Treat Population

Group: Strata = Ig use

Variable	Statistics	Placebo (N=8)	X4P-001 (N=6)
Total Infection Score - by 3-month interval [2]			
0 - <= 3 months		14.00 (1.616,26.384)	5.89 (-9.253,21.035)
3 - <= 6 months		12.50 (-0.320,25.320)	4.84 (-5.919,15.605)
6 - <= 9 months		17.50 (7.398,27.602)	0.00 (0.000,0.000)
9 - <= 12 months		17.75 (2.801,32.705)	6.67 (-8.510,21.858)
Total Infection Score - by 6-month interval [2]			
0 - <= 6 months		13.25 (2.453,24.047)	7.90 (-6.786,22.586)
6 - <= 12 months		17.67 (5.500,29.839)	2.50 (-2.274,7.276)

For the subgroup of patients 12-18 years of age, there is a numerical trend towards a lower total infection score for mavorixafor-arm compared to placebo. Furthermore, a tendency towards a lower total infection score for treatment months 7-12 in the mavorixafor arm is observed.

Table 49: Total Infections Score by Subgroup and Treatment: Age 12-18 years

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Table 14.2.3.2.2
Summary and Analysis of Total Infections Score by Subgroup and Treatment - Randomized Placebo-Controlled Period
Intent-to-Treat Population

Group: Group: Age 12-<18 years

Variable	Statistics	Placebo (N=8)	X4P-001 (N=7)
Total Infection Score - by 3-month interval [2]			
0 - <= 3 months		5.50 (0.156,10.844)	2.86 (-1.780,7.495)
3 - <= 6 months		5.00 (0.356,9.644)	7.43 (-1.740,16.597)
6 - <= 9 months		10.00 (3.555,16.445)	2.29 (-3.307,7.879)
9 - <= 12 months		5.56 (0.471,10.640)	3.49 (-1.019,7.996)
Total Infection Score - by 6-month interval [2]			
0 - <= 6 months		5.25 (2.162,8.338)	5.14 (0.150,10.136)
6 - <= 12 months		7.85 (3.182,12.519)	2.88 (-0.124,5.883)

Pre-defined and post-hoc subgroup analyses

Annualised Infection Rate

Annualised infection rate, defined as the rate of infections per person per year of exposure, was on the one hand contributing to the total infection score and on the other hand an additional pre-specified secondary endpoint, not included in the formal testing hierarchy.

The mean (SD) annualised infection rate was 2.41 (3.106) in the mavorixafor arm and 4.73 (4.160) in the placebo arm. Treatment with mavorixafor showed lower annualised infection rates over the entire

12-month treatment period, which was determined to be statistically significant in a descriptive analysis (p-value 0.0072).

Reduction in annualised infection rate was consistently observed across subgroups in the mavorixafor arm, with numerically lower infection rates in both Ig and non-Ig users, patients below and above 18 years of age, US- and non-US patients, patients with R334X mutation or other mutations.

Table 50: Summary and Analysis of Annualised Infection Rate Based on Adjudicated Events – Randomized Placebo-Controlled Period – ITT Population

Statistics	Placebo (N=17) n (%)	Mavorixafor (N=14) n (%)
Summary of annualised infection rate		
N	17	14
Mean (SD)	4.73 (4.160)	2.41 (3.106)
Median	2.95	1.30
Min, max	1.0, 13.6	0.0, 11.8
Number of infections		
N	17	14
Mean (SD)	4.8 (4.18)	1.6 (1.50)
Median	3.0	1.0
Min, max	1, 13	0, 5
Number of infections, n (%)		
0	0	3 (21.4)
1	2 (11.8)	6 (42.9)
2	5 (29.4)	2 (14.3)
3	3 (17.6)	1 (7.1)
4	2 (11.8)	1 (7.1)
≥5	5 (29.4)	1 (7.1)
Proportion of patients with		
≥5 infections, n (%)	5 (29.4)	1 (7.1)
<5 infections, n (%)	12 (70.6)	13 (92.9)
P-value[a]		0.1329
Negative binomial model		
LS mean (SE)	4.2 (0.72)	1.7 (0.48)
Ratio[b]		0.417
95% CI of the ratio		0.220, 0.789
P-value		0.0072

CI=confidence interval; ITT=Intent-to-Treat; LS=least squares; SD=standard deviation, SE=standard error.
[a] The comparison between groups was performed using Cochran-Mantel-Haenszel statistics, stratified by Ig Use.
[b] Ratio refers to mavorixafor Negative Binomial LS Mean to Placebo Negative Binomial LS Mean based on annualised infection rate.

Annualised infection rate was assessed over 3- and 6-month intervals. The difference between mavorixafor – and placebo arm was more pronounced during months 7-12 of treatment (Table 51).

Table 51: Summary and Analysis of Annualised Infection Rate by 6-Month Intervals Based on Adjudicated Events – Randomized Placebo-Controlled Period – ITT Population

Statistics	Placebo (N=17) n (%)	Mavorixafor (N=14) n (%)
Annualised infection rate – by 6-month interval[a]		
0 to ≤6 months	3.9 (0.86)	2.3 (0.73)
6 to ≤12 months	4.3 (0.80)	0.9 (0.43)

CI=confidence interval; HR=hazard ratio; ITT=Intent-to-Treat; LS=least squares; SD=standard deviation, SE=standard error.
[a] LS Mean (SE)

Infection characteristics by treatment group- Adjudicated by Independent Adjudication Committee

Severity of infectious events was contributing to the key secondary endpoint total infection score. Patients in the mavorixafor arm were observed to have fewer severe infection events. Adjudicated infection-related events are provided in Table 52.

The number of patients prescribed topical and oral antibiotics for infection-related events was 6 (42.9%) in the mavorixafor arm compared to 12 (70.6%) in the placebo arm. The number of patients requiring hospitalisation was low overall, with 2 patients in the mavorixafor group and 1 patient in the placebo group.

Table 52: Summary of Adjudicated Infection-Related Events – Randomized Placebo-Controlled Period – ITT Population

Statistics	Placebo (N=17) n (%)	Mavorixafor (N=14) n (%)
Patients with at least 1 infection, n (%)	17 (100)	11 (78.6)
Summary of number of infections		
N	17	14
Mean (SD)	4.8 (4.18)	1.6 (1.50)
Median	3.0	1.0
Min, Max	1, 13	0, 5
Number of infections, n (%)		
0	0	3 (21.4)
1	2 (11.8)	6 (42.9)
2	5 (29.4)	2 (14.3)
3	3 (17.6)	1 (7.1)
4	2 (11.8)	1 (7.1)
≥5	5 (29.4)	1 (7.1)
Site of infection, n (%)		
Upper respiratory tract infection	13 (76.5)	7 (50.0)
Ear infection	1 (5.9)	0
Skin and skin structure	6 (35.3)	2 (14.3)
Urinary tract	1 (5.9)	0
Lower respiratory tract	3 (17.6)	0
Digestive system	2 (11.8)	2 (14.3)
Nervous system	0	0
Other	4 (23.5)	2 (14.3)
Severity based on treatment[a]		

Statistics	Placebo (N=17) n (%)	Mavorixafor (N=14) n (%)
N	17	11
Mean (SD)	1.9 (0.75)	2.1 (1.22)
Median	2.0	2.0
Min, max	1, 4	0, 4
Severity based on treatment, n (%)		
Level 0	0	1 (7.1)
Level 1	4 (23.5)	2 (14.3)
Level 2	11 (64.7)	5 (35.7)
Level 3	1 (5.9)	1 (7.1)
Level 4	1 (5.9)	2 (14.3)
≥Level 2	13 (76.5)	8 (57.1)
Severity based on CTCAE Grade, n (%)		
Grade 1	8 (47.1)	8 (57.1)
Grade 2	3 (17.6)	2 (14.3)
Grade 3	4 (23.5)	1 (7.1)
Grade 4	1 (5.9)	0
Grade 5	0	0
≥Grade 3	5 (29.4)	1 (7.1)
Total duration of infection (days)[b]		
N	17	14
Mean (SD)	49.1 (40.20)	14.1 (13.17)
Median	32.0	8.5
Min, max	8, 134	0, 43
Total duration of infection, n (%)		
0-2 days	0	3 (21.4)
3-5 days	0	0
6-10 days	1 (5.9)	5 (35.7)
>10 days	16 (94.1)	6 (42.9)
Infection-free time[c]		
N	17	14
Mean (SD)	317.6 (40.16)	303.9 (96.98)
Median	332.0	351.0
Min, max	216, 369	48, 365
Annual rate of infection		
N	17	14
Mean (SD)	4.727 (4.1601)	2.411 (3.1059)
Median	2.954	1.303
Min, max	1.00, 13.57	0.00, 11.78

CTCAE=Common Terminology Criteria for Adverse Events; ITT=Intent-to-Treat; SD=standard deviation; SE=standard error.
Note: Percentages of patients are based on the number of patients in each analysis group.
[a] Based on the highest severity. Applies to both numeric and categorical summary of severity.
[b] For patients with multiple infections, the durations of multiple infections are summed up to represent the total duration.
[c] Infection-free time is calculated as the cumulative amount of time (days) that a patient is not otherwise identified as having an infection.

The adjudicated infection-related events by infection location are summarised in Table 53.

Table 53: Summary of Adjudicated Infection-Related Events by Infection Location – Randomized Placebo-Controlled Period – ITT Population

Analysis Infection Location	Placebo (N=17) n (%) Patients, n (%)	Infections	Mavorixafor (N=14) n (%) Patients, n (%)	Infections
Any infection	17 (100)	81	11 (78.6)	22
Ear, inner	1 (5.9)	1	0	0
Gastrointestinal system	2 (11.8)	3	2 (14.3)	2
Lower respiratory system	3 (17.6)	5	0	0
Skin	6 (35.3)	24	2 (14.3)	2
Upper respiratory system	13 (76.5)	36	7 (50.0)	13
Urinary tract	1 (5.9)	2	0	0
Other	4 (23.5)	10	2 (14.3)	5
Cellulitis	1 (5.9)	1	0	0
Conjunctivitis	2 (11.8)	2	0	0
Lymphadenitis	0	0	1 (7.1)	1
Oral candidiasis	1 (5.9)	5	0	0
Vulvovaginal candidiasis	1 (5.9)	2	1 (7.1)	4

Note: Percentages are based on the number of patients in each analysis group.
Note: If a patient had 2 or more events for the same category, the patient is counted only once for that category. The same patient may appear in different categories.

Qualitiy of life questionaires

The exploratory results of quality of life (assessed by 36-Item Short Form Survey, EQ-5D-5L, Life Quality Index, and Dermatology Life Quality Index) were similar between the two treatment groups and remained relatively stable during the study period.

Patients exit interviews

Fourteen (64%) of the 22 patients (9 in the mavorixafor group and 13 in the placebo group) participated in the exit interview and shared insights about their experience with WHIM syndrome and study treatment and gave examples of changes during the study. Seven (78%) respondents in the mavorixafor group reported improvements in daily life, no negative impacts were reported. Improvements were reported by 10 (77%) respondents from the placebo group, some negative impacts were reported in this group.

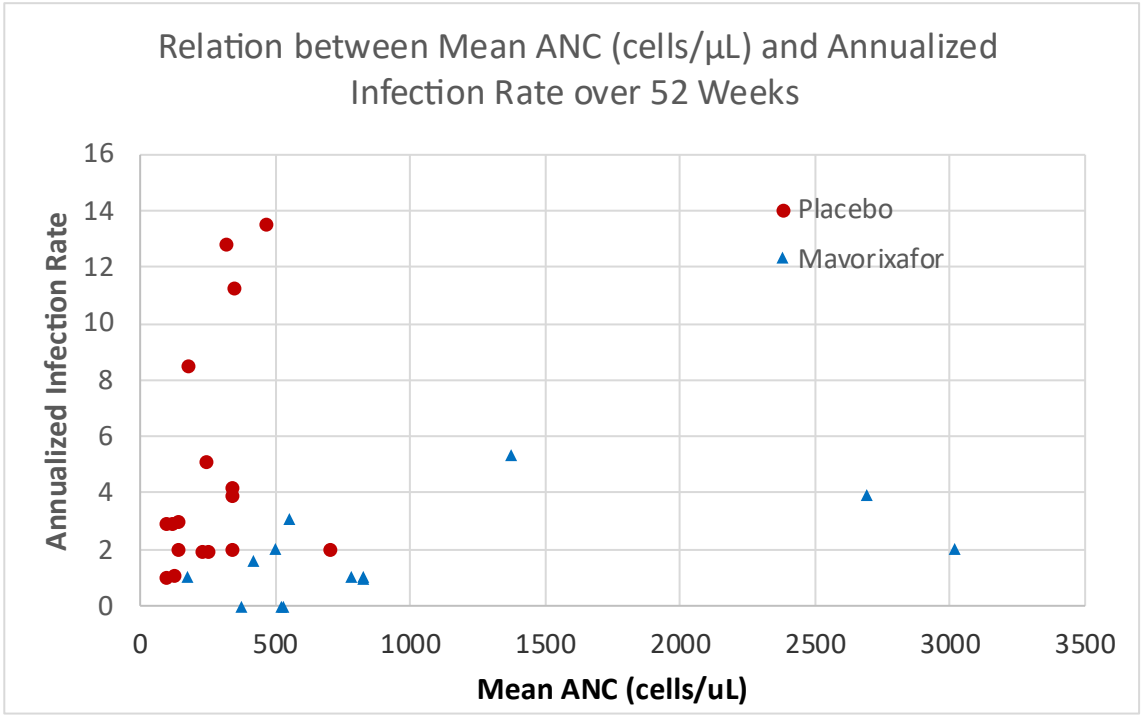
In the mavorixafor arm, 51% rated overall symptoms by WHIM syndrome to be improved in comparison to 36% in the placebo arm. For infections, 55% of the mavorixafor arm and 36% of the placebo arm saw an improvement of this symptom. For the global impression of change in warts, 33% of patients in the mavorixafor arm declared an improvement in comparison to 45% in the placebo arm.

Relationship between mean ANC values and annualised infection rate

To illude the assumed relationship of ANC values and infection rate, a plot of the mean ANC against annualised infection rate for the mavorixafor and placebo arm at Week 52 (*post hoc* analysis) is provided in Figure 24.

1 of 17 patients in the placebo group had ANC counts above 500 cells/µL at week 52. In contrast, 9 of 13 patients in the mavorixafor group had ANC counts above 500 cells/µL at week 52. Patients with ANC over 500 cells/µL had lower annualised infection rates.

Figure 24: Relationship between mean ANC (cells/µL) and annualised infection rate over 52 weeks

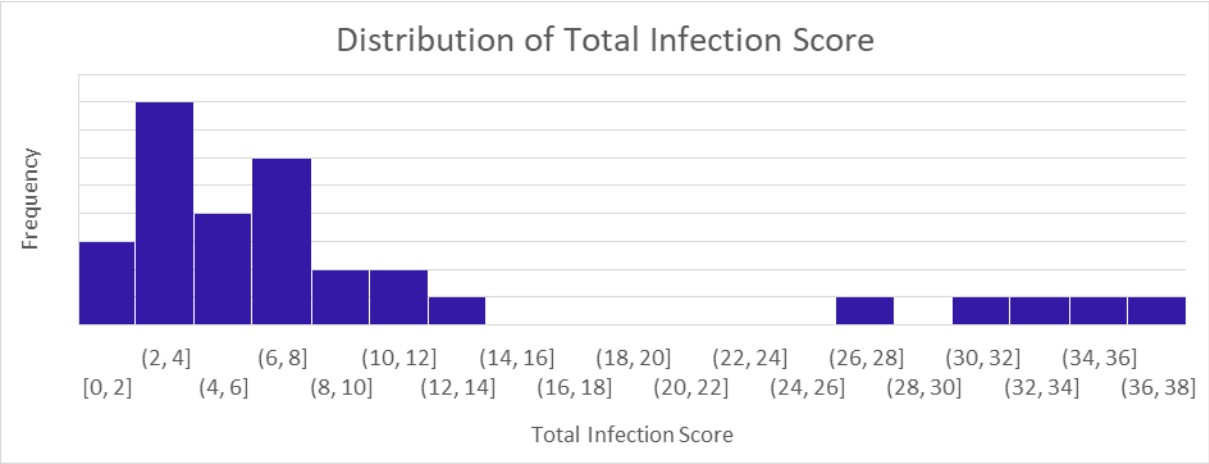


Note: Annualised infection rate is calculated by the total infection score over 52 weeks, weighted by event severity based on the adjudicated infection event data. Note: Blue triangles=mavorixafor, red dots=placebo.
Note: Excludes Week 52 data from 3 placebo patients who received mavorixafor at Week 52

Discussion of non-significant results regarding infections

The lack of significance in the original analysis of covariance (ANCOVA) score was driven largely by its non-normal distribution (ANCOVA analysis of total infection). Upon examination post database lock, the total infection score data exhibited markedly skewed distributions, with many data points concentrated near either 0 (lowest value) or 36 (highest value). This was further exacerbated by data from one outlier participant who was treated for only 31 days. Figure 25 shows the distribution of total infection scores.

Figure 25: Distribution of Total Infection Score



Upon the CHMP's request, the applicant provided further non-parametric and sensitivity analyses for infection data.

Table 54: Summary of post-hoc and prespecified analyses for infection data

Analysis	Title	Pre-specified or post-hoc	P-value
1). Original ANCOVA analysis for total infection score	Summary and Analysis of Total Infections Score	Pre-specified	0.2068
2). Negative Binomial regression on annualized infection rate	Summary and Analysis of Annualized Infection Rate based on Adjudicated Events	Pre-specified	0.0072*
3). Win-ratio analysis of composite endpoint	Unmatched Win Ratio Analysis of the Composite Endpoint Without Strata Considering Infection Score before Warts Score	Post-hoc (per FDA recommendation, included in the initial submission)	0.0003*
4). Sensitivity analysis of ANCOVA by excluding 1 outlier	Summary and Analysis of Total Infections Score on Subjects with more than 3 Months of Treatment	Post-hoc (included in the initial submission)	0.0245*
5). ANCOVA analysis on ranks	Rank Summary and Analysis of Total Infections Score	Post-hoc	0.0490*
6). Wilcoxon rank sum test	Wilcoxon rank-sum test Summary and Analysis of Total Infections Score	Post-hoc	0.0267*
7). Van Elteren test with WEIGHTS =STRATUM and RANKS=OVERALL options	Van Elteren test stratified by baseline Ig use Summary and Analysis of Total Infections Score	Post-hoc	0.0301*

Note: "*" represents p-values that are <0.05.

Vaccine titer levels

In study X4P-001-103, vaccine response was explanatorily evaluated, using HPV, tetanus, and pertussis vaccines.

Human papilloma virus

There was no significant difference in anti-HPV-16 and anti-HPV-18 antibody titers between the mavorixafor and placebo arm. Patients who had received HPV vaccines prior to the study had significantly higher anti-HPV-16 and anti-HPV-18 antibody titers at baseline (Week 0) compared with those that did not receive HPV vaccines prior to the study. For both, mavorixafor and placebo arms, anti-HPV-16 and anti-HPV-18 antibody titers were significantly increased at week 52 compared with baseline titers.

Table 55: Anti-HPV-16 and anti-HPV-18 antibody titer in fold change from baseline in the mavorixafor -/ and placebo arm.

	Anti-HPV-16 antibody titer		Anti-HPV-18 antibody titer	
	Placebo	Mavorixafor	Placebo	Mavorixafor
Week 0	1.0	1.0	1.0	1.0
Week 26	1.2	1.2	1.2	1.2
Week 39	1.2	1.3	1.3	1.3
Week 52	1.3	1.4	1.3	1.4
Mean	1.2	1.3	1.3	1.3

Fold change was calculated by dividing the values for Weeks 26, 39, and 52 respectively by baseline values (Week 0).

Tetanus vaccination

For patients in the mavorixafor arm, stronger increases in tetanus titer levels compared with those in the placebo arm could be observed (overall MMRM result for change in tetanus IgG / quant. (in U/ml): 1.73 vrs 1.06 in the mavorixafor-/ and placebo arm, respectively, descriptive p= 0.0387).

Pertussis vaccination

Titers of pertussis vaccine showed a numerical stronger increase in the mavorixafor arm compared to the placebo arm (descriptive p value=0.1698).

Pharmacodynamic results

In the 2 patients treated with mavorixafor 200 mg, ANC change from baseline was >2 fold, and TATANC was >22 hours.

Time Course of ANC and ALC During Dosing Interval

Arithmetic mean (SD) pre dose ANC (trough values) in the mavorixafor arm was 971.7 (1072.9) cells/µL at Week 13 and 794 (804.5) cells/µL at Week 52. ANC rose to a mean (SD) maximum of 1604.6 (1614.8) cells/µL at Week 13 and 1456.3 (1156.6) cells/µL at Week 52, at 4 hours post dose for each visit. ANC in the mavorixafor arm returned to pre dose levels by the end of the 24 hour dosing interval. In the placebo arm, pre dose levels were lower, at approximately 300 cells/µL and showed almost no increase during the dosing interval. The evolution of ALC mirrored the time course of ANC levels.

Results from the Open Label Extension Period (OLE) of pivotal study X4P-001-103

Data cut-off for the ongoing uncontrolled OLE period for this submission was 31 August 2023 and included supportive efficacy estimates from 27 patients who either continued open- label mavorixafor treatment or crossed over from placebo to open-label mavorixafor. Safety and tolerability were the primary objectives, with ANC, ALC and clinical findings as secondary endpoints.

Effects on neutrophils in the OLE

In the OLE, the effect on neutrophils was assessed by a single measurement of peripheral blood ANC instead of calculation of the duration above a certain threshold TAT_{ANC} as in the randomised controlled period. For patients continuing mavorixafor from the former mavorixafor-arm, mean ANC of OLE week 13 to OLE week 52 were between 0.3 to 0.67 G/L. For patients switching from the former placebo arm

to open-label mavorixafor, an increase from a baseline mean ANC of 0.18 G/L to week 13-week 52 ANC of 0.3 G/L to 0.9 G/L was observed (Table 56).

Table 56: Summary of Observed and Change from Baseline Values for Neutrophils (ANC) in OLE (Safety Population)

Visit	Statistics	Open label extension (OLE) up to database cut-off 31 August 2023					
		Placebo to Mavorixafor (N=16)		Mavorixafor to Mavorixafor (N=11)		Overall (N=27)	
		Actual	Change[a]	Actual	Change[a]	Actual	Change[a]
OLE Baseline	n	16	-	11	-	27	-
	Mean (SD)	0.329 (0.4040)	-	0.690 (0.4906)	-	0.476 (0.4683)	-
	Median	0.180	-	0.500	-	0.330	-
	Min, max	0.03, 1.62	-	0.06, 1.49	-	0.03, 1.62	-
OLE Week 13	n	11	11	7	7	18	18
	Mean (SD)	0.883 (0.7438)	0.510 (0.7217)	0.434 (0.2844)	-0.229 (0.4896)	0.708 (0.6361)	0.223 (0.7268)
	Median	0.610	0.150	0.400	-0.200	0.465	0.070
	Min, max	0.21, 2.32	-0.34, 1.98	0.04, 0.88	-1.06, 0.47	0.04, 2.32	-1.06, 1.98
OLE Week 26	n	12	12	6	6	18	18
	Mean (SD)	0.483 (0.2941)	0.253 (0.4068)	0.407 (0.2557)	-0.147 (0.3676)	0.457 (0.2767)	0.120 (0.4295)
	Median	0.440	0.190	0.440	-0.080	0.440	0.160
	Min, max	0.18, 1.21	-0.63, 0.87	0.00, 0.70	-0.75, 0.21	0.00, 1.21	-0.75, 0.87
OLE Week 39	n	11	11	6	6	17	17
	Mean (SD)	0.602 (0.6140)	0.352 (0.6180)	0.342 (0.1566)	-0.212 (0.4622)	0.510 (0.5096)	0.153 (0.6185)
	Median	0.400	0.270	0.365	-0.075	0.400	0.090
	Min, max	0.05, 2.12	-0.30, 1.89	0.10, 0.52	-0.85, 0.24	0.05, 2.12	-0.85, 1.89
OLE Week 52 (EOT)	n	6	6	6	6	12	12
	Mean (SD)	0.560 (0.5236)	0.410 (0.5710)	0.873 (0.6655)	0.348 (0.5348)	0.717 (0.5939)	0.379 (0.5284)
	Median	0.345	0.140	0.675	0.310	0.490	0.185
	Min, max	0.13, 1.48	0.01, 1.45	0.25, 1.86	-0.20, 1.27	0.13, 1.86	-0.20, 1.45

ALC=absolute lymphocyte count; EOT=end of treatment; max=maximum; min=minimum; NA=not applicable; OLE=open-label extension; RCP=randomized-controlled period; SD=standard deviation

Note: Baseline is based on the baseline visit values. Baseline is defined as the most recent non-missing measurement on or before the date of the first administration of the study drug or placebo. For open-label extension period placebo to mavorixafor group and mavorixafor to mavorixafor group, baseline is the most recent non-missing measurement on or before the date of the first administration of mavorixafor in open- label extension period. For open-label extension period of the three placebo subjects who took mavorixafor at Week 52, baseline is the most recent non-missing measurement on or before the date of the first administration of placebo in placebo-controlled period.

[a] Represents change from baseline.

Effects on lymphocytes in the OLE

Both patients remaining on mavorixafor and patients crossing over from placebo to mavorixafor in the open-label period showed levels of median ALC between 0.665 to 0.955 G/L in the OLE week 13- to week 52 ALC measurements.

Table 57: Summary of observed and change from baseline values for lymphocytes (ALC) in OLE (Safety Population)

Visit	Statistics	Open label extension (OLE) up to database cut-off 31 August 2023					
		Placebo to Mavorixafor (N=16)		Mavorixafor to Mavorixafor (N=11)		Overall (N=27)	
		Actual	Change[a]	Actual	Change[a]	Actual	Change[a]
Lymphocytes (10^9/L)							
OLE Baseline	n	16	-	11	-	27	-
	Mean (SD)	0.540 (0.3737)	-	0.892 (0.2743)	-	0.683 (0.3749)	-
	Median	0.405	-	0.780	-	0.620	-
	Min, max	0.29, 1.68	-	0.62, 1.51	-	0.29, 1.68	-
OLE Week 13	n	11	11	6	6	17	17
	Mean (SD)	0.930 (0.5499)	0.318 (0.2962)	0.677 (0.1776)	-0.095 (0.1859)	0.841 (0.4631)	0.172 (0.3272)
	Median	0.680	0.300	0.665	-0.035	0.680	0.120
	Min, max	0.40, 2.32	-0.29, 0.74	0.42, 0.94	-0.44, 0.06	0.40, 2.32	-0.44, 0.74
OLE Week 26	n	12	12	6	6	18	18
	Mean (SD)	1.068 (0.5172)	0.526 (0.2863)	0.753 (0.2787)	-0.088 (0.2218)	0.963 (0.4681)	0.321 (0.3953)
	Median	0.955	0.535	0.655	-0.080	0.890	0.355
	Min, max	0.49, 2.43	0.00, 1.08	0.44, 1.15	-0.34, 0.29	0.44, 2.43	-0.34, 1.08
OLE Week 39	n	11	11	6	6	17	17
	Mean (SD)	1.029 (0.4228)	0.472 (0.3330)	0.935 (0.2100)	0.093 (0.2741)	0.996 (0.3573)	0.338 (0.3571)
	Median	0.800	0.410	0.955	0.110	0.950	0.340
	Min, max	0.58, 1.80	0.08, 1.10	0.57, 1.20	-0.27, 0.42	0.57, 1.80	-0.27, 1.10
OLE Week 52 (EOT)	n	6	6	6	6	12	12
	Mean (SD)	0.697 (0.1194)	0.275 (0.1892)	0.978 (0.6848)	0.160 (0.6819)	0.838 (0.4912)	0.218 (0.4809)
	Median	0.735	0.310	0.645	-0.100	0.690	0.070
	Min, max	0.50, 0.82	0.05, 0.45	0.57, 2.32	-0.23, 1.54	0.50, 2.32	-0.23, 1.54

ALC=absolute lymphocyte count; EOT=end of treatment; max=maximum; min=minimum; NA=not applicable; OLE=open-label extension; RCP=randomized-controlled period; SD=standard deviation

Note: Baseline is based on the baseline visit values. Baseline is defined as the most recent non-missing measurement on or before the date of the first administration of the study drug or placebo. For open-label extension period placebo to mavorixafor group and mavorixafor to mavorixafor group, baseline is the most recent non-missing measurement on or before the date of the first administration of mavorixafor in open- label extension period. For open-label extension period of the three placebo subjects who took mavorixafor at Week 52, baseline is the most recent non-missing measurement on or before the date of the first administration of placebo in placebo-controlled period.

[a] Represents change from baseline.

Effects on warts in the OLE

Based on central review, at OLE baseline the mean (SD) CGI-S was similar between the two patient groups. By Week 26 of the uncontrolled OLE, both groups had experienced an improvement in warts. The mean total wart change score reported in patients in the mavorixafor-to-mavorixafor group was -3.8 (1.33) vrs -2.2 (2.669) in comparison to in the placebo-to-mavorixafor group.

Table 58: Summary of Total Wart Change Score Based on CGI-C From Central Review for the Target Regions (ITT Population)

Visit	Statistics	Randomized controlled period (RCP)		Open label extension (OLE) up to database cut-off 31 August 2023		
		Placebo (N=17) n (%)	Mavorixafor (N=14) n (%)	Placebo to Mavorixafor (N=16) n (%)	Mavorixafor to Mavorixafor (N=11) n (%)	Overall (N=27) n (%)
(RCP or OLE) Baseline CGI-S	n	17	13	16	11	27
	Mean (SD)	4.9 (1.58)	5.7 (2.56)	4.6 (1.75)	5.8 (2.52)	5.1 (2.15)
	Median	5.0	6.0	4.0	5.0	5.0
	Min, max	3, 8	3, 10	3, 8	3, 10	3, 10
(RCP or OLE) Week 26 total wart change score[a]	n	17	12	12	6	18
	Mean (SD)	-0.4 (1.50)	-0.2 (1.64)	-2.2 (2.66)	-3.8 (1.33)	-2.7 (2.40)
	Median	0.0	0.0	-1.5	-4.0	-2.5
	Min, max	-4, 2	-4, 3	-6, 1	-6, -2	-6, 1

(RCP or OLE) Baseline CGI-S	n	17	13	16	11	27
	Mean (SD)	4.9 (1.58)	5.7 (2.56)	4.6 (1.75)	5.8 (2.52)	5.1 (2.15)
	Median	5.0	6.0	4.0	5.0	5.0
	Min, max	3, 8	3, 10	3, 8	3, 10	3, 10
(RCP or OLE) Week 26 total wart change score[a]	n	17	12	12	6	18
	Mean (SD)	-0.4 (1.50)	-0.2 (1.64)	-2.2 (2.66)	-3.8 (1.33)	-2.7 (2.40)
	Median	0.0	0.0	-1.5	-4.0	-2.5
	Min, max	-4, 2	-4, 3	-6, 1	-6, -2	-6, 1

CGI-C=Clinical Global Impression of Change; CGI-S=Clinical Global Impression of Severity; ITT=Intent-to- Treat; max=maximum; min=minimum; OLE=open-label extension; RCP=randomized-controlled period; SD=standard deviation

Note: Baseline is based on the baseline visit values. Baseline is defined as the most recent non-missing measurement on or before the date of the first administration of the study drug or placebo. For OLE, placebo- to-mavorixafor group and mavorixafor-to-mavorixafor group, baseline is the most recent non-missing measurement on or before the date of the first administration of mavorixafor in the OLE.

Note: The total wart change score is calculated by summing the Regional Wart Change Scores from all 3 target regions.

Note: For patients without warts at baseline and with no new wart developed during treatment, the CGI-C is considered as no change.

Note: The missing total wart change score is imputed with the multiple imputation method (under missing at random assumption) using the SAS PROC MI procedure. Descriptive statistics are based on observed values.

[a] Represents change from baseline. Cross-reference:

Local dermatologist review observed an improvement in warts in the OLE (Table 59).

Table 59: Summary of Total Wart Change Score Based on CGI-C from Local Dermatologist Review of Warts for All Regions (ITT Population)

Visit	Statistics	Randomized controlled period (RCP)		Open label extension (OLE) up to database cut-off 31 August 2023		
		Placebo (N=17) n (%)	Mavorixafor (N=14) n (%)	Placebo to Mavorixafor (N=16) n (%)	Mavorixafor to Mavorixafor (N=11) n (%)	Overall (N=27)
(RCP or OLE) Baseline CGI-S	n	17	14	16	11	27
	Mean (SD)	28.50 (8.839)	28.36 (7.662)	28.63 (10.436)	31.55 (12.612)	29.81 (11.232)
	Median	25.00	25.50	24.00	26.00	25.00
	Min, max	23.0, 57.0	23.0, 50.0	23.0, 64.0	23.0, 62.0	23.0, 64.0
Number of regions with warts at baseline	Mean (SD)	3.76 (5.460)	3.14 (3.416)	3.94 (6.126)	4.73 (5.479)	4.26 (5.775)
(RCP or OLE) Week 26 total wart change score[a]	n	17	12	12	6	18
	Mean (SD)	-1.03 (3.319)	0.67 (3.367)	-0.89 (1.380)	-2.17 (4.446)	-1.31 (2.726)
	Median	0.00	0.00	-0.33	0.00	0.00
	Min, max	-11.0, 6.0	-4.0, 10.0	-4.0, 1.0	-10.0, 1.0	-10.0, 1.0
(RCP or OLE) Week 52 total wart change score[a]	n	17	11	8	7	15
	Mean (SD)	-0.41 (2.599)	-0.18 (3.459)	-0.42 (0.850)	-2.86 (3.288)	-1.56 (2.566)
	Median	0.00	0.00	0.00	-2.00	-1.00
	Min, max	-6.0, 7.0	-5.0, 8.0	-2.0, 0.7	-8.0, 0.0	-8.0, 0.7
OLE Week 26 Year 2 total wart change score[a]	n	-	-	4	2	6
	Mean (SD)	-	-	-0.50 (1.000)	-6.00 (7.071)	-2.33 (4.320)
	Median	-	-	0.00	-6.00	-0.50
	Min, max	-	-	-2.0, 0.0	-11.0, -1.0	-11.0, 0.0
OLE Week 52/EOT Year 2 total wart change score[a]	n	-	-	1	1	2
	Mean (SD)	-	-	0.00 (NA)	3.00 (NA)	1.50 (2.121)
	Median	-	-	0.00	3.00	1.50
	Min, max	-	-	0.0, 0.0	3.0, 3.0	0.0, 3.0

CGI-C=Clinical Global Impression of Change; CGI-S=Clinical Global Impression of Severity; EOT=end of treatment; ITT=Intent-to-Treat; max=maximum; min=minimum; NA=not applicable; OLE=open-label extension; RCP=randomized-controlled period; SD=standard deviation

Note: Baseline is based on the baseline visit values. Baseline is defined as the most recent non-missing measurement on or before the date of the first administration of the study drug or placebo. For OLE, placebo- to-mavorixafor group and mavorixafor-to-mavorixafor group, baseline is the most recent non-missing measurement on or before the date of the first administration of mavorixafor in the OLE.

Note: The total wart change score is calculated by summing the Regional Wart Change Scores from all 3 target regions.

Note: For patients without warts at baseline and with no new wart developed during treatment, the CGI-C is considered as no change.

Note: The missing total wart change score is imputed with the multiple imputation method (under missing at random assumption) using the SAS PROC MI procedure. Descriptive statistics are based on observed values.

Effects on infections in the OLE

The total infection score remained in the same range for patients continuing mavorixafor in the OLE. The total infection score declined for patients crossing over from placebo from mean 12.63 (SD 11.514) to 4.09 (SD 4.119) with mavorixafor treatment. The effect was more pronounced after six months of treatment (Table 60).

Table 60: Summary of Total Infection Score (ITT Population)

Statistics	Randomized controlled period (RCP)		Open label extension (OLE) up to database cut-off 31 August 2023		
	Placebo (N=17) n (%)	Mavorixafor (N=14) n (%)	Placebo to Mavorixafor (N=16) n (%)	Mavorixafor to Mavorixafor (N=11) n (%)	Overall (N=27) n (%)
Previous 12 months infection rate					
n	17	14	-	-	-
Mean (SD)	1.24 (1.147)	1.00 (1.359)	-	-	-
Median	1.00	0.00	-	-	-
Min, max	0.0, 3.0	0.0, 4.0	-	-	-
Total infection score					
n	17	14	16	11	27
Mean (SD)	12.63 (11.514)	6.30 (9.053)	7.93 (8.409)	4.09 (4.119)	6.37 (7.144)
Median	6.02	3.03	4.86	2.88	2.91
Min, max	2.2, 36.6	0.0, 35.3	0.0, 26.9	0.0, 12.5	0.0, 26.9
Total infection score by 6-month intervals[a]					
0 to ≤6 months	10.94 (4.955,16.927)	7.81 (2.052,13.576)	16 12.71 (6.462,18.964)	11 4.07 (1.490,6.656)	27 9.19 (5.163,13.224)
6 to ≤12 months	13.90 (7.475,20.332)	1.87 (0.108,3.631)	15 2.00 (0.037,3.963)	9 4.00 (-0.676,8.676)	24 2.75 (0.792,4.708)
12 to ≤18 months	-	-	10 0.60 (-0.757,1.957)	6 5.24 (-3.414,13.902)	16 2.34 (-0.589,5.272)
18 to ≤24 months	-	-	4 0.00 (0.000,0.000)	2 1.00 (-11.706,13.706)	6 0.33 (-0.524,1.190)
24 to ≤30 months	-	-	1 0.00 (0.000,0.000)	1 0.00 (0.000,0.000)	2 0.00 (0.000,0.000)

Statistics	Randomized controlled period (RCP)		Open label extension (OLE) up to database cut-off 31 August 2023		
	Placebo (N=17) n (%)	Mavorixafor (N=14) n (%)	Placebo to Mavorixafor (N=16) n (%)	Mavorixafor to Mavorixafor (N=11) n (%)	Overall (N=27) n (%)
30 to ≤36 months	-	-	1 0.00 (0.000,0.000)	- NA (NA,NA)	1 0.00 (0.000,0.000)

CI=confidence interval; ITT=Intent-to-Treat; NA=not applicable; OLE=open-label extension; RCP=randomized- controlled period; SD=standard deviation

Note: Total infection score is based on adjudicated total infection score.

Note: previous 12 months infection rate is based on patient's medical records from the 12 months preceding the drug treatment (including the screening period prior to the first dose).

[a] For RCP, data are presented as mean with 95% CI from T distribution. For OLE, data are presented as M, Mean with 95% CI from T distribution. Note: M represents the number of patients that are at risk of infection for each of the time intervals.

Annualised infection rate in the OLE

In the OLE, the annualised infection rate was 2.82 in the placebo-to-mavorixafor and 1.52 in the mavorixafor-to-mavorixafor patients. The annualised infection rate in the second 6-month interval during the OLE was 0.80 in the placebo-to-mavorixafor group.

5.3.3. Clinical studies in special populations

No study was performed in special populations.

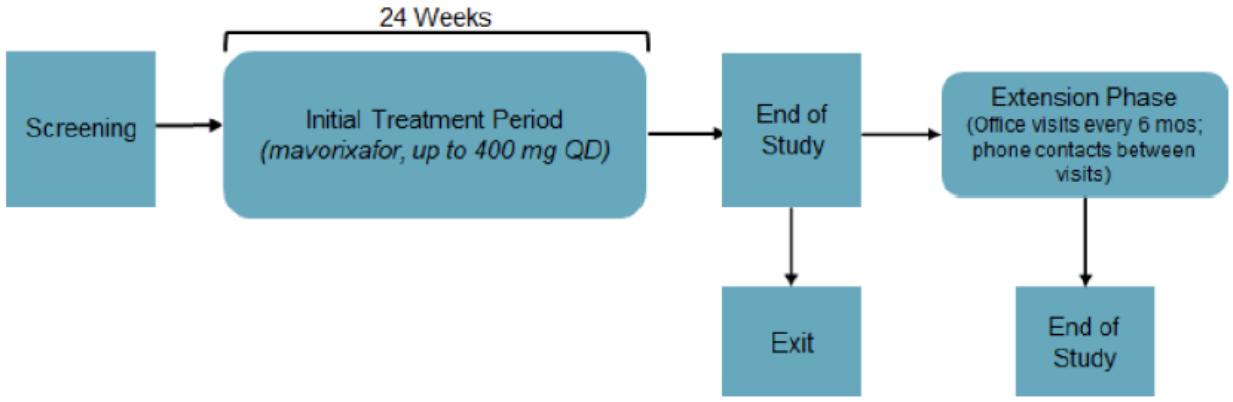
5.3.4. In-vitro biomarker test for patient selection for efficacy

Central sanger sequencing was performed for selection of patients based on detection of a mutation in line with WHIM syndrome as part of clinical routine diagnostics to establish the diagnosis.

5.3.5. Supportive study 001-MKKA

Completed phase II study X4P-001-MKKA is an uncontrolled, open-label, dose-escalation study with a 24-week treatment period and an extension phase until the end of the study (Figure 26) in patients older than the age of 18 with genotype confirmed WHIM syndrome and an absolute neutrophil count ≤400/µL and /or absolute lymphocyte count ≤650/µL in two independent blood samples. The concomitant use of immunoglobulin treatment was prohibited. The primary endpoint of this study was the mean value of the area under the plasma concentration-time curve for ANC (AUC_{ANC}) and /or the area under the plasma concentration-time curve for ALC (AUC_{ALC}) collected over a 24-hour period above clinically meaningful thresholds for the mavorixafor-treated patients over six months. In the X4P-001-MKKA study, the clinically meaningful threshold for ANC was defined as ANC ≥600/µL and for ALC ≥1000/µL. Statistical methods were descriptive. Exploratory endpoints were TAT_{ANC}, with the threshold of 500 cells/ µL, TAT_{ALC} with the threshold of 1000 cells/µL, incidence and severity of infections, change in number and severity of skin and genital warts over the treatment period and antibody levels following revaccination.

Figure 26: Overall Design Study X4P-001-103–Initial Treatment Period and Extension Phase,



Abbreviations: $AUC_{ANC/ALC}$=area under the curve for absolute neutrophil count and absolute lymphocyte count; QD=once daily.
*Dose escalations may be conducted in both treatment periods based on $AUC_{ANC/ALC}$ values, safety data, and review of clinical efficacy, up to a maximum dose of 400 mg daily.

From 17 January 2017 to 16 June 2022, 8 patients were enrolled in two study sites in the United States and in Australia. Doses were initially escalated from 50 mg mavorixafor QD to a maximum daily dose of 400 mg.

Neutrophil-responses to the 50 to 200 mg dose level were not shown. For 300 mg and 400 mg doses, mean ANC levels rose above the threshold. The mean AUC_{ANC} at 300/400 mg was 27477.00 (cells·hour/µL) at all visits in the initial treatment period of the uncontrolled study and 10357.88 (cells·hour/µL) at extension visits. The mean AUC_{ALC} at 300/400 mg was 14232.17 (cells·hour/µL) at all visits in initial the treatment period and 7023.12 (cells·hour/µL) at the extension visits, with a 2.6- to 2.9-fold increase in ANC and ALC during the extension phase.

Mean TAT_{ANC} was 14.0±9.2 hours at the combined 300/400 mg dose levels compared with 8.8±9.6 hours excluding data during infection events. The longest mean TAT_{ALC} was achieved at the combined 300/400 mg QD dose level with17.8±6.3 hours.

Mean infection scores were lowest at the 300/400 mg dose levels with an 84% reduction in infection score compared with the 50/100/150 mg doses (3.7% versus 23.5%).

Further descriptive analysis for annualised infection rate shows a reduction from 4.5 (SE 1.068) in the 12 months before mavorixafor-treatment to median 1.97 (SE 0.5495) at the dose levels 300/400 mg QD. The number of cutaneous warts counted was reduced by 79% at the 400 mg dose level by the end of the study.

The majority of patients had protective titers against haemophilus, rubella and measles at baseline and were not revaccinated.

No conclusions could be drawn from quality-of-life assessments due to low completion rates.

5.3.6. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

5.3.7. Patient experience data (PED)

Input from the patient organisation "International Patient Organisation for Primary Immunodeficiencies (IPOPI)" was received on 10 February 2025 according to the MAA:

Current treatments for WHIM syndrome focus on managing symptoms, such as infections, through prophylactic antibiotics, immunoglobulin therapy, or granulocyte-colony stimulating factors. However, these therapies do not address the underlying disease or prevent the development of HPV-related manifestations like warts in a population already at an increased risk for malignancies. There is a pressing need for more effective treatments that not only reduce infections but also protect against cancer. WHIM syndrome requires personalized treatment strategies due to the variability in presentation and severity. Each patient may exhibit different symptoms, so case-by-case medical counseling is essential, especially when considering CXCR4 antagonists. Treatment should also be closely monitored for potential cardiovascular side effects. Furthermore, reproductive health must be a key consideration due to the genetic nature of the disorder, with counseling necessary regarding the risks of passing on the condition and the effects of potential treatments on fertility.

5.3.8. Healthcare professional engagement

Input from the "European Academy of Allergy and Clinical Immunology (EAACI)" was received on 24 March 2025 according to the MAA:

WHIM syndrome has a clear genetic and functional basis, justifying a CXCR4 targeted approach in order to relief symptoms, prevent complications and improve quality of life through the re-balance of a dysregulated immune system function. There are no labeled treatments, and available approaches are mostly symptomatic. Mavorixafor represents an orally administered targeted treatment option that showed promising results in phase II and phase III clinical trials, going beyond the increase of neutrophils and lymphocytes count. Oral administration also represents a strength, considering that other CXCR4 antagonists are injectable since designed for episodic administration. While its use for patients with WHIM syndrome is supported by evidence and by clinicians who had the chance to use it for this purpose, being the most valuable available treatment and the only specifically approved for the disease, more data on long term usage in a real-life setting are needed, particularly for establishing treatment duration guidelines.

5.3.9. Overall discussion and conclusions on clinical efficacy

5.3.9.1. Discussion

Design and conduct of the clinical studies

The applicant conducted one supportive study and one pivotal study in patients with WHIM syndrome for the MAA.

Study X4P-001-MKKA (supportive study)

The completed uncontrolled phase II dose finding study X4P-001-MKKA including 8 patients above 18 years of age with WHIM syndrome, provided activity data for the dose level 300 / 400 mg mavorixafor QD. The exploratory endpoints in the supportive study were TAT_{ANC} and TAT_{ALC} with thresholds of ≥600/µL for ANC and for ≥1000/µL for ALC.

Study X4P-001-103 (pivotal study)

The clinical eligibility criteria chosen (ANC ≤ 400 cells/µL) were broad to cover a wide spectrum of patients from the age of 12 years affected by WHIM Syndrome and ultimately increase feasibility. Exclusion of patients with severe cytopenia, active infections, patients under antibiotic prophylaxis, or with QT interval prolongation >450 ms were agreed.

For study X4P-001-103, only patients with proven confirmation of the CXCR4 mutation were eligible (only *"patients with clinical diagnosis of WHIM syndrome" and "genotype-confirmed mutation of*

CXCR4 consistent with WHIM phenotype 4" (inclusion criterion #2)). WHIM syndrome is an inherited autosomal dominant monogenetic disease and the mechanism of action of mavorixafor relies on antagonism of the activated CXCR4-receptor due to mutation in *CXCR4*. The CHMP agreed that the indication wording does not need to mention a mandatory positive result regarding CXCR4 mutation test since genotyping of *CXCR4* is part of the clinical diagnostic work-up to confirm WHIM syndrome. However, there are case reports describing patients with WHIM-symptoms lacking *CXCR4* variants, estimated to account for approximately 3% of WHIM patients. The CHMP acknowledged that there is a lack of proof and doubt about the effectiveness in patients without a GOF-CXCR4 alteration irrespective of clinical presentation. Hence, a warning is implemented in Section 4.4 of the SmPC to warn prescribers that the efficacy and safety of mavorixafor have not been established in patients with WHIM-syndrome who do not carry pathogenic CXCR4 variants.

Comedication potentially influencing study estimates including antibiotic prophylaxis and G-CSF, was prohibited except immunoglobulin treatment, started before randomisation in the certain stratum.

Time in hours above the absolute neutrophil count threshold of 500 neutrophils /µl (TAT_{ANC}) was agreed on as a primary endpoint by the CHMP scientific advice. It was preferred to a 24h direct AUC okcomparison between mavorixafor and placebo group to emphasise the maintenance over the day of sufficiently high neutrophil counts. The applicant was alerted that the 500 neutrophils /µl threshold is rather unambitious, and results could be considered insufficient in case the effects on warts and infections do not show an improvement. In summary, the principle of a primary haematological endpoint to reach statistical significance in combination with clinically meaningful but not necessarily fully powered secondary endpoints was accepted in previous CHMP scientific advices, reflecting the limited sample size for an RCT in this ultra-orphan disease setting.

A clinical composite endpoint was chosen as a key secondary endpoint based on total infection score and total wart change score to increase the power of the statistical test to demonstrate efficacy in clinical endpoints. An ANCOVA model was applied to assess the contribution of mavorixafor (compared to placebo) to infections and to warts measured by the composite endpoint (rank sum of the individual ranked component total infection score and total ward change score).

The third key secondary endpoint in the testing hierarchy, severity of cutaneous warts and change over time for three target skin areas was assessed by a combination of a standardised definition of the three target areas in projection of the human body and severity on a five-tier scale (CGI-S). The degree of change over time was represented by a four-tier scale (CGI-C). However, in a pilot study to provide evidence of reliability, inter-rater reliability has not been shown for both, CGI-S and CGI-C with low concordance rates between different reviewers (agreement for CGI-S: 59%; for CGI-C: 72%). Only weak evidence for intra-rater reliability for the CGI-S was provided (68%), while the intra-rater reliability for CGI-C was high (80 an 97% for central reviewer A and B) questioning the methodological reliability of this efficacy assessment.

The assessment of the key secondary clinical endpoint total infection score was based on a patient related self-reporting system including a daily diary with potential further remote and in-patient treatment in case of infection-related signs or symptoms. Severity scoring was done on a five-tier scale, based on the intensity of the chosen treatment with slightly more granularity in the low and intermediate severity level in comparison to CTCAE.

Skin swab analyses were planned for exploratory research purposes. However, due to technical difficulties and methodological issues, no reliable data could be generated to date, and consequently, no corresponding report was included in the MAA submission.

For all primary and key secondary endpoints, intercurrent events were handled with a treatment policy strategy. It was agreed that this is the most reasonable approach as it reflects the real-world

treatment effect in routine clinical practice.

The CHMP requested clarifications regarding the changes made to the key secondary endpoints while the study was ongoing. The applicant clarified that the changes were made to improve statistical power after engagement with FDA before unblinding and before data analyses. The changes were not considered to affect study integrity.

Pivotal multiregional study X4P-001-103 was conducted from November 2019 to October 2022 in 20 sites and could enrol 31 patients. The amount of screening failures was low (4 patients). Three patients (21.4%) discontinued from the randomised-controlled period from the mavorixafor arm due to patient request (2 patients, 14.3%) and eligibility for early release (1 patient; 7.1%) compared to none in the placebo-arm. A total of 11 and 17 patients in the mavorixafor and placebo arms, respectively, completed the 52 weeks of treatment in the RCP. Consequently, drop- out rate was higher in the mavorixafor arm with cautious interpretability due to low sample size. There were 2 patients in the mavorixafor group who did not have sufficient dense samples to enable TAT calculation at Week 39 and one at Week 52, therefore they did not contribute to the TAT_{ANC} analysis at those specific visits.

Important baseline characteristics including age (median 17.5 versus 23 years in the mavorixafor and placebo arm, respectively), proportion of patients below 18 years of age (50 versus 47.1 in the mavorixafor and placebo arm, respectively), disease characteristics as baseline neutrophils (0.125 versus 0.206 G/L in the mavorixafor and placebo arm, respectively), median time since WHIM syndrome symptoms (13.46 versus 16.6 years in the mavorixafor and placebo arm, respectively) and diagnosis (8.32 versus 8.51 years in the mavorixafor and placebo arm, respectively) did not show a meaningful imbalance. Patients affected by infections over the past 12 months prior to study enrolment tended to be in favour of the mavorixafor arm (42.9 versus 64.7% of patients in the mavorixafor and placebo arm, respectively), while patients affected by warts at baseline (78.6 versus 64.7 % of patients in the mavorixafor and placebo arm, respectively) were numerically in favour of the placebo arm. In general, the median severity and frequency especially of infections appeared to be low (median number of infection events 2.0 per year for both arms, mean 2.3 and 1.9 events/ year). Only 31 patients from 20 sites were randomised due to the ultra rarity of the disease. Given the limited number of patients, it cannot be concluded whether the study population is fully representative for the target population with regard to the baseline infection burden. The CHMP considered however that the risk was sufficiently low to not further pursue the issue.

Efficacy data and additional analyses:

Study X4P-001-MKKA

The completed uncontrolled phase II dose finding study X4P-001-MKKA including 8 patients above 18 years of age with WHIM syndrome, provided activity data for the dose level 300 / 400 mg mavorixafor QD. The exploratory endpoints in the supportive study, TAT_{ANC} and TAT_{ALC} with thresholds of ≥600/µL for ANC and for ≥1000/µL for ALC, demonstrated promising mean time above threshold of 14.0 hours for ANC and 17.8 hours for ALC with a weak correlation with mavorixafor AUC0-24 (r=0.224). A numerical reduction in total infection score (-84%), annualised infection rate (-59%) and wart burden in comparison to 12 months pre-study derived from medical records could be observed at the 300/400 mg dose level in the uncontrolled open-label single arm trial.

Study X4P-001-103:

The primary efficacy endpoint was met, predefined as the time in which the neutrophil count is measured above a threshold of ≥500 cells/µL in a 24-hour in patient assessment (TAT_{ANC}), assessed at baseline and four times in the randomised-controlled period (every 3 months). Patients in the mavorixafor arm experienced a statistically significant longer TAT_{ANC} of 15.04 hours (SE 1.891)

compared to 2.75 hours (SE 1.518) of patients in the placebo arm (p<0.0001) with a significantly different increase from baseline (d0) of 12.78 hours (SE 1.891) in the mavorixafor arm compared to 0.49 hours (SE 1.518) in the placebo arm (p<0.0001). The effect was reproducible for each of the three monthly 24h-measurements, indicating a sustained effect, except for the week 52 measurement, where medication errors lead to false treatment of four patients. *Post-hoc* per protocol analysis provided a significant difference also for week 52-measurements. The difference between the arms remained statistically significant at 100 cell-tier thresholds from 500-1000 cells/µL with 5.24 hours above a threshold of 1000 neutrophils/µL in the mavorixafor arm compared to 0.45 hours in the placebo arm (p=0.0312). In the two patients treated with mavorixafor 200 mg, ANC change from baseline was >2 fold, and TAT_{ANC} was >22 hours. Arithmetic mean pre dose ANC in the mavorixafor arm was 971.7 (SD 1072.9) cells/µL at Week 13 and 794 (SD 804.5) cells/µL at Week 52. ANC in the mavorixafor arm returned to pre dose levels by the end of the 24-hour dosing interval. In the placebo arm, pre dose levels were lower at approximately 300 cells/µL and showed almost no increase during the dosing interval.

The first key secondary endpoint in the testing hierarchy, TAT_{ALC} (hours) above a prespecified threshold of ≥ 1000 lymphocytes/µL was reached with statistical significance in the overall analysis with a time above threshold of 15.8 hours (SE 1.385) compared to 4.55 hours (SE 1.148) in the placebo arm (p<0.0001). The finding was supported by sensitivity analyses according to change from baseline and in an analysis of the assessment days (week 13- 52) separately. Concerning T- cell subsets, the mean increase shown in comparison to baseline was 5.4-fold for CD4+ T-cells and 4.5-fold for CD8+ T-cells, with no clear percentage shift for any of the T-cell subsets (CD3+). According to B-Lymphocytes (CD19+), subsets of naïve B-cells (42-fold), unswitched memory cells (16.4-fold) and switched memory cells (6.4-fold) showed increases from baseline. No clear treatment effect of mavorixafor on serum immunoglobulin G levels could be observed in the RCP.

The 2nd key secondary composite endpoint of total infection score and total wart change score (sum of ranks for the individual components), assessed by ANCOVA was the first endpoint to evaluate *clinical* benefit. The composite endpoint had a positive trend but failed to meet statistical significance (LS mean 26.7 vrs 33.4; difference in composite rank sum 6.6 (SE 4.52), p=0.1422). However, in a *post-hoc* WIN ratio analysis, prioritizing the total infection score first and total wart change score second, the subsequently performed analysis showed statistical significance. The CHMP acknowledged that this analysis was recommended by FDA prior to unblinding study data. WIN ratio analysis is a not uncommonly used tool for the assessment of composite endpoints in the orphan setting. The reasoning, that frequent infections are the more significant manifestation of WHIM syndrome can be followed. The CHMP considered that the Win-Ratio analysis showed that the benefit of mavorixafor is driven by its effects on infections. While this analysis was considered reasonable especially considering the very limited sample size, it was only a *post-hoc* analysis providing supportive evidence. As only 22 of 31 patients were affected by warts at baseline, this might have impaired sensitivity, especially in a study with a low sample size. From a clinical point of view, the lack of a demonstration of mavorixafor's activity against warts remains.

The 3rd endpoint in the testing hierarchy, the second *clinical* endpoint, total wart change score by blinded independent review did not show a difference between the arms neither at 26 nor at 52 weeks of treatment. Local dermatologist review of warts did not demonstrate a difference between mavorixafor- or placebo-treated patients in terms of change in wart affection. The lack of a difference remained in a sensitivity analysis excluding patients without any warts at baseline (4 patients from mavorixafor-/ and 5 from placebo-arm) and in a sensitivity analysis for the total wart change score based on CGI-C scores from central review of the target regions with missing total wart change score imputed with zero. The mean burden of warts affecting the patients in both arms at baseline was low, the change in wart affection measured at the end of the 52-week RCP was low in both arms, too.

Support for a potential impact of mavorixafor on warts comes from the observational finding that less patients developed new warts in the mavorixafor arm (21.4% vrs 41.2%) and results of the uncontrolled OLE with an overall mean total wart change score of -2.7 (SD 2.40) with improvement of warts with longer exposure. However, an effect of mavorixafor on warts based on the study results cannot be concluded and the absence of difference in total wart change scores between mavorixafor and placebo arms at Week 52 is adequately reflected in SmPC Section 5.1.

The 4th key secondary endpoint, total infection score, was numerically 4.85 points lower in the mavorixafor arm (LS mean 7.41 (95% CI: 1.64, 13.19) vrs 12.27 (95% CI: 7.24, 17.30); 2-sided p value=0.21). As a component of the score, infection rate tended to favour the mavorixafor arm. Upon the CHMP's request, evaluation of infections was further discussed and additional *post hoc* analyses (Wilcoxon rank sum test; van Elteren test, ANCOVA analysis on ranks) were provided. Infection score data are very screwed and consequently assuming a normal distribution seems less appropriate and may have resulted in the failure to establish a significant treatment effect on total infection score based on the primary analysis. Although *post hoc*, all conducted additional/sensitivity analyses not relying on this assumption supported the conclusion on a benefit. The numerical improvements for total infection score were also observed in the open label extension period.

The annualised infection rate, an exploratory secondary endpoint, was numerically lower in the mavorixafor arm (p=0.0072), with a more pronounced effect in the 6–12-month period. Results on this endpoint were included in the SmPC Section 5.1, as considered clinically relevant. The trend to a lower infection-score and annualised infection rate was also eminent in the subgroup of patients 12-<18 years of age, in the stratum of patients receiving immunoglobulins. Further supportive evidence came from lower rates of repeat infections, prescriptions of topical or oral antibiotics and the duration of infection. In addition, severity of infections was lower in the mavorixafor arm (Grade 3 and 4: 7.1% in the mavorixafor arm versus 29.4% in the placebo arm). The findings from the OLE according to infections supported the RCP results for additional 12 months. The mean total infection score for the placebo-to-mavorixafor group was 7.93 (SD of 8.409) during the OLE period. Similar to patients in the mavorixafor group in the RCP, patients who transitioned to mavorixafor treatment in the OLE experienced a lower median total infection score of 2.00 (minimum of 0.037, maximum of 3.963) in the 6 to 12 months following initiation of mavorixafor treatment. Additionally, the OLE data showed that mavorixafor treatment decreased the annualised infection rate with initial treatment (annualised infection rate of 2.82 observed in placebo to mavorixafor patients) and maintained that effect with longer term treatment (annualised infection rate of 1.52 in the mavorixafor-to-mavorixafor patients). The annualised infection rate in the second 6-month interval during the OLE was 0.80 for the placebo to mavorixafor group. To contextualise the observed infection rates in the patients treated with mavorixafor in the OLE, the mean infection rate for the placebo group in the RCP of 4.73 can be used as the background rate of infection for estimating the predicted infection rate if these patients were untreated.

The exploratory endpoint $AUC_{ANC,}$ which was a first key secondary endpoint in the version 1 of the protocol, showed a statistically significant difference between treatment groups (LS Mean 8.56 (95% CI 8.22, 8.89) versus 9.58 (9.18, 9.98); p<0.001). Sustained effect on neutrophils counts was observed in the open label extension period.

In terms of response to HPV 16/18-vaccination, no contribution of mavorixafor to the antibody titre could be isolated. For tetanus-/ and pertussis vaccination responses, numerically higher antibody titres were found in the mavorixafor arm. Especially for WHIM patients, an effect on HPV would have been likely beneficial as HPV-associated warts are a mainstay of the syndrome. In the pivotal study, this was not the case. It is noticeable, that patients from both arms responded to the Gardasil vaccine (1.3-fold increase of titres (Ln)). Remarkably, for tetanus and pertussis vaccine, patients from the mavorixafor arm had higher titre responses. In a request for clarification, the applicant stated that

interpretation of HPV vaccine antibody titres is complex, as it is influenced by factors such as pre-existing HPV exposure, vitamin D status, and age. Furthermore, the humoral immune response to HPV vaccination is generally less robust and consistent than that observed with tetanus vaccination. There is no universal reference range for anti-HPV antibody titres, and no minimum antibody level has been established that correlated with protective immunity. Hence, no conclusion can be drawn on the effect of mavorixafor on HPV vaccination. Furthermore, considering also the lack of effects on warts, it remained questionable whether the treatment provides protection against potential complications such as HPV-associated squamous cell carcinomas which affects up to 16% of patients and other malignancies, which affect up to 30% of patients by the age of 30.

Overall, considering that the efficacy was mainly established on the PD endpoints TAT_{ANC} and TAT_{ALC}, upon the CHMP's request, the applicant agreed to revise the indication *in patients 12 years of age and older for the treatment of WHIM syndrome to increase the number of circulating mature neutrophils and lymphocytes*.

5.3.9.2. Conclusions on the clinical efficacy

The pivotal study X4P-001-103 was positive for the primary endpoint (TAT_{ANC}) and the key secondary endpoint (TAT_{ALC}). The second key secondary endpoint, a composite endpoint of total infection score and total wart change score, was not formally met in terms of the pre-specified testing hierarchy, hence, all clinical estimates remained descriptive from a methodological point of view. A *post-hoc* WIN ratio analysis prioritising infections led to significance. No improvement in warts could be demonstrated with mavorixafor treatment. It remained questionable whether the treatment with mavorixafor provides protection against potential complications such as HPV-associated squamous cell carcinoma. Impact on long term sequelae like malignancies is not predictable.

Hence, the CHMP concluded that the efficacy of mavorixafor is shown *in patients 12 years of age and older for the treatment of WHIM syndrome (warts, hypogammaglobulinemia, infections and myelokathexis) to increase the number of circulating mature neutrophils and lymphocytes.*

The CHMP considers the following Specific obligation necessary to generate long-term follow up efficacy data in the context of a marketing authorisation under exceptional circumstances:

- In order to investigate the long-term safety and efficacy of mavorixafor in the treatment of WHIM syndrome (warts, hypogammaglobulinemia, infections and myelokathexis) to increase the number of circulating mature neutrophils and lymphocytes in patients 12 years of age and older, the MAH shall conduct and submit the results of a non-interventional study based on a registry in patients collecting both safety and efficacy endpoints.

5.4. *Clinical safety*

Please refer to the table of studies in section 5.1.2. .

For the purpose of this document, the following definitions apply:

'Adverse event – AE' means any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

'Serious adverse event – SAE' means any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death. The definition (in line with ICH E2A) includes important medical events that may not be

immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

'Adverse Drug Reaction – ADR' means any untoward and unintended response to a medicinal product related to any dose administered, for which, after a thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or findings from epidemiological studies and/or on an evaluation of causality from individual case reports.

5.4.1. Safety data collection

The integrated safety analyses comprised 2 pooled groups:

- Group 1 included:
  - Patients who received ≥1 dose of mavorixafor in Study X4P-001-MKKA
  - Patients who received ≥1 dose of study intervention (placebo or mavorixafor) during the RCP of Study X4P-001-103
- Group 2 included:
  - Patients who received ≥1 dose of mavorixafor in Study X4P-001-MKKA
  - Patients who received ≥1 dose of mavorixafor during either the RCP or OLE of Study X4P-001-103

The integrated safety evaluations include patient disposition, demographics and baseline characteristics, medical history, prior and concomitant medications, extent of study drug exposure, adverse events (AEs), clinical laboratory assessments, ECG findings, and vital signs.

5.4.2. Patient exposure

The safety database for mavorixafor comprises 380 participants who have received ≥1 dose of mavorixafor, including 38 participants with WHIM syndrome, 43 participants with chronic neutoprenia, and 172 healthy participants. In combination with other oncology therapeutics, mavorixafor had been administered to 115 participants in various oncology indications.

The data from 2 studies of patients with WHIM syndrome have been pooled for an integrated summary of safety (ISS) with a database cut-off 06 September 2024.

Table 61: Exposure to Mavorixafor for Patients with WHIM Syndrome

Minimum duration of exposure	Study X4P-001-MKKA	Study X4P-001-103 RCP and OLE [a]	Total
	N	n	n
All exposed	8	30	38
6 months	6	25	31
1 year	5	23	28
2 years	5	15	20
3 years	5	5	10
4 years	3	1	4
5 years	2	0	2

OLE=open-label extension; RCP=randomized placebo-controlled period
a. Data for the OLE of Study X4P-001-103 as of database cut-off of 06 September 2024.

Table 62: Overall Extent of Exposure for Patients with WHIM Syndrome

	X4P-001-MKKA	X4P-001-103 (PCP)		X4P-001-103 (OLP)		Group 1			Group 2
Parameter	Mavorixafor (N=8)	Placebo (N=17)	Mavorixafor (N=14)	Placebo to Mavorixafor (N=16)	Mavorixafor to Mavorixafor (N=11)	Total (N=27)	Placebo (N=17)	Mavorixafor (N=22)	Mavorixafor (N=38)
Duration of study drug exposure (months) [1]									
n	8	17	14	16	11	27	17	22	38
Mean (SD)	31.343 (22.6980)	12.023 (0.6225)	10.276 (3.3921)	21.548 (11.9030)	18.882 (13.2785)	20.462 (12.3019)	12.023 (0.6225)	17.937 (16.9246)	24.929 (15.9104)
Median	42.891	11.959	11.795	23.967	17.840	23.524	11.959	11.877	24.181
Min, Max	0.20, 56.25	11.04, 14.03	1.02, 12.22	1.61, 43.07	1.05, 37.78	1.05, 43.07	11.04, 14.03	0.20, 56.25	0.20, 56.25
Total actual dose (mg) [2]									
n	8	17	14	16	11	27	17	22	38
Mean (SD)	317681.3 (251596.42)	122729.4 (32052.10)	113478.6 (45408.05)	235318.8 (158939.55)	216354.5 (181672.56)	227592.6 (165403.96)	122729.4 (32052.10)	187734.1 (180237.19)	270398.7 (192949.90)
Median	409475.0	141400.0	140800.0	251900.0	111200.0	227600.0	141400.0	142900.0	224150.0
Min, Max	1200, 670600	55000, 149600	12800, 149000	19200, 529200	12000, 507600	12000, 529200	55000, 149600	1200, 670600	1200, 670600

Note: PCP = Placebo-Controlled Period, OLP = Open-Label Extension Period

Note: Group 1 comprises subjects who received at least one dose of mavorixafor in Study X4P-001-MKKA, and subjects who received at least one dose of study treatment (placebo or mavorixafor) in Study X4P-001-103 during PCP. Group 2 includes subjects with WHIM syndrome who received at least one dose of mavorixafor in studies X4P-001-MKKA, and X4P-001-103 during either PCP or OLP.

[1] Duration of study drug exposure (in months) is calculated as (last dosing date - first dosing date + 1)/30.4375.

[2] Total actual dose (mg) is defined as sum of actual administered doses (mg) received during treatment.

[3] Actual dose intensity = total dose received (mg) / duration of treatment (days).

[4] Relative dose intensity = total actual dose (mg) / total planned dose (mg) * 100. Total planned dose (mg) = assigned dose (mg) * duration of study drug exposure (days), where assigned dose can be the modified dose by physician decision.

[5] Duration of treatment (in months) at certain dose level is defined as a continuous variable by the time a subject has been exposed to a different dose level. Patients with dose reduced to <=200mg were also included in the report.

Note: Some patient's compliance rate is high due to the number of returned tablets is missing.

Table 63: Summary of Patient Disposition (Safety Population)

Preferred Term	MKKA	103 (RCP)		103 (OLE)			Group 1 [a]		Group 2 [b]
	Mvx (N=8)	Pbo (N=17)	Mvx (N=14)	Pbo to Mvx (N=16)	Mvx to Mvx (N=11)	Total (N=27)	Pbo (N=17)	Mvx (N=22)	Mvx (N=38)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Completed study	6 (75.0) [c]	17 (100) [d, e]	11 (78.6) [d]	0	0	0	17 (100) [d, e]	17 (77.3) [d]	6 (15.8) [e, f]
Discontinued study	2 (25.0)	0	3 (21.4)	7 (43.8)	6 (54.5)	13 (48.1)	0	5 (22.7)	18 (47.4)
Reason for Discontinuation from Study									
Adverse event [g]	1 (12.5)	0	0	2 (12.5)	1 (9.1) [g]	3 (11.1)	0	1 (4.5)	4 (10.5)
Death	0	0	0	0	0	0	0	0	0
Protocol violation	0	0	0	0	0	0	0	0	0
Study termination by sponsor	0	0	0	0	1 (9.1)	1 (3.7)	0	0	1 (2.6)
Physician decision	0	0	0	0	0	0	0	0	0
Withdrawal by subject	1 (12.5)	0	2 (14.3)	2 (12.5)	2 (18.2)	4 (14.8)	0	3 (13.6)	7 (18.4)
Lost to follow up	0	0	0	1 (6.3)	0	1 (3.7)	0	0	1 (2.6)
Protocol-specified withdrawal criterion met	0	0	1 (7.1)	0	0	0	0	1 (4.5)	0
Other	0	0	0	2 (12.5)	2 (18.2)	4 (14.8)	0	0	5 (13.2)

103=Study X4P-001-103; MKKA=Study X4P-001-MKKA; n=number of patients; OLE=open-label extension; RCP=randomized placebo-controlled period.

a. Group 1 comprises patients who received ≥1 dose of mavorixafor in Study X4P-001-MKKA and patients who received ≥1 dose of study intervention (placebo or mavorixafor) during the RCP of Study X4P-001-103.

b. Group 2 comprises patients who received ≥1 dose of mavorixafor in Study X4P-001-MKKA and patients who received ≥1 dose of mavorixafor during either the RCP or OLE of Study X4P-001-103.

c. For Study XP4-001-MKKA, report initiation phase only (6 patients completed study, 2 patients discontinued study, 5 patients entered extension phase and completed extension phase).

d. For Study X4P-001-103, 'Completed study' in RCP means completed Week 52 treatment in RCP.

e. One participant in the placebo group during the RCP of Study X4P-001-103 completed the RCP but did not enter the OLE.

f. In Group 2, 'Completed study' means completed the initiation phase in Study X4P-001-MKKA or completed the OLE in Study X4P-001-103.

g. One patient had a TEAE that emerged during the RCP but led to discontinuation during the OLE.

Table 64: Patient Exposure (Cut off 14 May 2025)

	Patients enrolled	Patients exposed*	Patients exposed to the proposed dose range	Patients with long term** safety data (>=6months)	Patients with long term** safety data (>=12 months)
Blinded studies (placebo-controlled)	31	30	30	25	23
Blinded studies (active -controlled)	N/A	N/A	N/A	N/A	N/A
Open studies	8	8	8	6	5
Post marketing	21	21	21	11	0
Compassionate use	N/A	N/A	N/A	N/A	N/A

* Received at least 1 dose of active treatment
** In general this refers to 6 months and 12 months continuous exposure data, or intermittent exposure.

For Group 1, the mavorixafor group, the median duration of treatment was 11.88 months, and the median daily dose was 365.7 mg/day. For the placebo group, the median duration of treatment was 11.96 months.

The median duration of treatment for Group 2 was 24.18 months, and the median daily dose was 385.2 mg/day.

5.4.3. Adverse events

Table 65: Summary of adverse events (Safety population) 14 May 2025 cut-off

	MKKA		103 (RCP)				103 (OLE)						Group 1 [a]				Group 2 [b]	
	Mvx (N=8)		Pbo (N=17)		Mvx (N=14)		Pbo to Mvx (N=16)		Mvx to Mvx (N=11)		Total (N=27)		Pbo (N=17)		Mvx (N=22)		Mvx (N=38)	
	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]
Any TEAE	7 (87.5)	[113]	17 (100)	[146]	14 (100)	[89]	16 (100)	[211]	10 (90.9)	[76]	26 (96.3)	[287]	17 (100)	[146]	21 (95.5)	[202]	37 (97.4)	[489]
Grade ≥3 [c]	2 (25.0)	[4]	5 (29.4)	[14]	7 (50.0)	[14]	9 (56.3)	[14]	2 (18.2)	[9]	11 (40.7)	[23]	5 (29.4)	[14]	9 (40.9)	[18]	18 (47.4)	[41]
Treatment related [c]	4 (50.0)	[14]	3 (17.6)	[14]	7 (50.0)	[14]	12 (75.0)	[41]	2 (18.2)	[3]	14 (51.9)	[44]	3 (17.6)	[14]	11 (50.0)	[28]	23 (60.5)	[72]
Grade ≥3 and TR	0 (0)	[0]	0	[0]	1 (7.1)	[2]	0	[0]	1 (9.1)	[1]	1(3.7)	[1]	0	[0]	1 (4.5)	[2]	1 (2.6)	[2]
Serious	3 (37.5)	[5]	2 (11.8)	[2]	5 (35.7)	[10]	9 (56.3)	[12]	3 (27.3)	[6]	12 (44.4)	[18]	2 (11.8)	[2]	8 (36.4)	[15]	17 (44.7)	[33]
Serious and TR	0 (0)	[0]	0	[0]	0	[0]	1 (6.3)	[1]	0	[0]	1 (3.7)	[1]	0	[0]	0	[0]	1 (2.6)	[1]
Leading to DC [d]	1 (12.5)	[1]	0	[0]	0 [d]	[0]	2 (12.5)	[2]	0	[0]	2 (7.4)	[2]	0	[0]	1 (4.5)	[1]	4 [d] (10.5)	[4]
TR leading to DC	1 (12.5)	[1]	0	[0]	0	[0]	1 (6.3)	[1]	0	[0]	1 (3.7)	[1]	0	[0]	1 (4.5)	[1]	2 (5.3)	[2]
Leading to death	0 (0)	[0]	0	[0]	0	[0]	0	[0]	0	[0]	0	[0]	0	[0]	0	[0]	0	[0]

103=Study X4P-001-103; MKKA=Study X4P-001-MKKA; DC=discontinuation; [e]=number of events; n=number of patients; OLE=open-label extension; RCP=randomized placebo-controlled period; TEAE=treatment-emergent adverse event; TR=treatment related.
TEAEs were defined as any event that occurred or worsened on or after the first dose of study drug day up to 30 days following the last dose of study drug.
Participants reporting more than one TEAE within a SOC or PT were counted only once for that SOC or PT at the highest severity for the TEAE.
An AE was considered as treatment-related if it was definitely, probably, or possibly related to the study drug. AEs with missing or unknown relationship to the study drug were considered as treatment-related if there was a relationship with the onset of AE after the first dose of study drug.

a. Group 1 comprises patients who received ≥1 dose of mavorixafor in Study X4P-001-MKKA and patients who received ≥1 dose of study intervention (placebo or mavorixafor) during the RCP of Study X4P-001-103.
b. Group 2 comprised patients who received ≥1 dose of mavorixafor in Study X4P-001-MKKA and patients who received ≥1 dose of mavorixafor during either the RCP or OLE of Study X4P-001-103.
c. TEAEs with missing severity or relationship were counted as Grade 3 or treatment related, respectively
d. One patient had a TEAE that emerged during the RCP but led to discontinuation during the OLE.

Table 66: Treatment Emergent Adverse Events by SOC and PT Occurring in ≥2 Patients (>5% of Patients) in Any Treatment Group (Safety Population)

System Organ Class Preferred Term	MKKA		103 (RCP)				103 (OLE)						Group 1 [a]				Group 2 [b]	
	Mvx (N=8)		Pbo (N=17)		Mvx (N=14)		Pbo to Mvx (N=16)		Mvx to Mvx (N=11)		Total (N=27)		Pbo (N=17)		Mvx (N=22)		Mvx (N=38)	
	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]
Any Event	**7 (87.5)**	**[113]**	**17 (100)**	**[146]**	**14 (100)**	**[89]**	**16 (100)**	**[187]**	**10 (90.9)**	**[68]**	**26 (96.3)**	**[255]**	**17 (100)**	**[146]**	**21 (95.5)**	**[202]**	**37 (97.4)**	**[457]**
Blood and lymphatic system disorders	**0**	**[0]**	**0**	**[0]**	**4 (28.6)**	**[7]**	**2 (12.5)**	**[5]**	**4 (36.4)**	**[4]**	**6 (22.2)**	**[9]**	**0**	**[0]**	**4 (18.2)**	**[7]**	**9 (23.7)**	**[16]**
Anaemia	0	[0]	0	[0]	1 (7.1)	[1]	1 (6.3)	[1]	2 (18.2)	[2]	3 (11.1)	[3]	0	[0]	1 (4.5)	[1]	4 (10.5)	[4]
Iron deficiency anaemia	0	[0]	0	[0]	0	[0]	2 (12.5)	[4]	2 (18.2)	[2]	4 (14.8)	[6]	0	[0]	0	[0]	4 (10.5)	[6]
Thrombocytopenia	0	[0]	0	[0]	3 (21.4)	[3]	0	[0]	0	[0]	0	[0]	0	[0]	3 (13.6)	[3]	3 (7.9)	[3]
Congenital, familial and genetic disorders	**0**	**[0]**	**0**	**[0]**	**1 (7.1)**	**[1]**	**0**	**[0]**	**1 (9.1)**	**[1]**	**1 (3.7)**	**[1]**	**0**	**[0]**	**1 (4.5)**	**[1]**	**2 (5.3)**	**[2]**
Ear and labyrinth disorders	**2 (25.0)**	**[4]**	**3 (17.6)**	**[3]**	**0**	**[0]**	**1 (6.3)**	**[1]**	**0**	**[0]**	**1 (3.7)**	**[1]**	**3 (17.6)**	**[3]**	**2 (9.1)**	**[4]**	**3 (7.9)**	**[5]**
Ear pain	0	[0]	2 (11.8)	[2]	0	[0]	1 (6.3)	[1]	0	[0]	1 (3.7)	[1]	2 (11.8)	[2]	0	[0]	1 (2.6)	[1]
Eye disorders	**1 (12.5)**	**[1]**	**3 (17.6)**	**[4]**	**2 (14.3)**	**[4]**	**3 (18.8)**	**[5]**	**1 (9.1)**	**[1]**	**4 (14.8)**	**[6]**	**3 (17.6)**	**[4]**	**3 (13.6)**	**[5]**	**7 (18.4)**	**[11]**
Gastrointestinal disorders	**6 (75.0)**	**[16]**	**2 (11.8)**	**[3]**	**5 (35.7)**	**[6]**	**13 (81.3)**	**[22]**	**3 (27.3)**	**[4]**	**16 (59.3)**	**[26]**	**2 (11.8)**	**[3]**	**11 (50.0)**	**[22]**	**26 (68.4)**	**[48]**
Nausea	4 (50.0)	[6]	0	[0]	1 (7.1)	[1]	3 (18.8)	[3]	0	[0]	3 (11.1)	[3]	0	[0]	5 (22.7)	[7]	8 (21.1)	[10]
Diarrhoea	0	[0]	0	[0]	0	[0]	5 (31.3)	[5]	2 (18.2)	[2]	7 (25.9)	[7]	0	[0]	0	[0]	7 (18.4)	[7]

System Organ Class Preferred Term	MKKA		103 (RCP)				103 (OLE)						Group 1 [a]				Group 2 [b]	
	Mvx (N=8)		Pbo (N=17)		Mvx (N=14)		Pbo to Mvx (N=16)		Mvx to Mvx (N=11)		Total (N=27)		Pbo (N=17)		Mvx (N=22)		Mvx (N=38)	
	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]
Vomiting	0	[0]	1 (5.9)	[1]	2 (14.3)	[2]	1 (6.3)	[1]	2 (18.2)	[2]	3 (11.1)	[3]	1 (5.9)	[1]	2 (9.1)	[2]	5 (13.2)	[5]
Dyspepsia	3 (37.5)	[5]	0	[0]	1 (7.1)	[1]	0	[0]	0	[0]	0	[0]	0	[0]	4 (18.2)	[6]	4 (10.5)	[6]
Gastrooesophageal reflux disease	0	[0]	0	[0]	1 (7.1)	[1]	2 (12.5)	[2]	0	[0]	2 (7.4)	[2]	0	[0]	1 (4.5)	[1]	3 (7.9)	[3]
Abdominal discomfort	0	[0]	0	[0]	0	[0]	2 (12.5)	[2]	0	[0]	2 (7.4)	[2]	0	[0]	0	[0]	2 (5.3)	[2]
Abdominal pain	1 (12.5)	[1]	0	[0]	0	[0]	1 (6.3)	[1]	0	[0]	1 (3.7)	[1]	0	[0]	1 (4.5)	[1]	2 (5.3)	[2]
Dry mouth	2 (25.0)	[3]	0	[0]	0	[0]	0	[0]	0	[0]	0	[0]	0	[0]	2 (9.1)	[3]	2 (5.3)	[3]
General disorders and administration site conditions	**3 (37.5)**	**[4]**	**2 (11.8)**	**[2]**	**2 (14.3)**	**[2]**	**2 (12.5)**	**[2]**	**1 (9.1)**	**[1]**	**3 (11.1)**	**[3]**	**2 (11.8)**	**[2]**	**5 (22.7)**	**[6]**	**8 (21.1)**	**[9]**
Pyrexia	2 (25.0)	[2]	0	[0]	1 (7.1)	[1]	0	[0]	0	[0]	0	[0]	0	[0]	3 (13.6)	[3]	3 (7.9)	[3]
Immune system disorders	**0**	**[0]**	**0**	**[0]**	**0**	**[0]**	**2 (12.5)**	**[3]**	**0**	**[0]**	**2 (7.4)**	**[3]**	**0**	**[0]**	**0**	**[0]**	**2 (5.3)**	**[3]**
Drug hypersensitivity	0	[0]	0	[0]	0	[0]	2 (12.5)	[2]	0	[0]	2 (7.4)	[2]	0	[0]	0	[0]	2 (5.3)	[2]
Infections and infestations	**6 (75.0)**	**[56]**	**17 (100)**	**[98]**	**11 (78.6)**	**[29]**	**16 (100)**	**[88]**	**9 (81.8)**	**[37]**	**25 (92.6)**	**[125]**	**17 (100)**	**[98]**	**17 (77.3)**	**[85]**	**36 (94.7)**	**[210]**
Upper respiratory tract infection	3 (37.5)	[4]	7 (41.2)	[14]	3 (21.4)	[6]	7 (43.8)	[20]	2 (18.2)	[5]	9 (33.3)	[25]	7 (41.2)	[14]	6 (27.3)	[10]	15 (39.5)	1[35]
COVID-19	1 (12.5)	[1]	5 (29.4)	[5]	4 (28.6)	[4]	6 (37.5)	[6]	2 (18.2)	[2]	8 (29.6)	[8]	5 (29.4)	[5]	5 (22.7)	[5]	13 (34.2)	1[13]
Sinusitis	3 (37.5)	[9]	2 (11.8)	[6]	0	[0]	4 (25.0)	[6]	1 (9.1)	[1]	5 (18.5)	[7]	2 (11.8)	[6]	3 (13.6)	[9]	8 (21.1)	[16]
Lower respiratory tract infection	1 (12.5)	[1]	3 (17.6)	[3]	0	[0]	4 (25.0)	[6]	2 (18.2)	[3]	6 (22.2)	[9]	3 (17.6)	[3]	1 (4.5)	[1]	7 (18.4)	[10]

System Organ Class Preferred Term	MKKA		103 (RCP)				103 (OLE)						Group 1 [a]				Group 2 [b]	
	Mvx (N=8)		Pbo (N=17)		Mvx (N=14)		Pbo to Mvx (N=16)		Mvx to Mvx (N=11)		Total (N=27)		Pbo (N=17)		Mvx (N=22)		Mvx (N=38)	
	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]
Bronchitis	2 (25.0)	[2]	4 (23.5)	[5]	1 (7.1)	[1]	2 (12.5)	[2]	1 (9.1)	[6]	3 (11.1)	[8]	4 (23.5)	[5]	3 (13.6)	[3]	6 (15.8)	[11]
Cellulitis	3 (37.5)	[4]	3 (17.6)	[4]	1 (7.1)	[1]	1 (6.3)	[4]	1 (9.1)	[1]	2 (7.4)	[5]	3 (17.6)	[4]	4 (18.2)	[5]	6 (15.8)	[10]
Nasopharyngitis	2 (25.0)	[3]	7 (41.2)	[8]	1 (7.1)	[2]	2 (12.5)	[5]	2 (18.2)	[2]	4 (14.8)	[7]	7 (41.2)	[8]	3 (13.6)	[5]	6 (15.8)	[12]
Pneumonia	1 (12.5)	[1]	1 (5.9)	[1]	0	[0]	3 (18.8)	[7]	2 (18.2)	[2]	5 (18.5)	[9]	1 (5.9)	[1]	1 (4.5)	[1]	6 (15.8)	[10]
Urinary tract infection	1 (12.5)	[1]	2 (11.8)	[4]	1 (7.1)	[2]	2 (12.5)	[4]	2 (18.2)	[2]	4 (14.8)	[6]	2 (11.8)	[4]	2 (9.1)	[3]	5 (13.2)	[9]
Pharyngitis	2 (25.0)	[2]	0	[0]	0	[0]	1 (6.3)	[1]	1 (9.1)	[1]	2 (7.4)	[2]	0	[0]	2 (9.1)	[2]	4 (10.5)	[4]
Rhinitis	0	[0]	0	[0]	2 (14.3)	[2]	2 (12.5)	[2]	1 (9.1)	[1]	3 (11.1)	[3]	0	[0]	2 (9.1)	[2]	4 (10.5)	[5]
Conjunctivitis	1 (12.5)	[1]	3 (17.6)	[3]	0	[0]	2 (12.5)	[2]	0	[0]	2 (7.4)	[2]	3 (17.6)	[3]	1 (4.5)	[1]	3 (7.9)	[3]
Ear infection	1 (12.5)	[2]	2 (11.8)	[5]	0	[0]	2 (12.5)	[2]	0	[0]	2 (7.4)	[2]	2 (11.8)	[5]	1 (4.5)	[2]	3 (7.9)	[4]
Herpes zoster	0	[0]	1 (5.9)	[2]	0	[0]	2 (12.5)	[2]	1 (9.1)	[1]	3 (11.1)	[3]	1 (5.9)	[2]	0	[0]	3 (7.9)	[3]
Influenza	1 (12.5)	[1]	1 (5.9)	[1]	0	[0]	1 (6.3)	[1]	1 (9.1)	[1]	2 (7.4)	[2]	1 (5.9)	[1]	1 (4.5)	[1]	3 (7.9)	[3]
Otitis media	3 (37.5)	[4]	1 (5.9)	[1]	0	[0]	0	[0]	0	[0]	0	[0]	1 (5.9)	[1]	3 (13.6)	[4]	3 (7.9)	[4]
Folliculitis	1 (12.5)	[8]	0	[0]	0	[0]	1 (6.3)	[1]	0	[0]	1 (3.7)	[1]	0	[0]	1 (4.5)	[8]	2 (5.3)	[9]
Gastroenteritis	0	[0]	1 (5.9)	[3]	0	[0]	1 (6.3)	[1]	1 (9.1)	[1]	2 (7.4)	[2]	1 (5.9)	[3]	0	[0]	2 (5.3)	[2]
Gingivitis	0	[0]	0	[0]	0	[0]	0	[0]	2 (18.2)	[2]	2 (7.4)	[2]	0	[0]	0	[0]	2 (5.3)	[2]
Localised infection	1 (12.5)	[1]	1 (5.9)	[1]	1 (7.1)	[1]	0	[0]	0	[0]	0	[0]	1 (5.9)	[1]	2 (9.1)	[2]	2 (5.3)	[2]

System Organ Class Preferred Term	MKKA		103 (RCP)				103 (OLE)						Group 1 [a]				Group 2 [b]	
	Mvx (N=8)		Pbo (N=17)		Mvx (N=14)		Pbo to Mvx (N=16)		Mvx to Mvx (N=11)		Total (N=27)		Pbo (N=17)		Mvx (N=22)		Mvx (N=38)	
	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]
Oral herpes	0	[0]	1 (5.9)	[1]	0	[0]	2 (12.5)	[2]	0	[0]	2 (7.4)	[2]	1 (5.9)	[1]	0	[0]	2 (5.3)	[2]
Otitis media acute	1 (12.5)	[1]	0	[0]	0	[0]	1 (6.3)	[1]	0	[0]	1 (3.7)	[1]	0	[0]	1 (4.5)	[1]	2 (5.3)	[2]
Viral infection	1 (12.5)	[2]	0	[0]	0	[0]	0	[0]	1 (9.1)	[1]	1 (3.7)	[1]	0	[0]	1 (4.5)	[2]	2 (5.3)	[3]
Acarodermatitis	0	[0]	2 (11.8)	[3]	0	[0]	1 (6.3)	[1]	0	[0]	1 (3.7)	[1]	2 (11.8)	[3]	0	[0]	1 (2.6)	[1]
Skin infection	1 (12.5)	[1]	2 (11.8)	[5]	0	[0]	0	[0]	0	[0]	0	[0]	2 (11.8)	[5]	1 (4.5)	[1]	1 (2.6)	[1]
Tinea versicolour	0	[0]	2 (11.8)	[3]	0	[0]	1 (6.3)	[1]	0	[0]	1 (3.7)	[1]	2 (11.8)	[3]	0	[0]	1 (2.6)	[1]
Injury, poisoning and procedural complications	**4 (50.0)**	**[12]**	**5 (29.4)**	**[7]**	**1 (7.1)**	**[1]**	**1 (6.3)**	**[1]**	**1 (9.1)**	**[2]**	**2 (7.4)**	**[3]**	**5 (29.4)**	**[7]**	**5 (22.7)**	**[13]**	**7 (18.4)**	**[16]**
Skin laceration	0	[0]	2 (11.8)	[2]	0	[0]	0	[0]	0	[0]	0	[0]	2 (11.8)	[2]	0	[0]	0	[0]

System Organ Class Preferred Term	MKKA		103 (RCP)				103 (OLE)						Group 1 [a]				Group 2 [b]	
	Mvx (N=8)		Pbo (N=17)		Mvx (N=14)		Pbo to Mvx (N=16)		Mvx to Mvx (N=11)		Total (N=27)		Pbo (N=17)		Mvx (N=22)		Mvx (N=38)	
	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]
Investigations	**0**	**[0]**	**2 (11.8)**	**[2]**	**2 (14.3)**	**[4]**	**7 (43.8)**	**[12]**	**2 (18.2)**	**[2]**	**9 (33.3)**	**[14]**	**2 (11.8)**	**[2]**	**2 (9.1)**	**[4]**	**10 (26.3)**	**[18]**
Blood creatinine increased	0	[0]	0	[0]	0	[0]	4 (25.0)	[4]	0	[0]	4 (14.8)	[4]	0	[0]	0	[0]	4 (10.5)	[4]
Lipase increased	0	[0]	0	[0]	1 (7.1)	[1]	1 (6.3)	[2]	0	[0]	1 (3.7)	[2]	0	[0]	1 (4.5)	[1]	2 (5.3)	[3]
Platelet count decreased	0	[0]	0	[0]	1 (7.1)	[3]	1 (6.3)	[4]	0	[0]	1 (3.7)	[4]	0	[0]	1 (4.5)	[3]	2 (5.3)	[7]
Weight decreased	0	[0]	0	[0]	0	[0]	1 (6.3)	[1]	1 (9.1)	[1]	2 (7.4)	[2]	0	[0]	0	[0]	2 (5.3)	[2]
Metabolism and nutrition disorders	**0**	**[0]**	**0**	**[0]**	**2 (14.3)**	**[3]**	**2 (12.5)**	**[2]**	**0**	**[0]**	**2 (7.4)**	**[2]**	**0**	**[0]**	**2 (9.1)**	**[3]**	**4 (10.5)**	**[5]**
Musculoskeletal and connective tissue disorders	**2 (25.0)**	**[6]**	**2 (11.8)**	**[2]**	**3 (21.4)**	**[6]**	**3 (18.8)**	**[3]**	**2 (18.2)**	**[3]**	**5 (18.5)**	**[6]**	**2 (11.8)**	**[2]**	**5 (22.7)**	**[12]**	**8 (21.1)**	**[18]**
Arthralgia	2 (25.0)	[3]	1 (5.9)	[1]	0	[0]	0	[0]	1 (9.1)	[1]	1 (3.7)	[1]	1 (5.9)	[1]	2 (9.1)	[3]	3 (7.9)	[4]
Back pain	1 (12.5)	[1]	0	[0]	0	[0]	1 (6.3)	[1]	0	[0]	1 (3.7)	[1]	0	[0]	1 (4.5)	[1]	2 (5.3)	[2]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**[0]**	**0**	**[0]**	**2 (14.3)**	**[2]**	**4 (25.0)**	**[5]**	**0**	**[0]**	**4 (14.8)**	**[5]**	**0**	**[0]**	**2 (9.1)**	**[2]**	**6 (15.8)**	**[7]**
Basal cell carcinoma	0	[0]	0	[0]	0	[0]	2 (12.5)	[2]	0	[0]	2 (7.4)	[2]	0	[0]	0	[0]	2 (5.3)	[2]
Nervous system disorders	**0**	**[0]**	**5 (29.4)**	**[7]**	**4 (28.6)**	**[7]**	**3 (18.8)**	**[4]**	**1 (9.1)**	**[1]**	**4 (14.8)**	**[5]**	**5 (29.4)**	**[7]**	**4 (18.2)**	**[7]**	**8 (21.1)**	**[12]**
Headache	0	[0]	2 (11.8)	[4]	1 (7.1)	[2]	3 (18.8)	[4]	0	[0]	3 (11.1)	[4]	2 (11.8)	[4]	1 (4.5)	[2]	4 (10.5)	[6]
Dizziness	0	[0]	1 (5.9)	[1]	2 (14.3)	[2]	0	[0]	0	[0]	0	[0]	1 (5.9)	[1]	2 (9.1)	[2]	2 (5.3)	[2]
Product issues	**0**	**[0]**	**0**	**[0]**	**1 (7.1)**	**[1]**	**2 (12.5)**	**[2]**	**0**	**[0]**	**2 (7.4)**	**[2]**	**0**	**[0]**	**1 (4.5)**	**[1]**	**3 (7.9)**	**[3]**

System Organ Class Preferred Term	**MKKA**		**103 (RCP)**				**103 (OLE)**						**Group 1** [a]				**Group 2** [b]	
	Mvx (N=8)		**Pbo (N=17)**		**Mvx (N=14)**		**Pbo to Mvx (N=16)**		**Mvx to Mvx (N=11)**		**Total (N=27)**		**Pbo (N=17)**		**Mvx (N=22)**		**Mvx (N=38)**	
	n (%)	**[e]**	**n (%)**	**[e]**	**n (%)**	**[e]**	**n (%)**	**[e]**	**n (%)**	**[e]**	**n (%)**	**[e]**	**n (%)**	**[e]**	**n (%)**	**[e]**	**n (%)**	**[e]**
Product after taste	0	[0]	0	[0]	1 (7.1)	[1]	2 (12.5)	[2]	0	[0]	2 (7.4)	[2]	0	[0]	1 (4.5)	[1]	3 (7.9)	[3]
Psychiatric disorders	**0**	**[0]**	**0**	**[0]**	**0**	**[0]**	**2 (12.5)**	**[4]**	**2 (18.2)**	**[5]**	**4 (14.8)**	**[9]**	**0**	**[0]**	**0**	**[0]**	**4 (10.5)**	**[9]**
Renal and urinary disorders	**0**	**[0]**	**0**	**[0]**	**1 (7.1)**	**[2]**	**2 (12.5)**	**[2]**	**1 (9.1)**	**[1]**	**3 (11.1)**	**[3]**	**0**	**[0]**	**1 (4.5)**	**[2]**	**3 (7.9)**	**[5]**
Haematuria	0	[0]	0	[0]	1 (7.1)	[1]	2 (12.5)	[2]	0	[0]	2 (7.4)	[2]	0	[0]	1 (4.5)	[1]	3 (7.9)	[3]
Reproductive system and breast disorders	**2 (25.0)**	**[2]**	**1 (5.9)**	**[2]**	**0**	**[0]**	**1 (6.3)**	**[1]**	**1 (9.1)**	**[2]**	**2 (7.4)**	**[3]**	**1 (5.9)**	**[2]**	**2 (9.1)**	**[2]**	**4 (10.5)**	**[5]**
Respiratory, thoracic and mediastinal disorders	**3 (37.5)**	**[5]**	**6 (35.3)**	**[9]**	**2 (14.3)**	**[3]**	**5 (31.3)**	**[6]**	**1 (9.1)**	**[1]**	**6 (22.2)**	**[7]**	**6 (35.3)**	**[9]**	**5 (22.7)**	**[8]**	**11 (28.9)**	**1[15]**
Epistaxis	0	[0]	1 (5.9)	[1]	2 (14.3)	[3]	1 (6.3)	[1]	0	[0]	1 (3.7)	[1]	1 (5.9)	[1]	2 (9.1)	[3]	3 (7.9)	[4]
Dyspnoea	1 (12.5)	[1]	0	[0]	0	[0]	1 (6.3)	[1]	0	[0]	1 (3.7)	[1]	0	[0]	1 (4.5)	[1]	2 (5.3)	[2]
Rhinitis allergic	0	[0]	0	[0]	0	[0]	1 (6.3)	[1]	1 (9.1)	[1]	2 (7.4)	[2]	0	[0]	0	[0]	2 (5.3)	[2]

System Organ Class Preferred Term	MKKA		103 (RCP)				103 (OLE)						Group 1 [a]				Group 2 [b]	
	Mvx (N=8)		Pbo (N=17)		Mvx (N=14)		Pbo to Mvx (N=16)		Mvx to Mvx (N=11)		Total (N=27)		Pbo (N=17)		Mvx (N=22)		Mvx (N=38)	
	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]
Skin and subcutaneous tissue disorders	**4 (50.0)**	**[6]**	**3 (17.6)**	**[6]**	**8 (57.1)**	**[11]**	**6 (37.5)**	**[14]**	**1 (9.1)**	**[2]**	**7 (25.9)**	**[16]**	**3 (17.6)**	**[6]**	**12 (54.5)**	**[17]**	**18 (47.4)**	**[33]**
Eczema	0	[0]	1 (5.9)	[1]	1 (7.1)	[2]	2 (12.5)	[3]	0	[0]	2 (7.4)	[3]	1 (5.9)	[1]	1 (4.5)	[2]	3 (7.9)	[5]
Dermatitis psoriasiform	1 (12.5)	[1]	0	[0]	1 (7.1)	[1]	0	[0]	0	[0]	0	[0]	0	[0]	2 (9.1)	[2]	2 (5.3)	[2]
Dry skin	1 (12.5)	[1]	0	[0]	1 (7.1)	[1]	0	[0]	0	[0]	0	[0]	0	[0]	2 (9.1)	[2]	2 (5.3)	[2]
Pityriasis	0	[0]	0	[0]	2 (14.3)	[2]	0	[0]	0	[0]	0	[0]	0	[0]	2 (9.1)	[2]	2 (5.3)	[2]
Psoriasis	0	[0]	1 (5.9)	[1]	0	[0]	2 (12.5)	[3]	0	[0]	2 (7.4)	[3]	1 (5.9)	[1]	0	[0]	2 (5.3)	[3]
Rash	0	[0]	0	[0]	2 (14.3)	[2]	0	[0]	0	[0]	0	[0]	0	[0]	2 (9.1)	[2]	2 (5.3)	[2]

103=Study X4P-001-103; MKKA=Study X4P-001-MKKA; [e]=number of events; n=number of patients; OLE=open-label extension; PT=Preferred Term; RCP=randomized placebo-controlled period; SOC=System Organ Class; TEAE=treatment-emergent adverse events.

The table is sorted by decreasing frequency of PT (in Group 2) within SOC which is sorted alphabetically

TEAEs were defined as any event that occurred or worsened on or after the first dose of study drug day up to 30 days following the last dose of study drug.

Participants reporting more than one TEAE within a SOC or PT were counted only once for that SOC or PT at the highest severity for the TEAE.

An AE was considered as treatment-related if it was definitely, probably, or possibly related to the study drug. AEs with missing or unknown relationship to the study drug were considered as treatment-related if there was a relationship with the onset of AE after the first dose of study drug.

AEs are coded with MedDRA version 25.0

a. Group 1 comprises patients who received ≥1 dose of mavorixafor in Study X4P-001-MKKA and patients who received ≥1 dose of study intervention (placebo or mavorixafor) during the RCP of Study X4P-001-103.

b. Group 2 comprised patients who received ≥1 dose of mavorixafor in Study X4P-001-MKKA and patients who received ≥1 dose of mavorixafor during either the RCP or OLE of Study X4P-001-103.

c. One event of platelet count decreased occurred in the OLE prior to the patient receiving mavorixafor

Table 67: Treatment-Related Treatment-Emergent Adverse Events by SOC and PT (Safety Population)

System Organ Class Preferred Term	MKKA		103 (RCP)				103 (OLE)						Group 1				Group 2	
	Mvx (N=8)		Pbo (N=17)		Mvx (N=14)		Pbo to Mvx (N=16)		Mvx to Mvx (N=11)		Total (N=27)		Pbo (N=17)		Mvx (N=22)		Mvx (N=38)	
	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]
Any Event	**4 (50.0)**	**[14]**	**3 (17.6)**	**[14]**	**7 (50.0)**	**[14]**	**12 (75.0)**	**[42]**	**1 (9.1)**	**[2]**	**13 (48.1)**	**[44]**	**3 (17.6)**	**[14]**	**11 (50.0)**	**[28]**	**23 (60.5)**	**[72]**

System Organ Class Preferred Term	MKKA		103 (RCP)				103 (OLE)						Group 1				Group 2	
	Mvx (N=8)		Pbo (N=17)		Mvx (N=14)		Pbo to Mvx (N=16)		Mvx to Mvx (N=11)		Total (N=27)		Pbo (N=17)		Mvx (N=22)		Mvx (N=38)	
	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]
Eye disorders	**0**	**[0]**	**0**	**[0]**	**1 (7.1)**	**[1]**	**1 (6.3)**	**[3]**	**0**	**[0]**	**1 (3.7)**	**[3]**	**0**	**[0]**	**1 (4.5)**	**[1]**	**2 (5.3)**	**[4]**
Dry eye	0	[0]	0	[0]	1 (7.1)	[1]	0	[0]	0	[0]	0	[0]	0	[0]	1 (4.5)	[1]	1 (2.6)	[1]
Retinal aneurysm	0	[0]	0	[0]	0	[0]	1 (6.3)	[1]	0	[0]	1 (3.7)	[1]	0	[0]	0	[0]	1 (2.6)	[1]
Uveitis	0	[0]	0	[0]	0	[0]	1 (6.3)	[2]	0	[0]	1 (3.7)	[2]	0	[0]	0	[0]	1 (2.6)	[2]
Gastrointestinal disorders	**3 (37.5)**	**[10]**	**0**	**[0]**	**2 (14.3)**	**[3]**	**9 (56.3)**	**[11]**	**0**	**[0]**	**9 (33.3)**	**[11]**	**0**	**[0]**	**5 (22.7)**	**[13]**	**14 (36.8)**	**[24]**
Nausea	2 (25.0)	[4]	0	[0]	1 (7.1)	[1]	2 (12.5)	[2]	0	[0]	2 (7.4)	[2]	0	[0]	3 (13.6)	[5]	5 (13.2)	[7]
Diarrhoea	0	[0]	0	[0]	0	[0]	3 (18.8)	[3]	0	[0]	3 (11.1)	[3]	0	[0]	0	[0]	3 (7.9)	[3]
Dyspepsia	2 (25.0)	[4]	0	[0]	1 (7.1)	[1]	0	[0]	0	[0]	0	[0]	0	[0]	3 (13.6)	[5]	3 (7.9)	[5]
Abdominal discomfort	0	[0]	0	[0]	0	[0]	2 (12.5)	[2]	0	[0]	2 (7.4)	[2]	0	[0]	0	[0]	2 (5.3)	[2]
Gastrooesophageal reflux disease	0	[0]	0	[0]	0	[0]	2 (12.5)	[2]	0	[0]	2 (7.4)	[2]	0	[0]	0	[0]	2 (5.3)	[2]
Abdominal distension	0	[0]	0	[0]	0	[0]	1 (6.3)	[1]	0	[0]	1 (3.7)	[1]	0	[0]	0	[0]	1 (2.6)	[1]
Abdominal pain	0	[0]	0	[0]	0	[0]	1 (6.3)	[1]	0	[0]	1 (3.7)	[1]	0	[0]	0	[0]	1 (2.6)	[1]
Dry mouth	1 (12.5)	[2]	0	[0]	0	[0]	0	[0]	0	[0]	0	[0]	0	[0]	1 (4.5)	[2]	1 (2.6)	[2]
Vomiting	0	[0]	0	[0]	1 (7.1)	[1]	0	[0]	0	[0]	0	[0]	0	[0]	1 (4.5)	[1]	1 (2.6)	[1]
General disorders and administration site conditions	**0**	**[0]**	**0**	**[0]**	**0**	**[0]**	**1 (6.3)**	**[1]**	**0**	**[0]**	**1 (3.7)**	**[1]**	**0**	**[0]**	**0**	**[0]**	**1 (2.6)**	**[1]**
Fatigue	0	[0]	0	[0]	0	[0]	1 (6.3)	[1]	0	[0]	1 (3.7)	[1]	0	[0]	0	[0]	1 (2.6)	[1]
Infections and infestations	**1 (12.5)**	**[1]**	**2 (11.8)**	**[13]**	**0**	**[0]**	**3 (18.8)**	**[7]**	**0**	**[0]**	**3 (11.1)**	**[7]**	**2 (11.8)**	**[13]**	**1 (4.5)**	**[1]**	**4 (10.5)**	**[8]**
Cellulitis	0	[0]	1 (5.9)	[2]	0	[0]	1 (6.3)	[4]	0	[0]	1 (3.7)	[4]	1 (5.9)	[2]	0	[0]	1 (2.6)	[4]
Conjunctivitis	1 (12.5)	[1]	1 (5.9)	[1]	0	[0]	0	[0]	0	[0]	0	[0]	1 (5.9)	[1]	1 (4.5)	[1]	1 (2.6)	[1]
Fungal infection	0	[0]	0	[0]	0	[0]	1 (6.3)	[1]	0	[0]	1 (3.7)	[1]	0	[0]	0	[0]	1 (2.6)	[1]
Gastroenteritis	0	[0]	0	[0]	0	[0]	1 (6.3)	[1]	0	[0]	1 (3.7)	[1]	0	[0]	0	[0]	1 (2.6)	[1]

System Organ Class Preferred Term	MKKA		103 (RCP)				103 (OLE)						Group 1				Group 2	
	Mvx (N=8)		Pbo (N=17)		Mvx (N=14)		Pbo to Mvx (N=16)		Mvx to Mvx (N=11)		Total (N=27)		Pbo (N=17)		Mvx (N=22)		Mvx (N=38)	
	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]
Lower respiratory tract infection	0	[0]	1 (5.9)	[1]	0	[0]	1 (6.3)	[1]	0	[0]	1 (3.7)	[1]	1 (5.9)	[1]	0	[0]	1 (2.6)	[1]
Localised infection	0	[0]	1 (5.9)	[1]	0	[0]	0	[0]	0	[0]	0	[0]	1 (5.9)	[1]	0	[0]	0	[0]
Skin infection	0	[0]	1 (5.9)	[4]	0	[0]	0	[0]	0	[0]	0	[0]	1 (5.9)	[4]	0	[0]	0	[0]
Subcutaneous abscess	0	[0]	1 (5.9)	[1]	0	[0]	0	[0]	0	[0]	0	[0]	1 (5.9)	[1]	0	[0]	0	[0]
Tonsillitis	0	[0]	1 (5.9)	[1]	0	[0]	0	[0]	0	[0]	0	[0]	1 (5.9)	[1]	0	[0]	0	[0]
Upper respiratory tract infection	0	[0]	1 (5.9)	[2]	0	[0]	0	[0]	0	[0]	0	[0]	1 (5.9)	[2]	0	[0]	0	[0]
Investigations	**0**	**[0]**	**0**	**[0]**	**0**	**[0]**	**4 (25.0)**	**[6]**	**1 (9.1)**	**[1]**	**5 (18.5)**	**[7]**	**0**	**[0]**	**0**	**[0]**	**5 (13.2)**	**[7]**
Blood creatinine increased	0	[0]	0	[0]	0	[0]	2 (12.5)	[2]	0	[0]	2 (7.4)	[2]	0	[0]	0	[0]	2 (5.3)	[2]
Weight decreased	0	[0]	0	[0]	0	[0]	1 (6.3)	[1]	1 (9.1)	[1]	2 (7.4)	[2]	0	[0]	0	[0]	2 (5.3)	[2]
Electrocardiogram QT prolonged	0	[0]	0	[0]	0	[0]	1 (6.3)	[1]	0	[0]	1 (3.7)	[1]	0	[0]	0	[0]	1 (2.6)	[1]
Lipase increased	0	[0]	0	[0]	0	[0]	1 (6.3)	[2]	0	[0]	1 (3.7)	[2]	0	[0]	0	[0]	1 (2.6)	[2]
Metabolism and nutrition disorders	0	[0]	0	[0]	0	[0]	1 (6.3)	[1]	0	[0]	1 (3.7)	[1]	0	[0]	0	[0]	1 (2.6)	[1]
Decreased appetite	0	[0]	0	[0]	0	[0]	1 (6.3)	[1]	0	[0]	1 (3.7)	[1]	0	[0]	0	[0]	1 (2.6)	[1]
Musculoskeletal and connective tissue disorders	**0**	**[0]**	**0**	**[0]**	**0**	**[0]**	**2 (12.5)**	**[2]**	**0**	**[0]**	**2 (7.4)**	**[2]**	**0**	**[0]**	**0**	**[0]**	**2 (5.3)**	**[2]**
Back pain	0	[0]	0	[0]	0	[0]	1 (6.3)	[1]	0	[0]	1 (3.7)	[1]	0	[0]	0	[0]	1 (2.6)	[1]
Oligoarthritis	0	[0]	0	[0]	0	[0]	1 (6.3)	[1]	0	[0]	1 (3.7)	[1]	0	[0]	0	[0]	1 (2.6)	[1]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**[0]**	**0**	**[0]**	**0**	**[0]**	**1 (6.3)**	**[2]**	**0**	**[0]**	**1 (3.7)**	**[2]**	**0**	**[0]**	**0**	**[0]**	**1 (2.6)**	**[2]**
Skin papilloma	0	[0]	0	[0]	0	[0]	1 (6.3)	[2]	0	[0]	1 (3.7)	[2]	0	[0]	0	[0]	1 (2.6)	[2]

System Organ Class Preferred Term	MKKA		103 (RCP)				103 (OLE)						Group 1				Group 2	
	Mvx (N=8)		Pbo (N=17)		Mvx (N=14)		Pbo to Mvx (N=16)		Mvx to Mvx (N=11)		Total (N=27)		Pbo (N=17)		Mvx (N=22)		Mvx (N=38)	
	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]
Nervous system disorders	**0**	**[0]**	**1 (5.9)**	**[1]**	**2 (14.3)**	**[4]**	**2 (12.5)**	**[2]**	**0**	**[0]**	**2 (7.4)**	**[2]**	**1 (5.9)**	**[1]**	**2 (9.1)**	**[4]**	**4 (10.5)**	**[6]**
Headache	0	[0]	1 (5.9)	[1]	0	[0]	2 (12.5)	[2]	0	[0]	2 (7.4)	[2]	1 (5.9)	[1]	0	[0]	2 (5.3)	[2]
Dizziness	0	[0]	0	[0]	1 (7.1)	[1]	0	[0]	0	[0]	0	[0]	0	[0]	1 (4.5)	[1]	1 (2.6)	[1]
Dysgeusia	0	[0]	0	[0]	1 (7.1)	[1]	0	[0]	0	[0]	0	[0]	0	[0]	1 (4.5)	[1]	1 (2.6)	[1]
Syncope	0	[0]	0	[0]	1 (7.1)	[2]	0	[0]	0	[0]	0	[0]	0	[0]	1 (4.5)	[2]	1 (2.6)	[2]
Product issues	**0**	**[0]**	**0**	**[0]**	**1 (7.1)**	**[1]**	**2 (12.5)**	**[2]**	**0**	**[0]**	**2 (7.4)**	**[2]**	**0**	**[0]**	**1 (4.5)**	**[1]**	**3 (7.9)**	**[3]**
Product after taste	0	[0]	0	[0]	1 (7.1)	[1]	2 (12.5)	[2]	0	[0]	2 (7.4)	[2]	0	[0]	1 (4.5)	[1]	3 (7.9)	[3]
Renal and urinary disorders	**0**	**[0]**	**0**	**[0]**	**1 (7.1)**	**[1]**	**0**	**[0]**	**1 (9.1)**	**[1]**	**1 (3.7)**	**[1]**	**0**	**[0]**	**1 (4.5)**	**[1]**	**1 (2.6)**	**[2]**
Acute kidney injury	0	[0]	0	[0]	1 (7.1)	[1]	0	[0]	1 (9.1)	[1]	1 (3.7)	[1]	0	[0]	1 (4.5)	[1]	1 (2.6)	[2]
Respiratory, thoracic and mediastinal disorders	**1 (12.5)**	**[2]**	**0**	**[0]**	**0**	**[0]**	**1 (6.3)**	**[1]**	**0**	**[0]**	**1 (3.7)**	**[1]**	**0**	**[0]**	**1 (4.5)**	**[2]**	**2 (5.3)**	**[3]**
Epistaxis	0	[0]	0	[0]	0	[0]	1 (6.3)	[1]	0	[0]	1 (3.7)	[1]	0	[0]	0	[0]	1 (2.6)	[1]
Nasal dryness	1 (12.5)	[2]	0	[0]	0	[0]	0	[0]	0	[0]	0	[0]	0	[0]	1 (4.5)	[2]	1 (2.6)	[2]

System Organ Class Preferred Term	MKKA		103 (RCP)				103 (OLE)						Group 1				Group 2	
	Mvx (N=8)		Pbo (N=17)		Mvx (N=14)		Pbo to Mvx (N=16)		Mvx to Mvx (N=11)		Total (N=27)		Pbo (N=17)		Mvx (N=22)		Mvx (N=38)	
	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]	n (%)	[e]
Skin and subcutaneous tissue disorders	**1 (12.5)**	**[1]**	**0**	**[0]**	**4 (28.6)**	**[4]**	**2 (12.5)**	**[2]**	**0**	**[0]**	**2 (7.4)**	**[2]**	**0**	**[0]**	**5 (22.7)**	**[5]**	**7 (18.4)**	**[7]**
Dermatitis psoriasiform	1 (12.5)	[1]	0	[0]	1 (7.1)	[1]	0	[0]	0	[0]	0	[0]	0	[0]	2 (9.1)	[2]	2 (5.3)	[2]
Dry skin	0	[0]	0	[0]	1 (7.1)	[1]	0	[0]	0	[0]	0	[0]	0	[0]	1 (4.5)	[1]	1 (2.6)	[1]
Pruritus	0	[0]	0	[0]	1 (7.1)	[1]	0	[0]	0	[0]	0	[0]	0	[0]	1 (4.5)	[1]	1 (2.6)	[1]
Psoriasis	0	[0]	0	[0]	0	[0]	1 (6.3)	[1]	0	[0]	1 (3.7)	[1]	0	[0]	0	[0]	1 (2.6)	[1]
Rash	0	[0]	0	[0]	1 (7.1)	[1]	0	[0]	0	[0]	0	[0]	0	[0]	1 (4.5)	[1]	1 (2.6)	[1]
Rash macular	0	[0]	0	[0]	0	[0]	1 (6.3)	[1]	0	[0]	1 (3.7)	[1]	0	[0]	0	[0]	1 (2.6)	[1]
Uncoded	**0**	**[0]**	**0**	**[0]**	**0**	**[0]**	**1 (6.3)**	**[2]**	**0**	**[0]**	**1 (3.7)**	**[2]**	**0**	**[0]**	**0**	**[0]**	**1 (2.6)**	**[2]**
Uncoded	0	[0]	0	[0]	0	[0]	1 (6.3)	[2]	0	[0]	1 (3.7)	[2]	0	[0]	0	[0]	1 (2.6)	[2]

103=Study X4P-001-103; MKKA=Study X4P-001-MKKA; [e]=number of events; n=number of patients;

OLE=open-label extension; PT=Preferred Term; RCP=randomized placebo-controlled period; SOC=System Organ Class; TEAE=treatment-emergent adverse event.

The table is sorted by decreasing frequency of PT (in Group 2) within SOC which is sorted alphabetically

TEAEs were defined as any event that occurred or worsened on or after the first dose of study drug day up to 30 days following the last dose of study drug.

Participants reporting more than one TEAE within a SOC or PT were counted only once for that SOC or PT at the highest severity for the TEAE.

An AE was considered as treatment-related if it was definitely, probably, or possibly related to the study drug. AEs with missing or unknown relationship to the study drug were considered as treatment-related if there was a relationship with the onset of AE after the first dose of study drug.

AEs are coded with MedDRA version 25.0

a. Group 1 comprises patients who received ≥1 dose of mavorixafor in Study X4P-001-MKKA and patients who received ≥1 dose of study intervention (placebo or mavorixafor) during the RCP of Study X4P-001-103.

b. Group 2 comprised patients who received ≥1 dose of mavorixafor in Study X4P-001-MKKA and patients who received ≥1 dose of mavorixafor during either the RCP or OLE of Study X4P-001-103.

5.4.3.1. Adverse drug reactions

Table 68: Summary of ADRs initially proposed for inclusion by the applicant in the SmPC

System organ class	Adverse reaction	Frequency
Gastrointestinal disorders	Nausea	Very Common
	Diarrhoea	Very Common
	Dyspepsia	Very Common
	Abdominal pain (grouped term)	Very Common
	Vomiting	Very Common
Infections and infestations	Rhinitis	Very Common
Nervous system disorders	Dizziness	Common
Skin and subcutaneous tissue disorders	Rash (grouped term)	Common
	Pityriasis	Common

Abdominal pain: grouped terms of abdominal discomfort and abdominal pain; Rash: grouped terms of rash and rash macular.

Adverse drug reactions for mavorixafor for consideration for inclusion in the SmPC, Section 4.8 were determined based on medical evaluation of the following:

- TEAEs that occurred in ≥2 patients in the RCP of Study X4P-001-103 and were reported in a higher proportion of mavorixafor-treated patients compared with placebo patients
- TEAEs and other safety data from Group 2 in accordance with the criteria laid out in Table below.

Table 69: Criteria for Identification of Adverse Drug Reactions from Data from Group 2 Data

TEAE Category	ADR Review Parameters
All TEAE	≥20% or TEAE ≥Grade 3 with frequency of ≥2 patients
All TEAE	≥10% and <20%
All treatment related TEAE	≥5%
All SAE	Reviewed individually
All treatment related SAE	Reviewed individually
Deaths	Reviewed individually
Laboratory test results	≥Grade 3 results for all laboratory parameters (hematology and chemistry)
Vital signs and physical examinations	Review of clinically significant abnormal results
Important Medical Event (IME)[(1)]	Reviewed individually

TEAE=treatment emergent adverse event; ADR=adverse drug reaction

[1] In accordance with European Medicines Agency: Important medical event terms list 27-1_ime_list.xlsx (live.com)

Table 70: TEAEs Reported in ≥2 Patients in the RCP of Study X4P-001-103 and Reported in a Higher Proportion of Mavorixafor-Treated Patients Compared with Placebo Patients

System Organ Class Preferred Term	103 (RCP)			
	Pbo (N=17)		Mvx (N=14)	
	n (%)	[e]	n (%)	[e]
Any Event	**17 (100)**	**[146]**	**14 (100)**	**[89]**
Blood and lymphatic system disorders	**0**	**[0]**	**4 (28.6)**	**[7]**
Thrombocytopenia	0	[0]	3 (21.4)	[3]
Gastrointestinal disorders	**2 (11.8)**	**[3]**	**5 (35.7)**	**[6]**
Vomiting	1 (5.9)	[1]	2 (14.3)	[2]
Infections and infestations	**17 (100)**	**[98]**	**11 (78.6)**	**[29]**
Rhinitis	0	[0]	2 (14.3)	[2]
Dizziness	1 (5.9)	[1]	2 (14.3)	[2]
Respiratory, thoracic and mediastinal disorders	**6 (35.3)**	**[9]**	**2 (14.3)**	**[3]**
Epistaxis	1 (5.9)	[1]	2 (14.3)	[3]
Skin and subcutaneous tissue disorders	**3 (17.6)**	**[6]**	**8 (57.1)**	**[11]**
Pityriasis	0	[0]	2 (14.3)	[2]
Rash	0	[0]	2 (14.3)	[2]

103=Study X4P-001-103; [e]=number of events; n=number of patients; RCP=randomized placebo-controlled period.

TEAEs in Group 2 reported with a frequency ≥20% were considered ADRs as long as there was a possible causal relationship between the study drug and the AE such as biologic plausibility, mechanism of action of the study drug.

The TEAEs reported with frequency ≥10% and <20% were further analyzed for temporal relationship of the events, reported causality by the investigator, and other factors useful in determining causality such as biologic plausibility, consistency in pattern or trends across other populations.

Table 71: Evaluation of Identified Potential Adverse Drug Reactions

Data	RCP of study X4P-001-103	Group 2	Group 2
Criteria	**≥2 patients and a higher proportion of mavorixafor-treated patients compared with placebo patients**	**≥20% or TEAE ≥Grade 3 with frequency of ≥2 patients**	**≥10% and <20%**
TEAE identified	Pityriasis		
	Rash (grouped terms – rash, rash macular)		
	Rhinitis		
	Vomiting		
	Dizziness		
		Nausea	
		Diarrhea	

			Dyspepsia
			Abdominal pain (grouped terms – abdominal pain, abdominal discomfort)

5.4.4. AEs of special interest, serious adverse events and deaths, other significant events

AESIs

AESIs identified from nonclinical studies include specific ophthalmic events (retinal degeneration and atrophy), testicular toxicity and hepatotoxicity, and also malignancies.

Ophthalmic Events

Patients with WHIM Syndrome

In Group 1, TEAEs were reported for 3 patients (13.6%) with 5 TEAEs in the mavorixafor group and 3 patients (17.6%) with 4 TEAEs in the placebo group. No individual TEAE was reported more than once except for cataract which was reported for 1 patient with 2 TEAEs of cataract in the placebo group.

In Group 2, TEAEs were reported for 7 patients (18.4%) with 11 TEAEs.

Additionally, in Study X4P-001-103 post-baseline ophthalmological abnormalities were reported for similar proportions of patients compared with baseline. In Study X4P-001-MKKA post-baseline ophthalmological abnormalities for retinal examination were reported for 4 patients (there were no abnormalities reported at baseline). There were no shifts from normal baseline to clinically significant abnormal retinal examinations. Also, retinal photographs (images) of all patients in both Study X4P-001-103 and Study X4P-001-MKKA were reviewed by a fellowship-trained retinal expert at the Massachusetts Eye Research and Surgery Institution. It was concluded that there was no evidence of retinal toxicity related to the study drug, based on the color fundus photographs provided.

All X4-Sponsored Clinical Studies of Mavorixafor

TEAEs related to retinal events, dry eye, and ocular and conjunctival hyperaemia were reported for only a few patients with WHIM syndrome and a few patients with CN.

Specifically, retinal related TEAEs were reported for 2 patients in total across all studies: 1 patient in the OLE of Study X4P-001-103 (WHIM syndrome) and 1 patient with 3 TEAEs in Study X4P-001-RCCA (oncology).

Dry eye and ocular and conjunctival hyperaemia were reported in higher proportions of patients in oncology studies in which the patients were generally older and had more concomitant diseases. Conjunctival hyperaemia was reported by 15 healthy participants (100%) in Study X4P-001-REGA (healthy volunteers). Other TEAEs related to retinal events, dry eye and ocular hyperaemia were reported by 2 participants in total across studies with healthy volunteers.

Testicular toxicity

Patients with WHIM Syndrome

In pooled Group 1, no TEAEs were reported in the mavorixafor group, and 1 patient reported 2 Grade 1 TEAEs in the placebo group: benign prostatic hyperplasia and pruritus genital.

In pooled Group 2, a new TEAE was reported for 1 patient: mild (Grade 1) genital lesion which was considered not related to treatment with mavorixafor and remained ongoing at the data cutoff (06 September 2024).

Additionally, post-baseline testicular abnormalities were reported for 4 patients in Study X4P-001-103 (there were no abnormalities reported at baseline; assessments were not performed in Study X4P-001-MKKA): luteinizing hormone, testicular ultrasound evaluation (for 2 patients) and testosterone.

Non-WHIM Syndrome Studies

Across all non-WHIM syndrome studies, 6 male patients reported TEAEs in the SOC Reproductive system and breast disorders. The TEAEs were all reported in 2 oncology studies: X4P-001-RCCA (scrotal oedema, gynaecomastia, pelvic pain, and benign prostatic hyperplasia) and X4P-001-204 (erectile dysfunction and haematospermia). The TEAEs occurred during combination treatment of mavorixafor with another therapy and were mild (Grade 1), except for moderate (Grade 2) benign prostatic hyperplasia, and were considered not related to treatment. All TEAEs and resolved with the exception of benign prostatic hyperplasia.

Hepatotoxicity

Patients with WHIM Syndrome

In Group 1, 1 patient experienced a TEAE in the SOC of Hepatobiliary disorders. The 1 patient (4.5%), in the mavorixafor group, experienced Grade 3 cholecystitis which was not considered serious or related to treatment and resolved after surgery.

In Group 2, there were no new TEAEs in the SOC of Hepatobiliary Disorders (cholecystitis was reported for a total of 1 patient [2.6%] already noted above, i.e., included in Group 1).

Non-WHIM Syndrome Studies

Study X4P-001-104 in Chronic Neutropenia (CN)

Among the 43 patients with CN who were treated with mavorixafor in Part 1 and Part 2 of the study, no TEAEs have been reported in the SOC of Hepatobiliary disorders up to a database cutoff date of 06 September 2024. Non-serious TEAEs for liver enzyme abnormalities were reported for 4 patients (17.4%), all considered related to treatment with mavorixafor:

- One patient had severe (Grade 3) ALT increased, moderate (Grade 2) GGT increased and mild (Grade 1) AST increased.
- One patient had severe (Grade 3) ALT increased and severe (Grade 3) AST increased, moderate (Grade 2) bilirubin increased, and mild (Grade 1) GGT increased.
- One patient had mild (Grade 1) AST increased and mild (Grade 1) ALT increased
- One patient had moderate (Grade 2) ALT increased, moderate (Grade 2) AST increased and mild (Grade 1) GGT increased.

Oncology studies

In the studies oncology studies (X4P-103-RCCB, X4P-103-RCCA, X4P-103-MELA, X4P-100-204), 115 patients with advanced malignancies were treated with mavorixafor in combination with an active anti-cancer agent. TEAEs related to liver enzymes were reported for 28 patients and were considered treatment-related for 8 patients. There were no results for liver enzymes that met the criteria for Hy's Law. Notably, the oncology studies are confounded by underlying malignant disease and the use of mavorixafor in combination with agents known to cause hepatic adverse reactions.

Malignancies

In pooled Group 1, malignancies were reported for 2 patients in the mavorixafor group and no patients in the placebo group:

- 1 patient with a TEAE of Grade 3 vaginal cancer Stage 0 which was considered not related to treatment with mavorixafor and was resolved after a duration of 15 days, and
- 1 patient with an SAE of life threatening (Grade 4) malignant glioma which was considered not related to treatment with mavorixafor, led to discontinuation, and remained ongoing at the data cutoff date

In pooled Group 2, new malignancies were reported for 4 patients (in total, malignancies were reported for 6 patients including 2 patients with onset during the RCP of Study X4P-001-103 who are already noted above, i.e., included in Group 1, and continued in the OLE):

- 2 patients with TEAEs of moderate (Grade 2) basal cell carcinoma which were considered not related to treatment with mavorixafor and resolved after a duration of 56 days and 37 days, respectively; and
- 1 patient with an SAE of severe (Grade 3) pancreatic carcinoma which was considered not related to treatment with mavorixafor, led to discontinuation, and remained ongoing at the data cutoff date; and
- 1 patient with a TEAE of mild (Grade 1) skin papilloma which was considered related to treatment with mavorixafor and resolved after a duration of 1 day.

Deaths

No patient died in the 2 WHIM syndrome clinical studies or any other study or single patient IND or Special Access Scheme with mavorixafor in patients with WHIM syndrome, CN, or healthy participants.

Serious Adverse Events

In pooled Group 1, there was a higher frequency of SAEs reported in mavorixafor group (8 patients [36.4%] with 15 SAEs) compared with the placebo group (2 patients [11.8%] with 2 SAEs).

The SAEs were predominantly related to infections and blood disorders and in the majority of cases, were only reported in 1 patient each. In the RCP of Study X4P 001 103, SAEs were reported for more patients in the mavorixafor group (5 patients [35.7%]) compared with the placebo group (2 patients [11.8%]).

No SAEs were considered related to treatment with mavorixafor. No patient discontinued from the study due to an SAE. All SAEs were resolved at the data cutoff date of 06 September 2024 except Grade 3 malignant glioma which remained ongoing following onset during the RCP of Study X4P-001-103 (mavorixafor group) and led to discontinuation from the OLE.

In pooled Group 2, SAEs were reported for 17 patients (44.7%) with 33 SAEs.

In the OLE of Study X4P 001, 103 SAEs were reported for 11 patients (40.7%) treated with mavorixafor, and the occurrence of SAEs was higher in the placebo to mavorixafor group (9 patients [56.3%]) than in the mavorixafor-to-mavorixafor group (2 patients [18.2%]).

In pooled Group 2, there were 2 discontinuations due to malignancies reported as SAEs and considered not related to mavorixafor, and one SAE of oligoarthritis considered related to treatment with mavorixafor. Although oligoarthritis was considered related to treatment with mavorixafor by the study investigator, other factors may have contributed. The patient has a prior history of

arthralgia, and oligoarthritis is an autoimmune disease; autoimmune complications have been reported in patients with WHIM syndrome.

5.4.5. Discontinuation due to adverse events

In the Pooled Group 1, a TEAE leading to discontinuation was experienced by 1 patient (4.5%) in the mavorixafor group; with a TEAE of mild (Grade 1) dermatitis psoriasiform which was considered related to treatment with mavorixafor and resolved after a duration of ~3 months. This patient had previously experienced a similar rash during participation in a study investigating low dose plerixafor, another CXCR4 receptor antagonist.

In the Pooled Group 2, TEAEs leading to discontinuation were experienced by 4 patients (10.5%):

- 1 patient with a TEAE of mild (Grade 1) dermatitis psoriasiform (as noted in above, i.e., patient included [and discontinued] in Group 1),
- 1 patient with an SAE of mild (Grade 1) oligoarthritis which was considered related to treatment with mavorixafor and resolved after a duration of ~1 year and 4 months,
- 1 patient with an SAE of severe (Grade 3) pancreatic carcinoma which was considered not related to treatment with mavorixafor and remained ongoing at the end of study visit, and
- 1 patient with an SAE of life threatening (Grade 4) malignant glioma (with onset during the RCP of Study X4P 001 103) which was considered not related to treatment with mavorixafor and remained ongoing at the end of study visit.

5.4.6. Safety in special populations

Intrinsic Factors

Age

In Group 1, the incidence of TEAEs was similar for all age groups for the mavorixafor group and placebo group; TEAEs were reported for 93.3% to 100% of patients (note that there were only 2 patients aged >65 years and both were assigned to placebo treatment). There were no notable differences in the most commonly reported individual TEAEs, Grade >3 TEAEs, TEAEs leading to discontinuation, and SAEs for the age groups of 12 to <18 years and >18 to <65 years.

In Group 2, similar to Group 1, the incidence of TEAEs was similar for all age groups; TEAEs were reported for 95.2% to 100% of patients.

Sex

In Group 1, the incidence of TEAEs was similar for males and females for the mavorixafor group and placebo group; TEAEs were reported for 85.7% to 100% of patients. There were no notable differences in the most commonly reported individual TEAEs for males and females. There were no notable differences between males and females in Grade >3 TEAEs, TEAEs leading to discontinuation, and SAEs.

In Group 2, similar to Group 1, the incidence of TEAEs was similar for males and females; TEAEs were reported for 92.9% and 100% of patients, respectively.

Race

In the 2 clinical studies of patients with WHIM syndrome (Study X4P-001-MKKA and Study X4P-001-103) included only 2 non-white patients (1 patient categorized as Other, Arab and 1 patient as Other, Asian). Overall, the study population is consistent with the known prevalence of WHIM syndrome.

Due to the limited number of participants in the studies, it is difficult to compare the safety profiles by race.

Extrinsic Factors

Geographical region

The incidences of TEAEs, Grade >3 TEAEs, TEAEs leading to discontinuation, SAEs, and deaths were summarized by geographical region (US and RoW). The RoW comprised 11 countries: Italy, Israel, UK, France, Spain, Denmark, Austria, Australia, Russia, The Netherlands, and South Korea.

In Group 1, the incidence of TEAEs was similar for US and RoW for the mavorixafor group and placebo group; TEAEs were reported for 87.5% to 100% of patients. There were no notable differences in the most commonly reported individual TEAEs for US and RoW. There were no notable differences between US and RoW in Grade >3 TEAEs, TEAEs leading to discontinuation, and SAEs.

In Group 2, similar to Group 1, the incidence of TEAEs was similar for US and RoW; TEAEs were reported for 91.7% and 100% of patients, respectively.

Patients with renal impairment

The safety and efficacy of mavorixafor have not been established in patients with severe renal impairment (creatinine clearance 15 to less than 30 mL/min) or end-stage renal disease (creatinine clearance less than 15 mL/min). It is not recommended to administer mavorixafor to patients with severe renal impairment or end-stage renal disease. No dosage adjustment is recommended in patients with mild to moderate renal impairment (creatinine clearance 30 to less than 90 mL/min).

Patients with hepatic impairment

The safety and efficacy of mavorixafor have not been established in patients with moderate to severe hepatic impairment (Child Pugh score ≥7). Mavorixafor is not recommended for use in patients with moderate to severe hepatic impairment. No dosage adjustment is recommended in patients with mild hepatic impairment.

Use in Pregnancy and Lactation

Mavorixafor has not been administered to pregnant or lactating women. Pregnant women were excluded from all clinical studies conducted with mavorixafor therefore the safety is unknown in pregnant women.

Based on the mechanism of action of mavorixafor, developmental toxicity is anticipated with a CXCR4 antagonist as CXCR4 is critical during embryonic, foetal, and neonatal development.

Overdose

In clinical studies included in this MAA submission, there have been no cases of overdose. To date, the highest dose of mavorixafor administered to any patient with WHIM syndrome is 400 mg QD. This dose has been administered to patients for up to approximately 4 years.

Effect on Ability to Drive or Operate Machinery

Studies in WHIM Syndrome

For the 2 clinical studies of patients with WHIM syndrome (Study X4P-001-MKKA and Study X4P-001-103), the TEAEs most likely to affect ability to drive or operate machinery are those in the SOC of Nervous system disorders.

In Group 1, only headache and dizziness were reported for more than 1 patient. Headache was reported for 1 patient (4.5%) in the mavorixafor group compared with 2 patients (11.8%) in the placebo group, and dizziness was reported for 2 patients (9.1%) in the mavorixafor group compared with 1 patient (5.9%) in the placebo group.

In Group 2, headache and dizziness remained the only TEAEs that were reported for more than 1 patient. New TEAEs of headache were reported for 3 patients making a total of 4 patients (10.5%). No new TEAEs of dizziness were reported (a total of 2 patients [5.3%] reported dizziness).

Additionally, 2 TEAEs of severe (Grade 3) syncope were experienced by 1 patient (4.5%) with a history of ADHD and receiving treatment with lisdexamfetamine for which unexplained syncope has been reported; both events were considered related to treatment with mavorixafor and resolved the same day as onset.

5.4.7. Safety related to drug-drug interactions and other interactions

Mavorixafor is metabolised via hepatic enzymes, with CYP3A4 and, to a lesser extent, CYP2D6 primarily responsible for its metabolism. Please refer to the Clinical pharmacology Section 5.2.6.1. for discussion on DDI.

5.4.8. Vital signs and laboratory findings

Haematology

Table 72: Summary of Potentially Clinically Significant Laboratory Values (Safety Population)

Criteria	MKKA	103 (RCP)		103 (OLE)			Group 1 [a]		Group 2 [b]
	Mvx (N=8)	Pbo (N=17)	Mvx (N=14)	Pbo to Mvx (N=16)	Mvx to Mvx (N=11)	Total (N=27)	Pbo (N=17)	Mvx (N=22)	Mvx (N=38)
	n (%) [c]	n (%) [c]	n (%) [c]	n (%) [c]	n (%) [c]	n (%) [c]	n (%) [c]	n (%) [c]	n (%) [c]
Platelet count <50×10^9/L	0	2 (11.8)	2 (14.3)	1 (6.3)	0	1 (3.7)	2 (11.8)	2 (9.1)	3 (7.9)
WBC <2×10^9/L	7 (87.5)	17 (100)	10 (71.4)	12 (75.0)	9 (81.8)	21 (77.8)	17 (100)	17 (77.3)	29 (76.3)
ANC <1×10^9/L	7 (87.5)	17 (100)	12 (85.7)	14 (87.5)	10 (90.9)	24 (88.9)	17 (100)	19 (86.4)	33 (86.8)
ALC <0.5×10^9/L	6 (75.0)	14 (82.4)	0	6 (37.5)	4 (36.4)	10 (37.0)	14 (82.4)	6 (27.3)	16 (42.1)

103=Study X4P-001-103; MKKA=Study X4P-001-MKKA; ANC=absolute neutrophil count; ALC=absolute lymphocyte count; WBC=white blood cell

Table includes assessments that are on treatment. On-treatment duration is defined as the time from the first dose of study intervention to 30 days after the last dose of study intervention.

Laboratory parameters for which no patients had potentially clinically significant laboratory values are not included in the table

a. Group 1 comprises patients who received ≥1 dose of mavorixafor in Study X4P-001-MKKA and patients who received ≥1 dose of study intervention (placebo or mavorixafor) during the RCP of Study X4P-001-103.

b. Group 2 comprised patients who received ≥1 dose of mavorixafor in Study X4P-001-MKKA and patients who received ≥1 dose of mavorixafor during either the RCP or OLE of Study X4P-001-103.

c. Percentage is based on the number of patients in each group

Clinical Chemistry

Group 1: Study X4P-001-MKKA and Study X4P-001-103 RCP

No patients experienced a potentially clinically significant chemistry laboratory value.

Baseline values for chemistry parameters were categorized as normal for most patients in both the mavorixafor group and placebo group except lactate dehydrogenase which was categorized as normal for ~50% of patients in both groups and low for ~30% of patients in the mavorixafor group and ~40% of patients in the placebo group. There were no observable differences between the mavorixafor group and placebo group in shifts from baseline categories for lactate dehydrogenase.

For creatinine, 8 patients (36.4%) in the mavorixafor group shifted from normal to high compared with no patients in the placebo group. Mean (SD) creatinine, values at baseline were 61.43 (10.28) µmol/L for the mavorixafor group and 66.26 (19.01) µmol/L for the placebo group. Small increases in the average of all post-baseline values for mean (SD) creatinine, were recorded in both the mavorixafor group (8.60 [8.86] µmol/L) and the placebo group (1.01 [6.72] µmol/L). Acute kidney injury was reported as a TEAE for 1 patient (4.5%) in the mavorixafor group compared with no patients in the placebo group. Mild (Grade 1) acute kidney injury was considered related to treatment with mavorixafor ADR, not serious and was resolving after interruption of mavorixafor for 44 days followed by dose adjustments.

There were no observable differences between the mavorixafor group and placebo group in shifts from baseline categories for any other chemistry parameters.

Group 2: Study X4P-001-MKKA and Study X4P-001-103-RCP and OLE

In group 2, no patients experienced a potentially clinically significant chemistry laboratory value.

The mean baseline and change from baseline for clinical laboratory parameters and the baseline categories and shifts from baseline categories were similar to those described for Group 1.

There was 1 new TEAE of acute kidney injury reported by the patient who had experienced acute kidney injury in Group 1, i.e., there was a total of 2 TEAEs of mild (Grade 1) acute kidney injury, considered related to treatment with mavorixafor and not serious, experienced by 1 patient. The new TEAE was resolving after interruption of mavorixafor followed by dose reduction.

Hepatotoxicity

In pooled Group 1, in the mavorixafor group, bilirubin >1.5×ULN was reported for 3 patients (13.6%) and bilirubin >2.0×ULN was reported for 1 patient (4.5%). In the placebo group, ALP >1×ULN was reported for 1 patient (4.5%). There were no other results for liver enzymes that fell into any category of concern. The distribution of peak values for ALT and bilirubin was similar for the mavorixafor group and placebo group and values were below the thresholds of concern except for 1 patient, in the mavorixafor group. There were no results for liver enzymes that met the criteria for Hy's Law (defined as ALT >3×ULN with total bilirubin of <2×ULN).

In pooled Group 2, bilirubin >1.5×ULN was reported for 5 patients (13.2%) and bilirubin >2.0×ULN was reported for 2 patients (5.3%). Peak values for ALT and bilirubin were within the normal range for most patients and values were below the thresholds of concern except for 1 patient, in the mavorixafor group (already noted in Group 1). There were no results for liver enzymes that met the criteria for Hy's Law or Temple's Corollary Range (defined as ALT >3×ULN with total bilirubin of <2×ULN).

Vital Signs

Table 73: Summary of Potentially Clinically Vital Signs Values (Safety Population)

Criteria	MKKA	103 (RCP)		103 (OLE)			Group 1 [a]		Group 2 [b]
	Mvx (N=8)	Pbo (N=17)	Mvx (N=14)	Pbo to Mvx (N=16)	Mvx to Mvx (N=11)	Total (N=27)	Pbo (N=17)	Mvx (N=22)	Mvx (N=38)
	n (%) [c]	n (%) [c]	n (%) [c]	n (%) [c]	n (%) [c]	n (%) [c]	n (%) [c]	n (%) [c]	n (%) [c]
SBP <90 mmHg and >20 mmHg ↓ from BL	0	2 (11.8)	0	0	0	0	2 (11.8)	0	0
SBP >140 mmHg and >20 mmHg ↑ from BL	2 (25.0)	1 (5.9)	1 (7.1)	1 (6.3)	1 (9.1)	2 (7.4)	1 (5.9)	3 (13.6)	4 (10.5)
DBP <50 mmHg and >10 mmHg ↓ from BL	0	2 (11.8)	0	0	0	0	2 (11.8)	0	0
DBP >105 mmHg and >10 mmHg ↑ from BL	0	0	0	1 (6.3)	0	1 (3.7)	0	0	1 (2.6)

103=Study X4P-001-103; MKKA=Study X4P-001-MKKA; BL=baseline; DBP=diastolic blood pressure; n=number of patients; OLE=open-label extension; RCP=randomized placebo-controlled period; SBP=systolic blood pressure

Baseline is defined as the most recent non-missing measurement on or before the date of the first administration of study intervention. For participants in the OLE of Study X4P-001-103 OLP who transitioned from placebo to mavorixafor, baseline was the most recent non-missing measurement on or before the date of the first administration of mavorixafor. For participants in the OLE of Study X4P-001-103 OLP who continued mavorixafor, baseline was the most recent non-missing measurement on or before the date of the first administration of mavorixafor in the RCP.

Table includes assessments that are on treatment. On-treatment duration is defined as the time from the first dose of study intervention to 30 days after the last dose of study intervention.

Laboratory parameters for which no patients had potentially clinically significant laboratory values are not included in the table

a. Group 1 comprises patients who received ≥1 dose of mavorixafor in Study X4P-001-MKKA and patients who received ≥1 dose of study intervention (placebo or mavorixafor) during the RCP of Study X4P-001-103.

b. Group 2 comprised patients who received ≥1 dose of mavorixafor in Study X4P-001-MKKA and patients who received ≥1 dose of mavorixafor during either the RCP or OLE of Study X4P-001-103.

c. Percentage is based on the number of patients in each group

Electrocardiograms

Group 1: Study X4P-001-MKKA and Study X4P-001-103 RCP

Most patients had normal maximum QTcF values (≤450 ms for males, ≤460 ms for females) (18 patients [81.8%] in the mavorixafor group and 13 patients [76.5%] in the placebo group) and small changes from baseline (≤30 ms) (15 patients [68.2%] in the mavorixafor group and 9 patients [52.9%] in the placebo group). There were no changes from normal to clinically significant abnormal ECG values. Abnormal ECG values which changed from normal to abnormal not clinically significant were reported for similar proportions of patients in the mavorixafor group and placebo group (5 patients [22.7%] and 3 patients [17.6%], respectively). A maximum value for QTcF of >500 ms was reported for 1 patient each in the mavorixafor group (4.5%) and placebo group (5.9%), and maximum change from baseline for QTcF of >60 ms was reported for 1 patient (4.5%) in the mavorixafor group and 3 patients (17.9%) in the placebo group. There was no observable trend for the time to maximum QTcF value.

Group 2: Study X4P-001-MKKA and Study X4P-001-103-RCP and OLE

Most patients had normal maximum QTcF values (≤450 ms for males, ≤460 ms for females) (32 patients [84.2%]) and small changes from baseline (≤30 ms) (28 patients [73.7%]). There were no changes from normal to clinically significant abnormal ECG values. Abnormal ECG values which changed from normal to abnormal not clinically significant were reported for 3 more patients making a

total of 8 patients (21.2%). No more patients experienced a maximum value for QTcF of >500 ms or a maximum change from baseline for QTcF of >60 ms. There was no observable trend for the time to maximum QTcF value.

No TEAEs have been reported in the SOC of Cardiac disorders.

Study X4P 001 106

Study X4P 001 106 is a Phase 1, 2 part, SAD (Part 1), randomized, partially blind, placebo and moxifloxacin controlled, 3 period crossover (Part 2) thorough QT study in healthy volunteers. Results are presented in Section 5.2.3.2.

5.4.9. Post marketing experience

Mavorixafor was approved by the US FDA in April 2024 in patients 12 years of age and older with WHIM syndrome to increase the number of circulating mature neutrophils and lymphocytes. The first quarterly Periodic Adverse Drug Experience Report (PADER) for Xolremdi (mavorixafor) capsules, for oral use covers the reporting period from 26 April 2024 to 25 July 2024. Based on the information in the report and all the currently available data, no significant new safety data were identified that would change the safety profile of Xolremdi (mavorixafor) capsules, when used for its approved indication, at the recommended dose, and in the approved population in US.

Development Safety Update Report (DSUR)

Data intended for inclusion in the upcoming mavorixafor DSUR with a data cut-off date of 14 May 2025 were provided. These included safety data from the OLE of study X4P-001-103 (n=27), a study in patients with chronic neutropenia (n=43), and the ongoing WHIM syndrome Single Patient IND/Special Access Programme (n=5).

During the additional eight months of safety follow-up since the previous data cut-off date (06 September 2024), 32 new TEAEs were reported (increasing from 255 to 287 in total). Two non-treatment-related SAEs (oesophageal candidiasis and haemolytic anaemia) and two non-treatment-related AESIs (Grade 1 hepatomegaly and Grade 2 cholelithiasis) were observed. The classification of non-treatment-relatedness is considered acceptable. Nausea and diarrhoea were the most frequently reported TEAEs. No treatment-related SAEs, deaths, or TEAEs/treatment-related TEAEs leading to discontinuation of mavorixafor were reported in the OLE of the pivotal phase III study.

5.4.10. Overall discussion and conclusions on clinical safety

5.4.10.1. Discussion

5.4.10.1.1. Overall assessment of available safety data

Safety database

The clinical programme for mavorixafor comprises of a number of studies in different indications in small numbers of patients. Altogether across all studies, the safety database for mavorixafor comprised 380 participants who have received ≥1 dose of mavorixafor. In this aspect, the safety database could be considered of sufficient size. However, there were only 38 patients treated with mavorixafor in the proposed indication of WHIM syndrome. Most of the other patients exposed to mavorixafor were either healthy volunteers or patients with oncological diseases. The data from the two studies of patients with WHIM syndrome (studies X4P-001-MKKA and X4P-001-103) were pooled with a safety database cut-off 06 September 2024.

Exposure

The safety evaluation was primarily based on the single pivotal Phase 3 Study (X4P-001-103)

supported by the Phase 2 Study (X4P-001-MKKA). The applicant pooled the patients into two groups. The group 1, that consists of patients who received ≥1 dose of mavorixafor in Study X4P-001-MKKA and patients who received ≥1 dose of study intervention (placebo or mavorixafor) during the RCP of Study X4P-001-103 and provided a comparison of mavorixafor with placebo. The pooled group 2 provided longer term safety information for all patients treated with mavorixafor for WHIM syndrome and was therefore relevant for assessment of long-term safety of the product. The approach to pool the patients from these two studies was found reasonable, considering the very limited safety database. The applicant did not provide a stratified safety analysis by mavorixafor dose. This was acceptable given the limited number of WHIM syndrome patients exposed to doses other than 400 mg.

Acknowledging that the WHIM syndrome is an ultra-rare disease, the relevant safety database although limited in size, provided a reasonable amount of data to evaluate only very common safety aspects. Nevertheless, there are remaining uncertainties related to the safety risks as further outlined hereafter.

Of the 38 patients with WHIM syndrome (23 adult patients [aged >18 years] and 15 adolescents [aged <18 years]), all were treated with mavorixafor for up to 6 months, 28 patients for over 1 year, and 2 patients were treated for more than 5 years. The median duration of treatment for the pooled group 2 was 24.18 months. While this could have been sufficient, it was mainly driven by patients from the X4P-001-MKKA study and not the pivotal study. Therefore, the length of the follow-up for a reasonable number of participants in view of the intended use as a lifelong treatment was considered limited. During the procedure, the applicant provided updated safety data with a data cut-off date of 14 May 2025. However, the safety database was not considered comprehensive. In order to address these uncertaintities, additional data on the long-term use of mavorixafor will be collected in the registry-based study (SOB) in the context of a marketing authorisation under exceptional circumstances, as discussed in Section 9.6.3.1.

TEAEs

In the primary group of interest, the pooled Group 1, comparing mavorixafor with placebo, 21 patients (95.5%) in the mavorixafor group reported any TEAE compared with 17 patients (100%) in the placebo group. The TEAEs were considered related to treatment for 11 patients (50.0%) in the mavorixafor group compared with 3 patients (17.6%) in the placebo group.

In pooled Group 2, 37 patients (97.4%) reported any TEAE. The TEAEs were considered related to treatment with mavorixafor for 23 patients (60.5%).

In general, although treatment with mavorixafor appeared to be associated with less favourable overall safety compared to placebo, mavorixafor was nevertheless considered well tolerated. The most common risks associated with mavorixafor treatment included tolerability issues like rash and gastrointestinal toxicity. The most frequently reported TEAEs were due to infections. Due to the nature of WHIM syndrome, infection risk and development of infections are greatly increased in this patient population and therefore a high incidence of infections would be expected in both the mavorixafor group and placebo group.

Frequency of severe TEAEs (⩾Grade 3) in pooled Group 1 was higher in the mavorixafor group (40.9%) compared to the placebo group (29.4%). Two (2) TEAEs of Grade 3 syncope in mavorixafor group were considered related to the treatment in a patient with cofounding factors of history of ADHD and concomitant medication of lisdexamfetamine for which unexplained syncope is noted in the product information. Whether mavorixafor treatment contributed to these events is unclear, however, mavorixafor dose was not changed and both events resolved the same day as onset.

For the pooled group 1, the TEAEs by SOC reported in ≥50% of patients in either the mavorixafor group or placebo group, were Infections and infestations (17 patients [77.3%] and 17 patients

[100%], respectively), Skin and subcutaneous tissue disorders (12 patients [54.5%] and 3 patients [17.6%]), Gastrointestinal disorders (11 patients [50.0%] and 2 patients [11.8%]).

TEAEs were reported more frequently in the mavorixafor group than the placebo group in the SOC of Blood and lymphatic system disorders (4 patients [18.2%] compared with no patients, respectively) for the pooled group 1. The higher frequency of Blood and lymphatic system disorders in the mavorixafor group was predominantly due to the occurrence of thrombocytopenia which was reported in 3 patients (13.6%) in the mavorixafor group and 0 patients in the placebo group. TEAE of platelet count decreased was reported for 1 patient (4.5%) in the mavorixafor group compared with no patient in the placebo group. The TEAE of platelet count decreased was considered not related to mavorixafor, it was Grade 3 and SAE. Thrombocytopenia and decreased platelet count are discussed under *Laboratory findings.*

For the pooled group 2, the most frequently reported TEAEs by SOC, reported in ≥50% of patients treated with mavorixafor were: Infections and infestations (36 patients [94.7%]) and Gastrointestinal disorders (26 patients [68.4%]). For most patients, the Gastrointestinal disorders, were experienced within the first 6 months of treatment with mavorixafor.

Treatment related AEs

For pooled group 1, treatment-related TEAEs by SOC, reported in ≥2 patients in either the mavorixafor group or placebo group, were Skin and subcutaneous tissue disorders (5 patients [22.7%] and no patients), Gastrointestinal disorders (5 patients [22.7%] and no patients), Nervous system disorders (2 patients [9.1%] and 1 patient [5.9%]), and Infections and infestations (1 patient [4.5%] and 2 patients [11.8%], respectively). The following TEAEs were reported in more than 1 patient overall: nausea and dyspepsia were each reported for 3 patients (13.6%) in the mavorixafor group and no patients in the placebo group, dermatitis psoriasiform was reported for 2 patients (9.1%) in the mavorixafor group and no patients in the placebo group, and conjunctivitis was reported for 1 patient in each treatment group (mavorixafor and placebo).

In pooled Group 2, the most frequently reported treatment-related TEAEs by SOC, reported in ≥3 patients treated with mavorixafor, were: Gastrointestinal disorders (14 patients [36.8%]), Skin and subcutaneous tissue disorders (7 patients [18.4%]), Investigations (5 patients [13.2%]), Infections and infestations (4 patients [10.5%]), and Nervous system disorders (4 patients [10.5%]) and Product issues (3 patients [7.9%]).

Individual TEAEs considered related to treatment with mavorixafor that were reported by >1 patient were: nausea which was reported for 5 patients (13.2%); dyspepsia, and product after taste each reported for 3 patients (7.9%), and abdominal discomfort, dermatitis psoriasiform, gastro-oesphageal reflux disease, blood creatinine increased, weight decreased and headache each reported for 2 patients (5.3%).

Of note, treatment-related TEAEs were reported more frequently during the OLE of Study X4P-001-103, than RCP.

AEs of special interest

AESIs identified from nonclinical studies included specific ophthalmic events (retinal degeneration and atrophy), testicular toxicity, hepatotoxicity and malignancies.

The significance of the nonclinical findings of retinal degeneration and atrophy to humans is not certain. The retinal examinations showed no apparent adverse effects of mavorixafor on the retina and other ophthalmologic parameters assessed in the limited number of patients. There was also no evidence of retinal toxicity associated with mavorixafor treatment in non-WHIM studies, according to the studies that included retinal and ophthalmological examinations. The most commonly occurring

eye-related TEAEs across all mavorixafor studies were dry eye and ocular/conjunctival hyperemia. These events were reported more frequently in the studies of oncology studies and healthy volunteers compared with studies in patients with WHIM syndrome. Due to the nonclinical findings and limited experience in humans, the retinal degeneration and atrophy is included as important potential risks in the RMP and is reflected in the section 5.3 of the SmPC. This important potential risk will be further characterised in the registry-based study (SOB).

The implications for humans with respect to the testicular toxicity observed in animals remain unclear due to the limited exposure to mavorixafor and inadequate evaluation in the clinical studies. The reported TEAEs and sparse testicular assessments reported so far in the clinical studies overall did not show evidence of testicular toxicity associated with treatment with mavorixafor. However, additional testicular assessment that was performed, was first included in protocol version 3 of the pivotal study (X4P-001-103), finalised on 25 October 2021, so not all male participants up to 50 years of age had additional testicular assessment data. Furthermore, assessments included testicular examination, testicular ultrasound, and blood testing for hormones. However, the main outcome measures that would have been most relevant for testicular toxicity, the semen parameters, were not performed. Therefore, given the very limited number of patients exposed to mavorixafor and lack of thorough evaluation, the risk in humans cannot be ruled out and testicular toxicity is listed as an important potential risk in the RMP for mavorixafor and precautions for use regarding male fertitily implemented in SmPC Sections 4.6., 5.3. This important potential risk will be further characterised in the registry-based study (SOB).

The hepatotoxicity findings in animal studies warranted further characterisation of the risk of hepatotoxicity in humans. Overall, across studies of mavorixafor, there was no clear evidence of drug related hepatic injury. However, patient numbers and duration of exposure are limited and the interpretation of the events of liver enzyme abnormalities reported in the non-WHIM syndrome studies was difficult given the underlying disease and concomitant medications. Because of the current uncertainties with regards to the significance of hepatotoxicity findings in animal studies to humans that cannot be clarified with the currently available limited clinical data, the hepatotoxicity is included as an important potential risk in the mavorixafor RMP. This important potential risk will be further characterised in the registry-based study (SOB). A precautionary measure is implemented in SmPC Section 4.4 so that mavorixafor is not recommended for use in patients with moderate to severe hepatic impairment. A dedicated hepatic impairment (HI) study is ongoing, the applicant commited to submit the results of this study once they are available for assessment (final report expected in May 2026).

Mavorixafor can be considered as non-genotoxic based on the preclinical genotoxicity assessment. No carcinogenicity studies have been conducted. The MAH has committed to submit the results of the Tg.rasH2 mouse carcinogenicity study post-approval. In WHIM patients, malignancies associated with the HPV have been reported, in addition to acute myeloid leukaemia and B- or T-cell lymphomas. CXCR4, and predominantly overexpression of CXCR4, has been implicated in several cancers, and malignancies are generally associated in patients who have immunodeficiency. In the 2 clinical studies of patients with WHIM syndrome (Study X4P-001-MKKA and Study X4P 001-103), 6 patients treated with mavorixafor, reported 1 malignancy each which were considered SAEs for 2 patients (malignant glioma [Grade 4] and pancreatic carcinoma [Grade 3]), a severe (Grade 3) TEAE for 1 patient (vaginal cancer Stage 0) and mild (Grade 1) or moderate (Grade 2) TEAEs for 3 patients (basal cell carcinoma [2 patients] and skin papilloma). All these malignancies were considered not to be related with mavorixafor treatment. Overall, the data obtained from the limited number of patients with a relatively short duration of exposure and follow-up did not indicate that mavorixafor is associated with development of malignancy. However, longer follow-up is needed to characterise the effect of mavorixafor treatment with respect to malignancies. Long-term safety *including risk of*

malignancy was included in the RMP as missing information and will be further characterised in the registry-based study (SOB).

SAEs and Deaths

No TEAEs leading to death were reported in Study X4P-001-MKKA and Study X4P 001-103.

The SAEs were predominantly related to infections and blood disorders and were more frequently reported in mavorixafor group (8 patients [36.4%] with 15 SAEs) compared with the placebo group (2 patients [11.8%] with 2 SAEs). In the OLE of Study X4P 001 103, SAEs were reported for 11 patients (40.7%) treated with mavorixafor, and SAEs occurred more frequently for patients in the placebo to mavorixafor group (9 patients [56.3%]) than in the mavorixafor to mavorixafor group (2 patients [18.2%]). One SAE of oligoarthritis in pooled group 2 was considered related to treatment with mavorixafor and led to discontinuation of treatment.

Most SAEs were also reported as severe TEAEs (≥Grade 3) which were therefore reported similarly less frequently for the mavorixafor-to-mavorixafor group (1 patient [9.1%]) compared with the placebo to mavorixafor group (8 patients [50.0%]). These data were reassuring overall, as they suggest that the tolerability of mavorixafor is not worsened with longer-term treatment.

TEAEs leading to discontinuation

In the RCP of Study X4P-001-103, no TEAE led to treatment discontinuation. There was one TEAE of Grade 1 dermatitis psoriasiform, considered treatment related and leading to discontinuation in Study X4P-001-MKKA.

In Pooled Group 2, TEAEs leading to discontinuation were experienced by 4 patients (dermatitis psoriasiform already mentioned, oligoarthritis, pancreatic carcinoma and malignant glioma).

Overall, no concerns arose with regard to the treatment discontinuations due to AEs.

Safety in special populations

Subgroup analyses regarding safety differences according to intrinsic factors as age, sex and race as well as with respect to the extrinsic factor geographical regions (US and rest-of the world) were provided. Due to extreme rare disease and the very limited target population available for clinical studies, the information regarding safety differences in special population was sparse and could be only analysed descriptive from the available data. Overall, the discriminative power with respect to safety differences according to age, sex, race and geographical regions was low and interpretation of observed differences therefore remained inconclusive.

In clinical studies in patients with WHIM syndrome, only 2 patients were aged 65 years and older (in placebo group). These 2 patients were exposed to mavorixafor during the open label phase. No patients were aged 75 years and older. Therefore, it was not possible to determine with the data provided whether they responded differently from younger patients. For the age groups of 12 to <18 years and >18 to <65 years, there were no notable differences in the most commonly reported individual TEAEs, Grade >3 TEAEs, TEAEs leading to discontinuation, and SAEs. In summary, there were limited data in the older population as adequately reflected in SmPC Section 4.2.

The risk of embryo-foetal toxicity has been discussed under the non-clinical aspects Section 4.5.1. The embryo-foetal toxicity was included as an important potential risk in the mavorixafor RMP. Mavorixafor is contraindicated during pregnancy and other minimisation measures are implemented to avoid pregnancies in SmPC Section 4.6. In order to further mitigate this risk, an HCP guide and patient card were implemented.

Effect on Ability to Drive or Operate Machinery

Dizziness was reported with varying frequency across studies of mavorixafor for various indications. Furthermore, syncope or presyncope has been reported for 1 patient with WHIM syndrome, 1 patient with Waldenström macroglobulinemia and for 2 healthy volunteers. According to the applicant, mavorixafor does not cross the blood-brain barrier, and it is argued that there is no evidence of sedation, clinical effects on blood pressure, or adverse neurological effects that would result in diminished ability to drive or operate machinery. However, considering dizziness and syncope are reported as common ADRs in WHIM patients treated with mavorixafor, mavorixafor may have influence on the ability to drive and use machines as adequately reflected in the SmPC section 4.7.

Drug-drug interactions

Potential drug-drug interactions for mavorixafor are expected to be a particular concern. Taking a drug with such a potential for interaction over a very long period could be challenging, especially in the population where concomitant medication might be needed. DDIs are discussed in Section 5.2.6.1. of the clinical pharmacology and recommendations for concomitant use of medicinal products interacting with mavorixafor are implemented in SmPC Sections 4.2, 4.3 and 4.5 including the contraindication for the use of mavorixafor with medicinal products highly dependent on CYP2D6 for clearance.

Laboratory findings

With regards to the haematology parameters, in both Group 1 and Group 2, at baseline, patients in both the mavorixafor and placebo groups showed below normal levels of WBC counts (leukocytes, neutrophils, lymphocytes, monocytes), which would be expected in patients with WHIM syndrome.

Thrombocytopenia and decreased platelet count were reported as TEAEs in patients treated with mavorixafor. Three participants experienced SAEs of Thrombocytopenia and Platelet Count Decreased without clinical signs or symptoms of thrombocytopenia. None of the TEAEs of thrombocytopenia were considered treatment-related and none resulted in dose modification or discontinuation of mavorixafor. There were cofounding factors in 2 of the 3 TEAEs. The analysis of platelet counts of pooled Group 1 data showed no difference between treatment groups (mavorixafor versus placebo) with respect to the proportion of patients who shifted from normal to low platelet count and assessments of clinically significant platelet values (<50×109/L) post baseline showed no difference between mavorixafor and placebo groups. Considering also the lack of biologic plausibility, it was concluded that the available data do not suggest that there is an increased risk for thrombocytopenia/decreased platelet count with mavorixafor.

In pooled Group 2, the patterns in mean change from baseline and shifts of haematological parameters were similar to those reported in pooled Group 1.

For renal parameters, in pooled Group 1, the mean (SD) change from baseline in creatinine values was higher for the mavorixafor group (8.60 [8.857] µmol/L) compared with the placebo group (1.01 [6.718] µmol/L) together with a higher shift from normal to high in the mavorixafor group (8 patients [36.4%]) compared with the placebo group (0 patients). However, further assessment of the creatinine values in the 8 patients who shifted from normal at baseline to high at worst post baseline value showed that the worst post baseline value changes were negligible and marginally above the normal reference range and no patient in either group met the criteria for clinically significant laboratory values. However, one patient in Study X4P-001-103 (mavorixafor group) had a reported TEAE of acute kidney injury during the RCP and the OLE periods (2 events, both Grade 1, non serious).

For all other parameters, there were no differences in shifts from baseline to worst post baseline value.

In pooled Group 2, no notable and clinically relevant changes were reported including for patients who transitioned from placebo to mavorixafor.

The ECG results from Study X4P-001-MKKA and Study X4P-001-103-RCP and OLE overall did not show trend for QT prolongation with mavorixafor treatment and no TEAEs were reported in the SOC of cardiac disorders. A prolongation of QTc in a concentration dependent manner was observed at supratherapeutic doses in the thorough QT Study X4P-001-106. A potentially relevant effect on QT could therefore be possible in patients who have additional risk factors for QTc prolongation however, the risk may also be increased when mavorixafor is used concomitantly with other medications that either increase mavorixafor levels or are known to prolong the QT interval. It is therefore important to assess baseline QTc and monitor QTc during treatment, particularly in patients who have additional risk factors or take concomitant medications that are known to prolong QTc. It is also important to correct any modifiable factors like electrolyte abnormalities (i.e. hypokalaemia) that are known risk factors for QT prolongation. Precautions for use regarding the risk of QTc prolongation are implemented in the SmPC Sections 4.4 and 4.5 and recommendations for dose modification including reduction or discontinuation of mavorixafor in SmPC Section 4.2, and the corresponding sections of the package leaflet.

Co-medication with G-CSF was not allowed in the phase 3 study X4P-001-013. However, in case of acute, severe bacterial infections, G-CSF rescue therapy could be given for a limited period of time (two weeks) at the investigator's discretion. This was actually the case for one of 14 patients in the phase 3 study. Hence, based on the limited data available, no information on rescue medication was included in the product information.

There are no data available on the potential risk of rebound infections following cessation of mavorixafor, as no patient in the RCT discontinued mavorixafor. Discontinuation and withdrawal under real-life conditions under real-world conditions will be a part of the assessment of the registry-based study (SOB).

Post-marketing experience

New safety information Data from post-marketing experience become available during the review process. During the additional eight months of safety follow-up, 32 new TEAEs were reported (increasing from 255 to 287 in total). Two non-treatment-related SAEs (oesophageal candidiasis and haemolytic anaemia) and two non-treatment-related AESIs (Grade 1 hepatomegaly and Grade 2 cholelithiasis) were observed. Nausea and diarrhoea were the most frequently reported TEAEs. No new safety concerns were identified from the review of these data.

5.4.10.1.2. Adverse drug reactions in the SmPC

The ADRs proposed by the applicant for inclusion in the SmPC are described in section 5.4.3.1 of this report.

The initially proposed derivation of ADRs for the SmPC was not considered fully acceptable as it did not take into account data generated in HVs and in other patient groups. This was not considered acceptable, especially when there were so very few data in WHIM syndrome patients. In response to the request for a revised appraisal of ADRs, the applicant re-evaluated safety data from across the mavorixafor clinical development programme. Safety data from the CN Phase 2 study (X4P-001-104) and six healthy volunteer studies, including both monotherapy (Study X4P-001-REGA, Study X4P-001-105, and Study X4P-001-107) and in drug combination with moxifloxacin (Study X4P-001-106), with EE (Study X4P-001-108), and with CYP450 Cocktails (Study X4P-001-109) were considered suitable for further reevaluation. Oncology studies continued to be excluded from the applicant's appraisal due to their exploratory nature and the presence of confounding factors such as advanced disease and combination therapies.

Rash, vomiting and dizziness, nausea, diarrhoea, dyspepsia, and abdominal pain were confirmed to be retained as ADRs.

A new ADR of headache was identified (frequency very common). It met the required frequency thresholds in both CN and healthy volunteer populations and was supported by investigator causality assessments and a positive temporal relationship with mavorixafor administration, typically occurring within 1–2 days of dosing. The applicant proposed a hypothetical yet plausible off-target mechanism involving inhibition of the norepinephrine transporter, which may contribute to headache via increased synaptic norepinephrine levels and associated vasoconstriction.

Although there appeared to be a numerical imbalance between the mavorixafor (2 patients each) and placebo (no patient for both) groups, considering the relatively low reporting rate of pityriasis and rhinitis in the 2 participants each who received mavorixafor, and the presence of alternate aetiologies (confounding factors) in these 2 participants, there is insufficient evidence that mavorixafor is associated with pityriasis and rhinitis. Overall, there is no reasonable possibility that pityriasis and rhinitis are related to mavorixafor, and, thus, both were excluded as an ADRs from the proposed SmPC.

Further, upon the CHMP's request, the applicant agreed to add the following adverse reactions:

- psoriasiform dermatitis and dry skin

Mavorixafor is an antagonist of the CXCR4 receptor, which is expressed in normal cutaneous tissue. Published evidence indicates that CXCR4 exerts a negative regulatory effect on keratinocyte proliferation and may modulate psoriatic plaque formation.

In the clinical study, four subjects exposed or previously exposed to mavorixafor experienced dermatitis psoriasiform or dry skin, whereas no such events were reported in the placebo group. Notably, 2/2 TEAEs of dermatitis psoriasiform and 1/2 TEAEs of dry skin were assessed by the investigators as related to mavorixafor.

Considering the pharmacological target expression in the skin and the available clinical observations, a causal relationship between mavorixafor and dermatitis psoriasiform or dry skin is regarded as reasonably possible.

- epistaxis

In a phase I clinical study in healthy volunteers, epistaxis led to discontinuation of treatment in more than 10% of participants. As the nasal epithelium expresses CXCR4 receptors, the occurrence of nosebleeds may not be solely attributable to external factors such as nasal dryness or common cold. Considering the frequency, the temporal association with treatment, and the mechanistic plausibility related to CXCR4 expression in nasal tissue, a causal relationship between mavorixafor and epistaxis was considered reasonably possible.

- dizziness and syncope

In the clinical data, syncope and dizziness were reported predominantly in the mavorixafor-treated group and were mostly assessed by the investigators as related to study drug. These events were particularly noted in a participant concomitantly treated with aripiprazole, which is contraindicated due to its dependence on CYP2D6 metabolism — an enzyme inhibited by mavorixafor. Given the mechanistic plausibility and the observed temporal association, a reasonable possibility of a relationship between mavorixafor exposure and dizziness/syncope cannot be excluded.

5.4.10.2. Conclusions on clinical safety

The available safety data suggest a generally manageable and tolerable safety profile of mavorixafor in the treatment of patients with WHIM syndrome. Given the limited clinical safety database, the identification of the important potential risks for mavorixafor was based on non-clinical data. These important potential risks are embryo-foetal toxicity, testicular toxicity, hepatotoxicity, and retinal

degeneration and atrophy.

The characterisation of the safety profile of mavorixafor was considered limited, particularly on the long-term use given that this medicinal product is intended as a life-long treatment, to be administered every day throughout the subject life.

The CHMP considers the following Specific obligation necessary to generate long-term follow up safety data in the context of a marketing authorisation under exceptional circumstances:

In order to investigate the long-term safety and efficacy of mavorixafor in the treatment of WHIM syndrome (warts, hypogammaglobulinemia, infections and myelokathexis) to increase the number of circulating mature neutrophils and lymphocytes in patients 12 years of age and older, the MAH shall conduct and submit the results of a non-interventional study based on a registry in patients collecting both safety and efficacy endpoints.

6. Risk management plan

6.1. *Safety specification*

6.1.1. Proposed safety specification

The applicant proposed the following summary of safety concerns in the RMP (version 0.3, date of final sign-off: 20 February 2026):

Table 74: Summary of safety concerns in the proposed RMP

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

6.1.2. Discussion on proposed safety specification

The justification for the proposed important potential risks and missing information was based on non-clinical data. Considering the limited number of patients treated with mavorixafor in clinical studies and the limited duration of exposure, this approach was supported.

Upon the CHMP's request, the applicant has updated the RMP and added "Including risk of malignancy" to the missing information "Long-term safety". Specifying the potential risks for malignancy enables a more robust study design and methodologically robust regulatory assessments. The general term 'long-term safety' was too broad, so that specification – in this case malignancy – will improve the overall understanding and safety assessments after authorisation.

Upon the CHMP's request, the important potential risk "Developmental toxicity" was renamed to the common term "Embryo-foetal toxicity" in all relevant parts of the RMP, which covers toxicity in embryo/foetus/neonate/infant and child, and which is relevant for a CXCR4 inhibitor.

Related to the PRAC assessment of the pharmacovigilance plan, the inclusion of the planned hepatic impairment study to the pharmacovigilance plan was not considered appropriate and the study was

removed from the pharmacovigilance plan. Furthermore, in the product information, it is stated that mavorixafor is not recommended for use in patients with moderate to severe hepatic impairment. Thus, in accordance with the Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (Rev 2), the missing information "Use in patients with hepatic impairment" was removed from all relevant sections of the RMP.

All issues concerning the safety specification were considered resolved.

6.2. *Pharmacovigilance plan*

6.2.1. Proposed pharmacovigilance plan.

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

Table 75: 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 authorization				
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	Protocol Feasibility report Interim results	Within 6 months after commission decision Within 6 months of approval Within the annual reassessment procedure Further milestones to be agreed with CHMP and PRAC.

		Retinal degeneration and atrophy		
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				

6.2.2. Discussion on the Pharmacovigilance Plan

6.2.2.1. Routine pharmacovigilance activities

'QTc prolongation' is included as a safety concern to be reported in the PSUR. The applicant is reminded that the reporting in the PSUR should focus on adverse clinical outcome of QT prolongation for instance arrythmia.

6.2.2.2. Additional pharmacovigilance activities

A registry-based post-authorisation safety and efficacy study (category 2 PASS, specific obligation (SOB)) is included in Part III of the RMP. The PASS is planned to utilize data from an existing registry to evaluate long-term safety and efficacy of mavorixafor in patients with WHIM syndrome. Although the primary scope of the study will be focused on long-term safety, the PASS is also planned to include long-term efficacy objectives. The study will address all safety concerns included in the RMP. In addition, effectiveness of risk minimisation measures will be addressed as part of the study and in PSURs.

Decisions on study design, study duration and precise wording of objectives for the PASS are postponed to the protocol to be submitted within 6 months after Commission decision. With regard to data sources, the existing European Societies of immunodeficiencies (ESID) registry, which collects data from a wide range of countries including in the EU, is proposed to be utilised as a data source. As part of the ongoing study feasibility process, the applicant has agreed to prepare a systematic review of all potentially relevant data sources.

Given the extreme rarity of the disease and the overall scope of the PASS to broadly enable collection of as much descriptive information about the long-term safety profile as possible, the PRAC found the synopsis and proposed approach acceptable from a safety and pharmacovigilance perspective. Hence, the preliminary study synopsis, the suggested data source, as well as the applicant's commitment to carry out a full feasibility assessment, was considered to sufficiently address the PASS information requirements at this stage.

In addition, the SOB regarding "Submission of yearly updates on any new information concerning the safety and efficacy of mavorixafor" is included as a separate category 2 activity in the RMP Part III.

Both SOBs, the registry-based PASS and the submission of yearly updates on the latest information in safety and efficacy, are included in Annex II of the product information.

6.3. *Plans for post-authorisation efficacy studies*

Not applicable.

6.4. *Risk minimisation measures*

6.4.1. Proposed risk minimisation measures

Table 76: Planned routine risk minimisation measures

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 PL 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

6.4.2. Discussion on the risk minimisation measures

6.4.2.1. Routine risk minimisation measures

The proposed routine risk minimsisation measures are considered appropriate by the PRAC.

6.4.2.2. Additional risk minimisation measures

The current SmPC section 4.3 includes a contraindication for use during pregnancy. In addition, the SmPC section 4.6 includes advice that effective contraceptives should be used by female patients of childbearing potential for three weeks after cessation of treatment with mavorixafor. Further, it is stated that male patients with female partners of childbearing potential should use contraception during treatment and for at least three weeks after stopping treatment. In addition, considering the long-term treatment with mavorixafor, risk awareness beyond the initial prescription is considered needed as the compliance with the contraindication may be reduced with repeated prescription. Based on the current evidence, a negative effect on embryofetal development cannot be excluded and as such further guidance directed beyond the information included in the SmPC and the PL is needed.

Thus, the applicant has included additional risk minimisation measures in the form of an HCP guide and a patient card for the important potential risk 'embryo-foetal toxiciy'. The applicant has included key messages for both the HCP guide and the patient card, respectively. In addition, the applicant has provided a full wording of the patient card in Annex III of the product information, as the patient card is intended for distribution within the product package.

6.5. *RMP Summary and RMP Annexes overall conclusion*

Part VI and RMP Annexes are acceptable.

6.6. *Overall conclusion on the Risk Management Plan*

☒The CHMP and PRAC consider that the risk management plan version 0.3 signed 20.02.2026 is acceptable.

7. Pharmacovigilance

7.1. *Pharmacovigilance system*

The CHMP considers that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

7.2. *Periodic Safety Update Reports submission requirements*

The active substance is not included in the EURD list and a new entry will be required. The new list of Union reference dates (EURD list) entry uses the European birth date (EBD) or the international birth date (IBD) to determine the forthcoming Data Lock Points. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request an alignment of the PSUR cycle with the IBD. The IBD is 15.05.2015.

8. Product information

8.1. *Summary of Product Characteristics (SmPC)*

8.1.1. SmPC section 4.1 justification

The applicant applied for the following indication: *Xolremdi is indicated in adult and adolescent patients 12 years of age and older for the treatment of WHIM syndrome (warts, hypogammaglobulinemia, infections and myelokathexis).*

However, upon the CHMP's request, the applicant agreed to revise the wording of the indication since the proof of efficacy of mavorixafor in the treatment of WHIM syndrome was mainly established based on the PD endpoints TAT_{ANC} and TAT_{ALC}.

Therefore, the the finally agreed indication is *in patients 12 years of age and older for the treatment of WHIM syndrome (warts, hypogammaglobulinemia, infections and myelokathexis) to increase the number of circulating mature neutrophils and lymphocytes*.

8.2. *User consultation*

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

8.3. *Additional monitoring*

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Xolremdi (mavorixafor) is included in the additional monitoring list since:

- It contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;
- It is approved under exceptional circumstances (Regulation (EC) 726/2004 Article 14(8)).

Therefore, the summary of product characteristics and the package leaflet include a statement that this medicinal product is subject to additional monitoring and will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

9. Benefit-risk assessment

9.1. *Therapeutic context*

9.1.1. Disease and therapeutic indication

WHIM syndrome (acronym for warts, hypogammaglobulinemia, infections, myelokathexis) is an ultra-rare (1 per 5 million) autosomal dominant combined immunodeficiency disorder in which in most cases a mutant CXCR4 chemokine receptor causes abnormal apoptosis and lack of migratory function, with retention of mature WBCs in the bone marrow. However, gain-of-function pathogenic variants in the *CXCR4* gene are not present in all patients with WHIM syndrome. In such patients, enhanced leukocyte responsiveness to CXCL12 may be due to defects that affect CXCR4 internalisation and desensitisation. Clinical features vary and may include neutropenia, lymphopenia, hypogammaglobulinemia and warts due to human papillomavirus infection. Sequelae of infections like COPD and a highly increased cancer risk have been described.

The initially sought indication was:

> *"Xolremdi is indicated in adult and adolescent patients 12 years of age and older for the treatment of WHIM syndrome (Warts, Hypogammaglobulinemia, Infections and Myelokathexis)."*

During the procedure, upon the CHMP's request, the applicant agreed to revise the indication as follows:

> "*Xolremdi is indicated in patients 12 years of age and older for the treatment of WHIM syndrome (warts, hypogammaglobulinemia, infections and myelokathexis) to increase the number of circulating mature neutrophils and lymphocytes*."

9.1.2. Available therapies and unmet medical need

Mavorixafor is an orally bioavailable CXCR4 antagonist that blocks the binding of the CXCR4 ligand CXCL12. CXCR4/CXCL12 interaction plays a role in trafficking and homing of leukocytes to and from the bone marrow compartment. The CXCR4 receptor is known to be involved in endothelial and epithelial development and has broad expression by haematopoietic stem and progenitor cells and mature leukocytes.

The current standard of care for the management of patients with WHIM syndrome includes G-CSF and intravenous immunoglobulins, prophylactic and therapeutically used antibiotics and antivirals. These agents have some role to treat or prevent infections.

9.2. *Main clinical studies*

The pivotal phase 3 study X4P-001-103 is a randomised, double blind, placebo-controlled study with an open-label extension period. Duration of the double-blind RCP was 52 weeks followed by an open-label extension period. In total, 31 patients (adults and adolescents ≥12 years of age) were enrolled and randomised 1:1 to either placebo or mavorixafor. All adult patients and adolescents weighing >50 kg assigned to mavorixafor received a dose of 400 mg QD, adolescents weighing ≤50 kg received mavorixafor 200 mg QD. Primary endpoint was time above a threshold of 500/µl for neutrophiles, assessed for 24 hours four times in the study (i.e. every 13 weeks), key secondary endpoints were time above a threshold of 1000/µl for lymphocytes, a composite clinical endpoint of total wart change score and total infection score, total wart change score and total infection score.

For a detailed description of the main clinical study supporting this application, please refer to section 5.3.2. of this document.

9.3. *Favourable effects*

The primary endpoint for efficacy of study X4P-001-103 was the time above a threshold of ≥ 500 neutrophiles/ µL (TAT_{ANC}) over a 24-hour period, assessed four times during the 52-week randomised placebo-controlled study period in the ITT population. The primary endpoint was met with TAT_{ANC} of 15.04 hours (LS mean, SE 1.891) in the mavorixafor arm and 2.75 hours (SE 1.518) in the placebo arm (5.5-fold improvement; p <0.0001). The difference from baseline in TAT_{ANC} was 12.78 hours (SE 1.891) versus 0.49 hour (SE 1.518) for mavorixafor or placebo, respectively. The effect was reproducible in 3 of 4 three monthly measurements at week 13 (p<0.0001), week 26 (p<0.0002), week 39 (p<0.0001). A *post-hoc* defined sensitivity analysis, where a higher threshold for TAT_{ANC} of 1G/L was applied, showed that the time above threshold remained longer for the mavorixafor arm (5.24 hours) compared to the placebo arm (0.45 hour; p=0.0312).

The exploratory endpoint AUC_{ANC} showed a significant difference between treatment groups in favour of mavorixafor (LS Mean 8.56 (95% CI 8.22, 8.89) vs 9.58 (9.18, 9.98); p<0.001).

The 1st key secondary endpoint TAT_{ALC} (hours) above ≥ 1000 lymphocytes/µL, over a 24-hour period, assessed four times during the 52-week randomised placebo-controlled study period in the ITT population was statistically significant in favour of the mavorixafor arm 15.8 hours (SE 1.385) compared to 4.55 hours in the placebo arm (SE 1.148; p<0.0001).

The 2nd key secondary endpoint, a composite endpoint of 'total infection score and total wart change score', had a non-significant positive trend in favour of the mavorixafor arm compared to placebo (LS mean 26.7 versus 33.4; difference in composite rank 6.6 (SE 4.52), p=0.1422). A *post-hoc* defined WIN analysis prioritising infections showed a significant result in favour of mavorixafor (WIN ratio 2.30; 95% CI 1.34; 3.96; two-sided p-value 0.0025 for stratified, unmatched analysis).

The key secondary endpoint 'total infection score' was numerically lower in the mavorixafor arm (7.41 (95% CI: 1.64, 13.19) compared to the placebo arm (12.27 (95% CI: 7.24, 17.30); p=0.21). The contributing aspect of annualised infection rate was lower in the mavorixafor arm (LS mean 1.7 (SE 0.48)) compared to the placebo arm (4.2 (SE 0.72); p=0.0072). Patients in the mavorixafor arm experienced less severe infections (CTCAE Grade ≥3 events: 7.1% in the mavorixafor arm compared to 29.4% in the placebo arm).

The following *post-hoc* analyses provided further information regarding the favourable effects of mavorixafor on the infections:

- In the RCT, there was a trend for lower annualised infection rate, which was also observed across the subgroups of patients below and above 18 years of age and of patients receiving or not immunoglobulins.
- In the RCT, there were lower observational rates of repeat infections (7.1% in the mavorixafor arm presented ≥5 infections versus 29.4% in the placebo arm), shorter duration of infections (8.5 days in the maorixafor arm versus 32 days in the placebo arm) and lower use antibiotics (42.9% in the mavorixafor arm versus 70.6% in the placebo arm).
- In the uncontrolled OLE, the total infection score dropped to a median score of 2.91 (min. 0.0, max. 26.9).
- A non-parametric analysis (Wilcoxon rank sum test) on the total infection score indicated significant results in favour of mavorixafor (p=0.0267).

9.3.1. Uncertainties and limitations about favourable effects

The sample size of the pivotal study X4P-001-103 is relevantly limited (n=31). However, the design and conduct of clinical studies in WHIM syndrome are limited by the ultra-rare nature of the condition.

The primary and the 1st key secondary efficacy PD endpoints of prolongation of TAT_{ANC} and TAT_{ALC}, are not established surrogate endpoints. These endpoints are expected to correlate into clinically meaningful reduction of infection risk. Estimates for clinical endpoints remained descriptive and indicated favourable numerical trends on infections, supporting a meaningful treatment effect. Hence, the wording of the indication has been adequately revised to reflect the main proof of efficacy based on the PD endpoints.

All patients included in the pivotal study X4P-001-103 were confirmed to carry the respective CXCR4 alterations. However, there are single case reports describing patients with WHIM symptoms lacking CXCR4 variants, estimated to account for approximately 3% of WHIM patients. As genotyping of CXCR4 is part of the clinical diagnostic assessment to confirm typical WHIM syndrome, a warning is implemented in Section 4.4 of the SmPC to warn prescribers that the efficacy and safety of mavorixafor have not been established in patients with WHIM syndrome who do not carry pathogenic *CXCR4* gene variants.

Key secondary endpoint total wart change score by blinded independent review was without a difference between groups. Excluding patients without warts at baseline did not show a different result (two-sided p value 0.93). An effect of mavorixafor on warts based on the study results could not be concluded.

Responses to vaccination were numerically higher for the mavorixafor arm regarding tetanus (p=0.0387) and pertussis (p=0.1698), but not for HPV. Whereas an effect on HPV would have been likely beneficial in patients with WHIM syndrome as HPV-associated warts are a mainstay of the syndrome, no conclusion could be drawn on the effect of mavorixafor on HPV vaccination. Considering also the lack of effects on warts, it remained questionable whether the treatment provides protection against potential complications such as HPV-associated malignancies. Additional data on the long term efficacy including infections, warts, malignancies will be collected in the registry-based study (SOB) in the context of marketing authorisation under exceptional circumstances as discussed in Section 9.6.3. of this report.

9.4. *Unfavourable effects*

The most frequently reported TEAEs were due to infections. The most common risks associated with mavorixafor treatment included tolerability issues like rash and gastrointestinal toxicity. Headache, rash, nausea, diarrhoea, dyspepsia, abdominal pain and vomiting were included as adverse reactions under frequency very common.

Syncope and dizziness were reported predominantly in the mavorixafor-treated group and mostly assessed by the investigators as related to study drug. Given the mechanistic plausibility and the observed temporal association, dizziness and syncope were both listed as adverse reactions under frequency common.

In a phase I clinical study in healthy volunteers, epistaxis led to discontinuation of treatment in more than 10% of participants. Considering the frequency, the temporal association with treatment, and the mechanistic plausibility related to CXCR4 expression in nasal tissue, epistaxis was added as an adverse reaction under frequency common.

A total of 4 TEAEs of dermatitis psoriasiform or dry skin were reported in patients treated with

mavorixafor, of which 3 were considered related. No such events were reported in the placebo group. Considering the pharmacological target expression in the skin and the available clinical observations, dermatitis psoriasiform and dry skin were listed as adverse reactions under frequency common.

The SAEs were predominantly related to infections and blood disorders and were more frequently reported in mavorixafor group (8 patients [36.4%] with 15 SAEs) compared with the placebo group (2 patients [11.8%] with 2 SAEs). In the OLE of Study X4P-001-103, SAEs were reported for 11 patients (40.7%) treated with mavorixafor, and SAEs occurred more frequent for patients in the placebo to mavorixafor group (9 patients [56.3%]) than in the mavorixafor-to-mavorixafor group (2 patients [18.2%]).

No TEAEs leading to death were reported in Study X4P-001-MKKA and Study X4P 001-103.

Since mavorixafor is primarily metabolised by CYP3A4 and, to a lesser extent, CYP2D6, potential drug-drug interactions for mavorixafor were expected to be a concern and were investigated. Recommendations for concomitant use of medicinal products interacting with mavorixafor are implemented in SmPC Sections 4.2, 4.3 and 4.5 and in the corresponding sections of the package leaflet including the contraindication for the use of mavorixafor with medicinal products highly dependent on CYP2D6 for clearance (e.g. dextromethorphan, codeine, tramadol).

9.4.1. Uncertainties and limitations about unfavourable effects

The relevant safety database is limited in size and provides the reasonable amount of data to evaluate only very common safety aspects. The length of the follow-up for a reasonable number of participants in view of the intended use of the product as a lifelong treatment for WHIM syndrome was considered limited. The safety dataset was not considered comprehensive and additional data on the long-term safety including malignancy will be collected in the registry-based study (SOB) in the context of marketing authorisation under exceptional circumstances as discussed in Section 9.6.3 of this report.

AESIs identified from nonclinical studies included specific ophthalmic events (retinal degeneration and atrophy), testicular toxicity, hepatotoxicity and malignancies.

The significance of the nonclinical findings of retinal degeneration and atrophy to humans is not certain. Due to the nonclinical findings and limited experience in humans, retinal degeneration and atrophy was included as an important potential risk in the RMP and will be further characterised in the registry-based study (SOB). These findings are reflected in SmPC section 5.3.

The implications for humans with respect to the testicular toxicity observed in animals remain unclear due to the limited exposure to mavorixafor and inadequate evaluation in the clinical studies, as the evidence provided was mainly derived from preclinical studies. In animal models, no safe threshold could be determined, as testicular degeneration/ atrophy were already evident at the lowest dose tested. Independent datasets with the CXCR4 antagonist plerixafor showed impaired spermatogonial stem cells with maintenance and differentiation across species, supporting a plausible class-related risk. Human testicular exposure may be limited by P-gp at the blood–testis barrier, but this barrier matures at puberty; younger males may be more susceptible. Reversibility is uncertain because spermatogonial stem cell depletion may cross a threshold beyond which fertility does not recover with ongoing treatment. Given long-term use of mavorixafor in WHIM patients and acknowledging that the relevance of the findings to the humans is unknown, the potential risk for male fertility were addressed in the relevant sections of product information. Testicular toxicity is an important potential risk in the RMP and will be further characterised in the registry-based study (SOB).

The hepatotoxicity findings in animal studies warrant further characterisation of the risk of hepatotoxicity in humans. Hepatotoxicity is included as an important potential risk in the mavorixafor RMP and will be further characterised in the registry-based study (SOB). Mavorixafor is not

recommended for use in patients with moderate to severe hepatic impairment. The applicant has committed to provide the results of the hepatic impairment PK study in Q3 2026.

While mavorixafor has not been evaluated in long-term preclinical carcinogenicity studies and these studies are expected to be submitted post-approval, existing genotoxicity studies have not indicated a carcinogenic potential. The increased cancer risk observed in patients with WHIM syndrome is considered to be attributed to the disease itself, and not the to the treatment with mavorixafor. However, longer follow-up is needed to characterise the effect of mavorixafor treatment with respect to malignancies. Long-term safety including risk of malignancy was included in the RMP as missing information and will be further characterised in the registry-based study (SOB).

Clinical characterisation of the potential drug-drug interaction for mavorixafor and CYP2D6 precipitant will be performed *post* approval, the applicant has committed to submit the results for assessment when available (CSR is anticipated by September 2028).

As an inhibitor of CXCR4, which is essential for embryo/foetal development, mavorixafor is anticipated to result in embryo-foetal toxicity. This toxicity is an important potential risk in the RMP. Further, the use of mavorixafor is contraindicated during pregnancy and precautionary measures regarding the use of contraception methods are recommended. This risk is further mitigated through the implementation of additional risk minimisation measures (healthcare professional guide and patient card).

9.5. Effects Table

Table 77: Effects Table for Xolremdi in study X4P-001-103 (data cut-off: 11 November 2022 for the primary analysis on efficacy, 31 August 2023 for the OLE and 14 May 2025 for safety)

Effect	*Short description*	*Treatment*	*Control*	*Uncertainties/ Strength of evidence*	*Ref*
Favourable Effects					
Intent to treat population (ITT): 31 patients					
		Mavorixafor 400 mg QD or 200 mg QD (n=14)	**Placebo (n=17)**		
TAT_{ANC} (primary endpoint)	Time in hours for neutrophils above a threshold of 500/µl	15.04 h	2.75 h	**SoE:** 2-sided p-value <0.0001 **Unc:** SE 1.891 for mavorixafor; SE 1.518 for placebo	Study X4P-001-103
TAT_{ALC} (1st key secondary endpoint)	Time in hours for lymphocytes above a threshold of 1000/µl	15.80 h	4.55 h	**SoE:** 2-sided p-value p<0.0001 **Unc:** SE 1.385 for mavorixafor, SE 1.148 for placebo	Study X4P-001-103
Unfavourable Effects (pooled Group 1 safety population)					
		Mavorixafor (N=22)	Placebo (N=17)		

Effect	Short description	Treatment	Control	Uncertainties/ Strength of evidence	Ref
Treatment related TEAEs – no. (%)		11 (50)	3 (17.6)	**Unc:** limited size of the safety database. Limited safety data on the long-term use Important potential risks from non-clinical data: embryo-foetal toxicity, testicular toxicity, hepatotoxicity, and retinal degeneration and atrophy	Study X4P-001-103 and Study X4P-001-MKKA
Serious TEAE - no. (%)		8 (36.4)	2 (11.8)		
TEAE Gastrointestinal SOC - no. (%)		11 (50.0)	2 (11.8)		
TEAE Skin and subcutaneous tissue SOC - no. (%)		12 (54.5)	3 (17.6)		

Abbreviations: Ref: reference; Unc: uncertainties; SoE: strength of evidence

9.6. *Benefit-risk assessment and discussion*

9.6.1. Importance of favourable and unfavourable effects

The pivotal randomised placebo-controlled study X4P-001-103 in 31 patients with WHIM syndrome met its primary endpoint TAT_{ANC}, significantly increasing the duration of the neutrophil count above 500 µL. The first key secondary endpoint TAT_{ALC} (time above ≥ 1000 lymphocytes/µL) also met statistical significance. The overall strategy to reach significance in a PD endpoint in combination with clinically meaningful but not necessarily fully powered secondary endpoints was agreed, reflecting the limited sample size for a randomised controlled study in this ultra-rare orphan disease setting. Prolongation of TAT_{ANC} and TAT_{ALC} are not established surrogate endpoints but are expected to correlate to clinically meaningful reductions of the infection risk. The clinical composite endpoint (based on total infection score and total wart change score) which was the first endpoint to evaluate clinical benefit had a positive trend in favour of mavorixafor but failed to meet statistical significance. Hence, in the testing hierarchy, none of the predefined clinical endpoints reached statistical significance. While there were numerical improvements regarding infections in comparison with placebo, sensitivity analyses and non-parametric analyses according to total infection score, overall supported the results of the primary analysis, supporting a meaningful treatment effect of mavorixafor on infections. The numerical improvements for total infection score were also observed in the OLE period. An effect on warts could not be demonstrated. A preventive effect of mavorixafor on malignancies for WHIM patients cannot be derived. Additional data on the long-term efficacy will be collected in the registry-based study, as specific obligation (SOB), in the context of marketing authorisation under exceptional circumstances.

As the efficacy of mavorixafor in the treatment of WHIM syndrome was mainly established based on the PD endpoints TAT_{ANC} and TAT_{ALC}, upon the CHMP's request, the applicant agreed to revise the indication as follows: *in patients 12 years of age and older for the treatment of WHIM syndrome (warts, hypogammaglobulinemia, infections and myelokathexis) to increase the number of circulating mature neutrophils and lymphocytes*.

Only patients with proven confirmation of the CXCR4 mutation were included in the pivotal study

X4P-001-103. Whereas it is acknowledged that WHIM syndrome is caused, in most cases, by gain-of-function pathogenic variants in the *CXCR4* gene, not all patients with WHIM syndrome carry a *CXCR4* gene variant. Considering that mavorixafor is a CXCR4 antagonist, there is a lack of proof and doubt about the effectiveness in patients without a *CXCR4* gene variant. As genotyping of CXCR4 is part of the clinical diagnostic assessment to confirm typical WHIM syndrome, prescribers are warned that no clinical data are available in patients without a *CXCR4* gene variant in the SmPC section 4.4.

The available safety data suggest a generally manageable and tolerable safety profile of mavorixafor in the patients with WHIM syndrome. The most common risks associated with mavorixafor treatment included tolerability issues like rash and gastrointestinal toxicity. The safety profile of mavorixafor is not considered to be comprehensively characterised. Additional data on the long-term safety will be collected in a registry-based study, as a specific obligation (SOB), in the context of marketing authorisation under exceptional circumstances.

Given the limited clinical safety database, the identification of the important potential risks for mavorixafor was based on non-clinical data. These important potential risks are embryo-foetal toxicity, testicular toxicity, hepatotoxicity, and retinal degeneration and atrophy and are expected to be further characterised in the registry-based study (SOB). In order to address the potential risk for male fertility due to testicular toxicity, appropriate precautions for use in male patients were implemented in the product information. Further, due to the important potential risk of embryo-foetal toxicity, the use of mavorixafor is contraindicated during pregnancy and precautionary measures regarding the use of contraception methods are implemented. Efforts to further mitigate this risk through the implementation of additional risk minimisation measures (healthcare professional guide and patient card) have been agreed.

Because of the hepatic metabolism of mavorixafor, drug-drug interactions were expected to be a concern and, therefore, investigated. Recommendations for concomitant use of medicinal products interacting with mavorixafor are implemented in SmPC Sections 4.2, 4.3 and 4.5 and in the corresponding sections of the package leaflet, including the contraindication for the use of mavorixafor with medicinal products highly dependent on CYP2D6 for clearance (e.g. dextromethorphan, codeine, tramadol).

9.6.2. Balance of benefits and risks

The pivotal randomised controlled study X4P-001-103 in 31 patients with WHIM syndrome met the primary endpoint of TAT_{ANC}, significantly increasing the duration of neutrophil counts above 500/µL and 1st key secondary endpoint of TAT_{ALC}. Numerical improvements were observed for infections, supporting a meaningful treatment effect of mavorixafor on infections. An effect on warts could not be demonstrated and a preventive effect of mavorixafor on malignancies for WHIM patients cannot be derived. The wording of the indication was revised to reflect that the evidence of efficacy was mainly derived from the PD endpoints. Further, prescribers are warned that the efficacy and safety of mavorixafor in patients with WHIM syndrome without confirmed CXCR4 gain of function variant have not been established.

The available safety data suggest generally manageable and tolerable safety profile of mavorixafor in the treatment of WHIM syndrome.

The safety and efficacy dataset are not considered comprehensive. In particular, data on the long-term safety and efficacy of mavorixafor are considered limited, given that this medicinal product is intended as a life-long treatment to be administered every day throughout the subject life. Acknowledging that it is not feasible to generate comprehensive data due to the rarity of the disease, a marketing authorisation under exceptional circumstances has been applied for, aiming to collect additional data on

the long-term safety and efficacy in the registry-based study (SOB) as discussed under Section 9.6.3 of this report.

9.6.3. Additional considerations on the benefit-risk balance

9.6.3.1. Marketing authorisation under exceptional circumstances

9.6.3.1.1. Applicant's request for a Marketing Authorisation under exceptional circumstances

According to the applicant, the benefit-risk balance for Xolremdi is positive 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. The applicant requested during assessment, upon suggestion by CHMP, consideration of its application for a Marketing Authorisation under exceptional circumstances in accordance with Article 14(8) of Regulation (EC) No 726/2004 based on the following two grounds:

1. The indication for which Xolremdi is intended is encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence (inability to provide comprehensive efficacy and safety data due to rarity of the indication; see Annex I, Part II of the Directive 2001/83/EC).

Orphan drug designation was granted by the European Commission for mavorixafor for the treatment of patients with WHIM syndrome on 25 July 2019 (EU/3/19/2183).

The applicant stated that currently the true prevalence of the condition is not well-established due to underdiagnosis and delayed recognition; however, it is estimated to affect fewer than 1 in 1,000,000 individuals (Orphanet, 2024[57]; NORD, 2024[58]). A systematic literature review identified only 105 diagnosed cases globally of myelokathexis or WHIM syndrome or a germline CXCR4 mutation as of early 2019 (Heusinkveld et al., 2019[59]), corresponding to a prevalence of approximately 0.01 per 10,000 in the European Union (EU). In addition, the natural history study by Dotta et al (Dotta et al., 2019[5]) highlights that significant diagnostic delay, with symptom onset occurring at an average age of 2.2 years, but diagnosis not confirmed until an average of 12.5 years, further complicating patient identification. In a further publication by Geier et al (Geier et al., 2022[60]), median age at diagnosis was 5.5 years (range 2 weeks to 51 years). This rare disease landscape limits the pool of eligible participants for clinical studies, despite global outreach and the use of broad inclusion criteria.

The applicant stated that conducting additional clinical studies in this population is not feasible due to the rarity of the condition, which therefore limits timely identification of eligible patients and further constrains enrolment potential, and that given the low global prevalence of the condition, additional larger, statistically powered studies are not practically feasible.

The CHMP agreed that the applicant had sufficiently justified that the indication for which Xolremdi is intended is encountered so rarely that the applicant cannot reasonably be expected to provide

[57] Orphanet. Prevalence and incidence of rare diseases: Bibliographic data Prevalence, incidence or number of published cases listed by diseases (in alphabetical order). October 2024. https://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_alphabeti cal_list.pdf; Accessed 01 April 2025

[58] National Organization for Rare Disorders (NORD). (2024). WHIM syndrome. https://rarediseases.org/rare-diseases/whim-syndrome/. Accessed 09 July 2025.

[59] Heusinkveld LE, Majumdar S, Gao JL, McDermott DH, Murphy PM. WHIM Syndrome: from Pathogenesis Towards Personalized Medicine and Cure. J Clin Immunol. 2019;39(6):532-556

[60] Geier CB, Ellison M, Cruz R, Pawar S, Leiss-Piller A, Zmajkovicoa K, et al. Disease progression of WHIM syndrome in an international cohort of 66 pediatric and adult patients. J Clin Immunol. 2022; 42(8):1748-65. doi: 10.1007/s10875-022-01312-7.

comprehensive evidence.

2. Collecting information to provide comprehensive evidence would be contrary to medical ethics (Guideline on procedures for the granting of a marketing authorisation under exceptional circumstances, pursuant to Article 14(8) of Regulation (EC) 726/2004 - EMEA/357981/2005).

In accordance with ethical principles enshrined in the Declaration of Helsinki and International Council for Harmonisation Good Clinical Practice, the applicant stated that the benefits for a patient in enrolling in a clinical study should outweigh the risks of participation. There is an unmet need for a treatment for WHIM syndrome with no approved options currently available. Given the statistically significant and clinically relevant data on ANC and ALC and numerical evidence of benefit on infections from clinical studies conducted with mavorixafor, the applicant considered that conducting a further placebo-controlled study and thus withholding a potentially beneficial treatment would not be ethically appropriate in the approved indication.

The CHMP considered that the applicant had not sufficiently justified that collecting information to provide comprehensive evidence would be contrary to medical ethics considering that the demonstration of efficacy was established mainly on PD endpoints and the uncertainties that remain in terms of long-term safety and efficacy. Nevertheless, this ground was not further pursued by the CHMP since sufficient justification of the ground on the inability to provide comprehensive evidence due to rarity of the indication was provided.

9.6.3.1.2. Discussion on comprehensiveness of data in the context of a Marketing Authorisation under exceptional circumstances

With regards to the request for Marketing authorisation under exceptional circumstances, the CHMP considered that the following is to be accounted in terms of comprehensiveness of the dossier:

The natural history of the WHIM syndrome disease is very heterogeneous. Predictive or prognostic factors are not well understood. Symptom onset and burden vary widely between patients, with only 38% of patients presenting with all clinical features of WHIM. Disease progression and long-term outcomes are also different from what can be inferred from the limited data available on this ultra-rare disease.

This application was supported by a single pivotal randomised placebo-controlled study X4P001-103. The clinical inclusion criteria were broad to include many patients with WHIM syndrome in this ultra-orphan setting.

The efficacy was mainly based on PD endpoints which are not established surrogates but are expected to correlate to clinically meaningful reductions of infection risk. The estimates for clinical endpoints remained descriptive and indicated favourable numerical trends on infections, supporting a meaningful treatment effect. The efficacy was further supported by numerical, descriptive improvements for some of the exploratory endpoints (annualised infection rate and AUC_{ANC}) and *post hoc* defined analyses on infections. Sustained effects on neutrophils counts were provided for the 52-week treatment period and the open label extension period. The numerical improvements for total infection score were also observed in the open label extension period.

The CHMP agreed that the design and conduct of clinical studies in WHIM syndrome is limited by the ultra-rare nature of the condition and that the provision of a randomised controlled study with a direct statistically significant clinical meaningful endpoint is not considered feasible. Considering the data available, the CHMP agreed that efficacy has been shown based on the PD endpoints as adequately addressed in the wording of the approved indication. The CHMP considered that efficacy on the long-term use, especially in the prevention of WHIM syndrome sequelae due to recurrent infections, warts and malignancies is insufficiently characterised. These concerns are not expected to be addressed

within a reasonable timeframe. As a specific obligation, the applicant committed to conduct a registry-based safety study collecting data on the long-term efficacy of mavorixafor.

Regarding the safety, only 38 patients that have been treated with mavorixafor in the WHIM indication were treated with mavorixafor for up to 6 months, 28 patients for over 1 year, and 2 patients for more than 5 years, the median duration of treatment was 2 years. Most of the other patients exposed to mavorixafor (n=380) were either healthy volunteers or patients with oncology diseases. Acknowledging that the WHIM syndrome is an ultra-rare disease, the relevant safety database although limited in size, provided a reasonable amount of data to evaluate very common safety aspects. However, the length of the follow-up for a reasonable number of participants in view of the intended use of the product as a lifelong treatment for WHIM syndrome was considered limited. As a result, the CHMP considered that the long-term safety is insufficiently characterised. This concern is not expected to be adequately addressed within a reasonable timeframe. Nothwithstanding this, the applicant committed to conduct a registry-based safety study to collect data on the long-term safety of mavorixafor, as a specific obligation.

In conclusion, based on the above, the clinical data cannot be considered as sufficiently comprehensive.

Further, the CHMP agreed that the indication for which mavorixafor is intended is encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence.

9.6.3.1.3. Conclusions and recommendation on Marketing Authorisation under exceptional circumstances

As comprehensive data on the product are not available, as discussed above, a marketing authorisation under exceptional circumstances was suggested by the CHMP during the assessment, after having consulted the applicant.

The CHMP considers that the applicant has sufficiently demonstrated that it is not possible to provide comprehensive data on the efficacy and safety under normal conditions of use, because the applied for indication is encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence.

Considering the ultra-rarity of the disease with a prevalence of the condition reported by the applicant to approximately 0.01 per 10,000 in the EU and the delays in the diagnosis complicating the patient identification, the CHMP agreed that conducting additional placebo-contolled clinical studies in the patient population would not be feasible.

Efficacy of mavorixafor in the treatment of WHIM syndrome has been shown based on PD endpoints. The available safety data indicate a generally manageable and tolerable safety profile of mavorixafor in patients with WHIM syndrome. There is a positive benefit-risk balance for mavorixafor in patients 12 years and older for the treatment of WHIM syndrome to increase the number of circulating mature neutrophils and lymphocytes. However, the dataset was not considered comprehensive with regards to long-term effects (safety and efficacy).

Therefore, recommending a marketing authorisation under exceptional circumstances is considered appropriate. As a specific obligation, the applicant committed to conduct a registry-based safety study to further characterise the long-term safety and efficacy of mavorixafor. The applicant has provided a description of the annual strategy for the reporting of the long-term safety including malignancies and the reporting of the long-term efficacy including infections, warts and malignancies. A protocol will be submitted for agreement within 6 months following the EC decision. Furthermore, the applicant agreed to a second specific obligation to provide yearly updates on any new information concerning the safety and efficacy of Xolremdi within the annual reassessments.

9.7. *Benefit-risk conclusions*

9.7.1. At Day 210 – CHMP conclusions

The benefit/risk balance of Xolremdi is positive in the following indication:

Xolremdi is indicated in patients 12 years of age and older for the treatment of WHIM syndrome (warts, hypogammaglobulinemia, infections and myelokathexis) to increase the number of circulating mature neutrophils and lymphocytes.