Study Title:	A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Mavorixafor in Patients with WHIM Syndrome with Open-Label Extension
Investigational Drug:	Mavorixafor (X4P-001)
Phase:	3
IND #:	129092
EudraCT #:	2019-001153-10
CT.Gov #:	NCT03995108
Sponsor:	X4 Pharmaceuticals Incorporated 61 N Beacon Street, 4th Floor Boston, MA 02134
Protocol Number:	X4P-001-103
Protocol Version, Date:	Version 3.0, 20 October 2021

This study will be conducted according to the protocol and in compliance with Good Clinical Practice, the ethical principles stated in the Declaration of Helsinki, and other applicable regulatory requirements.

INVESTIGATOR'S AGREEMENT

I understand that all documentation provided to me by X4 Pharmaceuticals, Inc. (X4), or its designated representative(s) concerning this study will be kept in the strictest confidence. This documentation includes the study protocol, Investigator's Brochure, case report forms, and other scientific data.

This study will not commence without the prior written approval of a properly constituted Institutional Review Board (IRB)/Independent Ethics Committee (IEC). No changes will be made to the study protocol without the prior written approval of X4 and the IRB/IEC, except where necessary to eliminate an immediate hazard to the participant.

I have read, understood, and agree to abide by all the conditions and instructions contained in this protocol.

Investigator Signature	Date
Printed Name	

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LIST OF ABBREVIATIONS

The following abbreviations and specialist terms are used in this study protocol.

Abbreviation	Explanation
AC	Adjudication Committee
AE	Adverse event
AESI	Adverse event of special interest
AG	Anogenital
ALC	Absolute lymphocyte count
ALT	Alanine aminotransferase
AMC	Absolute monocyte count
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the curve
AUC_{ALC}	Area under the curve for absolute lymphocyte count
AUC_{ANC}	Area under the curve for absolute neutrophil count
AUC_{last}	Area under the plasma concentration curve to the last measurable concentration
BP	Blood pressure
CBC	Complete blood count
ccRCC	Clear cell renal carcinoma
CGI-C	Clinical Global Impression of Change
CGI-S	Clinical Global Impression of Severity
CI	Confidence interval
CLIA	Clinical Laboratory Improvement Amendments
ClinRO	Clinician-reported outcome
C_{max}	Maximum concentration
CTCAE	Common Terminology Criteria for Adverse Events
CXCL12	C-X-C motif chemokine ligand 12
CXCR4	C-X-C chemokine receptor type 4
CYP	Cytochrome P450
DMC	Data Monitoring Committee

Abbreviation	Explanation
ECG	Electrocardiogram
eCRF	Electronic case report form
EoRP	End of Randomized Period
EOS	End of Study
EOT	End of Treatment
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
Gardasil®9	HPV-9 valent vaccine, recombinant
GCP	Good Clinical Practice
GOF	Gain-of-function
G-CSF	Granulocyte-colony stimulating factor
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HPV	Human papillomavirus
HR	Heart rate
ICF	Informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IM	Intramuscular
IRB	Institutional Review Board
ITT	Intent-to-Treat
IV	Intravenous
IXRS	Interactive web response system
LFT	Liver function test
MMRM	Mixed-model repeated measures
NCI	National Cancer Institute
OCT	Optical coherence tomography
OTC	Over-the-counter
PD	Pharmacodynamic
P-gp	P-glycoprotein

Abbreviation	Explanation
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Severity
PI	Principal investigator
PK	Pharmacokinetic(s)
PRO	Participant-reported outcome
PT	Preferred Term
QD	Once daily
QoL	Health-related quality of life
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System Organ Class
SUSAR	Suspected, unexpected serious adverse reaction
$T_{1/2}$	Half-life
TAT	Time above threshold
TAT-ALC	Time above threshold-absolute lymphocyte count
TAT-ANC	Time above threshold-absolute neutrophil count
Tdap	Tetanus, diphtheria, and pertussis vaccine
TEAE	Treatment-emergent adverse event
TLT	Treatment-limiting toxicity
T_{max}	Time to maximum concentration
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WHIM	Warts, Hypogammaglobulinemia, Infections, and Myelokathexis
WOCBP	Women/woman of childbearing potential
X4	X4 Pharmaceuticals, Inc.

1. PROTOCOL SYNOPSIS

Name of Sponsor/Company:
X4 Pharmaceuticals, Inc. (X4)

Name of Investigational Product: mavorixafor (X4P-001)

Title of Study: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Mavorixafor in Participants with WHIM Syndrome with Open-Label Extension

Study number: X4P-001-103

Study period:	**Phase of development:**
Date first participant enrolled: Q3 2019 Estimated date last participant to complete initial 52-week Treatment Period: Q3 2022 Every effort should be made to schedule the last participant last visit before 30 September 2022.	3

Objectives and Endpoints:

Objectives	Endpoints
Randomized Placebo-Controlled Period	
Primary	
To demonstrate the efficacy of mavorixafor in participants with Warts, Hypogammaglobulinemia, Infections, and Myelokathexis (WHIM) syndrome as assessed by increasing levels of circulating neutrophils compared with placebo and relative to a clinically meaningful threshold.	Time above threshold-absolute neutrophil count (TAT-ANC; in hours) of ≥ 500 cells/µL over a 24-hour period, assessed 4 times throughout the study (every 3 months for 12 months) for the Intent-to-Treat (ITT) Population.
Key Secondary	
To demonstrate the efficacy of mavorixafor in participants with WHIM syndrome as assessed by increasing levels of circulating lymphocytes compared with placebo and relative to a clinically meaningful threshold.	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 participants with WHIM syndrome as assessed by a composite endpoint of infections and warts.	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 participants with WHIM syndrome as assessed by improvement in warts.	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 participants with WHIM syndrome as assessed by reduction in infections.	Total infection score for mavorixafor based on number and severity of infections adjudicated by a blinded, independent Adjudication Committee (AC) in the ITT Population.
Other Secondary Endpoints	
To demonstrate the efficacy of mavorixafor in participants with WHIM syndrome including as assessed by participant-reported outcomes.	Time to Early Release as confirmed by blinded independent AC in the ITT Population.
	TAT-ALC of ≥ 1000 cells/μL in participants with lymphopenia at baseline.
	Composite endpoint based on total infection score and total wart change score for participants with warts at baseline or participants with non-Ig use.
	Total infection score based on infections adjudicated by a blinded, independent AC for participants 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 participants with warts at baseline.
	Total wart change score (CGI-C) based on local dermatologist review of all regions for participants 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 participants vaccinated at Week 13 with tetanus, diphtheria, and pertussis vaccine (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 participants receiving vaccinations with HPV 9-valent vaccine, recombinant (Gardasil®9) 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 participants 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.
	Quality of life by treatment group as measured by the 36-Item Short Form Survey and EQ-5D-5L, Life Quality Index, for all participants.
	Quality of life by treatment group as measured by The Dermatology Life Quality Index.
	Quality of life by treatment group in adolescent participants 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 participants 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 participants with ANC $\geq$ 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 $\geq$ 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 participants 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.
	Eq-
To evaluate the safety and tolerability of mavorixafor in participants with WHIM syndrome.	Safety and tolerability of investigational product (mavorixafor or placebo).
To evaluate pharmacokinetics (PK) of mavorixafor in participants with WHIM syndrome.	PK of mavorixafor in adult and adolescent WHIM participants.
	Relationship between mavorixafor PK characteristics and safety and efficacy.
Open-Label Period	
Primary	
To evaluate the long-term safety and tolerability of mavorixafor in participants with WHIM syndrome.	Safety and tolerability of mavorixafor in participants with WHIM syndrome, as assessed by adverse events (AEs), clinical laboratory evaluations, vital signs, electrocardiogram (ECG) assessments, physical and ophthalmologic examinations.
Secondary	
To evaluate the long-term efficacy of mavorixafor in participants with WHIM syndrome.	Proportion of neutrophil responders, defined as participants with ANC ≥ 500 cells/μL threshold.
	Proportion of lymphocyte responders, defined as participants 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 participants vaccinated with 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 participants 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.
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	Change over time in PGI-S and PGI-C.
	Total infection score as adjudicated by an independent AC.

Methodology:

This is a Phase 3, 2-period study, with an initial 12-month, randomized, double-blind, placebo-controlled period (referred to as the **Randomized Placebo-Controlled Period**) followed by an open-label extension (referred to as the **Open-Label Period** hereafter).

Randomized Placebo-Controlled Period:

To be eligible for the study, participants must have a diagnosis of WHIM syndrome and a genotype-confirmed mutation of C-X-C chemokine receptor type 4 (*CXCR4*), be at least 12 years of age, and have a confirmed absolute neutrophil count (ANC) or total white blood cell (WBC) count ≤ 400 cells/μL at screening, as well as meet all other eligibility criteria.

The **Randomized Placebo-Controlled Period** comprises a 12-month (52-week) treatment period. Approximately 18 to 28 participants will be randomized 1:1 to mavorixafor or matching placebo and stratified according to the use of immunoglobulin (Ig) therapy, irrespective of the mode of administration (including subcutaneous or intravenous). The 2 strata are defined as (1) have received any Ig treatment within 5 months prior to screening visit/signing of the informed consent form (ICF), or (2) have not received any Ig treatment within 5 months prior to screening visit/signing of the ICF.

Both the baseline assessments for eligible participants and the administration of the first dose of study drug or placebo will occur during a time period of approximately 28 hours from Day -1 to Day 1. Specifically, the baseline assessments, including an electrocardiogram (ECG) and serial samples for ANC and absolute lymphocyte count (ALC), as well as total WBC count and absolute monocyte count (AMC), will be conducted over 24 hours prior to study drug administration. In the case of systemic infection between screening and baseline, the baseline visit may be postponed for up to 4 weeks or until the ANC has been confirmed to be ≤ 400 cells/μL. Systemic infections must be resolved prior to first study drug administration. If an infection occurs any time between the screening and the baseline visits, this event will be considered medical history, and the Investigator should record the event via the clinician-reported outcome (ClinRO) mechanism as well as record the event on the Medical History form of the electronic case report form (eCRF). Participants will be treated with oral mavorixafor 400 mg once daily (QD) except for adolescents weighing ≤ 50 kg, who will be treated with mavorixafor 200 mg QD.

Participants stratified to the no prior Ig stratum will not be treated with Ig during the duration of the study (including in the **Open-Label Period**). Participants in the prior Ig therapy stratum will continue on the same Ig treatment (ie, same dose, mode of administration, and frequency) as administered prior

to joining the study. During the study, administration of Ig must not occur within 4 days prior to each visit.

The first dose of study drug will be administered on the morning of Day 1, followed by an ECG at 2 hours postdose (± 30 minutes) and blood draws at 2 hours and 4 hours postdose (each ± 15 minutes) (prior to discharge).

At Weeks 1 and 4 (± 3 days), participants will have a telephone call from the Investigator or designee to evaluate safety and discuss study compliance, followed by scheduled study visits every 13 weeks (ie, Weeks 13, 26, 39, and 52 [± 14 days for all of these visits]). In order to avoid multiple needle sticks, blood sampling for pharmacokinetics (PK), ALC, AMC, ANC, and WBC count may require an indwelling catheter.

Participants will be contacted by phone approximately 72 to 24 hours prior to each scheduled study visit to check if the participant feels that he/she may have an ongoing infection, and to remind the participant not to take his/her study medication at home on the day of the visit, as the study medication will be administered during the visit. In the event of symptoms consistent with infection, the visits may be delayed until the symptoms of infection are cleared.

Rescue use of granulocyte-colony stimulating factor (G-CSF) for up to approximately 2 weeks is permitted after discussion with the Medical Monitor. If an Investigator decides that a participant requires ongoing, regularly scheduled treatment with G-CSF, then the participant must be discontinued from study treatment or be considered for Early Release (Section 5.4.1.1). In the event of rescue treatment with G-CSF or antibiotic therapy any time on or after conducting the baseline visit, visits for ANC measures must be delayed for no less than 14 days and no more than 28 days from the last dose of G-CSF, or no less than 7 days (or 5 half-lives) for the antibiotic in consideration, whichever is longer, and no more than 28 days from the last dose of antibiotics.

Participants will be vaccinated with tetanus, diphtheria, and pertussis (Tdap) and HPV 9-valent vaccine, recombinant (Gardasil®9) according to a predetermined schedule starting at Week 13. Vaccination will be according to respective vaccine schedules for all participants, unless not permitted per standard of care. Revaccination for Gardasil®9 will be per vaccine schedule for participants who have completed a full course of vaccination with Gardasil®9 prior to the study, unless not permitted per standard of care. Antibody-specific titers, including pertussis toxin, tetanus, human papillomavirus (HPV) 16, and HPV 18 will be collected in the **Randomized Placebo-Controlled Period** at baseline, and Weeks 26, 39, 52, and EOS.

In the **Randomized Placebo-Controlled Period**, information about potential infections will be collected via multiple sources: an electronic participant-reported outcomes (PRO) questionnaire, the ClinRO questionnaire, through information collected by the study team and entered into the Adverse Event of Special Interest – Infections eCRF, and in documents uploaded in the infection adjudication portal. Potential infection events will be evaluated by a blinded, independent Adjudication Committee (AC) as outlined in the AC Charter. The AC will evaluate all potential infection data and determine whether an event is consistent with infection, the characteristics of the infection, the severity of the infection, and whether a given participant may qualify for **Early Release** from the **Randomized Placebo-Controlled Period** to the **Open-Label Period** based on infection severity. The AC will be the final arbiter of infections for the purpose of the efficacy analysis.

The warts Clinical Global Impression of Severity (CGI-S) and Clinical Global Impression of Change (CGI-C), determined by blinded central review for the target skin regions, will be used for the composite clinical endpoint analysis. Electronic diaries that contain the PRO questionnaire will be distributed at the baseline visit for the **Randomized Placebo-Controlled Period** and will include a participant training session. The electronic diaries will be completed daily during both the **Randomized** and **Open-Label Periods**.

Participants should continue to receive **blinded** study drug administration through the Week 52 (ie, the End of Randomized Period [EoRP]) visit. Participants completing the EoRP have 3 options:

- Roll over to the **Open-Label Period:** For these participants, the last day of the EoRP visit is the last day of the **Randomized Placebo-Controlled Period**.
- End participation in the study: These participants and any participants who discontinue study at any time during the **Randomized Placebo-Controlled Period** will attend an End of Study (EOS) visit at 30 days (± 14 days) post–last dose of study treatment.
- Roll over to long-term follow-up: These participants will have a safety follow-up visit at 30 days (± 14 days) post–last dose of study treatment. The safety follow-up visit will be identical to the EOS in terms of timing and procedures performed.

For participants who discontinue study treatment during the **Randomized Placebo-Controlled Period**, every effort will be made to encourage participants to attend all planned visits (ie, Weeks 13, 26, 39, and 52 [± 14 days for all of these visits], as applicable).

For participants who prematurely discontinue from the study an EOT visit will be conducted followed by an EOS/Safety follow-up visit. Discontinued participants will not continue into the **Open-Label Period**.

Open-Label Period:

Only participants who complete the **Randomized Placebo-Controlled Period** or are granted **Early Release** due to significant or recurrent infections, as adjudicated by a blinded, independent AC, or participants for whom the blind was broken will be eligible for and offered the opportunity to be enrolled in the **Open-Label Period** and receive treatment with mavorixafor 400 mg QD (or 200 mg QD for adolescents weighing ≤ 50 kg) until commercial availability or study termination by the Sponsor.

Assessments made at the Week 52 visit of the **Randomized Placebo-Controlled Period** (ie, the EoRP) will serve as baseline values for the **Open-Label Period**. The **Open-Label Period** begins with the administration of the first dose of open-label study drug (24 hours after the final dose of blinded study drug). The **Open-Label Period** ICF must be signed prior to any **Open-Label Period** procedure. Open-label study drug should be dispensed only after all assessments pertaining to the EoRP have been completed. In Year 1, the schedule of telephone contacts and office visits will match that of the **Randomized Placebo-Controlled Period**, with telephone contacts from the Investigator or designee at Weeks 1 and 4 (± 3 days) to evaluate safety, then a schedule of office visits every 13 weeks (Weeks 13, 26, 39, and 52 [± 14 days]). From Year 2 onward, participants will attend visits every 6 months (Weeks 26 and 52 [± 14 days]) with phone contacts between office visits (ie, at Weeks 13 and 39 [± 3 days]) to evaluate safety between office visits. An EOS visit will be conducted at 30 days (± 14 days) post–end of treatment or for any participant who discontinues the study early. Participants completing or discontinuing the **Open-Label Period** may choose to roll over to the long-term follow-up. These participants will have a safety follow-up visit at 30 days (± 14 days) post–last dose of mavorixafor. The safety follow-up visit will be identical to the EOS in terms of timing and procedures performed.

During Year 1 of the **Open-Label Period**, the same antibody-specific titers as in the **Randomized Placebo-Controlled Period** will be collected every 3 months and at EOS; and then every 6 months and at EOS from Year 2 onward. Early Release participants rolling over to the **Open-Label Period** will continue their vaccination schedule from the **Randomized Placebo-Controlled Period**.

In the **Open-Label Period**, information about infections will be collected similarly to that in the **Randomized Placebo-Controlled Period** in the PRO(s), the ClinRO, and the eCRF and submitted in the infection adjudication portal.

Participants will be contacted by phone approximately 72 to 24 hours prior to each scheduled study visit to check if the participant feels that he/she may have an ongoing infection, and to remind the participant not to take his/her study medication at home on the day of the visit, as the study medication will be administered during the visit. In the event of symptoms consistent with infection, the visits may be delayed until the symptoms of infection are cleared. During the study, administration of Ig must not occur within 4 days prior to each visit.

Rescue use of G-CSF for up to approximately 2 weeks is permitted after discussion with the Medical Monitor. If an Investigator decides that a participant requires ongoing, regularly scheduled treatment with G-CSF, then the participant must be discontinued from study treatment. In the event of rescue treatment with G-CSF or antibiotic therapy, visits for ANC measures must be delayed for no less than 14 days and no more than 28 days from the last dose of G-CSF, or no less than 7 days (or 5 half-lives) for the antibiotic in consideration, whichever is longer, and no more than 28 days from the last dose of antibiotics.

In the event that the study, or study drug is discontinued for any reason, the EOT and EOS/Safety follow-up visits will be performed as specified in the Schedules of Events (Section 1.1).

For Both Study Periods:

It is recommended to use central laboratory analysis for determination of ANC values. Local laboratory analysis should be used only for unscheduled visits, repeated samples, or for central laboratory samples that could not be processed.

Infections are a designated outcome and will be reported as adverse events of special interest (AESIs); infections that meet the criteria for serious adverse events (SAEs) will be reported as SAEs. For the purposes of this study, types of infections will include any bacterial, fungal, viral, protozoan, or parasitic disease, excluding HPV-related muco-cutaneous warts or any HPV-induced lesions. Participants with chronic localized infections that do not cause systemic inflammation may be eligible after approval by the Medical Monitor.

In the event that the study is discontinued prematurely for any reason, the EOT and EOS/Safety follow-up visits will be performed as specified in the Schedules of Events (Section 1.1). If a participant cannot be seen, attempts will be made to contact the participant by telephone to inquire about reasons for stopping participation and to obtain updated information on any unresolved AEs.

All available safety data will be reviewed periodically by an independent Data Monitoring Committee (DMC) as outlined in the DMC Charter. The DMC will be unblinded to support review of potential safety concerns. The DMC is responsible for making recommendations for study continuance with or without modification as part of their review.

Optional Long-Term Follow-Up:

Participants who are not willing, interested, or eligible to transition into the **Open-Label Period**, or those who complete or drop out of the **Open-Label Period**, will have the option to participate in long-term follow-up via phone contacts. The phone contacts will occur every 3 months, will be used to follow participants for reporting of items described in Section 8.3.3, and will continue until participant dropout or termination by Sponsor. Participants who elect to participate in the long-term follow-up will have a safety follow-up visit in place of the EOS visit. The safety follow-up visit will be identical to the EOS in terms of timing and procedures performed. Follow-up phone contacts will commence after the completion of the safety follow-up visit (Table 2).

Number of participants (planned):

The planned enrollment is approximately 18 to 28 participants ≥ 12 years of age.

Diagnosis and main criteria for inclusion:

Participants with a clinical diagnosis of WHIM syndrome must meet all of the following criteria to be eligible for study participation:

1. Be at least 12 years of age.
2. Have signed the current approved Informed Consent Form. Participants under 18 years of age (in the Netherlands and other applicable regions, participants under 16 years of age) will sign an approved informed assent form and must also have a signed parental/legal guardian consent.
3. Have a genotype-confirmed mutation of *CXCR4* consistent with WHIM phenotype.
4. Agree to use a highly effective form of contraception, as detailed in Section 5.3.1.
5. Be willing and able to comply with this protocol.
6. Have a confirmed ANC ≤ 400 cells/µL during screening, obtained while participant has no clinical evidence of infection. Local laboratory may be used if central laboratory is not available.
    a. If the ANC is below the lower limit of detection for the laboratory and the total WBC count is ≤ 400 cells/µL, then the participant is considered eligible for the study.
    b. If the ANC is > 400 cells/µL in the context of a recent infection or inflammation prior to screening, it is acceptable to redraw a blood sample and confirm that the ANC meets inclusion criteria (≤ 400 cells/µL) once the infection or inflammatory episode is resolved.
    c. If the participant experiences an infection or inflammatory episode between screening and baseline that may impact the ANC, or receives G-CSF between screening and baseline, the baseline visit may be postponed for up to 4 weeks until the ANC has been confirmed to be ≤ 400 cells/µL.

The Medical Monitor should be notified and approve each rescreen occurrence.

Exclusion:

In the criteria below, “prior to Day 1” refers to Day 1 of treatment.

Participants with any of the following will be excluded from participation in the study:

1. Has known systemic hypersensitivity to the mavorixafor drug substance, its inactive ingredients, or the placebo.
2. Is pregnant or breastfeeding.
3. Has a known history of a positive serology or viral load for HIV or a known history of AIDS.
4. Has, at screening, laboratory tests meeting 1 or more of the following criteria:
    - A positive hepatitis C virus antibody with confirmation by hepatitis C virus ribonucleic acid polymerase chain reaction reflex testing.
    - A positive hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb).

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

5. Has, at screening, safety laboratory tests meeting 1 or more of the following criteria:
   - Hemoglobin < 8.0 g/dL
   - Platelets < 75,000 cells/µL
   - Estimated glomerular filtration rate based on the Modification of Diet in Renal Disease of ≤ 29 mL/min/1.73 m^2 (Stage 4 or 5 chronic kidney disease)
   - Serum aspartate aminotransferase > 2.5 × the upper limit of normal (ULN)
   - Serum alanine aminotransferase > 2.5 × ULN
   - 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)
6. Had surgery requiring general anesthesia within the 4 weeks prior to Day 1.
7. Received any of the following treatments:
   - Plerixafor within 6 months prior to Day 1.
   - Chronic or prophylactic use of antibiotics (systemic or inhaled) within 4 weeks prior to Day 1.
   - Chronic or prophylactic use of G-CSF or granulocyte macrophage-colony stimulating factor within 2 weeks of Day 1.
   - Chronic or prophylactic use of systemic glucocorticoid use (> 5 mg prednisone equivalent per day) within 2 weeks prior to Day 1.
   - 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.
8. Is currently taking or has, within 2 weeks prior to Day 1, received any medication that is prohibited (see Section 6.4.1), based on potential for drug-drug interactions.
9. Has, at the planned initiation of study drug, a clinically diagnosed active infection (excluding warts) that has the potential to raise the ANC counts.
10. Has had a total splenectomy within 1 year.
11. Has a current diagnosis of myelofibrosis.
12. Has a medical history of hematological malignancies.
13. Has any other medical or personal condition that, in the opinion of the Investigator, may potentially compromise the safety or compliance of the participant or may preclude the participant's successful completion of the clinical study.
14. Has corrected QT interval using Fridericia's formula of > 450 ms.

Note: Central results should be used for determination of screening laboratory values when possible. However, local laboratory analysis may be used if central laboratories are not available, or for unscheduled visits, repeated samples, or in place of central laboratory samples that could not be processed or were out of window.

Inclusion criteria for **Open-Label Period:**

1. Completed the **Randomized Placebo-Controlled Period** or
2. Granted Early Release from the **Randomized Placebo-Controlled Period**, as described in Section 5.4.1.1.
3. Blind broken (Section 12.3.1).

Investigational product, dosage, and mode of administration:

Mavorixafor is a second-generation, small-molecule, noncompetitive antagonist of the CXCR4 receptor.

The mavorixafor dose regimen for both the **Randomized Placebo-Controlled Period** and the **Open-Label Period** is 400 mg QD for adults. For adolescents (12-17 years of age) weighing > 50 kg at any time during the study, the mavorixafor dose will also be 400 mg QD. Adolescents weighing ≤ 50 kg at screening will receive mavorixafor 200 mg QD. If an adolescent participant's weight increases to > 50 kg at any time during the study, the dose will be increased to 400 mg. Mavorixafor is administered as 100-mg dose strength capsules by mouth on an empty stomach.

Duration of treatment:

Screening is planned for up to 38 days.

In the **Randomized Placebo-Controlled Period**, the planned duration of treatment is 52 weeks. Participants are expected to receive their randomly assigned treatment until the earliest of:

- Completion of study
- Discontinuation for any reason

In the **Open-Label Period**, participants may receive mavorixafor until commercial availability, study termination by the Sponsor, or discontinuation for any reason.

Reference therapy, dosage, and mode of administration:

Placebo (equivalent number of matching capsules)

Statistical methods:

Sample size: For sample size estimation, the following assumptions were used based on the results from the Phase 2 study: Mean mavorixafor time above threshold for ANC (hours) = 11.4; mean placebo time above threshold for ANC (hours) = 1.4; pooled standard deviation = 4.7.

Given a 1:1 (mavorixafor:placebo) randomization allocation, a total of 18 participants (n = 9 in each treatment group) will provide greater than 90% power using a 2-sample t-test on the mean time above threshold for ANC over a 24-hour period, given the null hypothesis that the difference between the 2 treatment groups is equal to zero with a 2-sided significance level (alpha) of 0.05.

Analysis populations: The ITT Population (all participants randomized to treatment and received at least 1 dose of study treatment) is the primary population for the analysis of efficacy endpoints (according to the treatment to which they were randomized). Sensitivity and confirmatory analyses may be performed using the Per Protocol Population, defined as all participants in the ITT Population without any major protocol violations (defined in the statistical analysis plan) that may impact the

assessment of efficacy and with at least 1 efficacy evaluation. The Safety Population is the primary population for the analysis of safety endpoints, defined as all participants who received at least 1 dose of study medication (analyzed according to the treatment they actually received).

General methods: A detailed statistical analysis plan will be finalized prior to database lock. Data summaries will be prepared and categorized by treatment group (mavorixafor, placebo) and study period (randomized, open-label). All data collected in this study will be documented using summary tables and figures, as appropriate, and presented in by-participant data listings.

Tabulations will be produced for appropriate disposition, demographic, baseline, efficacy, and safety parameters. Categorical variables will be summarized by frequency distributions (number and percentages of participants), and continuous variables will be summarized by descriptive statistics (mean, standard deviation, median, minimum, and maximum). Statistical hypothesis testing will be performed to evaluate the primary and secondary efficacy endpoints of the **Randomized Placebo-Controlled Period** of the study. Where appropriate, p-values and 95% confidence intervals will be reported. All statistical tests will be reported using 2-sided tests with alpha = 0.05, unless otherwise stated.

To control familywise type I error rate, the following key secondary endpoints will be tested in order after meeting the primary endpoint:

1. 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.
2. Composite Clinical Efficacy Endpoint for mavorixafor versus placebo based on total infection score and total wart change score in the ITT Population over 52 weeks.
3. Total wart change score for mavorixafor versus placebo based on central blinded, independent review of 3 target skin regions in the ITT Population at 52 weeks.
4. Total infection score for mavorixafor versus placebo based on infections adjudicated by a blinded, independent AC in the ITT Population over 52 weeks.

Data collected in the **Open-Label Period** will be presented and analyzed separately.

1.1. Schedules of Events

Table 1: Schedule of Events: Randomized Placebo-Controlled Period

Study Phase	Screening	Treatment Phase						EOS/Safety Follow-up[c]
Procedure \ Study Day/ Week	Day -28 to Day -1 (±10D)	Baseline (Day -1 to Day 1)[a]	Week 1 Week 4 (Phone contact) (± 3D)	Week 13 (± 14D)	Week 26 (± 14D)	Week 39 (± 14D)	Week 52 (EoRP/EOT)[b] (± 14D)	30 days post–end of treatment (± 14D)
General study procedures								
Informed consent	X							
Eligibility assessment	X	X						
Randomization[d]	X							
Vaccinations (Section 8.1.8)[e]				X	X	X		
Exit interview (Section 8.5)[f]							X[f]	
History and Baseline assessments								
Inclusion / Exclusion criteria determination	X							
Inclusion / Exclusion criteria confirmation[g]		X						
Medical history, including 12-month infection history, any infection that led to hospitalization, and wart history (Section 8.1.1)	X							
History of WHIM syndrome	X							
Medication and vaccine history (including HPV)	X							
Physical examination (Section 8.1.5)[h]	X	X		X	X	X	X	X

Study Phase	**Screening**	**Treatment Phase**						**EOS/Safety Follow-up[c]**
Study Day/ Week / **Procedure**	**Day -28 to Day -1 (±10D)**	**Baseline (Day -1 to Day 1)[a]**	**Week 1 Week 4 (Phone contact) (± 3D)**	**Week 13 (± 14D)**	**Week 26 (± 14D)**	**Week 39 (± 14D)**	**Week 52 (EoRP/EOT)[b] (± 14D)**	**30 days post–end of treatment (± 14D)**
Height (in adults, only at baseline)	X	X		X	X	X	X	
Body weight	X	X		X	X	X	X	X
Vital signs (HR, BP, temperature)	X	X		X	X	X	X	X
12-lead ECG (Section 8.1.7)[i]	X	X		X	X	X	X	
Ophthalmologic examination (Section 8.1.9.1)[j]	X	X			X		X	X
Female Tanner stage assessment (only participants 12-17 years of age)	X						X	
Male Tanner stage assessment (only participants 12-17 years of age)	X			X	X	X	X	
Male testicular safety assessment (only male participants < 50 years of age)[k]	X			X	X	X	X	
Male testicular ultrasound (only male participants < 50 years of age)[k]	X				X		X	
Laboratory (including sampling for clinical assessments)								
Genotyping for eligibility (Section 8.1.3)	X							
Serology for eligibility	X							
Hematology (Section 8.1.10)	X	X		X	X	X	X	X
Serum chemistry (Section 8.1.10)	X	X		X	X	X	X	X
Urinalysis (Section 8.1.10)	X	X		X	X	X	X	X
Pregnancy test (WOCBP only; Section 8.1.10.1)	X	X		X	X	X	X	X

Study Phase	**Screening**	**Treatment Phase**						**EOS/Safety Follow-up[c]**
Procedure \ **Study Day/ Week**	**Day -28 to Day -1 (±10D)**	**Baseline (Day -1 to Day 1)[a]**	**Week 1 Week 4 (Phone contact) (± 3D)**	**Week 13 (± 14D)**	**Week 26 (± 14D)**	**Week 39 (± 14D)**	**Week 52 (EoRP/EOT)[b] (± 14D)**	**30 days post–end of treatment (± 14D)**
PK sample collection (See Section 9 for time points)[l]		X		X	X	X	X	
ALC, AMC, ANC, and WBC sampling time above threshold and for AUCs (see Section 10.1 for time points)[m]		X[n]		X	X	X	X	
Biomarker collection: Lymphocytes and lymphocyte subpopulations (Section 10.5.1)[o]	X	X		X	X	X	X	X
Biomarker collection: Serum immunoglobulins (Section 10.5.2)		X		X	X	X	X	X
Biomarker collection: Vaccine antibody titers (Section 10.5.3)		X			X	X	X	X
Optional research blood: Lymphocytes and lymphocyte subpopulations (Section 10.5.1)[p]	X	X		X	X	X	X	X
Optional research blood: Antibodies to common pathogens and antibody repertoire[p]		X			X		X	
HPV skin swabs (Section 10.5.4)	X				X		X	
Participant-reported outcomes (to be completed prior to any other study-related procedures)								
Patient Global Impression of Severity (Study Operations Manual Section 15.3)		X					X	
Patient Global Impression of Change (Study Operations Manual Section 15.2)							X	

Study Phase	**Screening**	**Treatment Phase**						**EOS/Safety Follow-up[c]**
Procedure / **Study Day/ Week**	**Day -28 to Day -1 (±10D)**	**Baseline (Day -1 to Day 1)[a]**	**Week 1 Week 4 (Phone contact) (± 3D)**	**Week 13 (± 14D)**	**Week 26 (± 14D)**	**Week 39 (± 14D)**	**Week 52 (EoRP/EOT)[b] (± 14D)**	**30 days post–end of treatment (± 14D)**
QoL questionnaires (prior to any other procedures at all scheduled visits) (Section 10.4)		X			X		X	
PRO questionnaire via e-diary		Continuous (event-driven)						
ClinRO questionnaire in response to e-diary		Continuous (event-driven)						
Reporting infections instruction review		X		X	X	X	X	X
Clinical assessments of warts								
Local dermatological assessment of warts including CGI-S and CGI-C[r] (Section 10.3)	X[q]				X		X	
Photographs of hands and feet and target warts for central review	X[q]				X		X	
Safety and medications								
Study drug administration		Randomly assigned treatment (mavorixafor or placebo) QD						
Concomitant medication monitoring	Continuous from screening to EOS							
Adverse event monitoring	Continuous from informed consent to EOS							

Abbreviations: AE = adverse event; ALC = absolute lymphocyte count; AMC = absolute monocyte count; ANC = absolute neutrophil count; AUC = area under the curve; BP = blood pressure; CGI-C = Clinical Global Impression of Change; CGI-S = Clinical Global Impression of Severity; ClinRO = clinician-reported outcome; D = days; ECG = electrocardiogram; EoRP = End of Randomized Period; EOS = End of Study; EOT = End of Treatment; G-CSF = granulocyte-colony stimulating factor; HPV = human papillomavirus; HR = heart rate; ICF = informed consent form; Ig = immunoglobulin; OCT = optical coherence tomography; PK = pharmacokinetic; PRO = participant-reported outcome; QD = once daily; QoL = quality of life; Tdap = tetanus, diphtheria, and pertussis vaccine; WBC = white blood cell; WHIM = Warts, Hypogammaglobulinemia, Infections, and Myelokathexis; WOCBP = women of childbearing potential

Notes: The schedule is presented relative to study week and time of dosing. The calendar day of the first administration of study drug is designated Day 1. All weeks are relative to Week 1, defined as Day 1 through Day 7, inclusive. Predose and postdose intervals are relative to the time of oral administration,

designated time 0.

Unscheduled visits will be conducted in person or by a phone contact any time the participant identifies a potential infection, as described in Section 8.6.

[a] At baseline, the 24-hour in-residency evaluation will be conducted on Day -1 prior to study drug administration on Day 1 and conclude after laboratory collections at approximately 4 hours after the first dose of study drug administration on Day 1.

[b] If treatment is terminated prematurely for any reason, the EoRP visit will be performed within 14 days from last dose of study drug or last visit. Every effort should be made to schedule the last participant last visit before 30 September 2022.

[c] Participants who elect to participate in the long-term follow-up will have a safety follow-up visit in place of the EOS visit. The safety follow-up visit will be identical to the EOS in terms of timing and procedures performed.

[d] Randomization will occur during the screening period once eligibility has been established. The randomized blinded study drug assignment will be sent to the clinical site for the eligible participant to be administered at baseline Day 1.

[e] Vaccination will be according to respective vaccine schedules for all participants, unless not permitted per standard of care. Revaccination for Gardasil®9 will be per vaccine schedule for participants who have completed a full course of vaccination with Gardasil®9 prior to the study, unless not permitted per standard of care. Participants < 14 years of age will be vaccinated with Tdap at Week 13 and Gardasil®9 at Weeks 13 and 39 (all ± 14 days).

[f] The exit interview will be conducted at the EoRP, or within 2 weeks prior to the EoRP (Week 52), or within 30 days of the last dose of study drug for participants who terminate early from the study; and in any case prior to enrolling in the Open-Label Period.

[g] No additional assessments are performed at baseline confirmation, but review of all non-laboratory–based exclusion criteria should be reviewed, such as prohibited concomitant medications. The evaluation of eligibility of the participant from screening is reviewed and confirmed.

[h] Complete physical examinations will include measurement of body weight and height (for adults, height at baseline only) and examination of general appearance, skin, neck (including thyroid), eyes, nose, throat, heart, lungs, abdomen, lymph nodes, extremities, and nervous system.

[i] Standard 12-lead ECG will be obtained after the participant has been semi-recumbent or supine for approximately 10 minutes. ECGs will be obtained at screening, at baseline, at predose (on Day -1 or Day 1 prior to dosing), then at 2 hours postdose (± 30 min), then predose and 2 hours postdose (± 30 min) at every office visit thereafter.

[j] Prior to dosing, the ophthalmology examination is required only once, at either screening or baseline.

[k] Assessments will occur every 3 months (6 months for ultrasound) for male adolescents and adults up to 50 years of age. Baseline visit assessments will only apply to new participants enrolling after the approval of Protocol Amendment version 3.0. Assessments will include testicular examination, testicular ultrasound (Section 8.1.9.3), and blood testing for hormones including serum luteinizing hormone, follicle-stimulating hormone, total testosterone levels, and inhibin B. Fasting, morning blood draws are preferred to get more consistent results as values can vary by time of day. In the case of abnormal lab values/AEs, additional tests may be required and may include semen testing per World Health Organization standard.

[l] Participants who discontinue treatment but remain on study will not undergo blood sampling for PK analysis.

[m] In the event of rescue G-CSF, visits for ANC measures must be delayed for no less than 14 days and no more than 28 days from the last dose of G-CSF. Furthermore, in the event of antibiotic therapy to treat an acute infection or exacerbation, visits for ANC measures must be delayed for no less than 7 days (or 5 half-lives for the antibiotic in consideration), whichever is longer, and no more than 28 days from the last dose of antibiotics.

[n] ALC, AMC, ANC, and WBC sample collection 2 hours and 4 hours postdose (each ± 15 minutes) at baseline Day 1.

[o] Lymphocyte subpopulations samples will be collected at time 0 at screening and then, for all subsequent visits, at time point 0 (predose) and at approximately 4 hours (postdose).

[p] Only for participants weighing ≥ 45 kg (≥ 100 pounds). For participants weighing < 45 kg (< 100 pounds), see blood volume schedule in the participant ICF.

[q] Dermatologist examinations can be done either on site or remotely using video conference during home-health visits. The examination and collection of photographs and images during the screening period should be performed at least 7 days prior to the baseline visit to allow central review of the quality of baseline images. Examinations, photographs, or swabs may be repeated at baseline if assessment/photographs/swabs from screening are not sufficient.

[r] CGI-C will not be assessed at baseline (as no baseline evaluation is available for comparison).

Table 2: Schedule of Events: Open-Label Period – Year 1

Study Phase							EOS/Safety-Follow-up[c]
Procedure \ Study Day/ Week	EoRP Visit[a]	Phone contacts:[b] Weeks 1 and 4 (± 3D)	Week 13 (± 14D)	Week 26 (± 14D)	Week 39 (± 14D)	Week 52 (or EOT) (± 14D)	30 days post–end of treatment (± 14D)
General study procedures							
Informed consent[a]	X						
Eligibility assessment	X						
Study drug administration	400 mg mavorixafor QD in adults and adolescents (12-17 years of age) weighing > 50 kg at any time during the study (200 mg QD in participants 12-17 years of age weighing ≤ 50 kg)						
Vaccinations (Section 8.1.8)	Vaccination schedule continued from Randomized Placebo-Controlled Period, if relevant[d]						
History and Baseline assessments							
Physical examination (Section 8.1.5)	X		X	X	X	X	X
Height (only participants 12-17 years of age at Open-Label Period baseline visit)	X		X	X	X	X	
Body weight	X		X	X	X	X	X
Vital signs (HR, BP, temperature)	X		X	X	X	X	X
12-lead ECG at time 0 (predose) and 2 hours postdose (Section 8.1.7)[e]	X		X	X	X	X	
Ophthalmologic examination (Section 8.1.9.1)[f]	X			X		X	X
Female Tanner stage assessment (only participants 12-17 years of age)						X	
Male Tanner stage assessment (only participants 12-17 years of age)	X		X	X	X	X	X

Study Phase							**EOS/Safety-Follow-up[c]**
Procedure \ **Study Day/ Week**	**EoRP Visit[a]**	**Phone contacts:[b] Weeks 1 and 4 (± 3D)**	**Week 13 (± 14D)**	**Week 26 (± 14D)**	**Week 39 (± 14D)**	**Week 52 (or EOT) (± 14D)**	**30 days post–end of treatment (± 14D)**
Male testicular safety assessment (only male participants < 50 years of age)[g]			X	X	X	X	
Male testicular ultrasound (only male participants < 50 years of age)[g]				X		X	
Laboratory (including samples for clinical assessments)							
Hematology (Section 8.1.10)	X		X	X	X	X	X
Serum chemistry (Section 8.1.10)	X		X	X	X	X	X
Urinalysis (Section 8.1.10)	X		X	X	X	X	X
Pregnancy test (WOCBP only; Section 8.1.10.1)	X		X	X	X	X	X
Biomarker collection: Lymphocytes and lymphocyte subpopulations (Section 10.5.1)[h]	X		X	X	X	X	X
Biomarker collection: Serum immunoglobulins (Section 10.5.2)	X		X	X	X	X	X
Biomarker collection: Vaccine antibody titers (Section 10.5.3)	X		X	X	X	X	X
Optional research blood: Lymphocytes and lymphocyte subpopulations[i]	X		X	X	X	X	X
Optional research blood: Antibodies to common pathogens and antibody repertoire[i]				X		X	
HPV skin swabs	X			X		X	

Study Phase							**EOS/Safety-Follow-up[c]**
Procedure / **Study Day/ Week**	**EoRP Visit[a]**	**Phone contacts:[b] Weeks 1 and 4 (± 3D)**	**Week 13 (± 14D)**	**Week 26 (± 14D)**	**Week 39 (± 14D)**	**Week 52 (or EOT) (± 14D)**	**30 days post–end of treatment (± 14D)**
Participant-reported outcomes (to be completed prior to any other study-related procedures)							
Patient Global Impression of Severity (Study Operations Manual Section 15.3)	X					X	
Patient Global Impression of Change (Study Operations Manual Section 15.2)	X					X	
QoL questionnaires (prior to any other procedures; see Section 10.4)	X			X		X	
e-diary completion for infection episodes and central adjudication of infection events	Continuous						
Clinical assessments of warts							
Local dermatologist assessment of warts including CGI-S and CGI-C (Section 10.3)	X			X		X	
Photographs of hands and feet and target warts for central review	X			X		X	
Safety and medications							
Study visits			X	X	X	X	
Concomitant medication monitoring	Continuous from Day 1 through EOS						
Adverse event monitoring	Continuous from Day 1 through EOS						
Optional long-term follow-up via phone contacts[j]							
Concomitant medication monitoring	X		X	X	X	X	NA
Infection data	X		X	X	X	X	NA

Study Phase							
Procedure / Study Day/ Week	EoRP Visit[a]	Phone contacts:[b] Weeks 1 and 4 (± 3D)	Week 13 (± 14D)	Week 26 (± 14D)	Week 39 (± 14D)	Week 52 (or EOT) (± 14D)	EOS/Safety-Follow-up[c] 30 days post–end of treatment (± 14D)
Wart data	X		X	X	X	X	NA

Abbreviations: AE = adverse event; BP = blood pressure; CGI-C = Clinical Global Impression of Change; CGI-S = Clinical Global Impression of Severity; D = days; ECG = electrocardiogram; EoRP = End of Randomized Period; EOS = End of Study; EOT = End of Treatment; HPV = human papillomavirus; HR = heart rate; ICF = informed consent form; OCT = optical coherence tomography; PRO = participant-reported outcome; QD = once daily; QoL = quality of life; WOCBP = women of childbearing potential.

Note: The schedule is presented relative to study week and time of dosing. The calendar day of the first administration of study drug is designated Day 1. All weeks are relative to Week 1, defined as Day 1 through Day 7, inclusive. Predose and postdose intervals are relative to the time of oral administration, designated time 0.

[a] The Open-Label Period ICF must be signed prior to any Open-Label Period procedure. The EoRP visit assessments will carry over from the Randomized Placebo-Controlled Period and serve as baseline values; EoRP procedures will not be repeated in the Open-Label Period. The Open-Label Period begins with the administration of the first dose of open-label study drug (24 hours after the final dose of blinded study drug). Open-label study drug should be dispensed only after all assessments pertaining to the EoRP have been completed.

[b] Phone contacts will be for assessing safety (concomitant medications and AEs) and study compliance.

[c] Participants who elect to participate in the long-term follow-up will have a safety follow-up visit in place of the EOS visit. The safety follow-up visit will be identical to the EOS in terms of timing and procedures performed.

[d] In the event of Early Release in the Randomized Placebo-Controlled Period prior to receiving any vaccinations, participants will continue their vaccination schedule from the Randomized Placebo-Controlled Period (see Section 8.1.8).

[e] Standard 12-lead ECG will be obtained after the participant has been semi-recumbent or supine for approximately 10 minutes. ECGs will be obtained predose, and at 2 hours postdose (± 30 min) for the first year of the Open-Label Period from Week 13 visit onward.

[f] Pretreatment scans must occur prior to first dose of open-label drug as part of the EoRP visit and every 6 months thereafter. Other ophthalmologic assessments may be performed, if feasible. Other assessments may include OCT and/or autofluorescence.

[g] Assessments will occur every 3 months (6 months for ultrasound) for male adolescents and adults up to 50 years of age. Assessments will include testicular examination, testicular ultrasound (Section 8.1.9.3), and blood testing for hormones including serum luteinizing hormone, follicle-stimulating hormone, total testosterone levels, and inhibin B. Fasting, morning blood draws are preferred to get more consistent results as values can vary by time of day. In the case of abnormal lab values/AEs, additional tests may be required and may include semen testing per World Health Organization standard.

[h] Lymphocyte subpopulation samples will be collected predose at time point 0 and approximately 4 hours postdose.

[i] Only for participants weighing ≥ 45 kg (≥ 100 pounds). For participants weighing < 45 kg (< 100 pounds), see blood volume schedule in the participant ICF.

[j] Participants who are not willing, interested, or eligible to transition into the Open-Label Period, or those who complete or drop out of the Open-Label Period, will have the option to participate in long-term follow-up via phone contacts that will continue until participant dropout or termination by Sponsor. The phone contacts will be used to follow participants for reporting of items described in Section 8.3.3.

Table 3: Schedule of Events: Open-Label Period – Year 2 Onward

Study Phase	Active Phase[a]		EOS/Safety Follow-up[b]
Study Day/ Week / Procedure	Week 26 (± 14D)	Week 52 (or EOT) (± 14D)	30 days post–end of treatment (± 14D)
General study procedures			
Study drug administration	400 mg mavorixafor QD in adults and adolescents (12-17 years of age) weighing > 50 kg at any time during the study (200 mg QD in participants aged 12 to 17 weighing ≤ 50 kg)		
Vaccinations (Section 8.1.8)	Vaccination schedule continued from Randomized Placebo-Controlled Period, if relevant		
History and Baseline assessments			
Physical examination (Section 8.1.5)	X	X	X
Height (only participants 12-17 years of age at baseline visit for Year 2 onward)	X	X	
Body weight	X	X	X
Vital signs (HR, BP, temperature)	X	X	X
12-lead ECG at time 0 (predose) (Section 8.1.7)[c]	X	X	
Ophthalmologic examination (Section 8.1.9.1)[d]	X	X	X
Female Tanner stage assessment (only participants 12-17 years of age)		X	
Male Tanner stage assessment (only participants 12-17 years of age)	X	X	X
Male testicular safety assessment (only male participants < 50 years of age)[e]	X	X	

Study Phase	Active Phase[a]		EOS/Safety Follow-up[b]
Study Day/ Week / Procedure	Week 26 (± 14D)	Week 52 (or EOT) (± 14D)	30 days post–end of treatment (± 14D)
Male testicular ultrasound (only male participants < 50 years of age)[e]	X	X	
Laboratory (including samples for clinical assessments)			
Hematology (Section 8.1.10)	X	X	X
Serum chemistry (Section 8.1.10)	X	X	X
Urinalysis (Section 8.1.10)	X	X	X
Pregnancy test (WOCBP only; Section 8.1.10.1)	X	X	X
Biomarker collection: Lymphocytes and lymphocyte subpopulations (Section 10.5.1)[f]	X	X	X
Biomarker collection: Serum immunoglobulins (Section 10.5.2)	X	X	
Biomarker collection: Vaccine antibody titers (Section 10.5.3)	X	X	X
Participant-reported outcomes (to be completed prior to any other study-related procedures)			
Patient Global Impression of Severity (Study Operations Manual Section 15.3)		X	
Patient Global Impression of Change (Study Operations Manual Section 15.2)		X	
QoL questionnaires (prior to any other procedures; see Section 10.4)	X	X	
e-diary completion for infection episodes and central adjudication of infection events	Continuous		

Study Phase	Active Phase[a]		EOS/Safety Follow-up[b]
Study Day/ Week / Procedure	Week 26 (± 14D)	Week 52 (or EOT) (± 14D)	30 days post–end of treatment (± 14D)
Clinical assessments of warts			
Local dermatologist assessment of warts including CGI-S and CGI-C (Section 10.3)	X	X	
Photographs of hands and feet and target warts for central review	X	X	
Safety and medications			
Study visits	X	X	
Concomitant medication monitoring	Continuous through EOS		
Adverse event monitoring	Continuous through EOS		

Abbreviations: AE = adverse event; BP = blood pressure; CGI-C = Clinical Global Impression of Change; CGI-S = Clinical Global Impression of Severity; D = days; ECG = electrocardiogram; EoRP = End of Randomized Period; EOS = End of Study; EOT = End of Treatment; HR = heart rate; ICF = informed consent form; OCT = optical coherence tomography; PRO = participant-reported outcome; QD = once daily; QoL = quality of life; WOCBP = women of childbearing potential.

Note: The schedule is presented relative to study week and time of dosing. The calendar day of the first administration of study drug is designated Day 1. All weeks are relative to Week 1, defined as Day 1 through Day 7, inclusive. Predose and postdose intervals are relative to the time of oral administration, designated time 0.

[a] The Active Phase of the Open-Label Period will be repeated until mavorixafor is commercially available or the study is terminated by the Sponsor.

[b] Participants who elect to participate in the long-term follow-up will have a safety follow-up visit in place of the EOS visit. The safety follow-up visit will be identical to the EOS in terms of timing and procedures performed.

[c] Standard 12-lead ECG will be obtained after the participant has been semi-recumbent or supine for approximately 10 minutes. ECGs will be obtained predose on all scheduled visits.

[d] Ophthalmologic assessment will occur every 6 months thereafter from Year 2 onward in the Open-Label Period. Other ophthalmologic assessments may be performed, if feasible. Other assessments may include OCT and/or autofluorescence.

[e] Assessments will occur every 6 months for male adolescents and adults up to 50 years of age. Assessments will include testicular examination, testicular ultrasound (Section 8.1.9.3), and blood testing for hormones including serum luteinizing hormone, follicle-stimulating hormone, total testosterone levels, and inhibin B. Fasting, morning blood draws are preferred to get more consistent results as values can vary by time of day. In the case of abnormal lab values/AEs, additional tests may be required and may include semen testing per WHO standard.

[f] Lymphocyte subpopulation samples will be collected predose at time point 0 and approximately 4 hours postdose.

2. INTRODUCTION

2.1. Background Information

WHIM (**W**arts, **H**ypogammaglobulinemia, **I**nfections, and **M**yelokathexis) syndrome is a rare, autosomal dominant, combined primary immunodeficiency syndrome caused by inherited gain-of-function (GOF) mutations altering the C-X-C chemokine receptor type 4 (CXCR4) receptor carboxyl terminus (OMIM 2015). The disease is associated with significant morbidity and mortality, primarily due to bacterial, viral, and fungal infections; susceptibility to human papillomavirus (HPV) disease; and an increased risk of malignancies (Beaussant Cohen 2012; Al-Herz 2014; Dotta 2019). Key immunological features include chronic severe neutropenia, lymphopenia, marked reduction of B cells, and hypogammaglobulinemia (Al-Herz 2014). Some patients present congenital malformations such as tetralogy of Fallot (Beaussant Cohen 2012; Heusinkveld 2017), adding to the overall disease morbidity. Recently, WHIM syndrome has been recognized by the United States (US) Food and Drug Administration (FDA) as a severely debilitating or life-threatening hematologic disorder (FDA CDER 2019).

The immune defects in WHIM syndrome have been classified as both "antibody deficiency" and "defect in innate immunity" (Al-Herz 2014) and arise from the inappropriate retention of otherwise sufficiently functional white blood cells (WBCs) in the bone marrow, including neutrophil retention, which is known as myelokathexis (Zuelzer 1964). Additional in vitro studies have documented impaired interactions among T cells and B cells in patients with WHIM syndrome (Kallikourdis 2013). Together, these deficiencies underpin the WHIM syndrome symptomatology and can lead to life-threatening complications.

The precise incidence of WHIM syndrome is unknown but estimated to be less than 1 in 1 million (NORD 2016).

There have been no prospective natural history studies of WHIM syndrome. Cohort-level data are limited to 2 studies: 1 study of 8 patients from the French chronic neutropenia registry (Beaussant Cohen 2012) and a study of 21 patients first presented at the 2016 annual meeting of the European Society for Immunodeficiencies (Dotta 2016; Dotta 2019). To better understand the clinical picture of this syndrome, a review of 109 case studies within the medical literature, including the above-listed cohort studies, was carried out by X4 Pharmaceuticals, Inc. (X4) in 2017 (X4 Medical Affairs 2017; Ebrahim 2018). The findings reinforced the characteristics and complications detailed in smaller cohort studies and provided additional insight into the relative incidences of morbidities and complications in this clinically heterogeneous and likely underdiagnosed disease.

In 2003, GOF mutations in *CXCR4* were identified for the first time in patients with WHIM syndrome from 6 different pedigrees (Hernandez 2003). Frameshift, nonsense, or deletion mutations resulted in the truncation of 10 to 19 amino acids from the C-terminus of the CXCR4 receptor cytoplasmic domain. These mutant CXCR4 receptors show impaired desensitization and internalization upon binding of the C-X-C motif chemokine ligand 12 (CXCL12), causing retention of mature WBCs in the marrow and leading to the chronic peripheral neutropenia and lymphopenia observed in patients (Hernandez 2003; Balabanian 2005; Kawai 2009; McCormick 2009). CXCL12, also referred to as stromal cell-derived factor 1, is constitutively

expressed on bone marrow stromal cells and plays a central role in the homing of hematopoietic cells to the bone marrow, their subsequent release into the circulation, and their trafficking to tissues (Lapidot 2002; Gulino 2004). The most common *CXCR4* mutation is R334X, which has been reported in more than half of the pedigrees (McDermott 2010; Dotta 2019). *CXCR4* GOF mutations have been recognized as the molecular basis for immunodeficiency in WHIM syndrome by the classification of primary immunodeficiency diseases issued by The International Union of Immunological Societies (Al-Herz 2014).

The pattern of infections varies in individual patients. The most common severe infections affect the lower respiratory tract (pneumonia, bronchitis) and can be due to a range of gram-positive and gram-negative extracellular pathogens. Of note, it has been reported that among patients over 21 years of age, 6 of 22 patients (27%) progressed to bronchiectasis, contributing to the morbidity of the disease (Beaussant Cohen 2012). Both gram-positive and gram-negative extracellular pathogens have been identified as particularly problematic, including *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Proteus mirabilis*, and *Staphylococcus aureus* (Heusinkveld 2017). In addition, patients are susceptible to fungal and mycobacterial infections (Beaussant Cohen 2012), and their inability to clear HPV leads to treatment-resistant cutaneous and anogenital (AG) warts that can be oncogenic.

WHIM syndrome typically manifests in early childhood, marked by frequent and severe bacterial infections and the appearance of warts. However, the diagnosis of WHIM syndrome is often delayed: about half of the patients were diagnosed in adulthood within the dataset of cases evaluated by X4 (X4 Medical Affairs 2017). In a cohort study of 18 patients, clinical features first manifested at 2.2 ± 2.6 years of age; however, disease diagnosis was delayed until 12.5 ± 10.4 years of age (Dotta 2019). One of the challenges to diagnosis is the transient increase in neutrophil counts during severe infection (Wetzler 1990; Beaussant Cohen 2012; Dotta 2019), which may delay the diagnosis of neutropenia. Another challenge is the clinical heterogeneity of the disease, particularly in younger patients, providing further challenge to timely diagnosis and appropriate treatment.

Current expert opinion is that WHIM syndrome should be considered in any case of neutropenia associated with hypogammaglobulinemia *or* lymphopenia. Confirmatory *CXCR4* genetic testing is recommended even in cases in which the marrow appears normal (Heusinkveld 2017; Badolato 2017; Aghamohammadi 2017; ESID 2019). It is estimated that up to 30% of cases are sporadic, highlighting the importance of broad genetic testing in patients with chronic neutropenia even in the absence of incomplete clinical diagnostic criteria (Aghamohammadi 2017). The presence of a positive family history may facilitate the timely diagnosis of younger patients. The contribution of family history to diagnosis is illustrated by the X4 case dataset, in which a positive history was present in approximately one-third of cases overall and in close to half (n = 6) of the 14 patients diagnosed before the age of 7 years (X4 Medical Affairs 2017).

In conclusion, WHIM syndrome is a challenging combined primary immunodeficiency disorder, and while the acronym “WHIM” was coined for the characteristic clinical manifestations of the disease, the warts, hypogammaglobulinemia, infections, and myelokathexis elements incompletely describe the phenotype. In addition, cohort studies have shown that the definitive diagnosis may be delayed by the incomplete penetrance of the hypogammaglobulinemia, the transient rise in neutrophils during acute infection, the absence of warts in younger patients, and

the difficulty of identifying myelokathexis in a marrow biopsy (Heusinkveld 2017; Tassone 2009), further delaying diagnosis and timely management of infections and comorbidities.

2.1.1. Unmet Clinical Need

Despite improved knowledge of the disease, therapeutic choices are insufficient, and there are no approved treatments directed at the primary pathophysiology of the syndrome. Current off-label therapeutic options for WHIM patients include parenteral immunoglobulin (Ig) therapy, granulocyte-colony stimulating factor (G-CSF), antibiotic prophylaxis, and hematopoietic stem cell transplantation. In addition, plerixafor, a parenteral CXCR4 inhibitor, is being investigated in patients with WHIM syndrome.

G-CSF and Ig therapy are the most commonly prescribed treatments, but neither treatment has been evaluated in patients with WHIM syndrome. G-CSF treatment lacks proof of efficacy in the prevention of infectious episodes. Treatment with Ig may be helpful for protecting children from the development of bronchiectasis as well as more serious acute infections that have a potentially lethal course, such as *Mycobacterium* (Badolato 2017). However, both are nonspecific, difficult to administer, do not address the primary underlying defect, and have limited effectiveness in mitigating hematological defects and preventing infection (Kawai 2009; Beaussant Cohen 2012). Neither treatment addresses the increased susceptibility to HPV-related disease.

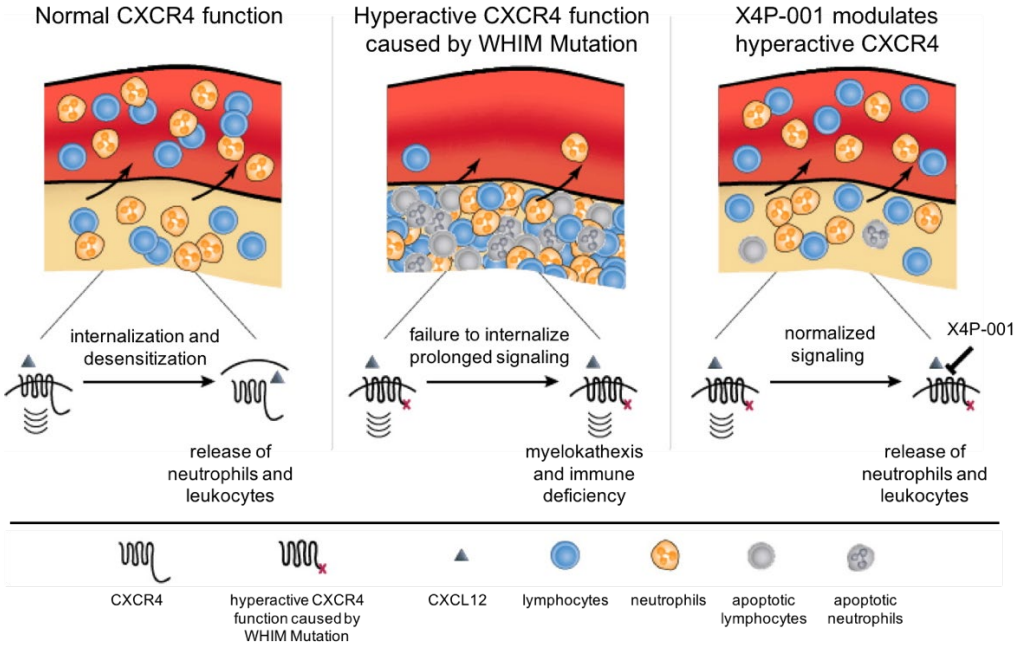
The challenges and limitations of the currently available treatment options illustrate that the primary underlying drivers of morbidity in WHIM syndrome remain unaddressed; namely, participant health-related quality of life (QoL) and vulnerability to life-limiting infection and malignancy.

2.2. Rationale for Mavorixafor in the Treatment of WHIM

Mavorixafor is a second-generation, small-molecule, noncompetitive antagonist of the CXCR4 receptor that acts by binding to extracellular domains of the receptor, resulting in specific and reversible inhibition of receptor signaling in response to its ligand CXCL12. Mavorixafor was discovered by the same laboratory that created plerixafor. Critical differences compared with plerixafor are that mavorixafor is orally bioavailable and has a half-life ($T_{1/2}$) of ~22.9 hours (see Investigator's Brochure), permitting QD oral dosing. In vitro studies have confirmed that mavorixafor is equally active in inhibiting the response to CXCL12 for both wild-type CXCR4 and for CXCR4 with the most common GOF mutations associated with primary immunodeficiency (AnorMED Study No. AOM 0050). Mavorixafor is currently in clinical development in participants with cancer (renal cell carcinoma, melanoma, and Waldenström's macroglobulinemia) and WHIM syndrome. The nonclinical pharmacology and clinical pharmacokinetic (PK) experience with mavorixafor are described in the Investigator's Brochure.

Figure 1 shows the effect of *CXCR4* mutation in WHIM syndrome and the expected effect of treatment with mavorixafor.

Figure 1: Effect of *CXCR4* Mutation in Participants with WHIM Syndrome and Hypothesized Effect of Mavorixafor Treatment



Abbreviation: WHIM = Warts, Hypogammaglobulinemia, Infections, and Myelokathexis.
CXCR4 antagonism by X4P-001 (mavorixafor) is predicted to modulate the enhanced and prolonged receptor signaling characteristic of WHIM syndrome, resulting in increased mobilization of neutrophils and lymphocytes from the bone marrow and normalization of bone marrow cellularity with decrease in hypermature and apoptotic cells.

As detailed in Section 2.1, WHIM syndrome is a disease of considerable morbidity and mortality, with no currently available therapy directed against the underlying mechanism of disease. Mavorixafor is an oral agent suitable for QD administration that directly and specifically targets the molecular basis of the disease and is expected to have efficacy at dose levels that will be safe and well tolerated.

For participants in this study, the potential clinical benefit of mavorixafor, an orally bioavailable, investigational treatment that directly targets the molecular pathogenesis of WHIM syndrome, outweighs its potential risks when these risks are appropriately monitored and managed, as described in Table 5 (see Section 4.5.7).

2.2.1. Overview of Clinical Development Program for Mavorixafor

X4 has initiated or completed the following studies of mavorixafor:

- X4P-001-REGA – a Phase 1 study in healthy volunteers comparing 2 different dosing regimens: 200 mg twice daily versus 400 mg once daily (QD).
- X4P-001-RCCA – a Phase 1/2 study of mavorixafor alone and in combination with axitinib in patients with advanced clear cell renal carcinoma (ccRCC).
- X4P-001-RCCB – a study adding mavorixafor to patients receiving nivolumab for the treatment of advanced ccRCC.
- X4P-001-MELA – a Phase 1b study of mavorixafor alone and in combination with pembrolizumab in patients with advanced melanoma.
- X4P-001-MKKA – a Phase 2 study of mavorixafor in adult patients with WHIM syndrome.
- X4P-001-204 – a Phase 1b open-label, multicenter, single-arm study of mavorixafor in combination with ibrutinib in patients with Waldenström's macroglobulinemia.
- X4P-001-104 – a Phase 1b, open-label, multicenter study of mavorixafor in patients with severe congenital neutropenia and chronic neutropenia disorders.

In addition, under the prior development program sponsored by AnorMed, 4 clinical studies were conducted, 2 in healthy volunteers and 2 in patients with HIV. PK and safety results from the prior development program are described in the Investigator's Brochure.

The data cutoff for Version 9.0 of the Investigator's Brochure is 04 May 2021. As of the data cutoff, there were 222 patients treated with mavorixafor in 12 clinical studies (n = 76 healthy volunteers, n = 16 HIV, n = 107 oncology, n = 23 WHIM syndrome). Overall, mavorixafor has been generally well tolerated in these populations.

Although the oncology populations include patients with recurrent disease and multiple comorbidities, no mavorixafor-related serious adverse events (SAEs) caused a fatal outcome in any of the oncology patients.

Clinical experience with mavorixafor in healthy volunteers and oncology populations is summarized in the Investigator's Brochure. Interim results from the Phase 2 study in patients with WHIM syndrome are described in the sections that follow.

2.2.2. Clinical Experience with Mavorixafor in WHIM Patients

Clinical experience with mavorixafor in WHIM patients is summarized in the Investigator's Brochure.

2.2.2.1. Disposition and Exposure

As of 14 May 2019, 8 adult patients with WHIM syndrome have been treated with mavorixafor 50 to 400 mg, with a median duration of treatment of 473 days (range 6 to 842 days).

Patients received doses of 50, 100, 150, 200, 300, and 400 mg. Not all patients received all doses. After September 2017, initial dosing was started using the 100-mg strength capsule

because it was determined by the Investigator and Sponsor that higher daily doses of 300 mg and 400 mg would be necessary to achieve the clinical threshold for absolute neutrophil count (ANC).

The mean age of patients was 35.5 years (range 18 to 57 years). The 8 patients who constituted the study population appeared to reflect the reported population with WHIM, being young (mean age 35.5 years), predominantly female (75%), and Caucasian (100%), with prior history of infection and warts, and 75% with the R334 variant *CXCR4* genotype. Overall, 6 of 8 patients had chronic ear and labyrinth disorders and 2 patients had prior malignancies. Seven of 8 patients had received prior treatment for WHIM, including G-CSF in 7 patients and plerixafor in 2 patients.

2.2.2.2. Pharmacokinetic and Pharmacodynamic Results

Phase 2 X4P-001-MKKA study PK data are available from 7 patients with WHIM syndrome at 6 dose levels. Administered mavorixafor doses ranged from 50 to 400 mg QD. Mavorixafor exhibited a multi-exponential distribution. The median time to maximum concentration (T_{max}) was consistent for all dose levels and occurred at approximately 1.50 hours, ranging from 1.25 to 2.0 hours postdose.

Mavorixafor displayed a biphasic elimination, characterized by an initial rapid elimination phase followed by a longer terminal elimination phase. When dose proportionality was assessed using Ln-transformed mavorixafor steady-state maximum concentration (C_{max}) and area under the plasma concentration curve to the last measurable concentration (AUC_{last}) and dose using a linear model, C_{max} increased proportionally with dose and AUC_{last} increased more than proportionally with dose. However, the number of patients at each dose was small and variability was high, leading to wide confidence intervals (CIs).

The human PK of mavorixafor has not been evaluated in children and adolescents (aged < 18 years). However, based on available data, we expect that the PK of mavorixafor in adolescents > 50 kg will be similar to that of adults. Indeed, mavorixafor is eliminated mainly by hepatic route in humans, and cytochrome P450 (CYP) 3A4/5 appears to be the predominant enzyme responsible for metabolism. Furthermore, hepatic metabolism in adolescents aged 13 years and older is considered to be similar to that of adults; therefore, it is anticipated that the PK of mavorixafor in adolescents weighing > 50 kg will be similar to that of adults. Finally, based on population PK modeling and simulations of adolescent exposures, exposures in adolescents weighing > 50 kg receiving adult doses of up to 400 mg are not anticipated to exceed observed exposures of mavorixafor in adult patients with renal cell carcinoma or WHIM.

A primary pharmacodynamic effect of CXCR4 antagonism is mobilization of WBC (including both myeloid and lymphoid cells) from the bone marrow into the peripheral circulation. The relationship between plasma drug levels and concurrent peripheral blood WBC counts was examined in Phase 1 studies with dense sampling. More specific data on neutrophils (ANC) and lymphocytes (absolute lymphocyte count [ALC]) were collected in Protocol X4P-001-MKKA in adult patients with WHIM.

2.2.2.3. Safety Data

Safety results of the Phase 2 study of mavorixafor in adult patients with WHIM syndrome, as of a database cutoff of 14 May 2019, show that 7 of 8 patients (87.5%) experienced at least 1

treatment-emergent adverse event (TEAE), with 2 (25%) patients experiencing a Grade 3 TEAE, cholecystitis in 1 patient and procedural pain in a second patient; neither of these events was considered by the Investigator to be study drug–related. No Grade 4 TEAEs or TEAEs with an outcome of death (ie, Grade 5 events) have been reported. The only TEAEs reported by > 1 patient included dry mouth, nausea, sinusitis, and upper respiratory tract infection (each 2 patients; 25%); all of these TEAEs were Grade 1 or 2 in intensity. One patient withdrew due to a study drug–related TEAE, dermatitis psoriasiform, which appeared during the first week of treatment. Overall, only 3 patients had TEAEs that were considered related to study drug, including nausea (2 patients) and conjunctivitis, dermatitis psoriasiform, dry mouth, dyspepsia, and nasal dryness (1 patient each). The frequency of TEAEs did not increase with dose. Two (25%) patients experienced an SAE, Grade 2 influenza and pyrexia in 1 patient and Grade 2 bronchitis in a second patient; all 3 events were considered unrelated to study drug.

The safety profile of mavorixafor in this patient population is emerging. Infections are the most common type of TEAEs in this patient population (given the underlying disease), followed by gastrointestinal disorders.

A detailed by-patient analysis of the clinical TEAEs for the Phase 2 patients revealed no TEAEs related to liver. As well, a detailed analysis of liver function tests (LFTs) revealed no clinically significant LFT abnormalities. One patient had an aspartate aminotransferase (AST) and alanine aminotransferase (ALT) reading that was above the upper limit of normal at 1 time point of laboratory testing. AST and ALT returned to within normal range at the next scheduled laboratory test.

There were no clinically meaningful findings in clinical chemistry or urinalysis and only the expected findings per the underlying disease (neutropenia, lymphopenia, and leukopenia) in hematology. There were no significant findings reported in electrocardiograms (ECGs) or ophthalmologic examinations.

After Data Monitoring Committee (DMC) review of the Phase 2 portion of the study, a dose of 400 mg QD was required to achieve both AUC_{ANC} and AUC_{ALC} above the levels considered clinically relevant in the majority of patients. Given the overall safety profile and the recommendation of the DMC, 400 mg QD has been selected as the dose for further investigation in Phase 3 (in adults and adolescents weighing > 50 kg at any time during the study).

2.2.2.4. Efficacy Data

Based on the pathophysiology of WHIM, clinical efficacy is expected to require mobilization of both lymphocytes and neutrophils above clinically relevant thresholds. ANC and ALC measurements were available from 7 evaluable patients with WHIM at doses ranging from 50 to 400 mg QD. No patient achieved area under the curve for absolute neutrophil count (AUC_{ANC}) above the target threshold of 14,400 cells·h/µL (which corresponds to a neutrophil count above 600 cells/µL over 24 hours) at doses below 300 mg of mavorixafor. At 300 mg, 4 of 7 patients achieved the target ANC response. At 400 mg mavorixafor, 2 of 3 patients who did not respond to 300 mg had ANC values that exceeded the threshold. For ALC, no patient treated with 50 mg mavorixafor achieved area under the curve for absolute lymphocyte count (AUC_{ALC}) above the threshold of 24,000 cells·h/µL (which corresponds to a lymphocyte count ≥ 1000 cells/µL over 24 hours), while the majority (ie, 75% at 100 mg) of patients had AUC_{ALC} above the threshold at the higher dose. Based on these data, 300 mg is considered the minimally effective dose in

WHIM, and a dose of 400 mg QD was selected as the Phase 3 dose in both adults and adolescents ages 12 to 17 weighing > 50 kg at any time during the study to achieve consistent elevations in ANC and ALC in the largest number of patients. Please refer to the latest version of the Investigator's Brochure for efficacy result details.

Efficacy results of the Phase 2 study of mavorixafor in adult patients with WHIM syndrome, as of a database cutoff of 14 May 2019, showed that mavorixafor 400 mg once daily reduced the yearly infection rate when comparing the rate 12 months prior to the trial (4.63 [95% CI, 3.3-6.3] events) to 2.14 (95% CI, 1.11-4.10) while on study treatment with mavorixafor. Additionally, mavorixafor up to 300 or 400 mg demonstrated an average of 75% reduction in the number of warts after 5 to 18 months on study, without the use of topical imiquimod or other treatment (Dale 2020).

It was also observed that no patient required G-CSF for infection events or prophylactic antibiotics on study and that the infection frequency was correlated with the time on treatment (Dale 2020).

2.2.2.5. Conclusions

Based on a thorough review of the data obtained through 14 May 2019, no significant risks have been identified that impact the benefit-risk of mavorixafor. The safety information obtained to date does not indicate any unfavorable changes in the benefit-risk profile of mavorixafor that would preclude further clinical development.

Based on a thorough review of the available safety information, treatment with mavorixafor is considered to be generally safe and well tolerated. With the proper management of risk, the Sponsor believes that the benefit-risk profile of mavorixafor is acceptable for investigational studies in patients with malignancies and in patients with WHIM syndrome.

A dose of 400 mg QD was required to achieve both AUC_{ANC} and AUC_{ALC} above the levels considered clinically relevant. Given the overall safety profile and the recommendation of the DMC, 400 mg QD has been selected as the dose for further investigation in the Phase 3 portion of this study (in adults and adolescents weighing > 50 kg at any time during the study).

3. STUDY OBJECTIVES AND ENDPOINTS

Table 4: Objectives and Endpoints

Objectives	Endpoints
Randomized Placebo-Controlled Period	
Primary	
To demonstrate the efficacy of mavorixafor in participants with Warts, Hypogammaglobulinemia, Infections, and Myelokathexis (WHIM) syndrome as assessed by increasing levels of circulating neutrophils compared with placebo and relative to a clinically meaningful threshold.	Time above threshold-absolute neutrophil count (TAT-ANC; in hours) of ≥ 500 cells/μL over a 24-hour period, assessed 4 times throughout the study (every 3 months for 12 months) for the Intent-to-Treat (ITT) Population.
Secondary	
To demonstrate the efficacy of mavorixafor in participants with WHIM syndrome as assessed by increasing levels of circulating lymphocytes compared with placebo and relative to a clinically meaningful threshold.	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 participants with WHIM syndrome as assessed by a composite endpoint of infections and warts.	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 participants with WHIM syndrome as assessed by improvement in warts.	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 participants with WHIM syndrome as assessed by reduction in infections.	Total infection score for mavorixafor based on number and severity of infections adjudicated by a blinded, independent Adjudication Committee (AC) in the ITT Population.
Other Secondary Endpoints	
To demonstrate the efficacy of mavorixafor in participants with WHIM syndrome including as assessed by participant reported outcomes.	Time to Early Release as confirmed by blinded independent AC in the ITT Population.
	TAT-ALC of ≥ 1000 cells/μL in participants with lymphopenia at baseline.
	Composite endpoint based on total infection score and total wart change score for

	participants with warts at baseline or participants with non-Ig use.
	Total infection score based on infections adjudicated by a blinded, independent AC for participants 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 participants with warts at baseline.
	Total wart change score (CGI-C) based on local dermatologist review of all regions for participants 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 participants 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 participants receiving vaccinations with HPV 9-valent vaccine, recombinant (Gardasil®9) 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 participants 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.
	Quality of life by treatment group as measured by the 36-Item Short Form Survey and EQ-5D-5L, Life Quality Index, for all participants.
	Quality of life by treatment group as measured by The Dermatology Life Quality Index.
	Quality of life by treatment group in adolescent participants 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 participants 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 participants with ANC $\geq$ 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 $\geq$ 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 participants 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.
	Absolute and fold change from baseline in absolute numbers of T, B, and natural killer lymphocyte subpopulations.
To evaluate the safety and tolerability of mavorixafor in participants with WHIM syndrome.	Safety and tolerability of investigational product (mavorixafor or placebo).
To evaluate pharmacokinetics (PK) of mavorixafor in participants with WHIM syndrome.	PK of mavorixafor in adult and adolescent WHIM participants.
	Relationship between mavorixafor PK characteristics and safety and efficacy.
Open-Label Period	
Primary	
To evaluate the long-term safety and tolerability of mavorixafor in participants with WHIM syndrome.	Safety and tolerability of mavorixafor in participants with WHIM syndrome, as assessed by adverse events (AEs), clinical laboratory evaluations, vital signs, ECG assessments, physical and ophthalmologic examinations.
Secondary	
To evaluate the long-term efficacy of mavorixafor in participants with WHIM syndrome.	Proportion of neutrophil responders, defined as participants with ANC ≥ 500 cells/μL threshold.
	Proportion of lymphocyte responders, defined as participants 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 participants vaccinated

	with 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 participants 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.

4. INVESTIGATIONAL PLAN

4.1. Study Design

This is a Phase 3, 2-period study, with an initial 12-month, randomized, double-blind, placebo-controlled period (referred to as the **Randomized Placebo-Controlled Period**) followed by an open-label extension (referred to as the **Open-Label Period** hereafter).

Randomized Placebo-Controlled Period:

To be eligible for the study, participants must have a diagnosis of WHIM syndrome and a genotype-confirmed mutation of C-X-C chemokine receptor type 4 (*CXCR4*), be at least 12 years of age, and have a confirmed absolute neutrophil count (ANC) or total white blood cell (WBC) count ≤ 400 cells/μL at screening as well as meet all other eligibility criteria.

The **Randomized Placebo-Controlled Period** comprises a 12-month (52-week) treatment period. Approximately 18 to 28 participants will be randomized 1:1 to mavorixafor or matching placebo and stratified according to the use of immunoglobulin (Ig) therapy, irrespective of the mode of administration (including subcutaneous or intravenous). The 2 strata are defined as (1) have received any Ig treatment within 5 months prior to screening visit/signing of the ICF, or (2) have not received any Ig treatment within 5 months prior to screening visit/signing of the ICF.

Both the baseline assessments for eligible participants and the administration of the first dose of study drug or placebo will occur during a time period of approximately 28 hours from Day -1 to Day 1. Specifically, the baseline assessments, including an electrocardiogram (ECG) and serial samples for ANC and absolute lymphocyte count (ALC), as well as total WBC count and absolute monocyte count (AMC), will be conducted over 24 hours prior to study drug administration. In the case of systemic infection between screening and baseline, the baseline visit may be postponed for up to 4 weeks or until the ANC count has been confirmed to be ≤ 400 cells/μL. Systemic infections must be resolved prior to first study drug administration. If an infection occurs any time between the screening and the baseline visits, this event will be considered medical history, and the Investigator should record the event via the ClinRO mechanism as well as record the event on the Medical History form of the eCRF. Participants will be treated with oral mavorixafor 400 mg once daily (QD) except for adolescents weighing ≤ 50 kg, who will be treated with mavorixafor 200 mg QD.

Participants stratified to the no prior Ig stratum will not be treated with Ig during the duration of the study (including in the **Open-Label Period**). Participants in the prior Ig therapy stratum will continue on the same Ig treatment (ie, same dose, mode of administration, and frequency) as administered prior to joining the study. During the study, administration of Ig must not occur within 4 days prior to each visit.

The first dose of study drug will be administered on the morning of Day 1, followed by an ECG at 2 hours postdose (± 30 minutes) and blood draws at 2 hours and 4 hours postdose (each ± 15 minutes) (prior to discharge).

At Weeks 1 and 4 (± 3 days), participants will have a telephone call from the Investigator or designee to evaluate safety and discuss study compliance, followed by scheduled study visits every 13 weeks (ie, Weeks 13, 26, 39, and 52 [± 14 days for all of these visits]). In order to avoid

multiple needle sticks, blood sampling for pharmacokinetics (PK), ALC, AMC, ANC, and WBC count may require an indwelling catheter.

Participants will be contacted by phone approximately 72 to 24 hours prior to each scheduled study visit to check if the participant feels that he/she may have an ongoing infection, and to remind the participant not to take his/her study medication at home on the day of the visit, as the study medication will be administered during the visit. In the event of symptoms consistent with infection, the visits may be delayed until the symptoms of infection are cleared.

Rescue use of granulocyte-colony stimulating factor (G-CSF) for up to approximately 2 weeks is permitted after discussion with the Medical Monitor. If an Investigator decides that a participant requires ongoing, regularly scheduled treatment with G-CSF, then the participant must be discontinued from study treatment or be considered for Early Release (Section 5.4.1.1). In the event of treatment with G-CSF or antibiotic therapy any time on or after conducting the baseline visit, visits for ANC measures must be delayed for no less than 14 days and no more than 28 days from the last dose of G-CSF, or no less than 7 days (or 5 half-lives) for the antibiotic in consideration, whichever is longer, and no more than 28 days from the last dose of antibiotics.

Participants will be vaccinated with tetanus, diphtheria, and pertussis (Tdap) and HPV 9-valent vaccine, recombinant (Gardasil®9) according to a predetermined schedule starting at Week 13. Vaccination will be according to respective vaccine schedules for all participants, unless not permitted per standard of care (see Section 8.1.8). Revaccination for Gardasil®9 will be per vaccine schedule for participants who have completed a full course of vaccination with Gardasil®9 prior to the study, unless not permitted per standard of care. Antibody-specific titers, including pertussis toxin, tetanus, human papillomavirus (HPV) 16, and HPV 18 will be collected in the **Randomized Placebo-Controlled Period** at baseline, and Weeks 26, 39, 52, and EOS.

In the **Randomized Placebo-Controlled Period**, information about potential infections will be collected via multiple sources: an electronic participant-reported outcomes (PRO) questionnaire, the clinician-reported outcomes (ClinRO) questionnaire, through information collected by the study team and entered into the Adverse Event of Special Interest – Infections electronic case report form (eCRF), and in documents uploaded in the infection adjudication portal. Potential infection events will be evaluated by a blinded, independent AC as outlined in the AC Charter. The AC will evaluate all potential infection data and determine whether an event is consistent with infection, the characteristics of the infection, the severity of the infection, and whether a given participant may qualify for **Early Release** from the **Randomized Placebo-Controlled Period** to the **Open-Label Period** based on infection severity. The AC will be the final arbiter of infections for the purpose of the efficacy analysis.

The warts Clinical Global Impression of Severity (CGI-S) and Clinical Global Impression of Change (CGI-C), determined by blinded central review for the target skin regions, will be used for the composite clinical endpoint analysis. Electronic diaries that contain the PRO questionnaire will be distributed at the baseline visit for the **Randomized Placebo-Controlled Period** and will include a participant training session. The electronic diaries will be completed daily during both the **Randomized** and **Open-Label Periods**.

Participants should continue to receive **blinded** study drug administration through the Week 52 (ie, the End of Randomized Period [EoRP]) visit. Participants completing the EoRP have 3 options:

- Roll over to the **Open-Label Period**: For these participants, the last day of the EoRP visit is the last day of the **Randomized Placebo-Controlled Period**.
- End participation in the study: These participants and any participants who discontinue study at any time during the **Randomized Placebo-Controlled Period** will attend an End of Study (EOS) visit at 30 days (± 14 days) post–last dose of study treatment.
- Roll over to long-term follow-up: These participants will have a safety follow-up visit at 30 days (± 14 days) post–last dose of study treatment. The safety follow-up visit will be identical to the EOS in terms of timing and procedures performed.

For participants who discontinue study treatment during the **Randomized Placebo-Controlled Period**, every effort will be made to encourage participants to attend all planned visits (ie, Weeks 13, 26, 39, and 52 [± 14 days for all of these visits], as applicable).

For participants who prematurely discontinue from the study an EOT visit will be conducted followed by an EOS/Safety follow-up visit. Discontinued participants will not continue into the **Open-Label Period**.

Open-Label Period:

Only participants who complete the **Randomized Placebo-Controlled Period** or are granted **Early Release** due to significant or recurrent infections, as adjudicated by a blinded, independent AC (Section 5.4.1.1), or participants for whom the blind was broken will be eligible for and offered the opportunity to be enrolled in the **Open-Label Period** and receive treatment with mavorixafor 400 mg QD (or 200 mg QD for adolescents weighing ≤ 50 kg) until commercial availability or study termination by the Sponsor (Figure 2).

Assessments made at the Week 52 visit of the **Randomized Placebo-Controlled Period** (ie, the EoRP) will serve as baseline values for the **Open-Label Period**. The **Open-Label Period** begins with the administration of the first dose of open-label study drug (24 hours after the final dose of blinded study drug). The **Open-Label Period** informed consent form (ICF) must be signed prior to any **Open-Label Period** procedure. Open-label study drug should be dispensed only after all assessments pertaining to the EoRP have been completed. In Year 1, the schedule of telephone contacts and office visits will match that of the **Randomized Placebo-Controlled Period**, with telephone contacts from the Investigator or designee at Weeks 1 and 4 (± 3 days) to evaluate safety, then a schedule of office visits every 13 weeks (Weeks 13, 26, 39, and 52 [± 14 days]). From Year 2 onward, participants will attend visits every 6 months (Weeks 26 and 52 [± 14 days]) with phone contacts between office visits (ie, at Weeks 13 and 39 [± 3 days]) to evaluate safety between office visits. An EOS visit will be conducted at 30 days (± 14 days) post–end of treatment or for any participant who discontinues the study early. Participants completing or discontinuing the **Open-Label Period** may choose to roll over to the long-term follow-up. These participants will have a safety follow-up visit at 30 days (± 14 days) post–last dose of mavorixafor. The safety follow-up visit will be identical to the EOS in terms of timing and procedures performed.

During Year 1 of the **Open-Label Period**, the same antibody-specific titers in the **Randomized Placebo-Controlled Period** will be collected every 3 months and at EOS; and then every 6 months and at EOS from Year 2 onward. Early Release participants rolling over to the **Open-Label Period** will continue their vaccination schedule from the **Randomized Placebo-Controlled Period**.

In the **Open-Label Period**, information about infections will be collected similarly to that in the **Randomized Placebo-Controlled Period** in the PRO(s), the ClinRO, and the eCRF and submitted in the infection adjudication portal.

Participants will be contacted by phone approximately 72 to 24 hours prior to each scheduled study visit to check if the participant feels that he/she may have an ongoing infection, and to remind the participant not to take his/her study medication at home on the day of the visit, as the study medication will be administered during the visit. In the event of symptoms consistent with infection, the visits may be delayed until the symptoms of infection are cleared. During the study, administration of Ig must not occur within 4 days prior to each visit.

Rescue use of G-CSF for up to approximately 2 weeks is permitted after discussion with the Medical Monitor. If an Investigator decides that a participant requires ongoing, regularly scheduled treatment with G-CSF, then the participant must be discontinued from study treatment. In the event of treatment with G-CSF or antibiotic therapy, visits for ANC measures must be delayed for no less than 14 days and no more than 28 days from the last dose of G-CSF, or no less than 7 days (or 5 half-lives) for the antibiotic in consideration, whichever is longer, and no more than 28 days from the last dose of antibiotics.

In the event that the study, or study drug is discontinued for any reason, the EOT and EOS/Safety follow-up visits will be performed as specified in the Schedules of Events (Section 1.1).

For Both Study Periods:

It is recommended to use central laboratory analysis for determination of ANC values. Local laboratory analysis should be used only for unscheduled visits, repeated samples, or for central laboratory samples that could not be processed.

Infections are a designated outcome and will be reported as adverse events of special interest (AESIs); infections that meet the criteria for serious adverse events (SAEs) will be reported as SAEs. For the purposes of this study, types of infections will include any bacterial, fungal, viral, protozoan, or parasitic disease, excluding HPV-related muco-cutaneous warts or any HPV-induced lesions. Participants with chronic localized infections that do not cause systemic inflammation may be eligible after approval by the Medical Monitor.

In the event that the study is discontinued prematurely for any reason, the EOT and EOS/Safety follow-up visits will be performed as specified in the Schedules of Events (Section 1.1). If a participant cannot be seen, attempts will be made to contact the participant by telephone to inquire about reasons for stopping participation and to obtain updated information on any unresolved AEs.

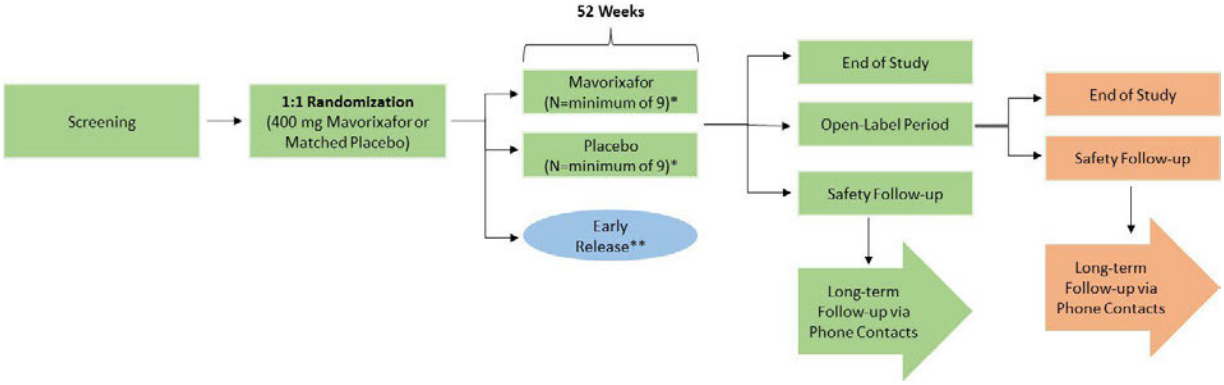
All available safety data will be reviewed periodically by an independent Data Monitoring Committee (DMC) as outlined in the DMC Charter. The DMC will be unblinded to support

review of potential safety concerns. The DMC is responsible for making recommendations for study continuance with or without modification as part of their review.

Optional Long-Term Follow-Up:

Participants who are not willing, interested, or eligible to transition into the **Open-Label Period**, or those who complete or drop out of the **Open-Label Period**, will have the option to participate in long-term follow-up via phone contacts. The phone contacts will occur every 3 months and will be used to follow participants for reporting of items described in Section 8.3.3 and will continue until participant dropout or termination by Sponsor. Participants who elect to participate in the long-term follow-up will have a safety follow-up visit in place of the EOS visit. The safety follow-up visit will be identical to the EOS in terms of timing and procedures performed. Follow-up phone contacts will commence after the completion of the safety follow-up visit (Table 2).

Figure 2: Schema for Study X4P-001-103: Randomized and Open-Label Periods



* Total enrollment is approximately 18 to 28 participants with a minimum of 9 participants for both treatment groups.
** Early release participants may roll over from the Randomized Placebo-Controlled Period to the Open-Label Period if meeting criteria described in Section 5.4.1.1.
Note: Participants aged 12-17 weighing ≤ 50 kg at screening will receive 200 mg mavorixafor or matched placebo in this study.

4.2. Number of Participants

The planned enrollment is approximately 18 to 28 participants ≥ 12 years of age.

4.3. Duration of Treatment

Screening is planned for up to 38 days.

In the **Randomized Placebo-Controlled Period**, the planned duration of treatment is 52 weeks. Participants are expected to receive their randomly assigned treatment until the earliest of the following:

- Completion of study
- Discontinuation for any reason

In the **Open-Label Period**, participants may receive mavorixafor until commercial availability, study termination by the Sponsor, or discontinuation for any reason.

4.4. Dose Adjustment Criteria

4.4.1. Dose Adjustments, Delays, or Stopping Due to Safety Events

If a participant receiving study treatment (mavorixafor or placebo) subsequently has a treatment-limiting toxicity (TLT) event (defined below) or any other AE, study treatment may, with agreement of the participant, the Investigator, and the Medical Monitor, be managed as follows:

- Study treatment may be held (dosing interrupted).
- If the event does *not* improve to Grade ≤ 1 within approximately 14 days, study treatment may be discontinued.
- If the event improves to Grade ≤ 1 within approximately 14 days of holding the study treatment, the participant may resume mavorixafor at the same dose.
- If there are any further Grade ≥ 2 recurrences, study treatment may be discontinued.
- In the case of documented safety concerns, it is acceptable for Investigators to reduce the dose of mavorixafor and inform the Medical Monitor.

A DMC may be consulted on an ad hoc basis for AEs and treatment alterations to determine necessary action to study treatment.

If there are any compliance issues related to the study drug, the Medical Monitor must be consulted. Additionally, if dosing is interrupted for an extended period, the study treatment may be discontinued.

A TLT is defined as one that meets both of the following criteria:

1. Assessed by the Investigator as related to mavorixafor (see Section 11.1.3).
2. Represents one of the following events (grading as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE NCICTCAE_2017], v5.0) (see Section 11.1.2):
    - Is a Grade 3 or Grade 4 clinical event.
        - Exception: Grade 3 nausea, vomiting, or diarrhea lasting < 48 hours in participants who have received suboptimal medical management.
    - Is a confirmed Grade 3 or Grade 4 laboratory event.
        - Exception: Grade 3 electrolyte abnormalities that persist < 72 hours and do not require hospitalization.
        - Exception: Grade 3 AST/ALT increases that persist < 5 days and with total bilirubin ≤ 1.5 × the upper limit of normal (ULN).
    - Is one of the other following events:
        - AST/ALT increased > 3 × ULN (Grade 2) with total bilirubin increased > 2 × ULN in the absence of cholestasis.
        - Testicular toxicity – confirmed treatment-emergent testicular toxicity.
        - Retinopathy – confirmed treatment-emergent retinopathy.
        - Platelets < 50,000 cells/µL (Grade 3) with bleeding or < 25,000 cells/µL (Grade 4) regardless of whether there is a confounding cause or not.

Participants who become pregnant will be discontinued from the study. The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed up and documented even if the participant was discontinued from the study (See Section 11.3.2 for a description of procedures to follow in case of a pregnancy).

4.4.2. Criteria for Dose Modifications Due to Concomitant Medications

Certain medications that are substrates, inhibitors, and/or inducers of CYPs or transporters are prohibited, as described in Table 5.

In the event that a strong CYP3A4 inhibitor/inducer substrate is required, the Investigator must contact the Medical Monitor before prescribing the medication. If Investigator and Medical Monitor conclude that one of these drugs must be used, the 400-mg QD dose of mavorixafor may be modified to 300 mg QD. Participants will return to the 400-mg QD dose once the strong inhibitor medication has been stopped. For adolescent participants aged 12 to 17 weighing ≤ 50 kg at screening, the dose of mavorixafor may be reduced from 200 mg to 100 mg if co-administration with a potent inhibitor of CYP3A4 and/or P-glycoprotein (P-gp) is necessary, but may be maintained at 200 mg QD with appropriate medical monitoring. In the event of other situations in which a dose reduction may be considered appropriate, the Investigator must consult the Medical Monitor.

In the event of an emergency in which a P-gp inhibitor cannot be avoided, the Investigator can prescribe the prohibited medication and hold the study treatment. The Investigator should report the emergency use of the prohibited medication to the Medical Monitor within 24 hours.

Finally, in the case of documented safety concerns, it is acceptable for Investigators to reduce the dose of mavorixafor and inform the Medical Monitor.

4.5. Rationale for the Study Design, Including the Choice of Control Groups

This is the second clinical study of mavorixafor in participants with WHIM syndrome. To minimize selection and assessment bias, the **Randomized Placebo-Controlled Period** of this study is placebo-controlled, randomized 1:1 (mavorixafor:placebo), double-blind, and stratified by Ig use within 5 months prior to screening visit/signing of the ICF. Treatment assignment will be performed by a centralized randomization procedure.

Rationale for specific elements of the study design is described in the sections that follow.

4.5.1. Rationale for Placebo Control

There are currently no approved therapies for the treatment of WHIM syndrome. Treatments have been used empirically in the treatment of WHIM syndrome without consistent results, including G-CSF and Ig. Neither of these are used globally for patient care (Badolato 2017). Therefore, placebo control is appropriate for this study.

The risk to participants is considered to be low, and provisions have been made for Early Release from the **Randomized Placebo-Controlled Period** in the event of (a) 1 and no more than 2 severe infections requiring hospitalization or (b) 4 moderate infections, defined as those requiring either intravenous (IV) antibiotic or G-CSF therapy, as described in Section 5.4.1.1. If medically justified in the opinion of the Investigator, participants experiencing infections may receive rescue therapy including G-CSF for up to approximately 2 weeks.

4.5.2. Rationale for Exclusions and Limitations

4.5.2.1. Ig Therapy During the Trial

Prophylactic administration of parenteral Ig substitution is one of the off-label therapeutic options in WHIM syndrome to raise IgG levels. Typically, Ig replacement therapy via the IV or subcutaneous route may be prescribed in WHIM patients who present with deficient antibody production and recurrent or unusually severe infection. However, evidence of efficacy using this treatment in WHIM participants is lacking (Badolato 2017). Because the use of Ig therapy may elevate vaccine titers, participants are stratified to prior Ig use and no prior Ig use based on treatment in the 5 months preceding screening.

Participants in the prior Ig therapy stratum will continue on the same Ig treatment (ie, same dose, mode of administration, and frequency) as administered prior to joining the study. Participants stratified to the no prior Ig use stratum will not be treated with Ig during the duration of the study (including in the **Open-Label Period**). During the study, administration of Ig must not occur within 4 days prior to each visit.

4.5.2.2. Rationale for Excluding G-CSF Therapy

Treatment with G-CSF increases neutrophil counts and may improve the outcome of infection (Badolato 2017; Dotta 2011; Heusinkveld 2017). Long-term use of G-CSF therapy could be a confounding element for the assessments of efficacy in this study and is therefore prohibited; however, rescue use of G-CSF for up to approximately 2 weeks is permitted after discussion with the Medical Monitor.

4.5.2.3. Rationale for Excluding Participants with Prior Plerixafor Treatment within 6 Months Prior to Day 1

Data show that plerixafor therapy is associated with clinical improvement in patients with WHIM syndrome, including infections and warts (McDermott 2014; McDermott 2019). While plerixafor has a short plasma $T_{1/2}$, it may take up to 6 months for ANC and ALC values to return to baseline values (McDermott 2014). Accordingly, participant exposure to plerixafor within 6 months of Day 1 is excluded.

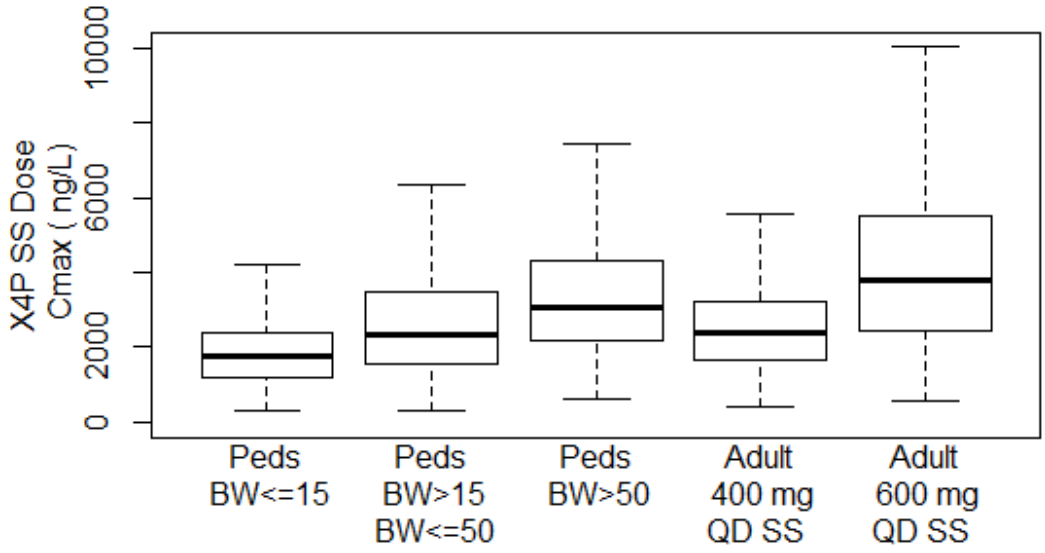
4.5.3. Rationale for Mavorixafor Dose and Duration of Treatment

4.5.3.1. Rationale for Mavorixafor Dose

Mavorixafor has been found to be well tolerated at doses up to 400 mg QD for durations of up to 426 days in patients with WHIM syndrome at the time of the interim analysis, and up to 873 days as of 14 May 2019 in an ongoing Phase 2 study of WHIM patients. AUC_{ALC} was consistently above the threshold for clinical relevance at doses of 100 mg and above, whereas AUC_{ANC} did not exceed the threshold in any patients at doses below 300 mg. Increasing the dose to 400 mg resulted in more patients achieving clinically relevant ANC thresholds over the dosing interval. A PK/pharmacodynamic (PD) analysis confirmed that mavorixafor C_{max} and AUC_{last} appear to correlate with AUC_{ANC}, whereas the AUC_{ALC} response to mavorixafor appears to be maximal by the 100-mg dose (Section 2.2.2.2). Thus, a dose of 400 mg mavorixafor appears to be required to achieve consistent clinically relevant elevations of both ANC and ALC across the

studied dose range. A population PK model of mavorixafor was developed based on adult data and scaled using allometry to simulate exposures in adolescents using standard age-weight tables. The results of the simulations demonstrated that the 400-mg adult dose is expected to provide mean mavorixafor exposures in simulated adolescent participants weighing more than 50 kg that were somewhat higher but still fall within the range of observed exposures in adult patients included in the model. Based on this model, doses of 200 mg in adolescent participants aged 12 to 17 weighing 50 kg or less will result in similar exposures to that in adults (Figure 3).

Figure 3: Box Plots of Mavorixafor (X4P-001) Simulated Exposures in Adolescents and Adults Following Weight-Based Dosing Compared with the Observed Exposures in Adults



Abbreviations: BW = body weight; C_{max} = maximum concentration; Peds = pediatric; QD = once daily.
Body Weight Range: Recommended X4P-001 dose for participants aged 12 to 17 weighing ≤ 50 kg at screening is 200 mg QD and for adolescents > 50 kg at any time during the study is 400 mg QD.

4.5.3.2. Rationale for Treatment Duration

At the time of the interim analysis of the Phase 2 study, 8 patients with WHIM syndrome had been on treatment with mavorixafor for a median of 1194 days (range: 6 to 1563 days). Five patients were ongoing in the extension phase and had been treated up to 28.6 months.

Moreover, data from the RCCA study support the long duration planned for the present study. As of 04 May 2021, 74 patients with advanced renal cell carcinoma had received mavorixafor and 62 patients were being treated at the 400-mg QD dose level. The duration of treatment ranged from 5 to 1372 days, inclusive of all dose levels (ie, 200, 400, and 600 mg), with a median duration of 167.5 days at the 400-mg dose level.

Therefore, based on the durations of exposure to date, the planned 52-week duration of treatment in the **Randomized Placebo-Controlled Period** is considered appropriate. In addition, the 52-week duration is intended to minimize variations due to seasonal variations and allow

sufficient observation on therapy to assess clinically relevant parameters such as rate and severity of annualized infections, change in warts, vaccine titers, and Ig levels.

4.5.4. Rationale for Enrolling Adolescent Participants

As previously described (Section 2.1), WHIM syndrome typically manifests in early childhood, yet diagnosis is delayed until 12.5 ± 10.4 years of age (Dotta 2019). Accordingly, adolescents 12 to 17 years of age are eligible for inclusion in the study as they may benefit from treatment.

Mavorixafor metabolism is expected to be similar in the adolescent (≥ 12 years) and adult participants in the study. CYP3A4/5 are the predominant enzymes responsible for mavorixafor metabolism. It has been established that hepatic metabolism in adolescents 13 years of age and older is expected to be similar to that of adults (Strolin Benedetti 2005).

4.5.5. Rationale for the ANC Threshold

Based on published data of WHIM patients treated with plerixafor (Dale 2011; McDermott 2011; McDermott 2014), baseline (pretreatment) ANC are typically ≤ 250 cells/µL, with modest variations over the course of a day.

In the proof-of-concept study conducted by the National Institutes of Health (McDermott 2014), 3 patients with WHIM syndrome were treated with plerixafor for 24 weeks. Concurrently, there was evidence of clinical efficacy, including

- decrease in the frequency and severity of infections;
- improved bone marrow histology, with decreases both in hypercellularity and in the frequency of hypermature, apoptotic neutrophils;
- improved response in generalized warts following localized treatment with imiquimod (McDermott 2014), suggesting improved immune function, with induction of an effective systemic anti-HPV response.

Although limited, these data suggest that in WHIM patients treated with a CXCR4 antagonist, achieving an ANC of 500 cells/µL reflects an improvement in the pathophysiology underlying WHIM syndrome and is sufficient to affect clinical outcomes.

The proposed ANC threshold is defined as 500 cells/µL. This is considered clinically meaningful because ANC < 500 cells/µL represents severe neutropenia (Grade 4) by the CTCAE and is associated with increased risk of morbidity and mortality. In addition, this threshold is in line with recent publications that suggested a relevant endpoint could be neutrophils ≥ 500 cells/µL at 12 hours postdose (McDermott 2019).

4.5.6. Rationale for Vaccination During the Study

Participants with WHIM are reported to have normal peak vaccine responses, but their titers have been shown to wane rapidly, within 12 months (Tassone 2009; Handisurya 2010). Tdap and HPV 9-valent vaccine, recombinant (Gardasil®9) vaccines will be administered during this study, independent of the participants' baseline vaccine titers. Vaccination will be according to respective vaccine schedules for all participants, unless not permitted per standard of care. Revaccination for Gardasil®9 will be per vaccine schedule for participants who have completed a

full course of vaccination with Gardasil®9 prior to the study, unless not permitted per standard of care.

Tdap provides protection from pertussis, which is important in this population because, in addition to bacterial pneumonia, other infections, such as pertussis, may cause further bronchial damage. Tdap is well tolerated.

Gardasil®9 will be beneficial to both male and female WHIM participants because of their susceptibility to HPV-related disease, including cervical, vulvar, vaginal, and anal cancer as well as precancerous or dysplastic lesions, and cutaneous, genital, and anal warts.

Gardasil®9 vaccinations will be administered in participants beyond the recommended age of 45 years. There is no known serologic correlative of immunity or minimum titers for HPV 16 and HPV 18 determined to be protective, and there is no evidence that the measurement of postvaccination antibody titers to monitor immunity is useful for determining which participants are protected against infection by the vaccine-targeted types (NCI 2020). Therefore, measuring vaccine titers prior to revaccination would not be informative for Gardasil®9.

4.5.7. Monitoring and Managing Previously Identified Risks Associated with Mavorixafor

Strategies for monitoring and managing previously identified risks associated with mavorixafor are described in Table 5. A detailed Schedule of Events is provided in Section 1.1.

Table 5: Monitoring and Management Procedures for Risks Identified for Mavorixafor

Potential risk	Clinical monitoring and risk management procedures
Participant monitoring and management to be conducted throughout the trial.	• The first dose of study drug will be administered by study personnel; the participants will be observed postdose. • Ongoing monitoring will be conducted for AEs. • Ongoing monitoring of all concomitant medications (prescription, over-the-counter, herbal, and vitamins) will be conducted to avoid potential drug-drug interactions. • Safety laboratory tests will be conducted throughout the study. • Regularly scheduled clinical evaluations, including vital signs and physical examinations will be conducted. • Scheduled ECGs will be performed throughout the study. • Criteria for discontinuing treatment in individual participants due to prespecified TLTs has been determined.

Potential risk	Clinical monitoring and risk management procedures
Mavorixafor is primarily metabolized through CYP3A4 and CYP2D6. Monitoring and management of con-medications should be conducted.	• Strong inhibitors and inducers of CYP3A4 and strong inhibitors of CYP2D6 are prohibited (FDA 2017). • If a strong inhibitor/inducer of CYP3A4 cannot be avoided, they are to be prescribed only with the approval of the Medical Monitor (see Section 4.4.2 for dose modification of mavorixafor if dosed with a strong CYP3A inhibitor). • Moderate inhibitors and inducers of CYP3A4 are to be prescribed only with the approval of the Medical Monitor. • Grapefruit, grapefruit juice, and Seville orange–containing products are prohibited.
Mavorixafor is a moderate inhibitor of CYP2D6 and a weak inhibitor (and possibly time-dependent inhibitor) of CYP3A. It is also an inducer of CYP1A2. Monitoring and management of con-medications should be conducted.	• Substrates of CYP3A, CYP2D6, or CYP1A2 considered sensitive/moderately sensitive or considered having a narrow therapeutic index are prohibited (FDA 2017). • Other CYP2D6 substrates should be administered only with the approval of the Medical Monitor.
Mavorixafor is possibly a substrate of P-gp.	• P-gp inhibitors are prohibited (FDA 2017).
In vitro studies suggest that mavorixafor is an inhibitor of P-gp, OAT1, OCT2, and MATE1.	• Avoid concomitant use of substrates of P-gp, OAT1, OCT2, and MATE1 with narrow therapeutic index (eg, digoxin for P-gp) (FDA 2017).
Emergency use of prohibited medication.	• If use of a prohibited medication cannot be avoided, the Investigator can prescribe the prohibited medication and hold the study treatment. • The Investigator should report the emergency use of the prohibited medication to the Medical Monitor within 24 hours.
AEs considered to be related and expected for mavorixafor can be found in the IB.	Guidelines for the management of AEs: • Participants who experience an AE should be carefully monitored for potential adverse reactions, and, if clinically significant, symptomatic treatment should be instituted per institutional standard of care.
All AEs should be reported to the Sponsor.	• The Sponsor will conduct a routine review of all reported AEs to determine safety risks and management. • Any risks that will potentially impact participant safety will be shared with the PI.

Potential risk	Clinical monitoring and risk management procedures
LFT abnormalities were observed in the animal model. Detailed information can be found in the IB.	• All clinical studies with mavorixafor have well-defined eligibility criteria. • Safety laboratory tests including monitoring of liver function will occur during the study.
Eye anomalies were observed in 1 animal model using a different salt form than that being studied in this protocol. Detailed information can be found in the IB.	• Ophthalmology examination and monitoring will occur during the study.
Embryo-fetal toxicity was observed in the animal model of an approved CXCR4 antagonist, Mozobil (plerixafor).	• WOCBP who are heterosexually active must agree to use an effective method of contraception, as detailed in Section 5.3.1, during the study and for 4 weeks after the last dose of study medication, or abstain from sexual intercourse for this time. • WOCBP partners of male participants should use an effective method of contraception, as detailed in Section 5.3.1, to prevent passage of study intervention through the ejaculate during the study and for 4 weeks after the last dose of study medication.
It has not been examined whether mavorixafor is excreted in human milk.	• Breastfeeding participants are excluded from study participation.
Testicular toxicity was observed at the highest dose tested in the chronic dog toxicology study	• Monitoring for testicular development via Tanner assessments (all participants up to the age of 17) and testicular safety monitoring (male study participants up to 50 years of age only) will be done every 3 months (6 months for ultrasound) including hormonal profile, testicular examination, and ultrasound.

Abbreviations: AE = adverse event; CXCR4 = C-X-C chemokine receptor type 4; CYP = cytochrome P450; ECG = electrocardiogram; IB = Investigator's Brochure; LFT = liver function test; P-gp = P-glycoprotein; PI = Principal Investigator; TLT = treatment-limiting toxicity; WOCBP = women of childbearing potential.

4.5.7.1. Rationale for Testicular Safety Evaluation

All of the Good Laboratory Practice repeated-dose toxicology studies conducted in rats and dogs with mavorixafor were initiated in prepubescent or peri-adolescent animals, thus supporting participant age groups of as young as 6.5 years of age based on the dog (Table 6) and 12.7 years based on the rat (Table 7). No histopathological effects on the central nervous system, including the cerebellum, were seen in any of these studies. However, testicular findings were recently reported in a study of dogs treated with mavorixafor for 39 weeks, specifically observations of seminiferous tubule degeneration and atrophy, which were considered adverse at higher drug levels. No adverse testicular findings were observed in rats treated chronically or in previous studies of shorter duration in dogs and rats. The reversibility of the testicular findings is unknown. The clinical relevance of these nonclinical findings in humans is unknown. However,

a potential effect on sperm production in males taking mavorixafor cannot be excluded (additional information is captured in the Investigator's Brochure).

Accordingly, adolescents and young adults will be carefully monitored for growth and development, with periodic (every 3 months) assessments while on study, as described in Table 1 and Table 5. Based on current knowledge of CXCR4 biology, no effect of drug on growth or maturation is expected in this age group.

The rationale supporting the safety of the medicinal product in pediatric participants is based on the following information and data:

Table 6: Comparative Ages of Beagle Dogs Used in Repeated-Dose GLP Toxicology Study Relative to Humans

Study No.	Duration	Age at initiation	Comparative human age
77401	4 weeks	5 to 7 months	6.3 to 8.8 years
7686-104	4 weeks	6 months	7.5 years
7686-107	13 weeks	7 to 8 months	8.8 to 10 years
7686-101	13 weeks	5 to 7 months	6.3 to 8.8 years
2847-001[b]	39 weeks	5.5 to 6.5 months	6.9 to 8.1 years

Abbreviations: GLP = Good Laboratory Practice; No. = number.
[a] The American Kennel Club generally states that a 1-year-old Beagle is equivalent to the 15-year-old child. Therefore, estimates of comparable human age are made based on the age of the dog in months/12 months and multiplied by 15. Also see, https://www.ajdesigner.com/fl_dog_age/dog_age.php.
[b] Draft report in progress: Mavorixafor (X4P-001): A 39-Week Oral (Capsule) Toxicity Study in Dogs.

Table 7: Comparative Ages of Rats Used in Repeated-Dose GLP Toxicology Study Relative to Humans

Study No.	Duration	Age at initiation	Comparative human age
77400	4 weeks	6 weeks	12.7 years
7686-100	13 weeks	6 to 7 weeks	12.7 to 14.8 years
7686-105	26 weeks	6 to 7 weeks	12.7 to 14.8 years

Abbreviations: GLP = Good Laboratory Practice; No. = number.
[a] To calculate the comparable human pubertal phase, 3.3 rat days = 1 human year (Sengupta 2013).

5. SELECTION AND WITHDRAWAL OF PARTICIPANTS

5.1. Randomized Placebo-Controlled Period

5.1.1. Participant Inclusion Criteria

Participants with a clinical diagnosis of WHIM syndrome must meet all of the following criteria to be eligible for study participation:

1. Be at least 12 years of age.
2. Have signed the current approved Informed Consent Form. Participants under 18 years of age (in the Netherlands and other applicable regions, participants under 16 years of age) will sign an approved informed assent form and must also have a signed parental/legal guardian consent.
3. Have a genotype-confirmed mutation of *CXCR4* consistent with WHIM phenotype.
4. Agree to use a highly effective form of contraception, as detailed in Section 5.3.1.
5. Be willing and able to comply with this protocol.
6. Have a confirmed ANC ≤ 400 cells/µL during screening, obtained while participant has no clinical evidence of infection. Local laboratory may be used if central laboratory is not available.
    a. If the ANC is below the lower limit of detection for the laboratory and the total WBC count is ≤ 400 cells/µL, then the participant is considered eligible for the study.
    b. If the ANC is > 400 cells/µL in the context of a recent infection or inflammation prior to screening, it is acceptable to redraw a blood sample and confirm that the ANC meets inclusion criteria (≤ 400 cells/µL) once the infection or inflammatory episode is resolved.
    c. If the participant experiences an infection or inflammatory episode between screening and baseline that may impact the ANC, or receives G-CSF between screening and baseline, the baseline visit may be postponed for up to 4 weeks until the ANC has been confirmed to be ≤ 400 cells/µL.

The Medical Monitor should be notified and approve each rescreen occurrence.

5.1.2. Participant Exclusion Criteria

In the criteria below, “prior to Day 1” refers to Day 1 of treatment.

Participants with any of the following will be excluded from participation in the study:

1. Has known systemic hypersensitivity to the mavorixafor drug substance, its inactive ingredients, or the placebo.
2. Is pregnant or breastfeeding.
3. Has a known history of a positive serology or viral load for HIV or a known history of AIDS.
4. Has, at screening, laboratory tests meeting 1 or more of the following criteria:

- A positive hepatitis C virus antibody with confirmation by hepatitis C virus ribonucleic acid polymerase chain reaction reflex testing.
- A positive hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb).
  - NOTE: If a participant tests negative for HBsAg, but positive for HBcAb, the participant would be considered eligible if the participant tests positive for hepatitis B surface antibody (also referred to as anti-HBsAg) on reflex testing.

5. Has, at screening, safety laboratory tests meeting 1 or more of the following criteria:
   - Hemoglobin < 8.0 g/dL
   - Platelets < 75,000 cells/μL
   - Estimated glomerular filtration rate based on the Modification of Diet in Renal Disease of ≤ 29 mL/min/1.73 m^2 (Stage 4 or 5 chronic kidney disease)
   - Serum aspartate aminotransferase > 2.5 × ULN
   - Serum alanine aminotransferase > 2.5 × ULN
   - 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)
6. Had surgery requiring general anesthesia within the 4 weeks prior to Day 1.
7. Received any of the following treatments:
   - Plerixafor within 6 months prior to Day 1.
   - Chronic or prophylactic use of antibiotics (systemic or inhaled) within 4 weeks prior to Day 1.
   - Chronic or prophylactic use of G-CSF or granulocyte macrophage-colony stimulating factor within 2 weeks of Day 1.
   - Chronic or prophylactic use of systemic glucocorticoid use (> 5 mg prednisone equivalent per day) within 2 weeks prior to Day 1.
   - 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.
8. Is currently taking or has, within 2 weeks prior to Day 1, received any medication that is prohibited (see Section 6.4.1), based on potential for drug-drug interactions.
9. Has, at the planned initiation of study drug, a clinically diagnosed active infection (excluding warts) that has the potential to raise the ANC counts.
10. Has had a total splenectomy within 1 year.
11. Has a current diagnosis of myelofibrosis.
12. Has a medical history of hematological malignancies.

13. Has any other medical or personal condition that, in the opinion of the Investigator, may potentially compromise the safety or compliance of the participant or may preclude the participant's successful completion of the clinical study.
14. Has corrected QT interval using Fridericia's formula of > 450 ms.

Note: Central results should be used for determination of screening laboratory values when possible. However, local laboratory analysis may be used if central laboratories are not available, or for unscheduled visits, repeated samples, or in place of central laboratory samples that could not be processed or were out of window.

5.2. Open-Label Period

5.2.1. Participant Inclusion Criteria

1. Completed the **Randomized Placebo-Controlled Period** or
2. Granted Early Release from the **Randomized Placebo-Controlled Period**, as described in Section 5.4.1.1.
3. Blind broken (Section 12.3.1).

5.3. Participant Restrictions During the Conduct of the Study

In the interest of their safety and to facilitate assessment of both safety and treatment effect, the participants in this study will be requested to agree to the following restrictions during the study:

- Not start any new prescription medications, except as prescribed or approved by the Investigator or if required in an emergency.
- Not take any over-the-counter (OTC) medications, except as instructed or approved by the Investigator.
- Not drink grapefruit juice or Seville orange–containing products, or eat grapefruit.
- Fasting:
  - No food or drink (except water) for 1 hour predose, and
  - No food or drink (except water) for 2 hours postdose.
  - Male participants up to the age of 50 should be fasted for 12 hours prior to each site visit.
- Must not become pregnant and male participants must not impregnate female partners (Section 5.3.1).

5.3.1. Contraception Guidance

A woman of childbearing potential (WOCBP) is defined as any female participant who has had menarche who is not postmenopausal or has not had a documented hysterectomy, bilateral tubal ligation, or bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be

used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient, and participants will be required to use a highly effective method of contraception.

All sexually active women of childbearing potential must use a highly effective method of contraception from screening, during participation in the study, and through at least 4 weeks after the last dose of study drug. Acceptable methods include:

- Systemic hormonal contraceptives when used with an additional barrier method (eg, male condom):
  - Combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation (either oral, intravaginal, or transdermal).
  - Progesterone-only hormonal contraception associated with inhibition of ovulation (either oral, injectable, or implantable).
- Intrauterine device.
- Intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- Vasectomized partner who has received a medical assessment of surgical success (when the partner is the sole partner).
- Sexual abstinence (refraining from heterosexual intercourse during the entire period of risk associated with the study treatment). The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant.
- Double barrier methods of contraception are acceptable, such as condoms with spermicide.

All WOCBP will have a urine pregnancy test done at the site at each office visit. Results must be obtained prior to dosing at every visit. A negative result is required to dispense study drug. The pregnancy test results will be maintained in the source documents. Confirmatory serum pregnancy tests may be performed per Investigator discretion. WOCBP must notify the site if a menstrual cycle is missed. Participants who become pregnant will be discontinued from the study.

All female participants who were not yet fertile when enrolled in the study should report the moment of menarche to the Investigator, and at each visit, the Investigator will inquire whether menarche has occurred in all female participants enrolled in the study who do not have menarche at screening.

Fertile males are required to use a male condom (with spermicide) with a sexual partner who is a WOCBP starting at screening, during participation in the study, and through 4 weeks after the last dose of study drug.

5.4. Participant Withdrawal or Termination of Participant, Study, or Study Site

5.4.1. Reasons for Withdrawal or Termination

To provide consistent accounting of participant disposition, when study treatment is discontinued in an individual participant for any reason, the Investigator will complete the appropriate eCRF and select the primary reason from the following standard categories:

- Completion – defined as completed 52 weeks of treatment and EoRP visit procedures (Section 1.1).
- TLT event – as defined in Section 4.4.1.
- AE – This includes any AE (clinical or laboratory; serious or non-serious; regardless of relation to study drug) that represents the reason study drug was discontinued, including the medical judgment of the Investigator based on the best interests of the participant.
- Participant request for study treatment discontinuation or withdrawing of consent.
- Lost to follow-up – The participant stopped coming for visits.
- Study termination by the Sponsor, for any reason (Section 5.4.3).
- Other reasons per the PI or Medical Monitor that define a need to discontinue participant engagement in the study (eg, low compliance, chemotherapy, etc).

5.4.1.1. Early Release from the Randomized Placebo-Controlled Period (Early Termination Due to Treatment for Infection)

The blinded, independent AC will evaluate the severity of infections using a treatment-based algorithm (see Section 10.2.3) that will be used to identify participants eligible for Early Release from the **Randomized Placebo-Controlled Period**, as follows:

- Participants who experience 1 and no more than 2 severe infections, characterized as Level 4 in the ClinRO, and defined as requiring hospitalization for more than 24 hours. This criterion recognizes that there are different levels of severity even among infections that result in hospitalization, and therefore allows the AC to permit Early Release after a single Level 4 infection.
- Participants who experience 4 moderate infections, characterized as Level 3 in the ClinRO, and defined as those requiring either IV antibiotic or G-CSF therapy.

Participants who meet either of the Early Release criteria, as confirmed by the blinded, independent AC, may be considered for Early Release from the **Randomized Placebo-Controlled Period**. The blinded, independent AC will meet on an ad hoc basis to approve Early Release cases. Further information is outlined in the AC Charter.

Upon Early Release, participants may either:

- enter the **Open-Label Period**, in which case, participants will complete an EoRP visit as early as clinically possible per the Investigator's judgment, or

- if not willing or eligible to transition into the **Open-Label Period**, participants may choose to participate in the long-term follow-up (Section 8.3.3). In this case, participants should complete a safety follow-up visit (Section 8.2.6). Or
- complete the EOS visit and terminate from the study.

5.4.2. Handling of Participant Withdrawals or Termination

In the event that the study is discontinued prematurely for any reason, the EOT and EOS/Safety follow-up visits will be performed as specified in the Schedules of Events (Section 1.1). If a participant cannot be seen, attempts will be made to contact the participant by telephone to inquire about reasons for stopping participation and get updated information on any unresolved AEs.

For participants who discontinue study treatment during the **Randomized Placebo-Controlled Period**, every effort will be made to have participants return for their scheduled office visit(s) (ie, Weeks 13, 26, 39, and 52 [± 14 days for all of these visits], as applicable). Discontinued participants will not continue into the **Open-Label Period**.

Participants who are not willing, interested, or eligible to transition into the **Open-Label Period**, or those who drop out of the **Open-Label Period**, will have the option to participate in long-term follow-up via phone contacts as described in Section 8.3.3 at time points specified in the Schedule of Events (Table 2) and will continue until participant dropout or termination by Sponsor.

5.4.3. Premature Termination or Suspension of Study/Study Site

The Sponsor reserves the right to discontinue or suspend the study (or any part of the study) for safety or administrative reasons at any time at an individual site or overall, in accordance with local laws and regulations. Should the study be terminated and/or the site closed for whatever reason, all study documentation must be archived, and study drug must be destroyed according to local policy or returned to the Sponsor or its representative, per Sponsor's instructions. Conditions that may warrant termination of the study or study site include but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to participants enrolled in the study
- The decision on the part of the Sponsor to suspend or discontinue testing the study treatment
- Low enrollment of participants
- Disbarment
- Failure of the Investigator to comply with GCP
- Submission of knowingly false information from the clinical trial site to the Sponsor or regulatory authorities
- Insufficient adherence to protocol requirements

If the study (or any part of it) is terminated prematurely or suspended, the Sponsor and the Investigator(s) will assure that adequate consideration is given to the protection of the participants' interests.

If the study (or any part of it) is terminated prematurely or suspended, the Investigator will promptly inform the site IRB/IEC. Review and approval by the site IRB/IEC may be required for resumption of the study in the event the study was suspended for safety reasons.

5.4.4. Completion of Randomized Placebo-Controlled Period

The participant will have completed the **Randomized Placebo-Controlled Period** after 52 weeks on treatment if rolling over to the **Open-Label Period**, following EOT/Safety follow-up if terminating or continuing in long-term follow-up, respectively, or prior to 52 weeks if the participant is granted Early Release (see Section 5.4.1.1).

5.4.5. Completion of Open-Label Period

Participants will have completed the **Open-Label Period** after completion of the EOS visit following study termination notification by the Sponsor.

6. TREATMENT OF PARTICIPANTS

6.1. Description of Study Drug

Mavorixafor is a second-generation, small-molecule, noncompetitive antagonist of the CXCR4 receptor that acts by binding to extracellular domains of the receptor, resulting in specific and reversible inhibition of receptor signaling in response to its ligand CXCL12. Physical, chemical, and formulation properties of mavorixafor are described in Section 7.

6.2. Dosing

The mavorixafor dose regimen for both the **Randomized Placebo-Controlled Period** and the **Open-Label Period** is 400 mg QD for adults. For adolescent participants weighing > 50 kg at any time during the study, the mavorixafor dose will also be 400 mg QD. Adolescent participants weighing ≤ 50 kg at screening will receive mavorixafor 200 mg QD. Mavorixafor is administered as 100-mg dose strength capsules by mouth on an empty stomach.

The following dosing considerations apply:

- If an adolescent participant turns 18 during the study, the dose will be adjusted to the full 400-mg daily dose at the next scheduled study visit.
- If an adolescent participant's weight increases from ≤ 50 kg to > 50 kg, the dose will be adjusted to the full 400-mg daily dose at the next scheduled study visit.
- If an adolescent weighs > 50 kg at randomization, but during the course of the study, the weight decreases to ≤ 50 kg, the dose will not be adjusted, and the participant will remain on the full 400-mg daily dose.

Participants randomized to placebo will receive an equivalent number of matching capsules in a double-blind fashion as a daily dose.

Dosing of **blinded** study drug is to continue through the End of the Randomized Period (Week 52). The **Open-Label Period** begins with the administration of the first dose of open-label study drug (24 hours after the final dose of blinded study drug). Open-label study drug should be dispensed only after all assessments pertaining to the EoRP have been completed.

6.3. Study Drug Administration

Participants will receive mavorixafor capsules (100-mg dose strength) or matched placebo according to treatment assignment.

Participants will be instructed to take all 2 or 4 capsules (depending on weight-based dosing) of mavorixafor within the same timeframe each day with water; capsules must not be opened. Participants should take mavorixafor in a fasted state as outlined in Section 6.3.3.

6.3.1. Randomization and Treatment Assignment

Participants will be randomized to receive up to 400 mg mavorixafor or matched placebo at a 1:1 allocation (see also Section 12.3). The randomization will be stratified into 2 categories: (1) have received any Ig treatment within 5 months prior to screening visit/signing of the ICF, or (2)

have not received any Ig treatment within 5 months prior to screening visit/signing of the ICF. Treatment assignment will be performed by a centralized randomization procedure.

Randomization will occur during the screening Period once eligibility has been established. The randomized blinded study drug assignment will be sent to the clinical site for the eligible participant to be administered at baseline Day 1. The active drug and the matched placebo are conditioned in identical packaging with blind labels so that the study site remains blind to the treatment arm after randomization.

Detailed instructions on participant randomization will be found in the interactive web response system (IXRS) Site User Guide.

6.3.2. Dosing Schedule

It is expected that the daily dose will be taken as follows:

- The daily dose should be taken in the morning, at the same time each day.
- The interval between successive doses should not be < 20 hours.
- If the interval between successive doses is delayed to > 30 hours, the dose should be omitted, and the usual schedule resumed the next day.
- At study visits with assessments over 24 hours (**Randomized Placebo-Controlled Period** Weeks 13, 26, 39, and 52), dosing (ie, administering the daily dose) must be held in the morning and delayed until after the time 0 blood samples have been obtained.
- Dosing of **blinded** study drug is to continue through the End of the Randomized Period (Week 52). The **Open-Label Period** begins with the administration of the first dose of open-label study drug (24 hours after the final dose of blinded study drug). Open-label study drug should be dispensed only after all assessments pertaining to the EoRP have been completed.
- Participants in the **Open-Label Period** should withhold the morning dose on the day of visit until after the time 0 blood samples have been obtained.

6.3.3. Food Restrictions

Absorption of mavorixafor is reduced when taken with food. Participants will be instructed to take mavorixafor in a fasted state as described in Section 5.3.

Participants for whom the scheduling requirements and eating restrictions represent significant difficulties should be discussed with the Medical Monitor to develop the most effective regimen possible.

6.4. Concomitant Medications and Procedures

Prior treatments for WHIM syndrome will be recorded in the eCRF.

From the screening through the last study visit, any concomitant medication used and any procedures (eg, imaging study, surgery, etc.) will be recorded in the eCRF, including dose,

dosage regimen, and indication (reason for its prescription). Any medications not listed in Section 6.4.2 are permitted, including inactivated vaccines such as HPV.

6.4.1. Restrictions Related to Drug Interactions

Restrictions related to drug interactions are detailed in Table 5.

6.4.2. Prohibited Medications, Treatments, and Procedures

The exclusion criteria specify treatments prohibited at the time of study entry, as described in Section 5.1.2, including the following:

- Ig therapy, only in participants stratified to the no prior Ig stratum (participants in the prior Ig therapy stratum will continue on the same Ig treatment [ie, same dose, mode of administration, and frequency] as administered prior to joining the study).
- Plerixafor within 6 months prior to Day 1.
- Chronic or prophylactic use of antibiotics (systemic or inhaled) within 4 weeks prior to Day 1.
- G-CSF or granulocyte macrophage-colony stimulating factor within 2 weeks prior to Day 1.
- Systemic glucocorticoid use (> 5 mg prednisone equivalent per day) within 2 weeks prior to Day 1.
- Topical and systemic treatments for warts should be discontinued prior to Day 1 of treatment and are prohibited throughout the **Randomized Placebo-Controlled Period**.
- Laser therapy, surgery, or bleomycin injections are not permitted.
- Any medication that is prohibited based on CYP and/or transporter interaction (see Table 5).

Participants who discontinue from the study prematurely and have completed the EOT/Safety follow-up visit may receive available or investigational treatment for their disease at any time based on the judgment of their physician.

6.4.3. Rescue Medications, Treatments, and Procedures

6.4.3.1. Rescue G-CSF

In some participants with WHIM syndrome presenting with febrile illness consistent with acute, severe bacterial infection, experienced clinicians may consider it prudent to administer G-CSF in addition to antibiotics and hospitalization. Provision is therefore made for participants meeting those criteria to be administered a course of G-CSF as rescue therapy until the acute process is resolved, stabilized, or determined not to reflect bacterial infection for up to approximately 2 weeks. If an Investigator decides that a participant requires ongoing, regularly scheduled treatment with G-CSF, then the participant must be discontinued from study treatment or be considered for Early Release (Section 5.4.1.1).

6.4.3.2. Therapy for Warts

Topical imiquimod treatment for warts is permitted in the **Open-Label Period**. Other treatments should be discussed with the Medical Monitor.

6.5. Study Treatment Compliance

Treatment compliance will be monitored by pill count at every applicable visit following baseline.

7. STUDY DRUG MATERIALS AND MANAGEMENT

7.1. Study Drug Properties

Physical and chemical properties of the study drug are described in Table 8, and formulation information is provided in Table 9. The placebo will be similar in color, shape, and composition but will contain no active ingredients.

Table 8: Physical and Chemical Properties of Active Ingredient (Drug Substance)

Name	**Mavorixafor (X4P-001)**
Drug class	Chemokine (C-X-C motif) receptor 4 (CXCR4) antagonist
INN	Not assigned
Molecular formula	$C_{21}H_{27}N_5$
Molecular weight	349.48 amu
Appearance	White to pale yellow solid
Solubility	Mavorixafor is freely soluble in the pH range 1.0 to 8.0 (> 100 mg/mL), sparingly soluble at pH 9.0 (10.7 mg/mL), and slightly soluble at pH 10.0 (2.0 mg/mL). Mavorixafor is only slightly soluble in water
Melting point	111.4 °C

Abbreviation: INN = international nonproprietary name.

Table 9: Formulation of Mavorixafor 100-mg Capsule

Name	**Mavorixafor 100-mg capsule**
Active ingredient	Mavorixafor
Excipients	Microcrystalline cellulose, dibasic calcium phosphate dihydrate, croscarmellose sodium, sodium stearyl fumarate, colloidal silicon dioxide, sodium lauryl sulfate
How supplied	Dispensing instructions will be provided in the Pharmacy Manual
Storage	5 °C ± 3 °C; protect from light and humidity
Administration	Oral

7.2. Study Drug Packaging and Labeling

Mavorixafor will be supplied as 100-mg hard gelatin capsules in 30-count bottles. The primary packaging is Oxy-Guard® 60-cc high-density polyethylene bottles with 33-mm caps and integrated foil induction seals. Rayon coil is placed above the capsules in each bottle, and 1 desiccant pack is positioned at the top of each bottle between the rayon coil and the cap.

Labels are applied to the outside of the bottles. All labels are compliant with local clinical study regulations.

7.3. Study Drug Storage

Mavorixafor should be stored at 5 °C ± 3 °C and protected from light and humidity (Table 9). Additional storage details are provided in the Pharmacy Manual.

7.4. Study Drug Preparation

There is no preparation needed.

7.5. Study Drug Accountability

Mavorixafor and matched placebo will be provided by the Sponsor. The Investigator at each study site is responsible for the control of study drug and will identify trained and experienced personnel to handle it in accordance with the protocol, appropriate Good Clinical Practice (GCP) principles, and the guidelines outlined in the Pharmacy Manual.

This may include:

- Storing the drug in a secure, controlled-access location.
- Storing the drug under the specified conditions, including daily monitoring and recording of storage temperature.
- Maintaining records of the receipt of study drug.
- Dispensing and administering study drug only in accordance with the protocol.
- Maintaining drug accountability records indicating the disposition of study drug, including a Drug Dispensing Log, which may contain the following information:
  - Identification of the participant to whom the study drug was dispensed.
  - Date(s) and quantity of the study drug dispensed to the participant.
  - Date(s) and quantity of the study drug returned by the participant at each study visit.
- Having all records and drug supplies available for inspection by the study monitor.

7.6. Study Drug Handling and Disposal

At the completion of the study, typical procedures for handling any remaining study drug include the following:

- Returning study drug to the study drug depot.
- Destroying study drug at the study site according to the site's institutional standard operating procedure.

8. STUDY PROCEDURES

The complete Schedules of Events are shown separately for the **Randomized Placebo-Controlled Period** and **Open-Label Period** in Section 1.1.

History, baseline, and safety assessments (eg, laboratory, ECG, ophthalmologic, etc.) are described in Section 8.1. Clinical assessments are described in Section 10, and safety assessments (AEs) are discussed in Section 11.

8.1. History, Baseline, and Safety Procedures

8.1.1. Demographic and Medical History, Including Infection and Wart History

Demographic data will include gender, date of birth, race, height, weight, and ethnicity.

A complete medical, surgical, infection, and treatment history will be obtained, including first diagnosis and end date (month and year), if applicable.

Specific histories to be collected include:

- History of WHIM syndrome.
- Infection history for the 12 months prior to dosing (including the screening period prior to first dose) from all possible sources of medical records, regardless of the severity of the infection, to be captured in the Prior Infections page of the eCRF.
- History of any infections that led to hospitalizations, to be captured in the Prior Infections page of the eCRF.
- History of cutaneous and AG warts.
- All other medical history should be captured in the Medical History form of the eCRF.

8.1.2. History of Medications and Vaccines

A complete history of WHIM medications will be obtained, including G-CSF, Ig, and all medication and procedures for warts.

History of vaccines will also be obtained, including COVID-19 and HPV, if relevant.

8.1.3. Genotyping

A blood sample will be collected during screening and submitted to the central laboratory for Sanger sequencing of the C-terminus of *CXCR4*. To be eligible, participants are required to have a genotype-confirmed mutation of *CXCR4* that is consistent with the WHIM phenotype. Participants may provide results from a blood sample analyzed by a local Clinical Laboratory Improvement Amendments (CLIA)–certified laboratory (or equivalent accreditation) for genetic confirmation of eligibility as an option to allow randomization and dosing. If randomization is based on genetic results from a local CLIA-certified laboratory (or equivalent accreditation) that is not the central laboratory for the study, then the participant's sample will additionally be collected and analyzed by Sanger sequencing performed by a central laboratory. If central

laboratory sequencing does not confirm a pathogenic mutation, then discontinuation of the participant from the study will be discussed with the Medical Monitor.

Provision will be made for replacing participants discontinued because their local mutation results could not be confirmed.

8.1.4. Vital Signs

Vital signs include heart rate (HR), blood pressure (BP), and temperature. Where feasible, vital signs should be measured before blood is drawn and after the participant has been sitting or semi-reclined quietly for 5 minutes with the BP cuff in place on the non-dominant arm. BP and HR measurements may be done manually or by automated recorder. Temperature will be obtained using an electronic (rapid reading) device.

Vital sign measurements will be assessed by the Investigator as either 'normal,' 'abnormal, not clinically significant,' or 'abnormal, clinically significant.' Clinically significant abnormal vital sign measurements will be reported as an AE and, if possible, should be repeated at clinically relevant intervals until resolved or stabilized. Any treatment should be captured as concomitant medication.

8.1.5. Physical Examination, Weight, and Height Assessments

Complete physical examinations will include, at a minimum, measurement of body weight and height (for adults, height at baseline only; for adolescent participants, height will be measured at post-baseline office visits, and growth charts for height and weight may be plotted) and examination of general appearance, orientation, skin, neck (including thyroid), eyes, nose, throat, heart, lungs, abdomen, lymph nodes, extremities, and nervous system.

Physical examination findings will be assessed by the Investigator as either 'normal,' 'abnormal, not clinically significant,' or 'abnormal, clinically significant.' Any clinically significant changes identified after the baseline examination will be recorded as AEs (see Section 11.2).

8.1.6. Tanner Stage Assessments

Female participants up to 17 years of age:

- Tanner staging will be based on genital appearance and pubic hair development yearly.

Male participants up to 17 years of age:

- Please refer to Section 8.1.9.3.

8.1.7. Electrocardiogram

Standard 12-lead ECG will be obtained after the participant has been semi-recumbent or supine for approximately 10 minutes. The following ECG parameters will be recorded: ventricular rate, RR interval, PR interval, QRS interval, QT interval, QTc interval, and QTcF.

QTc will be calculated using Fridericia's formula, which is $QTc = QT/RR^{1/3}$.

ECGs will be obtained at screening, at baseline, at predose (on Day -1 or Day 1 prior to dosing), then at 2 hours postdose (± 30 min), then predose and 2 hours postdose (± 30 min) at every office visit thereafter during the **Randomized Placebo-Controlled Period**.

ECGs will be obtained predose, and at 2 hours postdose (± 30 min) for the first year of the **Open-Label Period** from the Week 13 visit onward and predose only from Year 2 onward.

8.1.8. Vaccinations

In the **Randomized Placebo-Controlled Period**, participants ≥ 14 years of age will be vaccinated with Tdap at Week 13 and Gardasil®9 at Weeks 13, 26, and 39 (all ± 14 days). Participants < 14 years of age will be vaccinated with Tdap at Week 13 and Gardasil®9 at Weeks 13 and 39 (all ± 14 days). Vaccination will be according to respective vaccine schedules for all participants, unless not permitted per standard of care. Revaccination for Gardasil®9 will be per vaccine schedule for participants who have completed a full course of vaccination with Gardasil®9 prior to the study, unless not permitted per standard of care. Early Release participants will continue their vaccination schedule from the **Randomized Placebo-Controlled Period** if continuing into the **Open-Label Period**.

Antibody-specific titers, including pertussis toxin, tetanus, HPV 16, and HPV 18 will be collected in the **Randomized Placebo-Controlled Period** at baseline, and Weeks 26, 39, 52, and EOS. During Year 1 of the **Open-Label Period**, the same antibody-specific titers will be collected every 3 months and at EOS; and then every 6 months and at EOS from Year 2 onward.

8.1.9. Specialist Examinations

8.1.9.1. Ophthalmologic Examination

Ophthalmologic examination will be performed as scheduled (during screening or at baseline prior to dosing) and include the following elements: assessment of visual acuity (using Snellen examination, or local equivalent in countries outside the US), refraction (at screening only), assessment of color vision (using Ishihara Color Vision Test or local equivalent), slit lamp examination, and retinal examination with fundus photographs. All retinal photographs will be submitted to a central repository as soon as feasible after being performed to be reviewed for quality and completeness and central expert review. An optometrist may complete the exam if all requirements can be met, including use of appropriate equipment to obtain the retinal photographs.

Other ophthalmologic assessments may be performed, if feasible. Other assessments may include optical coherence tomography (OCT) and/or autofluorescence. These will be performed at the EoRP visit and every 6 months thereafter for participants in the **Open-Label Period**.

Retinal abnormalities noted at screening will be discussed with the Medical Monitor. Enrollment may proceed with the approval of the Medical Monitor.

8.1.9.2. Dermatologist Examination and Assessments

Dermatology examinations can be done either on site or remotely using video conference during home-health visits. The examination and collection of photographs and images during the screening period should be performed 7 days prior to the baseline visit to allow central review of the quality of baseline images.

Dermatologist examinations will be conducted at screening and every 6 months throughout the study to assess efficacy (ie, wart assessment), as described further in Section 10.3. Examinations,

scoring, photographs, and skin swabs for HPV-genotyping may be repeated at baseline if assessment, photographs, or skin swabs from screening are not sufficient. The Dermatology Manual provides guidance on the dermatology assessments.

8.1.9.3. Testicular Assessment

Testicular assessment will be performed for all male participants up to 50 years of age. Testicular volume assessments will be conducted as outlined in the schedule of assessments for the **Randomized Placebo-Controlled Period** (Table 1) and the **Open-Label Period** (Table 2 and Table 3). The following assessments should be performed every 3 months (Yu 2021) unless stated otherwise. In the case of abnormal lab values/AEs, additional tests to those outlined below may be required and may include semen testing per World Health Organization standard.

All testicular assessments/reports (redacted) will be submitted for a central expert review process as soon as feasible after being performed to be reviewed for quality and completeness and central expert review. Other testicular assessments may be requested by the central reviewer, if feasible.

1. Physical examination of genitalia and testicles/scrotum.
    a. Include estimated testis volumes based on Prader orchidometer comparisons.
    b. Include description of any abnormalities on physical examination of the testicles
2. Fasted endocrine evaluation of hypothalamic-pituitary-gonadal axis (H-P-G).
    a. Serum luteinizing hormone (LH)
    b. Serum FSH
    c. Serum total testosterone level
    d. Serum inhibin B level
3. Ultrasound evaluation of testicles every 6 months (to be conducted by local radiology/urology clinic).
    a. Provide assessment of appearance of testicular parenchyma of both testicles
    b. Provide measurements of each testicle in 3 dimensions (length, width, depth)
    c. Include description of any abnormalities on scrotal ultrasound examination
4. Tanner stage assessment.
    a. Up to 17 years of age, include Tanner staging based on genital appearance and pubic hair development. Do not use the testicular volume measurements for Tanner staging.

Findings on evaluation that might prompt additional assessments as determined by the central reviewer:

1. Palpable mass or abnormal contour on ANY testicular examination.
2. Two sequentially abnormal lab values for each test. Abnormal high or low is based on the testing center's normal reference range.
3. Abnormal appearance of testicular parenchyma on scrotal ultrasound (eg, testicular mass, parenchymal heterogeneity, testicular calcifications, atrophy, necrosis, or cystic changes).

8.1.10. Laboratory Assessments

The laboratory safety tests below will be performed as scheduled by a central laboratory facility. The Investigator may order additional local laboratory tests consistent with their routine standard of care (Table 10). Local tests can replace central laboratory results if not available or lost.

The participant informed consent form contains a cumulative summary of blood volume. For participants weighing < 45 kg (or < 100 pounds), alternative (pediatric) kits are to be used in order to take all precautions to not collect more than 3% of total blood volume over 24 hours as per widely used guidelines.

Table 10: Clinical Laboratory Tests

Hematology Panel	
HbA1c	WBC differential and absolute cell counts[a]
Hematocrit	RBCs
Hemoglobin	Basophils
Platelet count	Eosinophils
WBC count[a]	Lymphocytes/lymphocyte subsets (T, B, NK samples)
Serum testosterone[b]	Monocytes
Follicle-stimulating hormone[b]	Neutrophils
Luteinizing hormone[b]	
Inhibin B[b]	
Clinical Chemistry Panel	
Alanine aminotransferase	Inorganic phosphorus
Albumin	Lactate dehydrogenase (reflex isoenzymes[c])
Alkaline phosphatase	Lipase
Aspartate aminotransferase	Phosphorus
Bicarbonate	Potassium
Calcium	Sodium
Chloride	Total bilirubin (reflex direct/indirect[c])
Creatine kinase (reflex isoenzymes[c])	Total protein
Creatinine (calculated eGFR/creatinine clearance)	Urea
Gamma glutamyl transpeptidase	Uric acid
Glucose	
Urinalysis	
Bilirubin	Ketones
Glucose	Leukocyte esterase
Hemoglobin	Protein
Microscopic exam (WBC, RBC, cells, casts, crystals)	
Pregnancy Tests (WOCBP only)	
Beta-human chorionic gonadotropin	
Follicle-stimulating hormone[d]	
Serologic Tests	
HBsAg	HBsAb reflex testing (anti-HBsAg)
HBcAb	HCVAb

Abbreviations: eGFR = estimated glomerular filtration rate; HBcAb = hepatitis B core antibody; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HCVAb = hepatitis C virus antibody; NK = natural killer; RBC = red blood cell; WBC = white blood cell; WOCBP = women of childbearing potential.

[a] Clinical laboratory assessments will not be masked at screening. The 0-hour predose laboratory assessments at Baseline will not be masked, but they will be blinded to Investigator and Sponsor once study drug is administered.

[b] Only for males up to 50 years of age.

[c] If abnormal, reflex tests will be run.
[d] Optional to confirm menopausal status per Section 5.3.1.

8.1.10.1. Pregnancy Screen

All WOCBP will have a urine pregnancy test done at the site at each office visit. Results must be obtained prior to dosing at every visit. A negative result is required to dispense study drug. The pregnancy test results will be maintained in the source documents. Confirmatory serum pregnancy tests may be performed per Investigator discretion.

All female participants enrolled in the study who do not have menarche at screening should report the moment of menarche to the Investigator.

All WOCBP must notify the site if a menstrual cycle is missed.

8.1.10.2. Reporting of Laboratory Assessments

Results of safety laboratory tests (except serology) are expected to be available to the Investigator within 48 hours.

Procedures for the Investigator assessment of the results are detailed in Section 11.1.4. Procedures for the analysis of laboratory data are described in Section 11.1.2.2.

8.1.10.3. Repeating Abnormal Laboratory Tests

Laboratory tests showing abnormal or exclusionary values at screening may be repeated with approval of the Medical Monitor; however, exclusionary serologic results may not be repeated.

After dosing, abnormal laboratory tests assessed as 'clinically significant' values may be repeated as often as deemed clinically necessary by the Investigator until the test values are clinically acceptable or until an explanation other than drug effect or other etiology is given.

8.2. Office Visits

In the **Randomized Placebo-Controlled Period**, office visits are conducted as described in Section 4.1. In the **Randomized Placebo-Controlled Period**, the office visit occurring every 13 weeks at Weeks 13, 26, 39, and 52 (visits that include assessments over 24 hours) includes overnight assessments. In the **Open-Label Period**, office visits are conducted on the same schedule in Year 1. Only Week 26 and 52 visits will be overnight visits (for PK collection). From Year 2 onward, participants will attend visits every 6 months and there will be no overnight visits. Participants will also complete 1 EOS/Safety follow-up visit post–end of treatment as described in Section 4.1.

Participants will be contacted by phone approximately 72 to 24 hours prior to each scheduled office visit (Section 4.1).

When multiple clinical assessments and procedures are conducted at a given visit, the following order should be followed (assessments and procedures for each visit are as described in Table 1, Table 2, and Table 3):

- QoL questionnaires (starting at the baseline visit)
- Physical exam

- Vital signs
- ECG (predose)
- Blood draws/specimen collection
- Other clinical assessments
- Study drug administration
- ECG (2 hours postdose [± 30 min])
- Vaccine administration

8.2.1. Screening

Screening activities must be completed between Day -28 and Day -1.

All participants must provide written informed consent (or assent with parental/legal guardian consent) and the consent procedure recorded in the source documentation before the performance of any study-related procedures.

Participants assessed by the Investigator as eligible after completing screening will have all screening data entered into a web-based electronic data capture system. The data will be reviewed by the Medical Monitor or designee and any questions discussed with the site.

After acceptance, the Investigator and site pharmacy will be provided in writing (by email and/or fax) formal acknowledgment that the participant may be randomized to study treatment. Participants will be randomized to the study treatment upon confirmation of their eligibility, using the IXRS process.

Rescreening of participants, if needed, is allowed.

Procedures for the assessment of infections are presented in more detail in Section 10.2.

8.2.2. Baseline (Day -1 to Day 1)

The baseline visit is an overnight visit. The baseline visit will determine the predrug AUC_{ANC} over 24 hours prior to study drug administration, starting on Day -1 and concluding after the laboratory collections at 4 hours postdose (prior to discharge). Therefore, the duration of the overnight study visit will be approximately 28 hours.

The EoRP visit assessments in the **Randomized Placebo-Controlled Period** will serve as the baseline values for the **Open-Label Period**.

Diaries will be distributed at the baseline visit in the **Randomized Placebo-Controlled Period** (Section 10.2.1). Participants will be instructed on how to complete the diary and PRO questionnaire: When a participant experiences any new or worsening symptoms suggestive of an infection, the participant will contact the investigator site and, once the episode is resolved, the participant will complete a PRO questionnaire.

8.2.3. Office Visits Every 13 Weeks

The office visits occurring every 13 weeks at Weeks 13, 26, 39, and 52 in the **Randomized Placebo-Controlled Period** are visits that include assessments over 24 hours (Section 4.1 and Table 1).

During Year 1 of the **Open-Label Period**, office visits will occur every 13 weeks at Weeks 13, 26, 39, and 52 (Section 4.1 and Table 2); however, office visits from Year 2 onward in the **Open-Label Period** will occur every 6 months (Section 4.1 and Table 3).

8.2.4. End of Randomized Period (Week 52)/End of Treatment

The EoRP Week 52 visit is an overnight visit. If the randomized study is terminated prematurely for any reason, the EoRP/EOT visit will be performed within 14 days after the decision to terminate.

Exit interviews may be conducted at the EoRP/EOT visit or within 2 weeks prior, as described in Section 8.5.

Blinded study drug administration should continue through the EoRP visit. Participants completing the EoRP have 3 options:

- Roll over to the **Open-Label Period:** For these participants, the last day of the EoRP visit is the last day of the **Randomized Placebo-Controlled Period**.
- End participation in the study: These participants and any participants who discontinue study at any time during the **Randomized Placebo-Controlled Period** will attend an EOS visit at 30 days (± 14 days) post–last dose of study treatment.
- Roll over to long-term follow-up: These participants will have a safety follow-up visit at 30 days (± 14 days) post–last dose of study treatment. The safety follow-up visit will be identical to the EOS in terms of timing and procedures performed.

Open-label study drug should be dispensed only after all assessments pertaining to the EoRP have been completed.

The **Open-Label Period** ICF must be signed prior to any **Open-Label Period** procedure. Assessments required for beginning the **Open-Label Period** must be completed at the EoRP visit; the **Open-Label Period** begins the day after the EoRP with the administration of the first dose of open-label study drug.

8.2.5. End of Treatment (Open-Label Period)

Participants who complete Week 52 or those prematurely discontinuing the **Open-Label Period** will undergo an EOT visit, composed of the assessments described for the Week 52 visits shown in the Schedule of Events for the **Open-Label Period** (Table 2 and Table 3).

8.2.6. End of Study/Safety Follow-up Visit

Participants terminating the study (at any stage during the Randomized Period or Open-Label Period):

The EOS visit will occur 30 days post–end of treatment (± 14 days) or 30 days after discontinuation from the study. Participants who discontinue study at any time during the

Randomized Placebo-Controlled Period or **Open-Label Period** will attend an EOS visit approximately 30 days after their last dose of their randomly assigned study drug.

Participants rolling over to the long-term follow-up:

Participants who elect to participate in the long-term follow-up will have a safety follow-up visit in place of the EOS visit. The safety follow-up visit will be identical to the EOS in terms of timing and procedures performed.

8.3. Phone Contacts

8.3.1. Weeks 1 and 4 Phone Contact

During the **Randomized Placebo-Controlled Period** and Year 1 of the **Open-Label Period** Participants will be contacted by the Principal Investigator (PI) or designee at Weeks 1 and 4 (± 3 days) to evaluate safety and to review and discuss the study compliance.

8.3.2. Phone Contact for Participant Retention and Reporting Compliance

Study sites will contact the participants regularly during the entire course of the **Randomized** and **Open-Label Periods**. Sites will communicate with the participants on an approximately monthly basis during the **Randomized Placebo-Controlled Period** of the study. The aim of the calls will be to ensure ongoing participant understanding of the study, including reporting of infection events and study drug compliance, and to evaluate safety.

8.3.3. Optional Long-Term Follow-Up Via Phone Contacts

Participants who are not willing, interested, or eligible to transition into the **Open-Label Period**, or those who drop out of the **Open-Label Period**, will have the option to participate in long-term follow-up via phone contacts that will continue quarterly until participant dropout or termination by Sponsor. Participants who elect to participate in the long-term follow-up will have a safety follow-up visit in place of the EOS visit. The safety follow-up visit will be identical to the EOS in terms of timing and procedures performed. The ICF for this observational study must be signed prior to, or during the EOS, and in any case prior to any data collection. Participants will be encouraged to keep a diary to collect the information to provide to the site during phone calls.

The phone contacts will be used to follow participants for reporting of the following items:

- Concomitant medications
  - Start and stop dates
  - Route of administration
  - Dose and units
  - Indication
  - Frequency
- Infections
  - Date of first symptom related to the infection

  - Date of resolution
  - Diagnosis of infection
  - Cause of infection (ie, bacterial, fungal, viral, protozoan, parasitic, unknown)
  - Culture identified organism
  - No. of doctor visits associated with the infection event
  - Highest level of treatment for infection (Levels 0-4 as outlined in Section 10.2.3)
  - Was hospitalization required?
    - no. of days hospitalized
    - was admission to intensive care required?
    - was a visit to the emergency department required?
  - Antibiotic use (OTC/prescribed, route, duration)
  - System infection is located
- Wart assessment, as assessed by the patient
  - Resolution
  - Improvement
  - No change
  - Worsened
    - Treatment used for warts
- ANC information, if available, as reported by the patient
- Other information

Time points up to Week 52 are specified in the Schedule of Events (Table 2). Following quarterly phone calls will be identical.

8.4. Home-Health Visits

There will be an allowance for home-health visits if there are extenuating circumstances that would impede participants from coming to the study site for a scheduled visit. Home-health visits would be reviewed and approved by X4 on a case-by-case basis. Home-health visits will be an option applicable for all study visits, including screening and baseline.

8.5. Exit Interview

All participants will be invited to participate in an exit interview. The purpose of the exit interview is to capture, directly from the participant, whether they experienced a meaningful improvement from baseline. Specifically, the participants will be interviewed about their decision to enter the clinical study, the changes they experienced during the clinical study, and

their impressions about a treatment benefit. The data will capture the participant's perception of treatment benefit and will inform the participant-reported outcome measure content and scoring.

The exit interview will be conducted at the End of the Randomized Period, or within 2 weeks prior to the EoRP (Week 52) or within 30 days of the last dose of study drug for participants who terminate early from the study; and in any case prior to enrolling in the **Open-Label Period**. The interviews will follow a semi-structured interview guide and include questions about the participant's expectations about a meaningful improvement in their condition, whether they experienced a meaningful improvement in their condition, and their perception as to why they did or did not experience a meaningful improvement in their condition.

All interviewers will be blinded to the treatment assignment at the time of the interview. Informed consent will be documented prior to the interview. Interviews will be audio recorded unless the participant refuses to be audio recorded, in which case interviewer notes will serve as the source data for analysis. Subsequent transcripts will be generated from the interviews and translated into English for analysis. Qualitative data will be coded using ATLAS.ti software, which was designed for the systematic qualitative analysis of textual, graphical, audio, and vignette data (Muhr 2013). A qualitative coding dictionary will be developed for use in the analyses. Researchers from the vendor conducting the interviews will be blinded to treatment assignment during data analysis (coding qualitative data) but unblinded following database lock for treatment comparison analyses.

Participants entering the **Open-Label Period** will be eligible for the exit interview for up to 2 weeks prior to and including the EOT visit of the **Open-Label Period**. The interviews will follow the same structure and procedures as in the **Randomized Placebo-Controlled Period** exit interview with the exception that no blinding will be required for the **Open-Label Period** exit interview.

Any potential AEs reported during the interviews will be communicated to the Investigator for follow-up and documentation.

8.5.1. Participant Narratives

Detailed narratives will be prepared describing the participant's treatment course and corresponding responses. To maintain proper blinding, WBC and any other potentially unblinding data will be added post–database lock and will be included as part of the clinical study report. All data and information will be collected as part of the study and there will be no additional procedural requirements from the site.

8.6. Unscheduled Visits

Unscheduled visits may occur any time the participant identifies a potential infection. Unscheduled visits may also occur to monitor participant safety on the study. These visits may be in person or via telephone. If performed remotely, any clinically mandated laboratory tests may be performed using a local laboratory and entered as unscheduled test results (identified as infection related). These tests may include, at the Investigator's discretion, complete blood count (CBC), cultures, c-reactive protein, imaging studies including photographs of infections, particularly cutaneous infections, and any other relevant evaluations.

9. PHARMACOKINETICS

Blood samples will be analyzed for mavorixafor concentration using reversed-phase high-performance liquid chromatography with tandem mass spectrometry detection.

- PK sampling will be collected at baseline on Day -1 at time 0 and on Day 1 at 2 hours after the first administration of the study drug.
- Dense PK sampling will occur at all post-baseline office visits in the **Randomized Placebo-Controlled Period** (see Section 1.1) at the following time points:

  Time 0 (predose, up to 30 minutes prior), 30 minutes, 60 minutes (each ± 15 minutes), and 90 minutes, 2, 3, and 4 hours (each ± 15 minutes), and 8, 12, 16, and 24 hours (each ± 30 minutes).

The PK results for the **Randomized Placebo-Controlled Period** will not be reported to the Investigator or the Sponsor until the study is unblinded. To reduce participant burden, participants who prematurely discontinue study treatment but remain on study will not undergo blood sampling for PK analysis.

10. ASSESSMENT OF EFFICACY

10.1. ALC, AMC, ANC, and WBC Count

ALC, AMC, ANC, and WBC count will be measured for the calculation of times above thresholds and AUCs.

Participants are scheduled for blood sample collection at the following time points during the **Randomized Placebo-Controlled Period**:

- On baseline Day -1, for 24 hours before administration of study drug, sampling will be performed at time 0, 30 minutes, 60 minutes (each ± 15 minutes), 90 minutes, 2, 3, and 4 hours (each ± 15 minutes), and 8, 12, 16, and 24 hours (each ± 30 minutes). On baseline Day 1, sampling will be performed 2 hours and 4 hours (each ± 15 minutes) after the first administration of the study drug.
- On subsequent visits, sampling will be performed at time 0 (predose, up to 30 minutes prior), 30 minutes, 60 minutes (each ± 15 minutes), 90 minutes, 2, 3, and 4 hours (each ± 15 minutes), and 8, 12, 16, and 24 hours (each ± 30 minutes).

ALC, AMC, ANC, and WBC count will be determined by standard methods. Whole blood samples will be sent to a central laboratory selected by the Sponsor.

All individual values and the calculated time above threshold and AUCs for ALC, AMC, ANC, and WBC count will not be reported to either the Investigator or the Sponsor until the **Randomized Placebo-Controlled Period** is unblinded.

10.2. Assessment of Infection by Adjudication Committee

For the purposes of this study, types of infections will include any bacterial, fungal, viral, protozoan, and parasitic disease, excluding HPV-related muco-cutaneous warts. Information about infections will be similarly collected in an electronic PRO(s), the ClinRO, and the eCRF. The PRO questionnaire and subsequent ClinRO assessment should be completed in the event of a 'yes' response to the infection question in the participant diary, as described further in Section 10.2.1 and Section 10.2.2. A blinded, independent AC will review all potential infection data (ie, diary, PRO, ClinRO, rationale for antibiotic route of administration [see Section 10.2.3], and other case-specific data) and, based on a priori–defined rules, will adjudicate the infection and severity. The AC will determine the following:

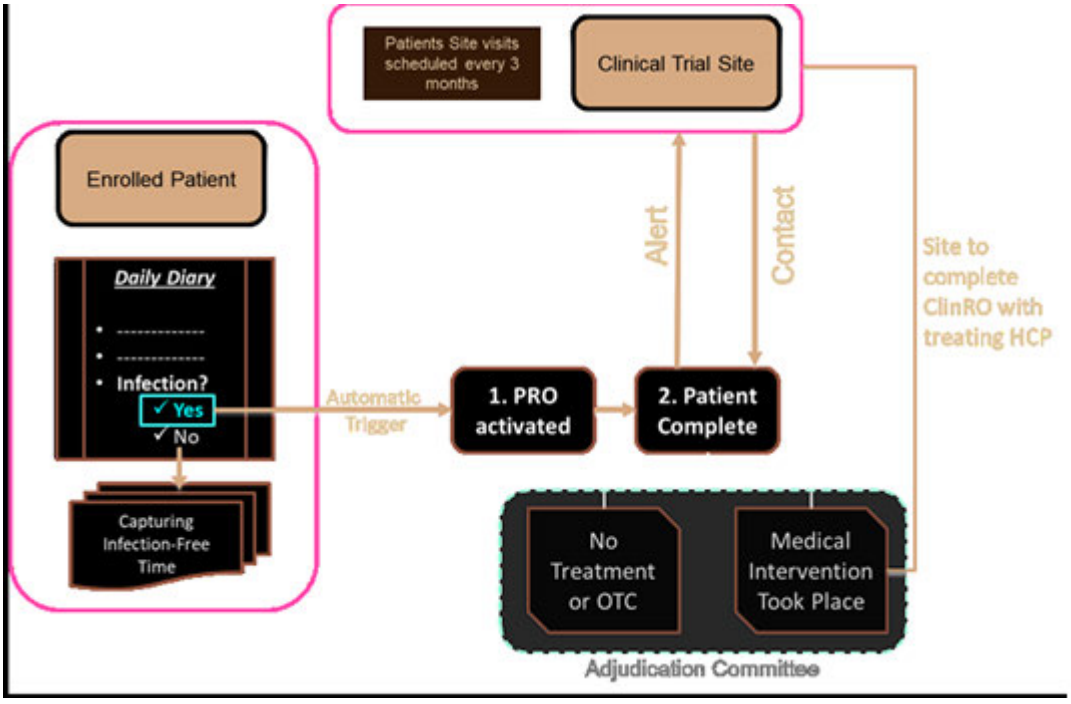
- Site of infection
- Duration of infection
- Severity of infection (treatment-based)
- Infection-free time

The AC will be the final arbiter of infections for the purpose of the efficacy analysis. Further information is outlined in the AC Charter.

10.2.1. Participant-Reported Potential Infections

Participants will complete a daily diary, which will include a question regarding whether the participant experienced an infection. A 'yes' response will trigger completion of the PRO. The PRO will capture infection severity, location, and frequency. Any activation of the PRO will trigger a telephone contact by the investigator, who will complete the ClinRO assessment. The process of collecting infection information via diary, PRO, and ClinRO is illustrated in Figure 4.

Figure 4: Data Collection Process for Infections: Diary, PRO, and ClinRO



Abbreviations: ClinRO = clinician-reported outcomes; HCP = health care provider; OTC = over-the-counter; PRO = participant-reported outcomes.

The treatment diary may be used to record the number of capsules taken, but the primary aim of the diary is to document the PRO questionnaire for any potential incidents of infections, not to document study drug compliance. Diaries also contain reminders on how to take the study drug. Diaries will be distributed at the baseline visit for the duration of the **Randomized Placebo-Controlled Period** and **Open-Label Period** and will include a participant training session. Participants will complete training modules during the baseline visit, which provide instruction on diary completion. Diaries will be reviewed with the participant at each study visit to remind the participant how to document infections on study.

10.2.2. Clinician-Reported Outcome of Infection

Whenever a participant identifies a potential infection, the participant will subsequently contact the investigator site and complete the PRO questionnaire via e-diary. The site personnel (eg, study coordinator, nurse, or physician), with oversight of the Investigator, will determine whether an in-person visit and/or special testing is needed. In-person visits may be performed at the investigational site if convenient, or by the participant's identified local cooperating physician. The site personnel, with oversight of the Investigator, will contact the local

cooperating physician to obtain all necessary data to complete the ClinRO. If telephone contact cannot be made, the site will attempt to obtain medical records from that visit. Infection severity will be characterized per the ClinRO. Assessment of any infection will include an evaluation for such as fever, malaise, and fatigue. If systemic symptoms are present, a CBC may be indicated based on clinical judgment, but the Investigator and Sponsor will remain blinded to the WBC count and differential results. The assessment of infection will be determined by the presumed site of infection, with documentation in source, as in the following examples:

- Upper respiratory tract infection
  - Includes sinusitis, nasopharyngitis, acute bronchitis, coryza, pharyngitis, and laryngitis
  - Need to clinically distinguish from noninfectious disorders, including allergy
  - Culture or antibiotic therapy rarely required
- Ear infection
  - Includes otitis externa, otitis media, and inner ear infections
  - Otoscopic examination, if performed
  - Antibiotics (systemic or topical), if indicated
- Skin and skin structure infection
  - Includes abscess, cellulitis, and erysipelas
  - Culture may be indicated, especially to rule out methicillin-resistant *Staphylococcus aureus*
  - Antibiotics (systemic or topical) often indicated
- Urinary tract infection
  - Urinalysis and culture, followed by antibiotics
- Lower respiratory tract infection
  - Imaging may be required
  - Sputum culture may be required
- Other infections
  - Medical imaging, blood tests, culture, and antibiotics may be required based on clinical judgment. Additionally, photographs taken by the participant or medical personnel may be useful to document the infection type and severity.

10.2.3. Severity of Infection

Infections will be categorized by the Investigator and recorded in the ClinRO. Infections will be scored in the Adverse Event of Special Interest – Infections eCRF page in the electronic database based on the following treatment-based scale:

- Level 0: No treatment
- Level 1: OTC medications, including nonprescription topical antibiotics
- Level 2: Oral or topical prescription antibiotics
- Level 3: Immune therapies, parenteral antibiotics (IV or intramuscular [IM])
- Level 4: Hospitalization required

The above severity scale is similar to the CTCAE severity scores for infections, which specifies that a Grade 2 event is characterized by the need for oral antibiotics and a Grade 3 event requires IV antibiotics. The above scale provides more granularity with the addition of scores of 0, 1, and 4.

To further inform the severity of infection, the Investigator will record additional data in the ClinRO for participants who require antibiotic treatment, whether local, oral, or parenteral (IV or IM), to capture the rationale for the route of antibiotic administration, as follows:

- OTC antibiotics (such as nonprescription topical antibiotics):
  - Minor infection with local symptoms
  - Unknown
- Oral antibiotics
  - Standard of care for this type of infection
  - Failed topical treatment
  - Unknown
- Parenteral antibiotics (IV or IM), excluding participants who are hospitalized (ie, ClinRO Level 4):
  - Standard of care for this type of infection
  - Failed oral therapy
  - Documented microorganism that is resistant to oral antibiotics
  - Unable to tolerate oral therapy
  - Unknown

In addition, if parenteral antibiotics are administered, the setting will be recorded as follows:

- In-patient hospital (hospitalization > 24 hours)
- Day hospital (hospitalization < 24 hours)
- Home health
- Unknown

All other standard information captured for any AE will also be collected in the AE pages of the eCRF.

10.3. Dermatological Assessment of Warts

10.3.1. Cutaneous Warts

Cutaneous warts will be evaluated and monitored by a dermatologist or trained study personnel at screening, Week 26, and Week 52 during the **Randomized Placebo-Controlled Period** and **Open-Label Period**.

Dermatologist examinations can be done either on site or remotely using video conference during home-health visits. The examination and collection of photographs and images during the screening period should be performed 7 days prior to the baseline visit to allow central review of the quality of baseline images.

Evaluation can be performed by a designee, under the supervision of the dermatologist, who has been trained in the conduct of this study. Examinations may be repeated at baseline if assessment, photographs, or skin swabs from screening are not sufficient. Guidance for these assessments is provided in the Dermatology Manual.

The following procedures will be completed by the dermatologist or trained study personnel:

- A study-supplied body diagram will be completed to indicate the locations of warts and their severity, and new warts will be noted. Details are provided in the Dermatology Manual.
- Standardized photographs (in duplicate) will be taken during dermatology visits for all participants. No photographs will be taken of the face or genitals. For all participants, regardless of wart presence, serial global photographs of both hands and feet as well as global and close-up photographs of 3 regions of interest, which may include a specific region on the hands and feet (eg, dorsum of hands, palmar aspect of hands, dorsum of feet, plantar aspect of feet, or other regions of interest with participant consent), will be selected at baseline and will be photographed at each dermatology visit. Regions of interest should be representative of the most severe wart lesions and will be identified according to a study-supplied body diagram and be evaluated for change and severity. Guidance is given in the Dermatology Manual if the participant is determined to have no warts. All details including CGI-S and CGI-C scale are provided in the Dermatology Manual.
- Additional areas of clinical significance, beyond the 3 regions of interest, excluding AG warts and face, may be photographed and scored for severity and change during the dermatology visits.
- Examinations, skin swabs, and photographs may be repeated at baseline if assessment, photographs, or skin swabs (see below) from screening are not sufficient.
- Complete CGI-S and CGI-C (change at follow-up visits only) for the 3 target skin regions, and for any other areas of clinical significance that have been identified.
- Skin swabs from healthy skin on the right hand, right foot, upper right chest, and inner cheek (oral swab) will be collected at each dermatology visit and stored for assessment of HPV types.
- Photographs of warts will be submitted for blinded, independent, central review.

10.3.2. Anogenital Warts

As part of medical history, participant-reported history of location and extent of AG warts will be collected. If a participant has a history of genital warts, a genital exam may be performed during each dermatology visit. This evaluation is optional, and participants may decline to participate. In addition, these evaluations are not meant to replace care provided by a participant's local provider. If performed, assessment of AG warts by the dermatologist will include a description of the number of lesions and size of the largest lesion(s) (up to 3). The dermatologist will complete assessments of CGI-S and CGI-C scores separately for AG warts.

10.4. Health-Related Quality-of-Life Questionnaires

Participants will complete the following validated health-related quality-of-life (QoL) questionnaires, as appropriate: 36-Item Short Form Survey, EQ-5D-5L, Life Quality Index, and Dermatology Life Quality Index (see Study Operations Manual Section 15, 15.1 through 15.7).

- The 36-Item Short Form Survey, EQ-5D-5L, and Life Quality Index will be completed for all participants.
- Both PGI-C and PGI-S questionnaires will be completed by all participants (Study Operations Manual Section 15.2 and Section 15.3, respectively)
- Adolescent participants (12-17 years of age) will also complete the Pediatric Quality of Life Inventory (Study Operations Manual Section 15.4).
- Additionally, the Dermatology Life Quality Index will be completed for all participants (Study Operations Manual Section 15.7).

QoL questionnaires must be completed prior to any other clinical procedures.

We understand that the responses to these questionnaires may differ depending on the health care systems and culture in different countries. Questionnaires will nevertheless be assessed in all participants, and participants will complete these forms according to their perspective of their situation.

10.5. Biomarker Assessments

10.5.1. Lymphocytes and Lymphocyte Subpopulations

Biomarker samples will be collected at time 0 at screening and then, for all subsequent visits, will be collected at predose (time point 0) and at approximately 4 hours postdose.

Assessments may include samples analyzed by flow cytometry for subpopulations of peripheral blood mononuclear cells. Candidate subsets may include but are not limited to the following:

- T- and B-cell subsets, including naïve and memory populations
- Plasmablasts
- Natural killer cells
- Monocytes and subsets
- CD34+ cells

These investigational assays will be performed by a central laboratory designated by the Sponsor. For participants who consent to future research and who weigh ≥ 100 pounds, a subset of peripheral blood mononuclear cells (PBMCs) may be isolated, frozen, and stored for future research to better understand the lymphocyte defect in participants with WHIM and the immune response to mavorixafor. The clinical significance of these tests is unknown at this time, and the results will not be assessed by the Investigator.

Detailed procedures for the collection, processing, storage, and shipment of these samples will be provided in the Laboratory Manual.

10.5.2. Serum Immunoglobulins

At each visit, serum will be obtained to determine total globulin, total immunoglobulin G (IgG), immunoglobulin A (IgA), immunoglobulin M (IgM), IgG1, IgG2, IgG3, and IgG4 concentrations.

10.5.3. Vaccine Antibody Titers

In participants vaccinated during the study with Tdap and/or Gardasil®9, antibody-specific titers, including pertussis toxin, tetanus, HPV 16, and HPV 18 will be collected in the **Randomized Placebo-Controlled Period** at baseline, and Weeks 26, 39, 52, and EOS. During Year 1 of the **Open-Label Period**, the same antibody-specific titers will be collected every 3 months, and at EOS; and then every 6 months and at EOS from Year 2 onward.

10.5.4. Skin Swabs

Metagenomic deep sequencing of human skin and oral samples will be performed to identify different types of pathogens, including HPV types present on the skin and oral mucosa. Swab locations will include the right hand, right foot, upper right chest, and inner cheek (oral swab) performed at screening and Weeks 26 and 52.

10.5.5. Research Blood

For participants who consent to future research and who weigh ≥ 100 pounds, samples including serum or peripheral blood mononuclear cells (PBMCs) may be collected and stored for future research to better understand the immunological response in participants with WHIM syndrome and in particular to explore the ability to produce antibodies to common pathogens and to study the antibody repertoire.

11. ASSESSMENT OF SAFETY

11.1. Adverse and Serious Adverse Events

11.1.1. Definitions

11.1.1.1. Adverse Event

An AE is any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory findings), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

An AE in a clinical study may be any of the following:

- An unfavorable and unintended symptom reported by the participant. Participants will be encouraged to report TEAEs spontaneously; general, non-directed questioning may also be used to elicit reports of AEs.
- Clinical sign detected by the Investigator. Observations by other study personnel will be reported to the Investigator for evaluation.
- Abnormal result from a laboratory study or other diagnostic procedure that meets at least one of the following criteria:
  - Results in termination of study drug;
  - Leads to treatment;
  - Leads to further diagnostic tests (other than a single repeat for confirmation);
  - Is assessed as “clinically significant” by the Investigator.

11.1.1.2. Serious Adverse Event

An AE or suspected adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it:

- Results in death.
- Is life-threatening. Life-threatening means that the participant was at immediate risk of death from the reaction as it occurred, ie, it does not include a reaction that hypothetically might have caused death had it occurred in a more severe form.
- Requires in-patient hospitalization or prolongation of existing hospitalization. Hospitalization admissions and/or surgical operations scheduled to occur during the study period but planned prior to study entry are not considered AEs if the illness or disease existed before the participant was enrolled in the study, provided that it did not deteriorate in an unexpected manner during the study (eg, surgery performed earlier than planned). Additional exclusions to SAE reporting include hospitalizations for
  - Elective procedures.

  - Social/administrative reasons in the absence of an AE.
  - Expected deterioration caused by progression of the disease under study.
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions.
- Is a congenital anomaly/birth defect.
- Is an important medical event. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in in-patient hospitalization or the development of drug dependency or drug abuse.

11.1.1.3. Adverse Drug Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility (see Section 11.1.3).

11.1.1.4. Suspected, Unexpected Serious Adverse Reaction

A **Suspected, Unexpected Serious Adverse Reaction** (SUSAR) is defined as an SAE that meets both of the following criteria with respect to study drug:

- Suspected: is assessed as related to study drug (see Section 11.1.3).
- Unexpected: Compared with the study drug–related AEs described in the Investigator's Brochure, the event meets any of the following criteria:
  - the event was not previously described;
  - the event is now characterized as more severe (see Section 11.1.2.1);
  - the event is now characterized more specifically (eg, an event of "interstitial nephritis" in a participant receiving an agent previously described as associated with "acute renal failure").

In clinical studies involving ill participants, events considered related to the natural history of the disease under study or to lack of efficacy (ie, the event is considered more likely related to those factors than to other factors, including study drug) are not considered "unexpected."

11.1.2. Classification of Adverse Events

11.1.2.1. Severity

The intensity (synonym: severity) of clinical AEs (ie, symptoms reported by the participant and/or signs observed by the Investigator) will be assessed by the Investigator using the NCI CTCAE (v5.0). Grades will be classified as Grade 1 to 5.

If the AE is not included in the NCI CTCAE, then the Investigator will contact the Medical Monitor, X4 Senior Medical Director, and/or the X4 pharmacovigilance team to determine an appropriate classification.

11.1.2.2. Grading of Laboratory Adverse Events

Treatment-emergent abnormal laboratory results will be reported as AEs when assessed as "clinically significant" using the procedures and criteria detailed in Section 11.1.4.

For the purposes of analyzing laboratory data, all laboratory results will be graded using NCI CTCAE (v5.0) and then summarized as "shift tables" comparing baseline and treatment-emergent results. This process will assure that the final study report contains complete and consistent analyses of safety laboratory tests.

11.1.3. Relationship to Study Drug

This determination is based on the Investigator's clinical judgment and experience regarding the likelihood that the study drug caused the AE and may include consideration of some or all of the following factors:

- Alternative possible causes of the AE, including the participant's underlying disease or comorbid conditions, other drugs, other host, and environmental factors;
- Temporal sequence between the exposure to study drug and the AE;
- Whether the clinical or laboratory manifestations of the AE are consistent with the known actions or toxicity of the study drug;
- Whether the AE resolved or improved with decreasing the dose or stopping the study drug (ie, de-challenge); or recurred or worsened with re-exposure to the drug (ie, re-challenge).

The causal relationship of the AE will be assessed. The following categories should be considered when evaluating the relationship of AEs and SAEs to the study treatment:

- **Definitely related:** Event can be fully explained by administration of the investigational product.
- **Probably related:** Event is most likely to be explained by the administration of the investigational product rather than the participant's clinical state or other agents and/or therapies.
- **Possibly related:** Event may be explained by the administration of the investigational product or the participant's clinical state or other agents and/or therapies.

- **Unlikely related:** Event can be fully explained by the participant's clinical state or other agents and or therapies rather than the investigational product.
- **Unrelated (or not related):** Event can be fully explained by the participant's clinical state or other agents and or therapies.

Related AEs may result during the use of the study drug as planned (per protocol), or from abuse, withdrawal, or over-dosage of the agent. The Investigator may change his/her opinion of causality in light of new or additional information and update the relationship to study drug at any time.

11.1.4. Clinical Laboratory Adverse Events

The Investigator will review the results of all safety laboratory tests (see Table 10) and designate any results outside of the reference range as *either* of the following:

- Abnormal, not clinically significant
- Abnormal, clinically significant

In making this judgment, the Investigator will consider all available information, including the participant's clinical condition, all available laboratory results, and the potential for false-positive test results. In addition, laboratory studies that result in the actions specified in Section 4.4.1 will be classified as "abnormal, clinically significant."

Any result assessed as "abnormal, clinically significant" will be recorded as an AE *unless* it is consistent with 1 or more of the following:

- Process noted in the medical history
- Ongoing AE already recorded or captured as part of diagnosis (eg, hemoglobin of 8 captured as part of new AE of anemia)
- Expected course of the primary disease under study

11.2. Recording Adverse Events

AEs spontaneously reported by the participant and/or in response to an open question from the study personnel or revealed by observation will be recorded during the study at the investigational site. Information about AEs and SAEs will be collected from the signing of consent form until the end of the study. Any untoward medical occurrence reported during the screening period will be recorded as medical history. The AE term should be reported in standard medical terminology when possible. For each AE, the Investigator will evaluate and report the onset (date and time), resolution (date and time), intensity, causality, action taken, serious outcome (if applicable), and whether it caused the participant to discontinue the study. Intensity will be assessed as described in Section 11.1.2.1.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity, whereas seriousness is defined by the criteria (Section 11.1.2.1). An AE of severe intensity may not be considered serious.

Should a pregnancy occur, it must be reported and recorded on the Sponsor's pregnancy form. Pregnancy in itself is not regarded as an AE unless there is a suspicion that an investigational product may have interfered with the effectiveness of a contraceptive medication.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) must be followed up and documented even if the participant was discontinued from the study.

All reports of congenital abnormalities/birth defects are SAEs. Spontaneous miscarriages should also be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

11.3. Reporting Adverse Events

Each participant must be carefully monitored for the development of any AEs. This information should be obtained in the form of non-leading questions (eg, "How are you feeling?") and from signs and symptoms detected during each examination, observations of study personnel, and spontaneous reports from participants and/or family members/caregivers (such as in the case of minors).

All AEs (serious and non-serious) should be reported in standard medical terminology when possible. Also, when possible, signs and symptoms indicating a common underlying pathology should be noted as 1 comprehensive event. For each AE, the Investigator will evaluate and report the onset, resolution, intensity, causality, action taken, serious outcome (if applicable), and whether or not it caused the participant to discontinue the study.

11.3.1. Serious Adverse Event Reporting

SAE reporting, including supporting materials, will be performed by the site using a system approved by the Sponsor; detailed training will be provided during site initiation. Contact information for guidance and assistance with SAE reporting will be provided in the Study Manual.

11.3.1.1. Procedures for Reporting Serious Adverse Events to the Sponsor

The initial notification of each SAE will be reported within 24 hours of the time the Investigator (or the Investigator's designee) becomes aware that the event has occurred and will include the following information (any items not available should be explicitly noted):

- Protocol number, study site, participant number;
- Investigator's name and contact information (phone, fax, email) and signature;
- Description of the event (ie, date and time of onset, initial assessment, treatments, and course);
- Current status of the participant and the event;
- Criteria by which the event was assessed as serious;
- Date of the first administration of study drug;
- Date of the last administration of study drug prior the event;

- Assessment of relationship of study drug to the event;
- Whether the study drug was discontinued or adjusted as a result of the event.

Thereafter, signed supplemental (follow-up) information will be provided as it becomes available to the Investigator (either directly or as a result of investigation into a query). Such information includes but is not limited to:

- Copies of relevant medical reports, including diagnostic procedures (eg, laboratory tests), surgical procedures, and consultations
- More definitive outcome for events previously reported as ongoing or unknown outcome

11.3.1.2. Requirements for Expedited and Periodic Reporting of Adverse Events

SUSARs are required to be reported immediately to regulatory authorities and to IRBs/IECs (typically within 7 days for fatal or life-threatening SUSARs; within 15 days for all other SUSARs). The Sponsor and the Investigator will work together to meet these reporting requirements.

11.3.1.3. Notification of Serious Adverse Events to the Investigator by the Sponsor

In accordance with regulatory requirements, the Sponsor will notify the Investigator of the occurrence of SUSARs reported by other Investigators in this or in other studies involving the study drug. The Investigator will promptly inform his/her IRB/IEC of such communications from the Sponsor and will document that notification in the Investigator's Regulatory Binder.

11.3.2. Reporting of Pregnancy

Pregnancies occurring in the participant or participant's partner while the participant is receiving study drug or within 1 month after the participant's last dose of study drug will not be considered serious but are to be reported using the same procedures as for SAEs described in Section 11.3.1.

Study drug must be discontinued immediately in the event of a pregnancy in the participant. The participant/participant's partner should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the participant/participant's partner until completion of the pregnancy and must notify the Medical Monitor of the outcome within 5 days. The Investigator will provide this information as a follow-up to the initial report.

If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, spontaneous abortion [any congenital anomaly detected in an aborted fetus will be documented], stillbirth, neonatal death, or congenital anomaly), then the Investigator should report it as such. Furthermore, all neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the Investigator suspects is related to in utero exposure to the study drug should also be reported.

11.3.2.1. Follow-Up and Outcome of Adverse Events

If possible, AEs will be followed until resolved either with or without sequelae, including for participants who prematurely discontinue study participation. For AEs that are assessed as

unrelated to the study drug and are not resolved at the EOS visit, follow-up may be limited with the approval of the Medical Monitor.

11.3.3. Time Period and Frequency for Event Assessment and Follow-Up

Procedures for the collection and recording of AEs are as follows:

- From the time of obtaining informed consent through EOS, there will be active surveillance to identify all AEs. Events will be recorded in the AE portion of the eCRF, with particular attention to whether the onset of the event was before or after the administration of the first dose of study drug. If an AE occurs any time between the screening visit and the baseline visit of the **Randomized Placebo-Controlled Period**, the Investigator should record the event on the Medical History form of the eCRF. Any SAE will be recorded on the corresponding eCRF page and will be reported to the Sponsor, as described in Section 11.3.
- After the EOS, surveillance will be passive (only events brought to the Investigator's attention will be considered), and only events assessed as SUSARs (see Section 11.1.1.4) will be recorded.

11.4. Infection-Related Outcomes

Infection-related events are common in participants with WHIM. Because infection events are typically associated with the disease under study and are being collected as an outcome, infections will be reported as adverse events of special interest (AESI); infections that meet the criteria for SAEs will be reported as SAEs.

If an infection meets serious criteria (see Section 11.1.1.2), the serious infection will be recorded on the corresponding eCRF page and will be reported to the Sponsor, as described in Section 11.3. Infections will be monitored and adjudicated by a blinded, independent AC in the **Randomized Placebo-Controlled Period** (see Section 10.2). If an infection occurs any time between the screening visit and the baseline visit of the **Randomized Placebo-Controlled Period**, the Investigator should record the event via the ClinRO questionnaire as well as record the event on the Medical History form of the eCRF.

Any infection that occurs after signing informed consent until administration of the first dose of investigational medication, will be reported as medical history and will be logged in ClinRO.

12. STATISTICS

12.1. Sample Size

Interim Phase 2 data (ie, Study X4P-001-MKKA) were used to estimate these Phase 3 sample size calculations. Results from in-residence sampling during exposure to the 300-mg and 400-mg doses (8 observations) were used for estimating the mavorixafor mean time above threshold for ANC. Results from the in-residence sampling during exposure to the 50-mg, 100-mg, and 150-mg doses (8 observations) were used for conservatively estimating the placebo mean time above threshold for ANC. The final analysis will be performed using the mean of 4 on-treatment time values determined over the 12-month Treatment Period; thus, it is expected that the variability within participants will be less than that observed in Phase 2. As a result, a pooled standard deviation between mavorixafor and placebo was used for the estimates, divided by the square root of 4 to account for multiple assessments per participant.

For sample size estimation, the following assumptions were used:

- Mean mavorixafor time above threshold for ANC (hours) = 11.4
- Mean placebo time above threshold for ANC (hours) = 1.4
- Pooled standard deviation = 4.7

Given a 1:1 (mavorixafor:placebo) randomization allocation, a total of 18 participants (n = 9 in each treatment group) will provide greater than 90% power using a 2-sample t-test on the mean time above threshold for ANC over a 24-hour period, given the null hypothesis that the difference between the 2 treatment groups is equal to zero with a 2-sided significance level (alpha) of 0.05. To account for potential dropout and to allow flexibility in enrollment, a total of 28 participants may be enrolled and randomized.

12.2. Populations for Analysis

The ITT Population is the primary population for the analysis of efficacy endpoints. Sensitivity and confirmatory analyses may be performed using the Per Protocol Population. The Safety Population is the primary population for the analysis of safety endpoints (Table 11). Further details are provided in the statistical analysis plan.

Table 11: Populations for Analysis

Population	Description
Safety Population	All participants who were randomized to treatment and received at least 1 dose of study treatment (either mavorixafor or placebo). Participants will be analyzed according to the treatment they actually received.
ITT Population	All participants randomized to treatment and received at least 1 dose of study treatment. Participants will be analyzed according to the treatment to which they were randomized.
Per Protocol Population	All participants in the ITT Population without any major protocol violations that may impact the assessment of efficacy (as defined in the SAP) and with at least 1 efficacy evaluation (ie, at least 1 post-baseline ANC assessment).

Abbreviations: ANC = absolute neutrophil count; ITT = Intent-to-Treat; SAP = statistical analysis plan.

12.3. Randomization and Blinding

The **Randomized Placebo-Controlled Period** of this study is double-blind. The Sponsor and study team, Investigator, and participant will be blinded to treatment allocation, all PK data, and all data related to ALC, AMC, ANC, WBC count, and lymphocyte subsets, once randomized. Clinical laboratory assessments will not be masked at screening or at baseline Day -1. All masking will occur after first dose is administered at baseline Day 1.

Participants will be randomized to receive up to 400 mg mavorixafor or matched placebo at a 1:1 allocation. The randomization will be stratified into 2 categories: (1) have received any Ig treatment within 5 months prior to screening visit/signing of the ICF, or (2) have not received any Ig treatment within 5 months prior to screening visit/signing of the ICF. Approximately 18 to 28 participants will be randomized. This approach will allow a reasonable balance of the number of treatment allocations within each stratum for statistical analysis, while still allowing flexibility of enrollment accounting for the prevalence of Ig use.

Treatment assignment will be performed by a centralized randomization procedure. Participants randomized to placebo will receive an equivalent number of matching capsules.

Detailed instructions on participant randomization will be found in the IXRS Site User Guide.

12.3.1. Breaking the Blind During the Randomized Placebo-Controlled Period

To maintain the overall quality of data collected during the **Randomized Placebo-Controlled Period**, breaking the blind should occur only in exceptional circumstances when knowledge of the actual treatment is essential for further management of the participant. If the Investigator decides it is medically necessary to unblind a participant's treatment assignment to appropriately manage the participant's AE, the Investigator will inform the Medical Monitor as soon as possible prior to breaking the blind. In case of emergency, when prior communication with the Medical Monitor is not feasible, the Investigator will inform the Medical Monitor promptly thereafter. Every effort must be made to avoid disclosing treatment assignment to site personnel and the Sponsor. The date and reason for breaking the blind will be recorded in the appropriate eCRF. When the blind is broken, the Investigator will notify the IRB/IEC.

Once the blind is broken, the participant may not continue randomized treatment but may roll over to the **Open-Label Period**.

Detailed instructions on breaking of the blind will be found in the IXRS Site User Guide.

12.3.2. Unblinding Procedures Upon Completion of the Randomized Placebo-Controlled Period

At the End of the Randomized Period (ie, once all participants have completed the EoRP visit at Week 52 or discontinued prematurely) or the EOT/Safety follow-up visit, following data cleaning and database lock, the study will be unblinded for all participants. Prior approval will be obtained from the Sponsor before unblinding.

12.4. Description of Statistical Methods

12.4.1. General Methods

A detailed statistical analysis plan (SAP) will be finalized prior to database lock.

This is a multicenter study with a double-blind, **Randomized Placebo-Controlled Period** and an **Open-Label Period**. Statistical hypothesis testing will be performed to evaluate the primary and secondary efficacy endpoints of the **Randomized Placebo-Controlled Period** of the study. Data summaries will be prepared and categorized by treatment group (mavorixafor, placebo) and study period (randomized, open-label).

All data collected in this study will be documented using summary tables and figures, as appropriate. Tabulations will be produced for appropriate disposition, demographic, baseline, efficacy, and safety parameters. Categorical variables will be summarized by frequency distributions (number and percentages of participants), and continuous variables will be summarized by descriptive statistics (mean, standard deviation, median, minimum, and maximum). Where appropriate, p-values and 95% CIs will be reported. All statistical tests will be reported using 2-sided tests with alpha = 0.05 unless otherwise stated.

All data will be provided in by-participant listings.

To control familywise type I error rate, the following key secondary endpoints will be tested in order after meeting the primary endpoint:

1. 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.
2. Composite Clinical Efficacy Endpoint for mavorixafor versus placebo based on total infection score and total wart change score in the ITT Population over 52 weeks.
3. Total wart change score for mavorixafor versus placebo based on central blinded, independent review of 3 target skin regions in the ITT Population at 52 weeks.
4. Total infection score for mavorixafor versus placebo based on infections adjudicated by a blinded, independent AC in the ITT Population over 52 weeks.

Data collected in the **Open-Label Period** will be presented and analyzed separately.

12.4.2. Procedures for Handling of Missing Data

Participants who discontinue the study drug will be encouraged to return for visits where the primary or secondary endpoints are collected. Imbalances in dropout rates and timing across treatment arms will be examined to assess whether there is bias in favor of mavorixafor treatment.

12.4.2.1. ANC Calculations

No imputation of missing assessments will be performed for the primary analysis of either time above threshold or AUC_{ANC}. The primary endpoint will be analyzed using mixed-model repeated measures (MMRM), a robust method of analysis that allows for missing data in the covariance for the repeated measures. An unstructured covariance matrix will be estimated and used in the analysis. Sensitivity analyses using multiple imputation may also be used to assess the robustness of the statistical analysis results on the primary endpoint. Details will be provided in the SAP.

12.4.2.2. Adverse Event Dates

When tabulating AE data, partial dates will be handled as follows in the determination of treatment emergence:

- If the day of the month is missing, the onset day will be set to the first day of the month unless it is the same month and year as the date of the first dose of study treatment. In that case, the event onset will be coded to Day 1 (the calendar day of administration of the first dose of study drug) in order to conservatively report the event as treatment emergent.
- If the onset day and month are both missing, the day and month will be assumed to be January 1, unless the event occurred in the same year as the date of the first dose of study treatment. In that case, the event onset will be coded to Day 1 (the calendar day of administration of the first dose of study drug) in order to conservatively report the event as treatment emergent.
- For AE end dates, an event missing the day of the month will be set to the last day of the month, and an event missing both day and month will be set to missing.

12.4.3. Multiple Comparison/Multiplicity

Multiplicity in this Phase 3 study is controlled by specifying a single primary endpoint and use of a hierarchical approach to the analysis of secondary endpoints. Each endpoint will be hierarchically tested at the 2-sided alpha-level of 0.05, in the order presented in Section 3. If the analysis for a specific endpoint is not statistically significant, results on subsequent endpoints will be considered descriptive.

12.4.4. Disposition and Baseline Evaluations

A tabulation of participant disposition will be presented and will include the number of participants enrolled in each period of the study, the number of participants randomized to each treatment group, and the number of participants dosed in each treatment. The number of participants in each analysis population, the number who discontinued treatment, the number who discontinued the study, and the reasons for discontinuation will also be presented.

Details for the summary of demographic and baseline characteristics, including medical history, will be provided in the SAP.

12.4.5. Pharmacokinetic Analyses

Standard non-compartmental analysis will be applied to derive PK parameters, including C_{max}, T_{max}, $T_{1/2}$, and AUC. Other parameters may be derived as appropriate. PK data will be summarized using descriptive statistics and graphical concentration-time plots. Additional by-participant listings and summaries may be created as outlined in the SAP.

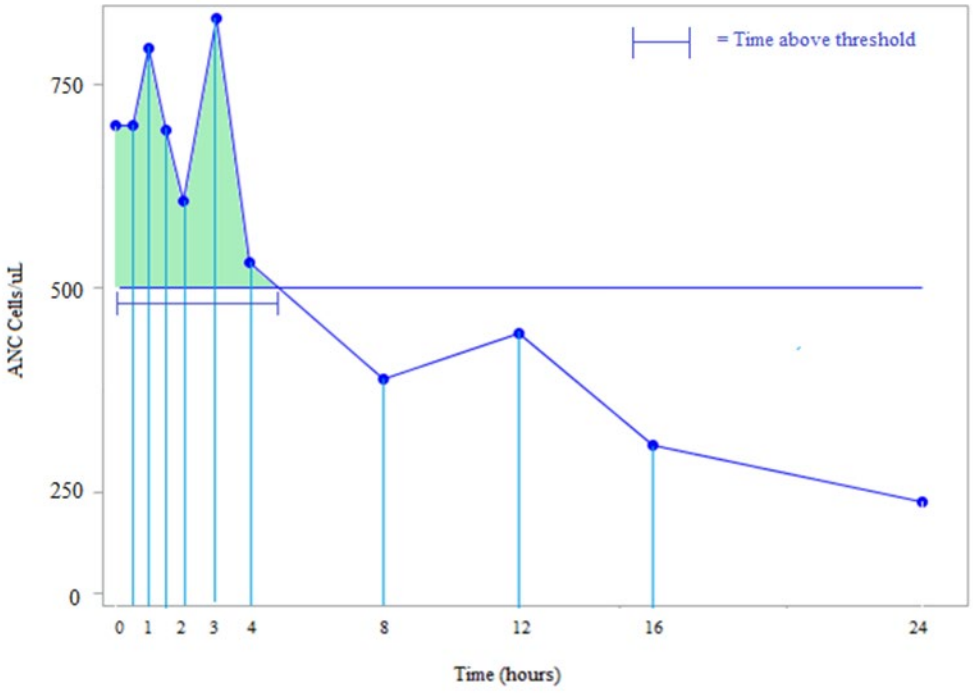
The PK and PD data may be combined with data from other studies and analyzed using population PK/PD analysis and reported outside of the clinical study report. This may include exploratory analyses to characterize participant factors associated with variability in PK, and to explore relationships between mavorixafor exposures and measures of efficacy and/or safety.

12.4.6. Efficacy Analyses

12.4.6.1. Analysis of Primary Endpoint

The primary endpoint analysis will compare the difference between mavorixafor and placebo with respect to the mean time above ANC threshold using MMRM analysis in the ITT Population. Time (in hours) above threshold will be calculated using a linear interpolation, such that the time between intervals where ANC values cross the threshold will be determined based on the slope between the 2 time points. The calculation of the time above threshold for a hypothetical set of ANC data is illustrated in Figure 5.

Figure 5: Calculation of Time Above Threshold for a Hypothetical Set of ANC Data



Abbreviation: ANC = absolute neutrophil count.

The model will use time above threshold as a dependent variable; treatment, visit, treatment*visit, prophylactic Ig use (randomization strata), and baseline time above threshold as covariates; and participant as the repeated random effect. The unstructured covariance matrix will be used. Two-sided p-values and 95% CIs associated with the least-square mean difference between groups will be presented overall and by visit. The primary analysis will be based on all data, with no imputation for missing data.

12.4.6.1.1. Sensitivity Analyses

Sensitivity analyses will be performed to assess the analysis assumptions and impact of missing data on the primary analysis. Supportive analyses will evaluate the use of different methods for handling missing data, including multiple imputation. A completers analysis will also be performed as supportive; only participants with at least 2 post-baseline ANC assessments collected will be included. A supportive analysis of time above threshold will be performed using an interval method, as opposed to linear interpolation; the duration is the cumulative sum of the intervals at which the ANC are above threshold, according to the specified time points. Additional details on sensitivity analyses will be included in the SAP.

12.4.6.2. Analysis of Key Secondary Endpoints

Key secondary efficacy endpoints represent objectively defined, verifiable clinical outcomes. A hierarchical approach to formal statistical testing will be used, with the hierarchy planned in the order of presentation of secondary endpoints in Section 3. The ITT Population is the primary population for analysis.

Time above threshold (TAT) of ALC will be analyzed using a similar MMRM model to that used for the primary endpoint of TAT of ANC, with factors of treatment, visit, treatment visit, prophylactic Ig use (randomization strata), and baseline TAT as covariates.

The 2-component composite score for each participant will be calculated by summing up the ranks of the 2 individual components (total infection score and 52-week total wart change score) according to the procedure described by O'Brien (O'Brien 1984). The comparison between mavorixafor and placebo will be performed based on analysis of covariance of the rank sum with treatment group and prophylactic Ig use as factors and covariate of the baseline rank sum (see SAP for details). The missing 52-week total wart change score will be imputed with the multiple imputation method (under missing at random assumption) using the SAS PROC MI procedure (see SAP for details). Sensitivity analysis, where the missing total wart change score will be imputed with 0, may be performed.

Baseline rank sum is the sum of the ranks for infection history and baseline warts for each participant. Each participant's infection history will be ranked based on their prior yearly infection rate only, due to the lack of information on infection event severity. Retrospective infection rates will be based on participant's medical records from the 12 months preceding the drug treatment (including the screening period prior to first dose). Each participant's baseline wart burden will be ranked based on the sum of baseline CGI-S for the 3 target skin regions.

The effect of treatment on warts will be assessed based on total wart change score using the blinded, centrally reviewed CGI-C at Week 52 for the 3 target skin regions. The total wart change score is calculated by summing the Regional Wart Change Scores from all 3 target skin

regions (see SAP for details). For participants without warts at baseline and with no new wart developed during the treatment, the CGI-C will be considered as no change.

The total wart change score will be analyzed using MMRM model with factors of treatment, visit, treatment*visit, prophylactic Ig use (randomization strata), and baseline CGI-S (sum in the 3 target areas) as covariate. The missing total wart change score will be 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 will be imputed with 0 may be performed.

The total infection score will be analyzed using a linear mixed model. Independent variables include treatment and prophylactic Ig use (randomization strata). Infection rate in the previous 12 months will be included as a covariate.

Additional details on the analysis of key secondary endpoints will be specified in the SAP.

12.4.6.3. Analysis of Other Secondary Endpoints

The other secondary endpoints will be analyzed to provide additional evidence of treatment effect.

Time to Early Release within the non-Ig use stratum of the ITT Population will be analyzed by a logrank test. A Cox proportional hazard model will be used for the estimation of the hazard ratio and its 95% CIs. Kaplan-Meier plots of time to Early Release will also be presented.

TAT-ALC of ≥ 1000 cells/μL over 26 weeks in participants with lymphopenia at baseline (ALC value < 1000 cells/μL at screening) will be analyzed with a similar model to that used for the ITT Population.

Composite endpoint based on total infection score and total wart change score for participants with warts at baseline or non-Ig use will be analyzed with a similar model to that used for the ITT Population.

Total infection score based on infections adjudicated by a blinded, independent AC for participants with and without Ig use will be analyzed with the following model: independent variables include treatment, prophylactic Ig use (randomization strata), and prophylactic Ig use by treatment interaction. Infection rate of previous 12 months will be included as a covariate.

Total wart change score based on blinded central review of 3 target skin regions for participants with warts at baseline will be analyzed with a similar model to that used for the ITT Population.

Total wart change score based on local dermatologist review of all regions for participants with warts at baseline will be analyzed with a similar model to that used for the target skin region analysis.

The sum of change from baseline in CGI-S in the target skin regions based on the blinded central review data will be analyzed using the MMRM model with factors of treatment, visit, treatment visit, prophylactic Ig use (randomization strata), and baseline CGI-S (sum in the target areas) as covariates. The missing sum of change from baseline will be imputed with the multiple imputation method (under missing at random assumption) using the SAS PROC MI procedure.

The annualized infection rate will be analyzed using a dispersion-adjusted negative binomial regression model. Independent variables including treatment, prophylactic Ig use (randomization

strata), and infection rate of previous 12 months will be included as covariates for ITT Population. The log-transformed exposure variable will be included in the model as the offset parameter. Subgroup analysis for the non-Ig use and Ig use strata will use the following model: independent variables include treatment, prophylactic Ig use (randomization strata), and prophylactic Ig use by treatment interaction; infection rate of previous 12 months will be included as a covariate.

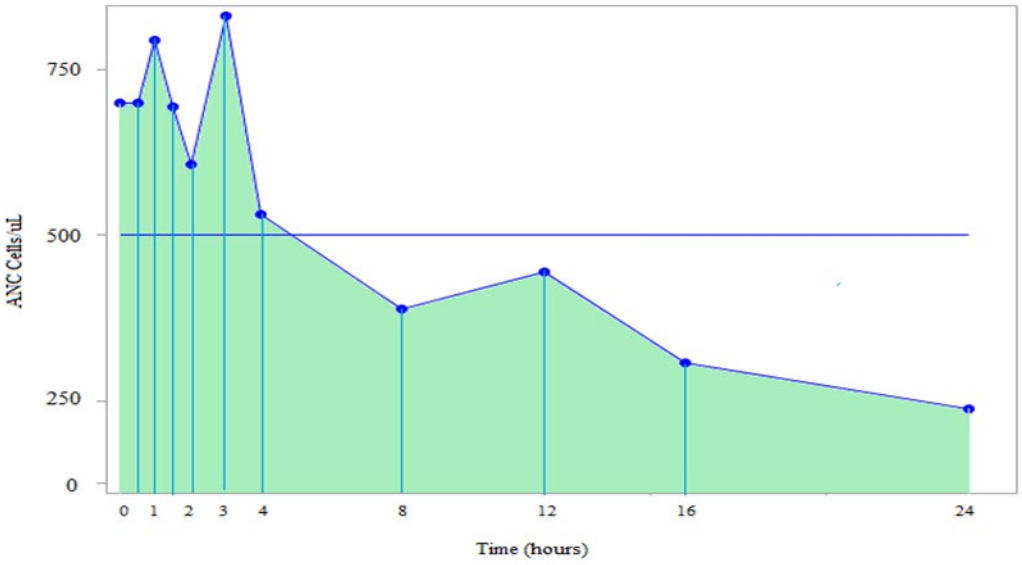
All potential infections (with the exception of warts) will be included, and the primary analysis will be based on the infections per the blinded, independent AC, as outlined in the AC Charter. Additional analysis may be performed on all participants and on infections with moderate or greater severity.

Clinical Global Impression of Change from baseline will be analyzed using a linear mixed model. Independent variables include treatment and prophylactic Ig use (randomization strata). Baseline Clinical Global Impression of Severity will be included as a covariate.

Patient Global Impression of Change from baseline will be analyzed using a linear mixed model. Independent variables include treatment, and prophylactic Ig use (randomization strata). Baseline Patient Global Impression of Severity will be included as a covariate.

The 24-hour AUC_{ANC} will be calculated using the trapezoidal method and compared between treatment groups using similar methods to that used for the primary endpoint. Figure 6 illustrates the calculation of the 24-hour AUC for a hypothetical set of ANC data.

Figure 6: Calculation of 24-Hour AUC for a Hypothetical Set of ANC Data



Abbreviations: ANC = absolute neutrophil count; AUC = area under the curve.

It is anticipated that the variability in data among participants in Phase 3 will be similar to that observed in Phase 2; thus, log-transformed values of the AUC_{ANC} will be used. The absolute values and fold change from baseline in ANC for each participant will be presented over time using graphical methods.

Vaccine titer levels at Week 52, including pertussis toxin, tetanus, HPV 16, and HPV 18, will be analyzed in logarithm 10 scale using an MMRM model similar to that used for the primary analysis, and geometric mean titers will be compared between mavorixafor and placebo. Fold change from baseline in antibody-specific titers will be presented by visit and treatment group, including the number of participants with increases in antibody titers to the therapeutic range, if applicable.

An ANC responder analysis will be performed. A responder is defined first as a participant with ANC above the threshold at least 50% of the time and then as a participant with ANC above threshold for the entire 24-hour period. For both responder criteria, a participant will be deemed an overall responder if they meet the definition at 2 consecutive visits. The proportion and percent of responders will be reported for each treatment group. The comparison between groups will be performed using Cochran-Mantel-Haenszel statistics. Response rate will also be summarized by time point.

If the between-groups comparison of AUC_{ANC} is statistically significant, the mavorixafor AUC_{ANC} will be analyzed relative to the prespecified clinically meaningful threshold of 500/µL. The analysis will be based on the ratio of the log-transformed AUC relative to the log-transformed threshold (ie, the log of the 24-hour AUC relative to the log of the threshold × 24). The analysis will be performed to determine whether the mean of the mavorixafor treatment arm, based on the per-participant average of the 4 AUCs taken during the 12-month treatment period, is significantly above 0 using a 1-sample t-test on the log-transformed ratio at α-level = 0.05, 2-sided.

The analysis for ALC will be performed using similar methods to those described for the associated ANC endpoints (ie, 24-hour AUC_{ALC}, ALC responder analyses). Absolute and fold change from baseline in ANC, ALC, AMC, and WBC count will be summarized over time.

The average duration of infections will be compared between treatment groups. In addition, the incidence, frequency, and duration of hospitalizations due to infections, as well as number of days missed from work/school, will be compared between treatment groups.

Quality-of-life assessments will be analyzed according to published guidelines for each assessment.

Endpoints and analyses, including additional supportive analyses, will be finalized in the SAP prior to unblinding.

12.4.6.4. Analysis of Exploratory Endpoints

The exploratory efficacy endpoints will be analyzed both to provide additional evidence of treatment effect and to generate additional hypotheses. Non-inferential, descriptive analyses will be presented by treatment group. Details will be specified in the SAP.

12.4.7. Safety Analyses

The objective of safety and tolerability (defined as any probably or definitely related AE leading to permanent discontinuation of study or study drug) will be assessed by analysis of AEs, clinical laboratory parameters, vital signs, and ECG assessments, as well as results from physical and ophthalmologic examination, and, for male study participants up to the age of 50 years old, testicular examinations.

12.4.7.1. Adverse Events

All AEs will be coded using the Medical Dictionary for Regulatory Activities coding system and displayed in tables and data listings using System Organ Class (SOC) and Preferred Term (PT). Analyses will be performed for TEAEs, defined as any AE that begins or worsens after administration of the first dose of study treatment. Summary tables will be presented by SOC and PT, indicating the number and percentage of participants with:

- Any TEAE
- AEs assessed as related to treatment
- SAEs
- AEs assessed as Grade ≥ 3 (severe or worse)
- AEs leading to withdrawal
- AEs leading to death

AEs will be summarized by participant incidence rates; therefore, in any tabulation, a participant contributes only once to the count for a given SOC and PT, regardless of the number of episodes.

12.4.7.2. Laboratory Tests

The actual value and change from baseline to each on-study evaluation will be summarized for each clinical safety laboratory parameter, including hematology and clinical chemistry assessments. In the event of repeat values, the last non-missing value per study day/time will be used. Shift tables of laboratory data based on NCI CTCAE grades from baseline to worst value and from baseline to last value on treatment will be presented. Similar shift tables of laboratory data based on the normal ranges will be used for tests that do not have CTCAE grades.

12.4.7.3. Electrocardiogram and Vital Signs

The actual value and change from baseline of ECG parameters and vital signs will be summarized descriptively by treatment group and visit.

ECG parameters include ventricular rate, RR interval, PR interval, QRS interval, QT interval, QTc interval, and QTcF. If not collected separately, the RR interval will be derived as follows: RR interval (seconds) = (60/ventricular rate).

12.4.7.4. Exposure and Participant Adherence

For both treatment arms, a descriptive summary of participant adherence to treatment will be produced to include duration of time on therapy, number of doses received, and actual and relative dose intensity. A summary of the number of participants completing this study (ie, receiving 52 weeks of treatment in the **Randomized Placebo-Controlled Period**) will be produced.

13. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Source documents are the originals of any documents used by the Investigator, hospital, or institution that verify the existence of the participant and substantiate the integrity of the data collected during the study.

13.1. Study Monitoring

Before an investigational site can enter a participant into the study, a representative of the Sponsor will assess the investigational study site for the following:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its designee

During the study, a monitor from the Sponsor or representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the participant's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each participant (eg, clinic charts)
- Record and report any protocol deviations not previously sent to the Sponsor
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to the Sponsor

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

13.2. Audits and Inspections

Authorized representatives of Sponsor or designee, a regulatory authority, or IRB/IEC may visit the study center to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and that data were recorded, analyzed, and accurately reported according to the protocol, International Council on Harmonisation (ICH) GCP, and any applicable regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

13.3. Institutional Review Board/Independent Ethics Committee

The PI must obtain IRB/IEC approval for the study. Initial approval and all materials approved by the IRB/IEC for this study, including the participant consent form and recruitment materials, must be maintained by the Investigator and made available for inspection.

14. QUALITY CONTROL AND QUALITY ASSURANCE

14.1. Study Monitoring

Monitoring and auditing procedures developed by the Sponsor or designee will be followed to comply with ICH GCP guidelines, as described in Section 13 and Section 16.

14.2. Case Report Form Completion

The Sponsor or designee will provide the study centers with eCRFs for each participant.

eCRFs will be completed for each study participant. It is the Investigator's responsibility to ensure the accuracy, completeness, and timeliness of the data reported in the participant's eCRF. Source documentation supporting the eCRF data should indicate the participant's participation in the study and should document the dates and details of study procedures, AEs, and participant status.

The Investigator, or designated representative, should complete the eCRF as soon as possible after information is collected, preferably on the same day that a participant is seen for an examination, treatment, or any other study procedure. Any outstanding entries must be completed immediately after the final examination. An explanation should be given for all missing data.

The Investigator must electronically sign and date the Investigator's Statement at the end of the eCRF to endorse the recorded data.

14.3. Electronic Records

All study data recorded on source documents are to be transcribed into the eCRFs. Any electronic study data are to be entered into a secure, validated data processing system and a backup maintained. Any changes to electronic study data will be documented.

14.4. Resolution of Deficiencies

The Investigator agrees to take promptly any reasonable steps requested by the Sponsor to resolve any deficiencies identified as a result of monitoring, audits, inspections, protocol deviations, or review of any other study documentation. Failure to take adequate remedial action can result in suspension or termination of the study at the site.

15. ETHICS

15.1. Ethics Review

The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of the participants. The study will only be conducted at study centers where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, Informed Consent Form, advertisements (if applicable), written information given to the participants (including diaries), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the Investigator.

The final study protocol, including the final version of the Informed Consent Form, must be approved or given a favorable opinion in writing by an IRB/IEC as appropriate. Written IRB/IEC approval must be received by the Sponsor or designee before a site can enroll any participant into the study.

The Investigator is responsible for informing the IRB/IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB/IEC must approve all advertising used to recruit participants for the study. The protocol (and other amended study documents) must be reapproved by the IRB/IEC upon receipt of amendments and annually, as local regulations require. The Investigator is also responsible for providing the IRB/IEC with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. The Sponsor will provide this information to the Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB/IEC according to local regulations and guidelines.

15.2. Ethical Conduct of the Study

The Sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, the ethical principles stated in the Declaration of Helsinki, and ICH GCP Guideline E6.

15.3. Written Informed Consent

The Investigator(s) at each center will ensure that the participant is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Participants must also be notified that they are free to discontinue from the study at any time. The participant should be given the opportunity to ask questions and allowed time to consider the information provided. This process should be recorded in the participant's source documentation.

An adult participant's signed and dated Informed Consent Form must be obtained before conducting any study procedures. A child participant's (< 18 years of age globally, < 16 years of age in the Netherlands and other applicable regions) signed and dated assent and the parent/guardian's signed and dated informed consent must be obtained before conducting any study procedures. Documentation of the consenting process must be recorded in the participant's source documents.

15.3.1. Consent Procedures and Documentation

The Investigator(s) must maintain the original, signed Informed Consent Form. A copy of the signed Informed Consent Form must be given to the participant, and this must be documented in the participant's source documents.

15.4. Confidentiality

In order to maintain participant privacy, all eCRFs, study drug accountability records, study reports, and communications will identify the participant by initials (as allowed by local regulations) and the assigned participant number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the participant's original medical records for verification of data gathered on the eCRFs and to audit the data collection process. The participant's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

16. DATA HANDLING AND RECORDKEEPING

16.1. Inspection of Records

All study data recorded on source documents are to be transcribed into the eCRFs. Any electronic study data are to be entered into a secure, validated data processing system and a backup maintained. Any changes to electronic study data will be documented.

16.2. Retention of Records

The Investigator will maintain all study records according to ICH GCP and applicable regulatory requirement(s). The Sponsor will inform all participating investigator sites of the data retention period applicable to the study, and when such data may be transferred or destroyed, in compliance with the applicable regulations and contractual agreements. If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. The Sponsor must be notified immediately by telephone or email and the notification confirmed in writing if a custodial change occurs.

16.3. Protocol Deviations

A protocol deviation is defined as an event in which the Investigator or site personnel or participant did not conduct the study according to this Protocol, including compliance requirements and agreements.

For any protocol deviation relating to individual participants, the event and relevant circumstances will be recorded on source documents and on the appropriate eCRF, reported to the Sponsor in a timely manner, and presented in the clinical study report.

Deviations that can be anticipated should, if possible, be discussed with the Sponsor before being implemented.

17. PUBLICATION POLICY

17.1. Publication and Data Sharing Policy

All information regarding the investigational product supplied by the Sponsor or designee to the Investigator is privileged and confidential information. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. It is understood that there is an obligation to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used toward the development of mavorixafor and may be disclosed to regulatory authorities, other Investigators, corporate partners, or consultants as required.

This study will be registered in a publicly accessible database before the recruitment of the first participant. Results from the study will be disclosed in the database and will include negative and inconclusive, as well as positive, results.

It is anticipated that the results of this study will be presented at scientific meetings and/or published in a peer-reviewed scientific or medical journal. A Publications Committee, comprising Investigators participating in the study and representatives from the Sponsor, as appropriate, will be formed to oversee the publication of the study results, which will reflect the experience of all participating study centers. Subsequently, individual Investigators may publish results from the study in compliance with their agreement with the Sponsor.

A prepublication manuscript is to be provided to the Sponsor at least 30 days prior to the submission of the manuscript to a publisher. Similarly, the Sponsor will provide any company-prepared manuscript to the authors for review at least 30 days prior to submission to a publisher.

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19. APPENDICES

19.1. Revision History and Sponsor Signature

Study Title	A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of Mavorixafor in Participants with WHIM Syndrome with Open-Label Extension
Protocol Number:	X4P-001-103
Protocol Version:	3.0
Date:	20 October 2021

The revision history is summarized in Table 12. Significant revisions made in each protocol version are provided in a separate Summary of Changes document.

Table 12: Protocol Revision History

Ver. No.	Date	Comment
1.0	24 April 2019	Initial submission to FDA
1.1	30 Jun 2020	Country Specific Protocol Amendment (Germany)
2.0	20 May 2020	Protocol Amendment 1
2.1	03 Aug 2020	Country Specific Protocol Amendment (UK)
2.2	13 Aug 2020	Country Specific Protocol Amendment (UK)
2.3	25 Aug 2020	Country Specific Protocol Amendment (Canada)
3.0	20 October 2021	Protocol Amendment 2

This protocol Version 3.0 has been prepared and approved by the Sponsor.