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.

Study Title:	A Phase 2, Open-Label, Multi-Center Trial of Mavorixafor in Patients with WHIM Syndrome
Investigational Drug:	Mavorixafor (X4P-001)
Phase	2
IND #:	129092
EudraCT#	2016-005028-26
ClinicalTrials.gov ID	NCT03005327
Sponsor:	X4 Pharmaceuticals, Inc. 61 North Beacon Street, 4th Floor Boston, MA 02134
Protocol Number:	X4P-001-MKKA
Protocol Version, Date:	Version 5.0, 21 December 2020 (US & Australia)
Replaces Version, Date:	Version 4.6, 10 April 2019 (US & Australia)

INVESTIGATOR STATEMENT

I understand that all documentation provided to me by X4 Pharmaceuticals, Inc. (X4), or its designated representative(s) concerning this study that has not been published previously will be kept in the strictest confidence. This documentation includes the study protocol, investigator 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 patient.

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

Abbreviation	Explanation
AE	Adverse event
AIDS	Acquired immune deficiency syndrome
ALC	Absolute lymphocyte count
ALT	Alanine transaminase
AMC	Absolute monocyte count
ANC	Absolute neutrophil count
AST	Aspartate transaminase
AUC	Area under the plasma concentration curve
BID	Twice daily
BP	Blood pressure
C_{max}	Maximum concentration
C_{min}	Minimum 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
DRC	Data Review Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
E_{max}	Maximum exposure
EOS	End-of-Study
EOT	End-of-Treatment
Gardasil®9, Gardasil 9	HPV 9-valent vaccine, recombinant
GCP	Good Clinical Practice
G-CSF	Granulocyte-colony stimulating factor
GM-CSF	Granulocyte macrophage-colony stimulating factor
GMP	Good Manufacturing Practice
HPV	Human papillomavirus
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IRB	Institutional review board
LFT	Liver function test
LQI	Life Quality Index

Abbreviation	Explanation
MM	Multiple myeloma
NCI	National Cancer Institute
NHL	Non-Hodgkin's lymphoma
NIH	National Institutes of Health
NOAEL	No observed adverse effect level
PBMC	Peripheral blood mononuclear cells
PD	Pharmacodynamic(s)
P-gP	P-glycoprotein
PHB	*p*-hydroxybenzoate salt
PK	Pharmacokinetic(s)
PT	Preferred term
QD	Once daily
SAE	Serious adverse event
SF-36	36-item Short Form Survey
SOC	System organ class
SUSAR	Suspected, unexpected serious adverse reaction
$T_{1/2}$	Half-life
TAT	Time above threshold
TDaP	Tetanus, diphtheria, and pertussis vaccine
TEAE	Treatment-emergent adverse event
T_{max}	Time to maximum concentration
TLT	Treatment-limiting toxicity
TMF	Trial master file
ULN	Upper limit of normal
WBC	White blood cell
WOCBP	Women of childbearing potential
WHIM	Warts, Hypogammaglobulinemia, Infections, and Myelokathexis

1. PROTOCOL SYNOPSIS

Study title	A Phase 2, Open-Label, Multi-Center Trial of Mavorixafor in Patients with WHIM Syndrome
Study number	X4P-001-MKKA
Sponsor	X4 Pharmaceuticals, Inc. 61 North Beacon Street, 4th Floor Boston, MA 02134
Phase	2
Planned study period (first enrollment-last patient out)	First patient in: Q1 2017 Expected last patient, last visit: Q1 2023 (study may end early if the product is commercially available or if the study is terminated by the Sponsor for any reason).
Study objectives	The primary objectives of the initial Treatment Period are: • To evaluate safety and tolerability of mavorixafor in patients with WHIM syndrome. • To assess the dose required to achieve a consistent increase in circulating neutrophils and lymphocytes in those patients. The objectives of the Extension Phase are: • To evaluate the safety of long-term treatment with mavorixafor. • To evaluate the efficacy of long-term mavorixafor treatment on infection rate, skin warts, vaccine titers, and neutrophil and lymphocyte counts.

Study design and plan	Protocol X4P-001-MKKA is a Phase 2 study with an initial 24-week Treatment Period and an Extension Phase. This study is designed to determine the safety, tolerability, and dose selection of mavorixafor for Phase 3 in patients with WHIM syndrome. Eligible patients will initiate treatment with mavorixafor at 50 mg once daily (QD) or a higher dose, with potential escalation based on area under the curve for absolute neutrophil count and absolute lymphocyte count ($AUC_{ANC/ALC}$) values to a maximum total daily dose of 400 mg. Additional twice daily (BID) dosing schedules may be explored but total daily dose will not exceed 400 mg daily. During the initial Treatment Period, patients will attend monthly office visits and will be monitored daily using an automated telephone- or web-based reporting system for temperature, activities of daily living, antibiotic usage, and unscheduled healthcare visits. Furthermore, patients will be admitted to a research unit at Weeks 5, 13, and 21 to permit collection of serial samples over 24 hours for determination of white blood cells (WBC), absolute neutrophil count (ANC), absolute lymphocyte count (ALC), absolute monocyte count (AMC), and plasma drug levels. In the event that a patient cannot return to the research unit, serial sampling may be done by a visiting nurse or by the patient's primary care physician. Patients may receive standard of care antibiotics in the event of infection, but may not receive routine extended prophylaxis with granulocyte-colony stimulating factor (G-CSF). In the event of an episode consistent with acute, severe bacterial infection, the Investigator may add *rescue therapy* consisting of a course of G-CSF (and/or immunoglobulin [Ig] therapy, if applicable) (see Section 7.4.4.2). During the initial Treatment Period, all available safety data will be reviewed approximately every 12 weeks by a Data Review Committee (DRC). After at least 4 patients have completed 24 weeks of treatment, the DRC will review all available data and make recommendations regarding the course of the study and the recommended Phase 3 dose. During the Extension Phase, the DRC will review data approximately every 6 months. During the Extension Phase, patients will have on-site visits every 6 months (±30 days) for the assessment of vital signs, safety laboratory tests, and pregnancy tests. In addition to evaluating safety, procedures every 12 months (±30 days) may include assessment of warts, ophthalmologic assessments, revaccination, and sampling for biomarkers including serum immunoglobulins, specific antibodies, and trough WBC, ANC, ALC, AMC, pharmacokinetics (PK), and quality of life evaluations. 24-hour serial ANC, ALC, AMC, and dense PK sampling are optional at these visits. Optional patient interviews may be conducted via

	telephone on an ad-hoc basis in the Extension Phase to gain insight about the patient's overall study experience and patient-reported perceived treatment effect. Subjects may also be asked to take part in optional pharmacogenetic research. Subjects who decline the pharmacogenetic research are eligible for the study if they meet all inclusion criteria and none of the exclusion criteria. The objective of the optional pharmacogenetic research is to assess how the genetic makeup of an individual affects his/her response to drugs, such as how CYP3A4*22 status may be associated with poor metabolism.
Planned number of patients	The maximum number of patients to be enrolled is up to 15 adult patients (aged ≥18 years).
Diagnosis and main inclusion criteria	Patients with a clinical diagnosis of WHIM syndrome must meet all of the following criteria to be eligible for study participation: 1. Be at least 18 years of age. 2. Has signed the current approved informed consent form. 3. Has a genotype-confirmed mutation of *CXCR4*. 4. Agree to use contraception as follows: • For women of childbearing potential (WOCBP), agree to use highly effective contraceptive methods from Screening, through the study, and for at least 4 weeks after the last dose of study drug (see Section 7.4.1.1 for the definition of non-childbearing potential). • For males, agree to use a condom with any WOCBP sexual partner from Day 1 of study treatment, through the study, and at least 4 weeks after the last dose of study drug. 5. Be willing and able to comply with this protocol. 6. Has confirmed ANC ≤400/µL *or* ALC ≤650/µL *or* both, where confirmation applies to each cell type separately and requires meeting the criterion on at least 2 independent blood samples collected over up to 14 days. ***Extension Phase.*** Any patients who complete the initial 24-week Treatment Period may continue to receive mavorixafor in the Extension Phase.

Exclusion criteria	Patients with any of the following will be excluded from participation in the study: 1. Has known systemic hypersensitivity to the mavorixafor drug substance or its inactive ingredients. 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 one or more of the following criteria: – A positive antibody test for hepatitis C virus, unless documented to have no detectable viral load on two independent samples. – A positive test for hepatitis B surface antigen. 5. Has, at Screening, safety laboratory tests meeting one or more of the following criteria: – Hemoglobin <8.0 g/dL. – Platelets <75,000/μL. – Creatinine >2.0 x the upper limit of normal (ULN). – Serum aspartate transaminase >2.5x ULN. – Serum alanine transaminase >2.5x ULN. – Total bilirubin >1.5x ULN (unless due to Gilbert's Syndrome, total bilirubin > 3.0x ULN and direct bilirubin > 1.5x ULN). 6. Has, within 2 months prior to Day 1, received Plerixafor (open-label or blinded) as treatment of WHIM Syndrome. 7. Has, within the 4 weeks prior to Day 1, had surgery requiring general anesthesia. 8. Has, within 2 weeks prior to Day 1, received any of the following treatments: – G-CSF or granulocyte macrophage-colony stimulating factor. – Immunoglobulin – Intravenous or subcutaneous (unless deemed necessary by the treating physician and after agreement from the Sponsor). – Corticosteroids (>10 mg prednisone equivalent per day).

	– Investigational therapies should be discussed with the Medical Monitor. 9. Is currently taking or has, within 2 weeks prior to Day 1, received any medication that is a strong inhibitor or inducer of cytochrome P450 (CYP) and/or P-glycoprotein. (see Sections 7.4.1.3 and 7.4.1.4). 10. Has, at the planned initiation of study drug, an uncontrolled and active infection (excluding warts), that has the potential to raise the ANC counts. 11. Has any other medical or personal condition that, in the opinion of the Investigator, may potentially compromise the safety or compliance of the patient, or may preclude the patient's successful completion of the clinical study.
Investigational Medicinal Product: dose/mode of administration/dosing schedule	The investigational agent is mavorixafor. Mavorixafor will be provided as 100 mg capsules. Previously, mavorixafor drug product was also available as a 25 mg hard gelatin capsule formulated with compendial pharmaceutical excipients. Mavorixafor is to be administered orally at a consistent time each morning (±2 hours) with no food or drink (except water) for at least 1 hr pre-dose and continuing for at least 2 hr post-dose. In the initial Treatment Period, 2 patients were treated at the initial proposed starting dose of 50 mg QD; this dose was determined to be a suboptimal dose. All subsequent patients received mavorixafor at a starting dose of 100 mg QD or a higher dose with potential escalation based on $AUC_{ANC/ALC}$ values to a maximum total daily dose of 400 mg. Additional BID dosing schedules may be explored but total daily dose will not exceed 400 mg daily. In the Extension Phase, all patients will receive mavorixafor; the dose will not exceed 400 mg daily. Dose-escalation may be continued during the Extension Period, if necessary, after prior approval from the Data Monitoring Committee, based on $AUC_{ANC/ALC}$ values, safety data, and review of clinical efficacy, up to a maximum dose of 400 mg daily.
Planned treatment duration per patient	Patients are expected to receive treatment for 24 weeks in the initial Treatment Period or until development of a treatment-limiting toxicity (see Section 5.7). In the Extension Phase, treatment may continue until commercial availability of mavorixafor or until the study is terminated by the Sponsor for any reason.

Efficacy Endpoints:	The primary endpoint of this study is the mean value of the AUC_{ANC} and/or AUC_{ALC} collected over a 24-hour period above clinically meaningful thresholds for the mavorixafor treated patients over 6 months. The ANC clinically meaningful threshold is defined as ANC ≥600/µL and the ALC clinically meaningful threshold is defined as ≥1000/µL.
	
	The exploratory endpoints are:
	
	• Time above threshold (TAT) of ANC, ALC, and AMC at different dose levels of mavorixafor, where:
	  • Time above threshold for ANC (TAT_{ANC}) is the time in hours over 24 hours during which the ANC is maintained above 500 cells/µL.
	  • Time above threshold for ALC (TAT_{ALC}) is the time in hours over 24 hours during which the ALC is maintained above 1000 cells/µL.
	  • Time above threshold for monocytes (TAT_{mono}) is the time in hours over 24 hours during which the monocytes count is maintained above the lower limit of normal corrected for age and sex per laboratory normal ranges.
	• Frequency and severity of infections, with diagnosis based on Investigator's clinical assessment and severity assessed as Grade 1 to 4 using National Cancer Institute Common Terminology Criteria for Adverse Events.
	• Number of warts – applicable only to patients with cutaneous warts at baseline, and comparing number at baseline to number at end of the Treatment Period.
	• Severity of genital warts – applicable only to patients with genital warts at baseline, and comparing number of lesions, size of largest lesion, and patient-reported morbidity at baseline to end of the Treatment Period.
	• Antibody levels following revaccination – applicable only to patients who were (a) previously administered approved vaccines, (b) found at baseline to have predefined sub-protective levels of antibody, and (c) agree to repeat administration of the vaccine after at least 12 weeks of treatment.
	• Frequency of events requiring rescue therapy (G-CSF and/or Ig).
	• Rate of infections.
	• Rate of hospitalization events as compared to baseline.

	• Circulating WBCs: – Absolute and fold change from baseline in total WBC counts, and in absolute numbers of lymphocytes, neutrophils, monocytes, and lymphocyte subpopulations cells. – Correlation of WBC, ANC, ALC, and AMC levels with plasma drug levels. • Ig and specific antibodies: – Changes from baseline in levels of total IgG, IgG subclasses, IgA, IgD, IgE and IgM. • Optional bone marrow aspirates (analyzed centrally by a blinded reviewer): – Change from baseline in cellularity. – Change from baseline in frequency of apoptotic cells. • Quality of life as assessed by the 36-item Short Form Survey, Life Quality Index, and HPV Impact Profile (if applicable), • Qualitative patient interviews conducted via telephone in the Extension Phase by a third party (optional) (see Section 7.1.5.3)
Statistical methods (includes sample size calculation)	**Sample Size:** Given the rarity of the disease under study, a traditional 3+3 dose escalation design was not selected. Alternatively, a small number of adult subjects (up to 15) will be treated with mavorixafor on an open-label basis, with safety data reviewed on an approximately every 12-week basis by the DRC. A sample size of up to 15 patients was considered adequate for the objectives of assessing safety, tolerability, and preliminary efficacy for planned Phase 3.

	Statistical Methods: All data collected in this study will be documented using summary tables, figures, and/or patient data listings. For continuous variables, descriptive statistics (number (n), mean, median, standard deviation, minimum and maximum) will be presented. For categorical variables, frequencies and percentages will be presented. For time-to-event variables, percentages of patients experiencing that event will be presented and median time to event will be estimated using the Kaplan-Meier method. As appropriate, a 95% CI will be presented. Graphical displays will be presented, as appropriate. For the primary efficacy endpoint, ANC and/or ALC will be analyzed as AUCs relative to pre-specified clinically meaning thresholds of 600/µL and 1000/µL, respectively. The 24-hour AUC will be calculated using the trapezoidal method with area above threshold being positive, and area below threshold, negative (see Section 10.4.2). Patients with AUC_{ANC} <2000 cell•hr/µL or AUC_{ALC} <5000 cell•hr/µL at the Week 5 or Week 13 evaluations will have mavorixafor daily dose increased up to a maximum total daily dose of 400 mg. Subsequent dose-escalations may be conducted in both treatment periods after prior approval from the Data Monitoring Committee, based on $AUC_{ANC/ALC}$ values, safety data and review of clinical efficacy, up to a maximum dose of 400 mg daily. Because ANC and ALC in WHIM patients are significantly impacted by acute infection, alone or with antibiotics, G-CSF, corticosteroids, epinephrine, or any other treatment that in the opinion of the investigator might impact cell counts, the planned in-residence stays should be delayed if necessary until therapy has been discontinued and the patient remained afebrile for at least 2 weeks. Sequential in-residence stays must be separated by at least 4 weeks and preferably 6 weeks. Planned in-residence stays should also occur no less than 14 days after any change of dose.
Schedules of events	The schedule of events is presented in Table 1-1 for the initial Treatment Period and in Table 1-2 for the Extension Phase.

Table 1-1: Schedule of Events –Initial Treatment Period

Procedure	Study Period / Visit											
		Initial Treatment Period[1]										
	Screen-ing[2]	Day 1	Week 2[3] (± 3D)	Week 3[3] (± 3D)	Week 4[3] (± 3D)	Week 5[4] (-7D/ +14D)	Week 9[3] (± 7D)	Week 13[4] (± 14D)	Week 17[3] (± 7D)	Week 21[4] (± 14D)	Week 25 (EOT) (± 7D)	EOS[5] [6]
Informed consent	X										X[6]	X[6]
General medical history	X											
History of WHIM syndrome	X											
Inclusion / exclusion criteria	X											
Genotyping for eligibility	X											
ANC and ALC for eligibility	X											
Serology	X											
Height	X	X				X		X			X	X
Body weight	X	X				X		X			X	X
Physical examination	X	X				X		X			X	X
Vital signs[7]	X	X	X	X	X	X	X	X	X	X	X	X
Safety laboratory tests[8]	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG[9]	X	X				X		X		X		
Ophthalmologic examination[10]	X							X			X	
Pregnancy test[11]	X	X[12]				X	X	X	X	X	X	X
Serial WBC, AMC, ANC, and ALC sampling (for time above threshold and AUC)[13]						X[14]		X		X		
Assessment of warts[15]	X	X				X		X[16]		X		

Procedure	Study Period / Visit											
		Initial Treatment Period[1]										
	Screen-ing[2]	Day 1	Week 2[3] (± 3D)	Week 3[3] (± 3D)	Week 4[3] (± 3D)	Week 5[4] (-7D/ +14D)	Week 9[3] (± 7D)	Week 13[4] (± 14D)	Week 17[3] (± 7D)	Week 21[4] (± 14D)	Week 25 (EOT) (± 7D)	EOS[5] [6]
Serum Ig and specific antibodies		X					X		X		X	
Revaccination								X				
Quality of life questionnaires		X		X		X	X	X	X	X	X	
PK and Biomarker Time 0 sample[17]		X					X		X		X	
PK dense sampling[17]						X		X		X		
Bone marrow aspirate *(optional)*[18]	X										X	
Study drug administration		X (Daily)										
Diary completion[19]		X (Daily)										
Concomitant medication monitoring	Continuous from Screening to EOS											
Adverse event monitoring	Continuous from Informed Consent to EOS											

Abbreviations: ALC=absolute lymphocyte count; AMC=absolute monocyte count; ANC=absolute neutrophil count; AUC=area under the curve; ECG=electrocardiogram; EOS=End-of-Study; EOT=End-of-Treatment; HR=heart rate; Ig=immunoglobulin; PK=pharmacokinetics; WBC=white blood cell count.

Note: Home-health visits are authorized if there are extenuating circumstances that would impede patients from coming to the study site for a scheduled visit. Requests for home health visits will 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.

1 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. Pre-and post-dose intervals are relative to the time of oral administration, designated 0 hr.

2 Screening Visit and Day 1 may be done during the same visit.

3 Depending upon patient situation the Week 2, 3, 4, 9 and 17 vital signs and blood draws could be done at either the study site or by a visiting research nurse in the subject's home.

4 In-residence visits are conducted at Week 5 + 14 days and Weeks 13 and 21 ±14 days. If a patient cannot return to the study site for an in-residence visit, a dense-sampling visit may be conducted by visiting research nurse or by the patient's primary care physician; however, in-residence visits at the study site are preferred. If a patient has their dose escalated during the Extension Phase, additional in-residence or dense-sampling visits may be conducted after the patient has received the escalated dose for at least 2 weeks. Additional in-resident or dense-sampling visits may also be conducted in the absence of dose escalation in order to collect additional data regarding a specific dose. Patients will have all of the same assessments conducted at the Weeks 5, 13 and 21 visits repeated at these additional in-residence or dense-sampling visit intervals.

5 The EOS visit is scheduled for 30 days ± 5 days after the last dose of study drug.

6 Patients may be considered eligible for the Extension Phase after the EOT or EOS visit; informed consent will be completed before entry into the Extension Phase.

[7] Vital signs comprise heart rate, blood pressure, and temperature. For patients dosed in clinic for PK dense sampling, vital signs will be performed and safety laboratory tests collected pre-dose.
[8] Safety laboratory tests – hematology and chemistry; see Section 7.2.1.1 for details. Safety laboratory tests may be conducted by a central or local laboratory.
[9] 12-lead ECG to be done pre-dose on Day 1 and at 2 hours post-dose during each in-residence dense PK sampling.
[10] Ophthalmologic examination – see Section 7.1.1.8 for details.
[11] Women of childbearing potential only.
[12] Women of childbearing potential (see Section 7.4.1.1 for definition) will have a urine or serum pregnancy test done at the site on Day 1 and the results obtained prior to dosing.
[13] Samples to be collected during an in-residence stay. See Section 7.1.4.1 for details of times for serial WBC, ANC, ALC, and AMC blood samples.
[14] WBC, ANC, ALC, and AMC performed by a Central Laboratory determined by the Sponsor.
[15] Wart assessment details are further described in Section 7.1.1.7.
[16] After consultation with the medical monitor, treatment with imiquimod to a sub-set of warts.
[17] See Section 7.1.2, and Section 7.1.3 for details of times and permitted variances for collection of PK and biomarker blood samples at time 0 and during dense sampling.
[18] Bone marrow aspirates are considered optional for this study (see Section 7.1.1.3).
[19] Daily diary for study drug administration, temperature, activities of daily living, antibiotic usage, and unscheduled healthcare visits for infection.

Table 1-2: Schedule of Events – Extension Phase

Procedure	Office Visits: Every 6 Months (±30 days)	Office Visits: Every 12 Months (±30 days)	End of Study (30 days ±5 days)
Body weight		X	X
Physical examination		X	X
Vital signs (HR, BP, temp)	X	X	X
Safety laboratory tests (Section 7.2.1.1)	X	X	X
Pregnancy test (WOCBP only)	X	X	X
Ophthalmological examination (Section 7.1.1.8)	X		
Mavorixafor metabolite assessment[1]		X[1]	
Trough WBC, ANC, ALC, AMC, and PK sampling		X	
ANC, ALC, and AMC sampling for time above threshold and AUC (*optional*) (Section 7.1.4.1)		X	
PK dense sampling (*optional*) (Section 7.1.2)		X	
Assessment of warts		X	
Serum Ig and specific antibodies		X	
Revaccination (*optional*) (Section 7.1.1.4)		X	
Biomarker Time 0 sample (Section 7.1.3)		X	
Study drug administration	Continuous		
Diary completion[2]	Continuous		
Concomitant medication monitoring	Continuous		
Adverse event monitoring	Continuous		
Quality of life questionnaires		X	
Pharmacogenetic sampling (optional)[3]	X[3]		
Qualitative patient interview conducted by a third party (optional) (Section 7.1.5.3)[4]	X[4]		
Research blood (optional)	X	X	

Abbreviations: ALC=absolute lymphocyte count; AMC=absolute monocyte count; ANC=absolute neutrophil count; AUC=area under the curve; BP=blood pressure; HR=heart rate; Ig=immunoglobulin; PK=pharmacokinetic; WBC=white blood cell; WOCBP=women of childbearing potential.

Note: Home-health visits are authorized if there are extenuating circumstances that would impede patients from coming to the study site for a scheduled visit. Requests for home health visits will 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.

1. A single sample will be obtained for evaluation of mavorixafor metabolites at the yearly visit (e.g., Month 12, 24, etc.), whichever occurs earliest for each patient after implementation of the v5.0 protocol amendment.
2. Daily diary for study drug administration, temperature, activities of daily living, antibiotic usage, and unscheduled healthcare visits for infection.
3. Optional assessment that may occur one time during the course of the study.
4. The qualitative patient interview can be performed by telephone at any time during the Extension Phase. For additional details see Section 7.1.5.3.

Table 1-3 Estimated Blood Volume - Initial Treatment Period

Tests	Vol (mL)	Scrn	Day 1	Study Week[2]							EOS	Total Vol (mL)
				2, 3, 4	5	9	13	Week 17	Week 21	Week 25 (EOT)		
WBC, ANC, ALC, and AMC Dense Sampling	2				20		20		20			60
Safety Laboratory Tests	8	8	8	24	8	8	8	8	8	8	8	96
Pharmacokinetic Samples[3]	2		2		22	2	22	2	22	2		74
Biomarker Samples	16		16			16		16		16		64
Pregnancy test (WOCBP only)[4]	0	0	0[5]		0	0	0	0	0	0	0	0
Serology	0	0										0
Serum Ig and Specific Antibodies	17		17			17		17		17		68
Total mL blood drawn		8	43	8/week	50	43	50	43	50	43	8	362

Abbreviations: ALC=absolute lymphocyte count; AMC=absolute monocyte count; ANC=absolute neutrophil count; EOS=End-of-Study; EOT=End-of-Treatment; Ig=immunoglobulin; PK=pharmacokinetics; WBC=white blood cell; WOCBP=women of childbearing potential.

1 The volumes shown are estimates; final volumes may vary, but will not be more than 15% greater than shown.

2 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.

3 See Section 7.1.2 for PK sampling times.

4 Pregnancy testing will be done at the central laboratory. Extra blood volume is not required.

5 Day 1 pregnancy test is done locally and may be performed on either a blood or urine sample.

Table 1-4: Estimated Blood Volume - Extension Phase

Tests	Vol (mL)	Office Visits: Every 6 months	Office Visits: Every 12 months	EOS	Total Vol (mL)
ANC, ALC, and AMC Dense Sampling (optional) (Section 7.1.4.1)	2		20		20
Safety Laboratory Tests (including trough WBC/ANC/ALC/AMC/pregnancy test/serology)	8	8	8	8	24
Trough PK sample	2		2		2
Serial PK Samples (optional) (Section 7.1.2)	2		22		22
Mavorixafor metabolite sample[1]	3		3[1]		3[1]
Biomarker Samples	16		16		16
Serum Ig and Specific Antibodies	17		17		17
Optional Research Blood (Section 7.1.4.3)	10[2]	10[2]	10[2]		10[2]
Total mL blood drawn		8	85[1]	8	101[1]

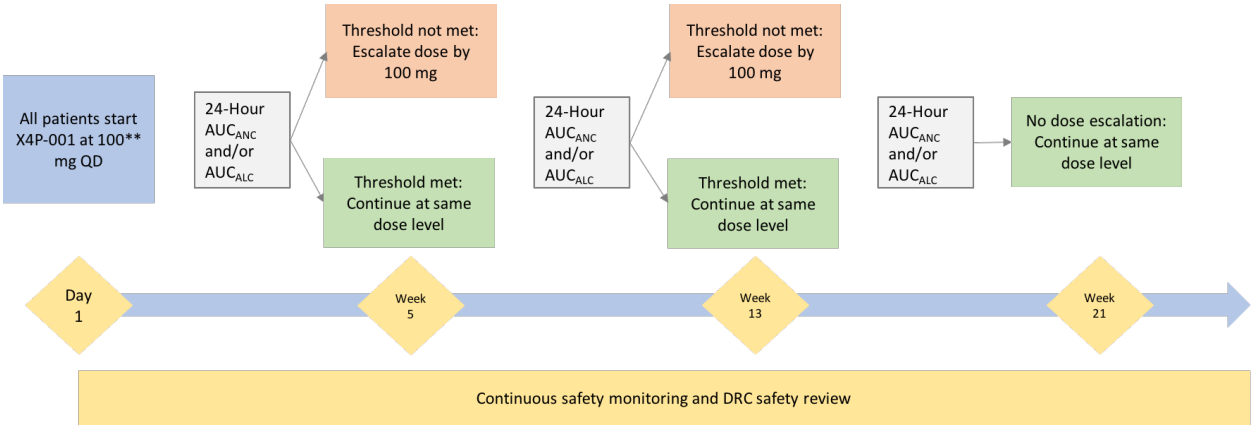
Abbreviations: ALC=absolute lymphocyte count; AMC=absolute monocyte count; ANC=absolute neutrophil count; EOS=End-of-Study; Ig=immunoglobin; PD=pharmacodynamics; PK=pharmacokinetic; WBC=white blood cell.
Notes: The volumes shown are estimates; final volumes may vary, but will not be more than 15% greater than shown. The total volume accounts for a 1-year period, one office visit for safety only and one more extensive office visit for safety, PK, and PD assessments at 6-month (±30 days) intervals to evaluate vital signs, safety laboratory parameters, and pregnancy tests) plus the EOS; amounts will be higher based on duration of participation.

[1] Optional serial dense sampling assessments blood volumes are included in the total blood volume estimate. A single 3 mL sample will be obtained for evaluation of mavorixafor metabolites at the yearly visit (e.g., Month 12, 24, etc.), whichever occurs earliest for each patient after implementation of the v5.0 protocol amendment. The total blood volumes do not show this 3 mL sample because it will occur only once in the study and not at every 12-month visit.

[2] For patients who consent to future research, blood may be collected and stored to better understand the immunological response in patients with WHIM syndrome. The total blood volumes do not show the research sample because it is optional. See Section 7.1.4.3.

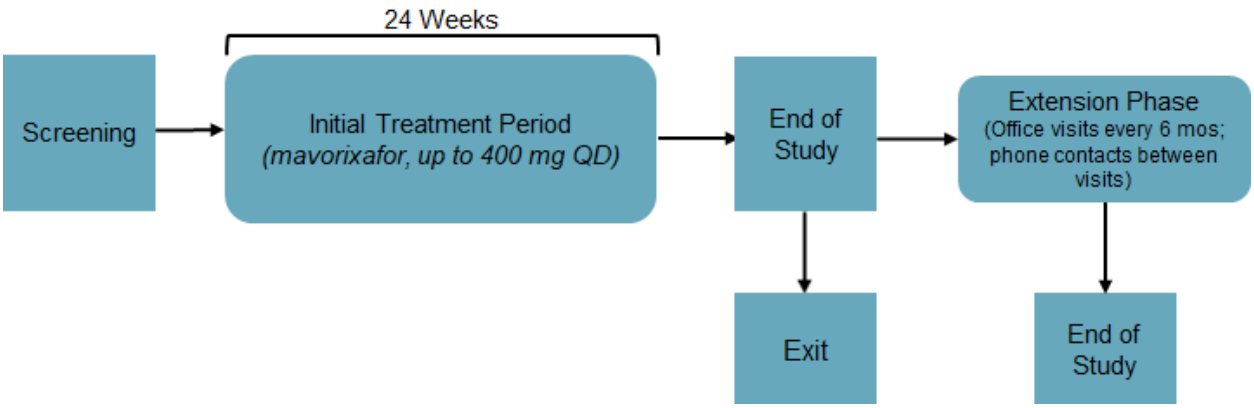
SCHEMATIC OF THE STUDY DESIGN

Figure 1-1: Dose Titration Strategy and Visit Schedule--Initial Treatment Period



Abbreviations: ALC=absolute lymphocyte count; ANC= absolute neutrophil count; AUC=area under the curve; DMC=Data Monitoring Committee; PD=pharmacodynamics; PK=pharmacokinetic; QD=once daily; SAE=serious adverse event.
Notes: Maximum daily dose not to exceed a total daily dose of 400 mg.
**In the initial treatment period, the first 2 patients were treated at the starting dose of 50 mg QD; this dose was determined to be a suboptimal dose as it did not increase ANC and ALC above pre-determined thresholds. All subsequent patients therefore received mavorixafor at a starting dose of at least 100 mg QD.
Based on the emerging safety PK and PD data, escalation may continue beyond the initial treatment period after approval from the DMC and even if patients meet the above-mentioned AUC threshold criteria to determine the Phase 3 dose that will provide the most consistent increase in circulating neutrophils and lymphocytes in the most number of patients. However, the maximum daily dose will be ≤400 mg. Patients who experience a ≥ Grade 3 treatment-related SAE will not be escalated.

Figure 1-2: Overall Study Design--Initial Treatment Period and Extension Phase



Abbreviations: AUCANC/ALC= area under the curve for absolute neutrophil count and absolute lymphocyte count; QD=once daily.
*Dose-escalations may be conducted in both treatment periods based on AUCANC/ALC values, safety data, and review of clinical efficacy, up to a maximum dose of 400 mg daily.

2. INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1. Background Information

WHIM (Warts, Hypogammaglobulinemia, Infections, and Myelokathexis) syndrome is exceedingly rare. The estimated incidence is 0.23 per million births, based on the identification of 8 patients in the French national registry (Table 5) [Beaussant-Cohen 2012]. WHIM syndrome is associated with significant morbidity and mortality [Beaussant-Cohen 2012].

In 1964, Zuelzer reported a young girl with severe non-cyclic neutropenia and frequent upper and lower respiratory tract infections. Of note, transient increases in circulating leukocytes had been observed during acute infection and were achieved experimentally following administration of bacterial endotoxin. The bone marrow demonstrated distinctive histopathological features, including dense hypercellularity and a predominance of hyper-mature neutrophils with highly condensed nuclear chromatin, increased segmentation, and cytoplasmic vacuoles [Zuelzer WW 1964]. Zuelzer hypothesized that in contrast to neutropenia associated with inadequate production, the mechanism here related to inappropriate retention of white blood cells in the bone marrow, and proposed the term myelokathexis. Subsequent studies demonstrated that in myelokathexis the marrow neutrophils have increased markers of apoptosis [Aprikyan 2000].

Based on clinical features noted in subsequent cases, the disease was designated WHIM syndrome [Al-Herz 2014]. In 2003 Hernandez and colleagues identified mutations in *CXCR4* (C-X-C chemokine receptor type 4) in patients with WHIM syndrome from 6 different pedigrees [Hernandez 2003]. The characteristic feature was frameshift or nonsense mutation that resulted in truncation of 10 to 19 amino acids from the C-terminus representing the cytoplasmic domain. Similar alternations were absent from >200 controls. The cognate ligand for CXCR4 is CXCL12 (also referred to as SDF-1α), which is constitutively expressed on bone marrow stromal cells and appears to cause direct and indirect cellular adhesive interactions, leading to retention of myeloid cells in the marrow [Gulino 2004]. A cell-line expressing CXCR4 from a WHIM patient demonstrated markedly increased and prolonged intracellular signaling in response to CXCL12 compared to wild type CXCR4, suggesting that the mutation could confer a pathologic response to a physiologic stimulus. Subsequent in vitro studies document impaired interactions among T cells and B cells from patients with WHIM syndrome, defining additional aspects of a broad primary immunodeficiency [Kallikourdis 2013].

In 2012, Cohen et al. published a summary of 51 previously reported cases plus 8 additional cases from the French Severe Chronic Neutropenia Registry [Beaussant-Cohen 2012]. Their report emphasized several distinctive features with manifestations differing across individual patients (Table 5). The findings from this literature review are further substantiated by the results from a recently published review of the literature that identified and analyzed 105 published cases of WHIM syndrome [Heusinkveld 2019]. Note that some of these 105 cases overlap with the patients identified in the aforementioned literature search. The literature review for all 105

patients [Heusinkveld 2019] included 62 females (59%), 41 males (39), and 2 individuals whose gender was not reported. The distribution of the patient population comprised 50% pediatric and 46% adult patients. The pediatric age distribution included 6 infants and 47 children (ages 1 to18 years) and 4 (4%) individuals whose age was not reported, while the adult population included 48 individuals. Finally, the literature provides 5 case reports of WHIM patients treated with hematopoietic stem cell transplant. Only 40 (38%) of the 105 cases presented all 4 classic manifestations of the WHIM tetrad, while other patients presented variable combinations of symptoms, including those outside of the WHIM tetrad. Warts affected 58 (55%) of WHIM patients.

Table 5: Reported Clinical Characteristics of Patients with WHIM Syndrome

Characteristic	Reported Cases 1964-2012 (N=51)	French Registry Cases (N=8)	Overall Frequency	Comment
Alive at last report	48	6	92%	
Age at last report				
≤17 yr	24	3	55%	
18-40 yr	17	2	30%	
41-76 yr	7	1	15%	
Died – age, cause	31 yr – meningitis 26 yr – lymphoma 54 yr – lymphoma	39 yr – metastatic vulvar cancer 41 yr – lymphoma c/b dissem atypical mycobacteria	8%	1/5 deaths due to infection 4/5 deaths were due to malignancy
CXCR4 mutation	42/44[1]	7/8	94%	2 patients were directly related
Myelokathexis	34/35	8/8	98%	The patient wo/ myelokathexis had typical R334X mutation
Warts	31/50	5/8	62%	
IgG <600 mg/dL	22/34	3/6	63%	
IgM <40 mg/dL	7/34	3/6	25%	
ANC <500/µL[2]	31/45	7/8	72%	
ALC <500/µL	7/29	7/8	38%	
Infections[3]				
PNA & bronchiectasis	3/46	4/8	13%	Age, median, 41 (range: 10-76)
PNA	27/46	–	50%	
Other respiratory[4]	9/46	–	17%	
Non-respiratory[5]	5/46	3/8	15%	
None	2/46	1/8	6%	

Abbreviations: ANC=, absolute neutrophil count; ALC=, absolute lymphocyte count; IgG=immunoglobulin G; IgM=immunoglobulin M; PNA=pneumonia; WBC=white blood cell.

1. Denominator represents number of patients for whom characteristic was reported as present or absent.
2. ANC was <1,500/µL for all 53 patients with at least one reported value. WBC counts in WHIM patients can be transiently elevated by acute infection, and patient status at the time lab data were obtained was often unclear.
3. Infection categories are hierarchical and mutually exclusive, emphasizing respiratory tract infection.

4. Other respiratory, either upper respiratory infection only or respiratory, not further specified.
5. Non-respiratory: cellulitis (2), enteritis (2), and one each, osteitis, phlegmon, urinary tract infection, and "numerous."

The most informative laboratory assessments in patients with WHIM syndrome are prospective baseline data from 9 patients studied over the course of one or more days from 4 published treatment studies [Dale 2011; McDermott 2011; McDermott 2014; McDermott 2019]. The key observations from those reports include:

- Absolute lymphocyte counts (ALC) nadir was 350-500/mm^3 with diurnal variation giving peak values of up to 900/mm^3. Such variation is consistent with observations in normal subjects [Suzuki 1997].
- Absolute neutrophil counts (ANC) were <100 to 250/mm^3, with some variation.

For these reasons, patients in this study are required to enter a research unit for a 24-hour pharmacokinetic (PK) and ANC/ALC assessment and resulting area under the curve (AUC) calculation (see Section 4.1). Overall, the clinical observations support the following key conclusions:

- The most common mutation (R334X), seen in 15 (56%) of 27 pedigrees, is c1000C>T (CXCR4^{R334X}) resulting in a nonsense codon at amino acid 334 and truncation of the 19 C-terminal residues.
- Among 54 patients with sequencing data for *CXCR4* as well as clinical features of WHIM syndrome, mutations were found in all but one pedigree (2 individuals). Those patients may have other defects in *CXCR4* or in signaling pathways that produce a similar phenotype [McDermott 2010].
- Onset of clinical symptoms of disease is usually in early childhood, marked by an increase in the frequency and severity of bacterial infections.
  - At presentation, most patients (78%, 14/18) experience a severe bacterial infection requiring hospitalization and intravenous antibiotic therapy [Dotta 2019].
  - As noted, patients with WHIM syndrome typically have severe neutropenia (ANC <200/µL). However, patients with WHIM syndrome appear to have a lower incidence of severe, life-threatening acute infections than patients who have similar counts associated with impaired neutrophil production. This is consistent with the observation that during acute infection, circulating white blood cell (WBC) counts can increase, presumably reflecting delayed release by other mechanisms.
  - 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 pathogens. Of note, 6 (27%)

of all 22 reported patients over 21 years of age had progressed to bronchiectasis contributing to the morbidity of the disease [Beaussant-Cohen 2012].

  - Other common infections include the upper respiratory tract (otitis media, sinusitis) and skin and underlying tissue (cellulitis, impetigo, folliculitis, and abscess); less common sites include joints (septic arthritis), gums (periodontitis), bone (osteomyelitis), urinary tract, and central nervous system (meningitis) [Tassone 2009].

- A unique and specific consequence of the immune disorder in WHIM syndrome is the inability to control human papilloma virus (HPV) infection, with some patients presenting with hundreds of HPV-induced warts, including cutaneous and genito-anal lesions. Cutaneous warts typically develop in mid-childhood between 5 and 10 years of age and are first noted on the hands and feet, whereas genital warts usually emerge in young adulthood after sexual debut. Morphology may range from flat warts to classic verruca to anogenital *condylomata acuminata* [Heusinkveld 2017]. Warts are treatment-refractory, and ano-genital warts are at high risk of malignant transformation [Beaussant-Cohen 2012; McDermott 2019] and contribute to the overall mortality of the syndrome. Severe herpes virus infections (including varicella zoster virus, herpes simplex virus type 1 [HSV-1], and herpes simplex virus type 2) were reported in over 10% of patients.
- The most common malignancy was lymphoma. In addition to the 3 fatal cases, there was a fourth patient with lymphoma alive (age 40) at last report. Of the 4 cases, 2 were noted to be Epstein-Barr virus-positive and one, Epstein-Barr virus-negative.
- Patients with WHIM syndrome may also have congenital malformations including Tetralogy of Fallot [Badolato 2012]. Cerebellar malformation with mild neuromotor deficits and psychopathological dysfunction [Galli 2019] add to overall disease morbidity.
- Treatment Experience – Immunoglobulin (Ig), granulocyte-colony stimulating factor (G-CSF) and antibiotic prophylaxis. Finally, because of the lack of effective therapies and the severity of the disease, a number of hematology teams in the United States and abroad have proposed hematopoietic stem cell transplantation as a viable treatment intervention for WHIM syndrome [Bhar 2015; Bies 2019; Dale 2020; Kriván 2010; Moiseeva 2019].

Case reports since the mid-1990s have described administration of G-CSF and Ig (intravenously or subcutaneously) with the goal of preventing or modulating infection. G-CSF consistently increases peripheral ANCs, but has little, if any, impact on lymphopenia. The clinical effect has been highly variable; among the 4 patients in the French registry treated with G-CSF, 3 were reported to show little benefit [Beaussant-Cohen 2012]. In addition, treatment-limiting complications, including bone pain, have been described [Amgen, Inc., 2015].

Immunoglobulin, as expected, raises Ig levels, but has no impact on circulating leukocytes. It has appeared to be helpful in young children, but long-term effectiveness has not been demonstrated. Although Ig replacement improves hypogammaglobulinemia and may be thought to be clinically beneficial, some treated patients still suffer recurrent infections, possibly because this treatment has no effect on associated monocytopenia or lymphopenia. Finally, warts remain refractory to all treatments including surgical resection [Badolato 2017].

2.1.1. Treatment Experience – Plerixafor

Plerixafor is a CXCR4 antagonist marketed as Mozobil® and is approved for treatment at 0.24 mg/kg actual body weight in combination with G-CSF for up to 4 consecutive days to mobilize hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with non-Hodgkin's lymphoma (NHL) and multiple myeloma (MM). Plerixafor has not been approved by any regulatory agency for treatment in WHIM patients or for long-term use. Investigational studies conducted by Dr. David Dale at the University of Washington and by Dr. David McDermott at the National Institutes of Health (NIH) in patients with WHIM syndrome have demonstrated that plerixafor at low doses can increase circulating levels of both neutrophils and lymphocytes [Dale 2011; McDermott 2011; McDermott 2014; McDermott 2019]. These studies provide proof-of-concept for the treatment of WHIM patients with a CXCR4 antagonist. This off-label treatment is not available to patients outside of a clinical trial [NCT00967785].

In 2 single dose, dose-escalation studies involving 9 patients with severe neutropenia and lymphopenia, typically with ANC <200/µL and ALC <500/µL, prior to treatment [McDermott 2011; McDermott 2014], single doses of plerixafor as low as 0.02 mg/kg (8% the approved dose) were highly effective at mobilizing neutrophils, lymphocytes (including all subpopulations), and monocytes from the bone marrow into the circulation (Table 6). Lymphocytes, especially B cells (CD19+), had the greatest relative increases. The duration of the effect was dose-dependent and also was consistent with the short half-life ($T_{1/2}$) of plerixafor (~5 hrs), supporting chronic dosing. All of these observations support the hypothesis that the mutations of *CXCR4* render the receptor hyper-reactive to its ligand and that modest levels of an effective antagonist can have a salutary effect.

Table 6: Estimated Changes in WBC in Patients with WHIM Syndrome during Treatment with Plerixafor[1]

Reference	N	Condition	Total WBC (10^6 / µL)	ANC (10^6 / µL)	ALC (10^6 / µL)	Notes
Dale, 2011	6	Baseline	900	250	410	
		Peak after 0.02 to 0.24 mg/kg	11.6x	8.2x	14x	incr B cells, 40x
McDermott, 2011	3	Baseline	1,102	150	350	
		Peak after 0.02 mg/kg	4,455	821	3,564	
		Peak after 0.16 or 0.24 mg/kg	8,100	2,310	4,696	incr CD4, 6.7x; incr CD8, 4.5x, incr CD19, 40x
McDermott, 2014	3	Baseline	~750	~150	350 – 900[2]	Same 3 patients as Dale 2011
		Peak after 1st dose 0.02 mg/kg	~3,000	250 – 600	~2,500	
		After 6 mo. 0.02 mg/kg BID				
		Post-dose peak	~4,000	600 – 1,700	~2,500	
		Post-dose trough	~2,000	400 – 800	~900	

Abbreviations: ALC=absolute lymphocyte count; ANC=absolute neutrophil count; BID=twice daily; WBC=white blood cells.

1. Data are presented differently in each report. In some instances, results shown have been read from graphs or calculated based on reported changes from baseline. For Dale 2011 and McDermott 2011, results shown represent mean counts or mean fold increases from baseline, as indicated. For McDermott 2014, results shown represent midrange of multiple values presented for each condition, with variability both within and among patients.
2. McDermott 2014 presents multiple pre-treatment values over 48 hrs showing diurnal variation with morning troughs <350/µL in all patients. Such variation is consistent with observations in normal subjects [Suzuki 1997].

Chronic administration of plerixafor is hampered by the fact that it has to be given by subcutaneous injection and has a very short $T_{1/2}$ of ~5 hrs. Additionally, as detailed above, the approved label (for MM and NHL indications) provides for up to 4 consecutive days of dosing in combination with G-CSF. During the investigational NIH dose-escalation study [McDermott 2011] conducted in 3 patients (ages 30 to 51 years) who self-administered plerixafor at 0.01 or 0.02 mg/kg twice daily (BID) for 6 months [McDermott 2014], both G-CSF and intravenous Ig were stopped. While there were quantitative differences among the leukocyte responses, several common themes emerged:

- The most profound and immediate response was an increase in ALC, particularly B cells (CD19+, CD27–, IgM+). This response was observed over months of treatment, but levels oscillated daily, with ALC peaking at 3 hr post-dose and returning to near baseline by 12 hr, prior to the next dose.
- In contrast, initial increases in ANC were modest, but levels became higher and more persistent with sustained treatment.

- Safety laboratory monitoring of hemoglobin, platelets, and liver function tests (LFTs) throughout the 6 months of treatment revealed no pattern of adverse effects.

When treatment with plerixafor was stopped at 6 months, circulating WBC counts approached baseline at variable rates ranging from 2 days to 35 days following the last dose, ranging from 20% to 80% above WBC baseline values. This post-treatment effect may relate to the observation that bone marrow aspirates at 6 months had areas of normal cellularity.

During the 6 months of treatment with plerixafor, each of the 3 patients had decreased frequency and morbidity from systemic infection compared to their pre-treatment experience. After treatment was discontinued for two to six months, patients appeared to return to their baseline pattern, indicating the need for chronic, life-long therapy. All patients entered the study with persistent warts unresponsive to the usual medical treatments. The first patient showed no improvement in their warts over the initial 4 months of plerixafor. Topical therapy with imiquimod (previously ineffective) was then added with good response not only at the lesions treated but at contralateral lesions as well, suggesting "an induced systemic anti-HPV immune response" [McDermott 2014]. The other 2 patients were treated with imiquimod and plerixafor and also showed improvement in their warts.

These proof-of-concept data suggest that treatment with a CXCR4 antagonist can improve both circulating leukocyte levels and clinical manifestations associated with WHIM syndrome and support the current study design of mavorixafor for the treatment of patients with WHIM syndrome.

2.2. Overview of Mavorixafor

Mavorixafor was previously under development for the treatment of HIV infection based on the role of CXCR4 in viral entry into the cell. That program, which is presented in detail in the Investigator Brochure, included nonclinical toxicology studies and clinical studies using the free base formulation, then designated AMD11070 (mavorixafor hereafter).

Throughout the prior clinical development program, the drug product used was capsules containing 100 mg of the free base. Lower dose capsules of 25 mg of the free base formulation have been used in the Dose-Escalation phase of the X4P-001-MKKA study. However, in the extension phase only 100 mg capsules will be used (see Section 6.1.2).

2.2.1. Prior Clinical Studies Conducted Using Mavorixafor

There is no prior clinical study experience with mavorixafor in patients with WHIM syndrome.

The 4 clinical studies conducted under the prior development program included Phase 1 and 2a studies involved a total of 55 healthy volunteers [Cao 2008; Nyunt 2008] and 16 HIV-infected patients [Moyle 2009; ACTG (DIAIDS) Protocol A5210]. Table 7 shows the protocol numbers, titles, and related publications; Table 8 summarizes the study populations, objectives, numbers, dose administered, and duration. These studies demonstrated the following:

- Oral administration of up to 400 mg BID for 3.5 days (healthy volunteers) and 200 mg BID for 8-10 days (healthy volunteers and HIV patients) was generally safe and well-tolerated with no pattern of adverse events (AEs) or clinically significant laboratory changes.
- $T_{1/2}$ of mavorixafor is ~23 hours, supporting the use of once daily (QD) dosing (see Investigator's Brochure).
- Pharmacodynamic activity, as assessed by increases in circulating WBC, was related to dose and duration of treatment.

Table 7: Prior Clinical Studies Conducted Using Mavorixafor – Protocol Number, Study Title, and Publication[1]

Protocol No.	Study Title	Publications
A5191	A Phase I, Dose-Rising Study of AMD11070 in HIV-Seronegative Men to Assess the Safety and Pharmacokinetics After Single or Multiple Doses	Stone 2007; Cao 2008
AMD-1001	Multicenter, dose-finding safety and activity study of AMD11070 in HIV-infected patients carrying X4-tropic virus	Moyle 2009
AMD-1002	A Study of the Pharmacokinetic Interaction between AMD11070 and Substrates of CYP 3A4 and 2D6 Enzymes in Healthy Volunteers	Nyunt 2008
ACTG A5210	Phase IB/IIA Dose-Finding Safety and Activity Study of AMD11070 (An Orally Administered CXCR4 Entry Inhibitor) in HIV-Infected Subjects	Johnson 2019

[1] All studies were conducted between 3 Sep 2003 and 13 Jul 2006.

Table 8: Prior Clinical Studies Conducted using Mavorixafor – Study Population, Objectives, and Exposures

Study ID	Study Population	Study Objective	Cohort (A5191 only)	N	Gender M/F[2]	Dose & Regimen (All oral)	Duration
A5191[1]	Healthy Volunteers	Dose escalation: Safety, PK	A-D	12[1]	43 M, 0 F[a]	Single Dose 50 to 400 mg	1 day
			F, G, I	18[1]		100 to 400 mg, BID	3.5 days (7 doses)
		Effect of food, of ritonavir	H, J, K	32[1]		≤3 doses, 200 mg or 400 mg each	≤3 doses over 6 to 17 days
A5210	HIV-infected	Safety Viral load reduction		6	3 M, 3 F	200 mg, BID	10 days
AMD-1001	HIV-infected	Safety Viral load reduction		10	9 M, 1 F	100 mg, BID (N=2) 200 mg, BID (N=8)	10 days
AMD-1002	Healthy Volunteers	Safety Drug-drug interaction		12	9 M, 3 F	200 mg, BID	8 days

Abbreviations: BID=twice daily; F=female; ID=identification; M=male; PK=pharmacokinetic(s).

1. Study A5191 enrolled 10 cohorts totaling 68 subjects representing 43 unique individuals. There were 3 subjects in each of the 4 single dose escalation cohorts (A-D) and 6 subjects in each of the 3 multiple dose escalation cohorts (F, G, I). No subject was enrolled in more than one of the dose escalation cohort.
2. Within each study the median age was ~40 years; overall age range was 19 to 58 years.

2.2.2. Clinical Pharmacology of Mavorixafor

2.2.2.1. Clinical Pharmacokinetics

In the 4 previous clinical studies conducted by AnorMed and NIH (Studies AMD1001, AMD1002, A5191, and A5210) using the freebase formulation in normal healthy volunteers and patients with HIV. Drug was administered orally in all studies; multiple dose studies were conducted using BID dosing. In single and multiple dose escalation studies, maximum concentration (C_{max}) and AUC increased more than dose-proportionally over 50 - 400 mg dose range. Mean terminal $T_{1/2}$ was 22.9 hr, supporting the QD dosing regimen.

After administration of a single dose of mavorixafor at 50 mg under fasted conditions, the PK parameters of mavorixafor are:

- Mean C_{max}: 134
- Mean AUC_{0-24}: 227 ng•hr/mL
- Mean AUC_{inf}: 235 ng•hr/mL
- Median T_{max}: 1.5 hr

Steady-state PK parameters were similar in healthy volunteers (AMD-1002) and in HIV infected patients (A5210 and AMD-1001). The results (mean ± SD) were derived from 26 subjects, including both healthy volunteers and HIV-infected subjects, who received mavorixafor at 200 mg BID for 8 to 10 days.

- AUC_{0-12hr}: 3735 ± 1755 ng•hr/mL
- C_{max}: 1223 ± 600 ng/mL
- Minimum concentration (C_{min}) at 12 hours: 74.3 ± 47.3 ng/mL
- Time to maximum concentration (T_{max}): 2.2 ± 0.9 hr

For 13 subjects, daily $C_{min(trough)}$ concentrations were determined. Overall, subjects reached steady state by Day 6, which is consistent with the $T_{1/2}$ of ~23 hr. Further, C_{min} and AUC_{0-12} were strongly correlated suggesting that monitoring C_{min} may provide a practical means for assessing drug exposure.

X4P-001-REGA study was a phase I study in 15 healthy volunteers comparing two different dosing regimens: 200 mg BID and 400 mg QD (10-day treatment). The study was prematurely discontinued on Day 3 due to an insufficient number of patients remaining on the trial to assess

the statistical endpoints. In this study, PK samples were collected from 0-12 hr for BID dosing and 0-24 hr for QD dosing. Preliminary PK results are listed below.

Following administration of mavorixafor 200 mg BID and 400 mg QD on Day 1, the mean C_{max} were 1070 ng/mL and 2662 ng/mL, respectively; the median T_{max} were 2.5 hr and 1.5 hr respectively. AUC_{0-12} was 3682 ng•hr/mL after 200 mg BID dose and AUC_{0-24} was 9421 ng•hr/mL after 400 mg QD dose. Comparing with results from Study A5191, the exposure in REGA study is higher.

2.2.2.2. Effect of Food on Absorption

In a food-effect study (A5191), 9 male subjects received mavorixafor in the fasted stated (fasting overnight after midnight until 2 hours post-dose) and in the fed state (low fat meal within 30 minutes prior to dosing), food had a significant negative effect on the bioavailability of mavorixafor. C_{max} and AUC_{0-12} in the fed state was 0.33x and 0.44x of that observed in the fasted state, respectively. T_{max} was delayed from 1 hr (fasted) to 3 hr (fed). $T_{1/2}$ was not changed.

2.2.2.3. Potential for Drug-Drug Interactions

Two clinical studies were conducted to assess the potential for drug-drug interactions. Ritonavir (a strong CYP3A4 inhibitor, P-glycoprotein [P-gp] inhibitor) resulted in a modest increase in mavorixafor plasma concentrations [A5191, Cao 2008]. The mean C_{max} and AUC of mavorixafor coadministered with the first dose of ritonavir were increased by 39% and 60%, respectively, compared to the administration of mavorixafor alone. Similar effects were seen after ritonavir had been administered BID for 14 days.

Study AMD-1002 assessed the effect of mavorixafor on metabolism of CYP3A4 and CYP2D6 substrates, using midazolam and dextromethorphan as substrates [Nyunt 2008]. Administration of mavorixafor had the following effects.

- The C_{max} for midazolam (a CYP3A4 substrate) was unaffected; AUC was 1.33x baseline.
- The C_{max} for dextromethorphan (a CYP2D6 substrate) was 2.5x baseline; the AUC, 2.86x.

The magnitude of the midazolam interaction was modest. The magnitude of the effect on dextromethorphan has significant potential to result in changes in clinical drug response, affecting either efficacy or toxicity. The clinical study protocols include detailed restrictions on concomitant medications to minimize the potential for drug-drug interactions.

Mavorixafor appeared to be a substrate of P-gp with an efflux ratio of 14. Inhibitors or inducers of P-gp may affect the concentration of mavorixafor in plasma or the distributions to tissues that express a high level of P-gp.

2.2.2.4. Clinical Pharmacodynamics

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 [Stone 2007]. After dosing, circulating WBC counts increased from baseline in all subjects, peaking between 2 and 4 h following dosing. The distribution of concurrent WBC-fold change from baseline versus drug concentration best fit a sigmoid maximum exposure (E_{max}) model.

- The estimated E_{max} was WBC increase to 2.03x baseline (95% CI, 1.95x to 2.11x).
- The estimated half maximal effective concentration was 39 ng/mL (95% CI, 28 to 50 ng/mL), which is below the observed steady-state $C_{min(12h)}$ for mavorixafor at 200 mg BID, the starting dose in the proposed oncology studies.

2.2.3. Clinical Safety Experience with Mavorixafor

2.2.3.1. Safety Experience – X4 Pharmaceuticals Clinical Development Program

As of 14 May 2020, the following studies have been initiated or completed:

- X4P-001-RCCA – a Phase 1/2 study of mavorixafor alone and in combination with Axitinib in patients with advanced renal cell carcinoma.
- X4P-001-RCCB – a study adding mavorixafor to patients receiving nivolumab for treatment of advanced clear cell renal cell carcinoma.
- X4P-001-MELA – a Phase 1b study of mavorixafor alone and in combination with pembrolizumab in patients with advanced melanoma.
- X4P-001-REGA – a Phase 1 study in healthy volunteers comparing 2 different dosing regimens of mavorixafor: 200 mg BID versus 400 mg QD.
- X4P-001-MKKA – a Phase 2 trial of mavorixafor in patients with WHIM (Warts, Hypogammaglobulinemia, Infections and Myelokathexis) Syndrome.
- X4P-001-103 – a blinded randomized study against placebo controlled Phase 3 trial of mavorixafor in patients with WHIM Syndrome.

Please refer to the current Investigator's Brochure for more information related to mavorixafor's clinical safety data.

2.2.3.2. Safety Experience – Prior Development Program

As of 14 May 2020, 194 patients were treated with mavorixafor in 10 clinical studies (n= 70 healthy volunteers, n= 16 HIV, n= 99 oncology, n= 9 WHIM syndrome). Section 2.2.3.2 summarizes the safety of the healthy volunteers and patients with HIV and Section 2.4 summarizeds the safety of ongoing WHIM and oncology studies.

An X4-sponsored study in 15 healthy volunteers has been completed (X4P-001-REGA). Further, under the prior development program (sponsored by AnorMed), 4 clinical studies were conducted with mavorixafor (then designated AMD-11070): AMD-1001, AMD-1002, A5191,

and A5210. Overall, these 5 studies involved a total of 70 healthy volunteers (Studies X4P-001-REGA, A5191, and AMD-1002) and 16 HIV-infected subjects (Studies AMD-1001 and A5210).

- The most common clinical treatment-emergent adverse events (TEAEs) across these 5 studies were in the gastrointestinal disorders system organ class (SOC). Across all studies, most of the events were mild and of brief duration; events such as diarrhea and nausea were typically assessed as moderate primarily because they were treated with routine medications.
- Furthermore, headache was reported in all studies. The events of headache were typically mild or moderate in severity and short-lived.
- Prompted by observations in the nonclinical toxicology studies in dogs, a detailed by subject analysis of clinical AEs related to the liver was performed. Across the studies, only 1 AE related to the liver was reported ("tender hepatomegaly"). This event occurred in an HIV-infected subject and was assessed as unrelated to study drug. The subject had pre-treatment transaminase levels 1.3× to 2.3× the upper limit of normal (ULN); these decreased to within normal limits during treatment. Total bilirubin was within normal limits during the entire study.
- There were no deaths and no discontinuations due to AEs. Two subjects discontinued for personal reasons after receiving 1 or 2 doses of mavorixafor.
- There was 1 serious adverse event (SAE), a grand mal seizure in a subject with a history of epilepsy; there were no events of seizure reported in other subjects. This SAE was the only clinical AE assessed as severe (Grade 3).
- There was one other clinically notable AE. A subject with baseline bradycardia experienced an episode of syncope upon standing rapidly. The episode resolved promptly without lying down. There were no events of syncope reported in other subjects.
- There were no laboratory abnormalities assessed as clinically significant. The primary treatment-related laboratory abnormalities observed were the pharmacologically expected increase in circulating neutrophils and lymphocytes. Treatment-emergent elevation in lipase was observed in one asymptomatic patient; the source of the enzyme (pancreas or salivary glands) was unclear.
- A detailed by-subject analysis of abnormal LFTs revealed no pattern of treatment-emergent LFT abnormalities suggesting a drug effect.

2.2.4. Treatment Effect of Mavorixafor in Prior Clinical Studies

There are no prior clinical studies of mavorixafor in patients with WHIM syndrome.

2.2.5. Nonclinical Toxicity Studies of Mavorixafor

Pivotal nonclinical toxicity studies were conducted in rats and Beagle dogs with mavorixafor administered orally in divided doses, BID. The no observed adverse effect level (NOAEL) in the 4-week rat study was 125 mg/kg/day. Adverse effects at 250 mg/kg/day included decreases in food consumption, body weight, and reticulocyte counts and minimal bone marrow hypocellularity; all except body weight were resolved following a 14-day recovery period.

The dose levels in the 13-week toxicity study in dogs were 10, 20, 35, and 70 mg/kg/day. Microscopic liver findings of pigment deposition and inflammation were reported in all dose groups and across males and females; these findings were typically assessed as minimal and not associated with histopathologic findings of necrosis or with LFT changes. The NOAEL (<10 mg/kg/day) reflected the finding of an isolated focus of liver necrosis (slight) in a single male animal dosed at 10 mg/kg/day. None of the remaining 11 animals (5 males and 6 females) in the 2 lowest dose groups had other liver-related findings and none, including the male with focal necrosis, had treatment-emergent increases in LFTs.

At the 2 highest dose levels (35 and 70 mg/kg/day), 4 of 12 animals were reported to have microscopic liver changes of multifocal necrosis (minimal to slight), further characterized as single cell necrosis in 2 animals. Two of the 12 animals in those dose groups (both 70 mg/kg/day) showed post-treatment increased alanine transaminase (ALT), rising to 1.4x above the upper range of controls in a male with no histologic findings, and to 2.4x in a female with multifocal single cell necrosis (slight). There were no elevations in bilirubin in any animal. One male (35 mg/kg/day) had “focally extensive (moderate)” necrosis and inflammation associated with macroscopic discoloration of the liver; transaminases were normal. On review, this lesion was qualitatively different from the microscopic multifocal lesions in other animals and had a subcapsular location, consistent with being secondary to external trauma.

The Sponsor has completed a 9-month preclinical good laboratory practice-compliant toxicology study (Study X4-TOX- 0001) in Beagle dogs with interim sacrifices at 3- and 6-months and terminal sacrifice at 9-months. In this study, the primary mavorixafor-related microscopic finding was dose dependent accumulation of pigment consistent with lipofuscin in multiple organs at doses of 3.8 mg/kg/day and above. Additional mavorixafor-related findings in the liver were primarily observed at doses of 34.1 mg/kg/day and included centrilobular hepatocellular atrophy and sinusoidal dilation, increased severity of mononuclear cell infiltration, and bile duct hyperplasia. Overall, there was no meaningful elevation of circulating hepatic enzymes reflective of liver injury or active inflammatory response in these animals.

During the earlier studies, a *p*-hydroxybenzoate salt (PHB) salt form of the drug (designated AMD11070PHB) was identified for future manufacturing and development purposes. However, animal toxicology studies (13- and 26-week duration) with AMD11070PHB demonstrated unexpected findings, including retinal changes in albino rats treated for 26 weeks and notable gastrointestinal intolerance and liver changes in Beagle dogs treated for 13 weeks (see Investigator’s Brochure). Although AMD11070PHB was never administered to humans and is

not proposed for use in any clinical studies with mavorixafor, these observations were carefully considered in the safety monitoring plans for all clinical studies with X4P-001 (see Section 8.6). Following these findings, however, close monitoring for eye toxicities and regularly scheduled ophthalmologic examination were part of all clinical studies with mavorixafor (see Table 17).

Regarding ophthalmology, the recently completed 9-month toxicology study in dogs showed no retinal findings, and the review of 194 clinical subjects found no retinal disorder, except for 1 patient in Study X4P-001-RCCA with Grade 1 age-related macular degeneration and Grade 1 retinal pigmentation at screening, and 1 patient in Study X4P-001-RCCA with Grade 1 retinal hemorrhage and Grade 1 retinal vein occlusion, both of which an ophthalmologist evaluated to be related to the patient's pre-existing conditions (diabetes mellitus and hypertension). Central review of retinal images in 23 subjects, including 3 patients exposed to mavorixafor for more than 2 years, showed no findings.

2.3. Clinical Experience with Related Compounds

The only approved agent that blocks the CXCR4 receptor is Mozobil® (plerixafor), which is an injectable drug with a very short $T_{1/2}$, and is approved for courses of up to 4 consecutive days in combination with G-CSF to mobilize hematopoietic stem cells to the peripheral blood for collection and subsequent autologous transplantation in patients with NHL and MM. Plerixafor is not approved as a treatment for patients with WHIM syndrome. However, investigational proof-of-concept studies conducted by Dr. David Dale at the University of Washington and by Dr. David McDermott at the NIH in patients with WHIM syndrome have demonstrated that plerixafor at low doses can increase circulating levels of both neutrophils and lymphocytes [Dale 2011; McDermott 2011] (see Section 2.1.1 for details).

2.4. Updated Clinical Experience with Mavorixafor in WHIM Patients

Prior to this clinical study, there was no experience with mavorixafor in patients with WHIM syndrome (Section 2.2.1).

Detailed below are the key findings based on the experience of mavorixafor in WHIM syndrome enrolled in the X4P-001-MKKA and X4P-001-103 studies:

The first 2 patients enrolled in this X4P-001-MKKA study received the starting dose of mavorixafor at 50 mg QD and were serially dose escalated to 100 mg QD and 150 mg QD based on their ANC and ALC not achieving the clinical threshold measured at the pre-determined time points. The Data Review Committee (DRC) met on 24 April 2017 and agreed to change the starting dose for additional patients to 100 mg QD as 50 mg QD did not provide sufficient pharmacodynamic changes in patients and was considered to be a suboptimal dose.

As of 14 May 2020, 9 patients with WHIM syndrome have been treated with mavorixafor in 2 clinical studies. The preliminary safety results show that treatment with mavorixafor is well tolerated.

- Eight patients with WHIM syndrome in Study X4P-001-MKKA were treated with mavorixafor administered at doses from 50 to 400 mg QD in an open-label 24-week period followed by an extension study.
- One patient with WHIM syndrome in Study X4P-001-103 was treated with mavorixafor administered at a dose of 400 mg QD or placebo for a 52-week treatment period followed by open-label mavorixafor 400 mg QD.

On the X4P-001-MKKA study, patients with WHIM syndrome have received mavorixafor for a median duration of 839 days (range 94 days to 2+ years) at doses of 50 to 400 mg QD. Mavorixafor has been well-tolerated with no serious Grade 4 or Grade 5 AEs reported in Study X4P-001-MKKA.

Seven of 8 (88.5%) patients in Study X4P-001-MKKA experienced at least 1 TEAE, 4 (50%) of whom experienced a total of 8 TEAEs that were considered as possibly related to study drug, including nausea and dyspepsia (2 patients each, 25%); and single instances of conjunctivitis, dermatitis psoriasiform, dry mouth, and nasal dryness (1 patient each, 12.5%). The frequency of TEAEs did not increase with dose.

Overall, 2 (25%) patients experienced a total of 5 Grade 3 TEAEs. The Grade 3 TEAEs involved single events (12.5%) of cholecystitis, cellulitis, otitis media, procedural pain, and tibia fracture; no Grade 3 events were considered by the Investigator to be treatment related. No Grade 4 TEAEs or TEAEs with an outcome of death (i.e., Grade 5 events) have been reported in Study X4P-001-MKKA.

All patients demonstrated a dose-dependent increase in ANC and ALC from screening values, with ALC increasing in greater proportion than ANC. Mavorixafor drug exposure showed a dose-dependent increase correlated with AUC of neutrophils. The DRC met on 29 November 2017 and agreed to escalate the maximum dose to 400 mg QD in order to assess if more consistent increases in ANC and ALC can be achieved. The basis for this recommendation comes from the experience of mavorixafor in oncology patients outlined below.

The interim results from the X4P-001-MKKA study are now published [Dale 2020].

Healthy Volunteers

As of 14 May 2020, a total of 70 healthy volunteers have been dosed with mavorixafor at daily doses ranging from 200 to 400 mg as monotherapy. In all studies, mavorixafor is considered to be generally safe and well tolerated, with most events being mild or moderate in severity and of brief duration. No deaths due to AEs occurred in any studies of healthy volunteers.

Patients with Solid Advanced Tumors

As of 14 May 2020, a total of 99 oncology patients have been dosed with mavorixafor at doses ranging from 200 to 600 mg QD as monotherapy or in combination with other agents. In all studies, mavorixafor is considered to be generally safe and well tolerated. The range of duration on treatment was 5 days to 3+ years across all patients enrolled in studies X4P-001-RCCA, X4P-001-RCCB, and X4P-001-MELA.

At the discretion of the Sponsor and with agreement from the Investigator(s) and Data Monitoring Committee, patients in the current Phase 2 study may have their dose escalated and have additional in-residence or dense-sampling visits conducted during the Extension Phase. Additional in-resident or dense-sampling visits may also be conducted in the absence of dose escalation in order to collect additional data regarding a specific dose.

3. OBJECTIVES AND PURPOSE

3.1. Primary Objective

The primary objectives of the initial Treatment Period are:

- To evaluate safety and tolerability of mavorixafor in patients with WHIM syndrome.
- To assess the dose required to achieve a consistent increase in circulating neutrophils and lymphocytes in those patients.

The objectives of the Extension Phase are:

- To evaluate the safety of long-term treatment with mavorixafor.
- To evaluate the efficacy of long-term mavorixafor treatment on infection rate, skin warts, vaccine titers, and neutrophil and lymphocyte counts.

4. STUDY DESIGN AND ENDPOINTS

4.1. Description of the Study Design

Protocol X4P-001-MKKA is a Phase 2 study with an initial 24-week Treatment Period and an Extension Phase.

The primary objectives of this Phase 2 study are to determine the safety, tolerability, and Phase 3 dose selection of mavorixafor in patients with WHIM syndrome. Up to 15 eligible adult patients (age 18 years or older) will be enrolled. Complete inclusion and exclusion criteria are presented in Section 5.1 and Section 5.2; the key disease-related eligibility criteria are:

- Has a genotype-confirmed mutation of *CXCR4* consistent with WHIM syndrome.
- Has ANC ≤400/µL or ALC ≤650/µL or both on at least 2 independent blood samples collected over a period of up to 14 days.

Two patients were treated at the initial proposed starting dose of 50 mg QD (see Section 2.2.3). This dose was determined to be a suboptimal dose. So, all additional eligible patients will initiate treatment with mavorixafor at 100 mg QD or a higher dose with the potential for dose escalation based on $AUC_{ANC/ALC}$ values to a maximum daily dose of 400 mg. During the scheduled Treatment Period, patients will be continuously monitored for safety including:

- Monthly office visits
- Daily monitoring of temperature, activities of daily living, antibiotic usage, and unscheduled healthcare visits – this information will be collected using an automated telephone- or web-based reporting system.

Patients are allowed to continue treatment in an Extension Phase, if regionally applicable, until it becomes available via an alternative mechanism (e.g., drug is commercially available, an expanded access program, etc. [see Section 7.3.1]) or until the study is terminated by the Sponsor for any reason. The dose of mavorixafor will not exceed 400 mg daily. During the Extension Phase, patients will have on-site visits every 6 months (±30 days) for the assessment of vital signs, safety laboratory tests, and pregnancy tests. In addition to evaluating safety, procedures every 12 months (±30 days) may include assessment of warts, ophthalmologic assessments, revaccination, and sampling for biomarkers including serum immunoglobulins, specific antibodies, and trough WBC, ANC, ALC, absolute monocyte count (AMC), PK, and quality of life evaluations. 24-hour serial ANC, ALC, AMC, and dense PK sampling are optional at these visits. Optional patient interviews may be conducted via telephone on an ad-hoc basis in the Extension Phase to gain insight about the patient's overall study experience and patient-reported perceived treatment effect.

Subjects may also be asked to also take part in optional pharmacogenetic research. Subjects who decline the pharmacogenetic research are eligible for the study if they meet all inclusion criteria and none of the exclusion criteria. The objective of the optional pharmacogenetic research is to

assess how the genetic makeup of an individual affects his/her response to drugs, such as how CYP3A4*22 status may be associated with poor metabolism.

Patients may receive standard of care antibiotics (and/or Ig therapy, if applicable, in the event of infection, but may not receive routine extended prophylaxis with G-CSF. In the event of an episode consistent with acute, severe bacterial infection, the Investigator may add *rescue therapy* consisting of a course of G-CSF and/or Ig therapy, if applicable (see Section 7.4.4.2). Prophylactic Ig therapy may be allowed after discussion with the Medical Monitor.

During the initial Treatment period, all available safety data will be reviewed approximately every 12 weeks by a DRC including participating Investigator(s), an independent physician with relevant experience in clinical research and/or immune deficiency diseases, the Medical Monitor, and a representative of the Sponsor. A detailed DRC charter will be prepared.

Patients will be admitted to a research unit at Weeks 5, 13, and 21 to permit collection of serial samples over 24 hours for determination of WBC, ANC, ALC, AMC, and plasma drug levels (PK). If patients cannot return to the study site for an in-residence visit, a dense-sampling visit may be conducted by visiting research nurse or by the patient's primary care physician; however, in-residence visits at the study site are preferred.

The decision for dose-escalation, if necessary, will be based on ANC and ALC analyzed as AUCs relative to pre-specified clinically meaning thresholds of 600/µL and 1000/µL, respectively. The 24-hour AUC will be calculated using the trapezoidal method with area above threshold being positive, and area below threshold, negative (see Section 10.4.2). Patients with AUC_{ANC} <2000 cell•hr/µL or AUC_{ALC} <5000 cell•hr/µL at the Week 5 or Week 13 evaluations will have mavorixafor daily dose increased to a maximum daily dose of 400 mg as indicated below:

- Planned doses: 100 mg QD, 200 mg QD, 300 mg QD, 400 mg QD.
- Based on the emerging safety, PK, and pharmacodynamic (PD) data, the planned dose may be omitted, an intermediate dose may be used to substitute the planned dose, or a BID dosing regimen may be explored. However, the maximum daily dose will be ≤400 mg.

Subsequent dose-escalations may be conducted in both treatment periods after prior approval from the Data Monitoring Committee, based on $AUC_{ANC/ALC}$ values, safety data, and review of clinical efficacy, up to a maximum dose of 400 mg daily. Dose-escalation may occur to determine the Phase 3 dose that will provide the most consistent increase in circulating neutrophils and lymphocytes in the most number of patients. Patients who experience a ≥ Grade 3 treatment-related SAE will not be escalated.

Because ANC and ALC in WHIM patients are significantly impacted by acute infection, alone or with antibiotics, G-CSF, corticosteroids, epinephrine, or any other treatment that in the opinion of the investigator might impact cell counts, the planned in-residence stays should be delayed if necessary until therapy has been discontinued and the patient remained afebrile for at least

2 weeks. Sequential in-residence stays must be separated by at least 4 weeks and preferably 6 weeks. Planned in-residence stays should also occur no less than 14 days after any change of dose.

After at least 4 patients have completed 12 weeks of treatment, the DRC will review all available data and make recommendations regarding the course of the study and the recommended Phase 3 dose.

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

4.2.1. Rationale for the ANC and ALC Threshold

Based on published data of WHIM patients treated with plerixafor [Dale 2011; McDermott 2011; McDermott 2014], baseline (pre-treatment) ANC are typically ≤250/µL, with modest variation over the course of the day; ALC ranges from 350 to 900/µL, representing physiologic diurnal variation. In the proof-of-concept study conducted by the NIH [McDermott 2014], 3 patients with WHIM syndrome were treated with plerixafor for 24 weeks (see Section 2.1.1 for details). Over that period, patients achieved a durable increase in circulating leukocyte trough values for ANC of approximately ≥600 cells/µL (clinically meaningful dose-escalation threshold; ≥500 cells/µL for TAT_{ANC} measurement) and for ALC, ≥1000 cells/µL. Concurrently, there was evidence of clinical efficacy, including:

- A 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 these ANC and ALC levels reflects a relevant improvement in the pathophysiology underlying WHIM syndrome and is sufficient to affect clinical outcomes.

Mavorixafor and plerixafor share the same mechanism of action; however, mavorixafor is orally bioavailable and has a $T_{1/2}$ suitable for once daily dosing (see Section 2.2.2.1).

4.2.2. Rationale for the AMC Threshold

The typical range of absolute monocyte count varies between both sex and age. AMC in patients between the ages of 12 and 18 usually ranges between 180 to 780 cells/µL and 190 to 720 cells/µL in males and females, respectively. In adult patients (≥ 18 years of age), AMC typically ranges between 290 to 950 cells/µL and 250 to 840 cells/µL in males and females, respectively.

4.2.3. Rationale for Study Structure

This is the first clinical study of mavorixafor in patients with WHIM syndrome.

Given the rarity of the disease under study as well as the known PK and PD profile of mavorixafor, a small number of patients (N=up to 15) are planned to be treated with mavorixafor on an open-label basis, with safety data reviewed on an approximately every 12-week basis by a DRC. Provision is made for dose escalation in individual patients, based on the $AUC_{ANC/ALC}$ values to a maximum total daily dose of 400 mg (see Section 4.2.1).

After at least 4 patients have completed the 24-week Treatment Period, the DRC will make recommendations regarding proceeding with a Phase 3 study. In addition, based on the experience in this study, a Phase 3 dose regimen for mavorixafor will be determined by the Sponsor with input from the DRC.

4.2.4. Rationale for Mavorixafor Dosing Regimen

Prior clinical studies demonstrated that mavorixafor is pharmacologically active at single doses of 50 mg (see Section 2.2.2.4). The hypersensitivity characteristic of the mutated *CXCR4* in WHIM patients appeared to respond to relatively low doses of plerixafor (0.01 to 0.02 mg/kg compared with the label dose of 0.24 mg/kg). Based on these observations, the proposed clinical starting dose of mavorixafor in the initial Treatment Period was 50 mg QD orally. This starting dose was supported by the normal healthy male volunteer study (A5191). In this study, a single 50 mg dose of mavorixafor showed a 1.3-fold increase in total WBC count; single doses of 100 mg and 200 mg resulted in an increased total WBC count of up to 1.5- to 1.8-fold. The concentrations of mavorixafor at 24 hours after a single dose of 50 mg QD and 200 mg QD ranged between approximately 1 ng/mL and 9 ng/mL, respectively.

The starting dose level of mavorixafor in the initial 2 patients was 50 mg QD. In both adults and adolescents, the predicted steady-state exposure for X4P 001 at 50 mg once daily was ~235 ng•hr/mL. This exposure represents a ~144-fold margin relative to the exposures associated with microscopic multifocal necrosis in the 13-week dog study ($AUC_{0\text{-}24hr}$: 33,822 ng•hr/mL) and a ~42-fold margin relative to the exposure at 10 mg/kg/day ($AUC_{0\text{-}24}$ of 9935 ng•hr/mL) based on the NOAEL dose in 13-week dog study is <10 mg/kg/day.

For additional subjects in this study, the starting dose of mavorixafor will be increased to 100 mg QD (see Section 2.4) or to a higher dose if emerging data (safety, PK, and PD) suggests that 100 mg QD is a suboptimal dose (i.e., not achieving the objective of consistent ANC/ALC target thresholds). In addition, if emerging data suggests that QD regimen is not sufficient, BID dose regimen may be explored. The maximum total daily dose will not exceed 400 mg daily.

4.2.5. Rationale for Mavorixafor Duration of Treatment

Patients will receive treatment for at least 24 weeks. This treatment duration was selected based on the results of a proof-of-concept study conducted by the NIH [McDermott 2014], in which 3 patients with WHIM syndrome were treated with plerixafor for 24 weeks (see Section 2.1.1 for

details). Over that period, there was evidence of efficacy, with a durable increase in circulating leukocytes in all patients, associated with a decrease in the rate of infections and improved response in generalized warts following localized treatment with imiquimod [McDermott 2014]. The latter suggests improved immune function, with induction of an effective systemic anti-HPV response. Of note, these patients also demonstrated improved bone marrow histology, with decreases both in hypercellularity and in the frequency of hypermature, apoptotic neutrophils.

Taken together, these changes support the hypothesis that CXCR4 antagonism reverses the primary pathophysiology underlying WHIM syndrome, i.e., hyperactive *CXCR4* response to physiologic levels of its ligand CXCL12.

The treatment duration of at least 24 weeks in the WHIM study is supported by the oncology clinical safety experience with mavorixafor to date. As of March 13, 2017, 6 patients in the oncology program have been treated with mavorixafor (at doses of 400 mg QD or greater) for 4-29 weeks. Three of the 6 patients have been on the treatment for approximately 6 months and treatment with mavorixafor is considered to be generally safe and well tolerated.

Patients may continue to receive treatment with mavorixafor in an Extension Phase, if regionally applicable. The first 2 patients' starting dose of 50 mg QD (see Section 2.2.3) and maximum dose of 150 mg QD was determined to be suboptimal. At the discretion of the Sponsor and with agreement from the investigator(s), these patients may have their dose escalated and have additional in-residence or dense-sampling visits conducted during the Extension Phase. Additional in-resident or dense-sampling visits may also be conducted in the absence of dose escalation in order to collect additional data regarding a specific dose.

4.3. Endpoints

4.3.1. Primary Endpoint

The primary endpoint of this study is the mean value of the AUC_{ANC} and/or AUC_{ALC} collected over a 24-hour period above clinically meaningful thresholds for the mavorixafor-treated patients over 6 months. The ANC clinically meaningful threshold is defined as ANC ≥600/μL and the ALC clinically meaningful threshold is defined as ≥1000/μL.

4.3.2. Exploratory Endpoints

- Time above threshold (TAT) of ANC, ALC, and AMC at different dose levels of mavorixafor, where:
    - Time above threshold for ANC (TAT_{ANC}) is the time in hours over 24 hours during which the ANC is maintained above 500 cells/μL.
    - Time above threshold for ALC (TAT_{ALC}) is the time in hours over 24 hours during which the ALC is maintained above 1000 cells/μL.

    - Time above threshold for monocytes (TAT_{mono}) is the time in hours over 24 hours during which the monocytes count is maintained above the lower limit of normal corrected for age and sex per laboratory normal ranges.

- Frequency and severity of infections, with diagnosis based on Investigator's clinical assessment and severity assessed as Grade 1 to 4 using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE).
- Number of warts – applicable only to patients with cutaneous warts at baseline, and comparing number at baseline to number at end of Treatment Period.
- Severity of genital warts – applicable only to patients with genital warts at baseline, and comparing number of lesions, size of largest lesion, and patient-reported morbidity at baseline to end of Treatment Period.
- Antibody levels following revaccination – applicable only to patients who were (a) previously administered approved vaccines, (b) found at baseline to have predefined sub-protective levels of antibody, and (c) agree to repeat administration of the vaccine after at least 12 weeks of treatment.
- Frequency of events requiring rescue therapy (G-CSF and/or Ig).
- Rate of infections.
- Rate of hospitalization events as compared to baseline.
- Circulating WBCs:
    - Absolute and fold change from baseline and in total WBC counts, and in absolute numbers of lymphocytes, neutrophils, monocytes, and lymphocyte subpopulations cells.
    - Correlation of WBC, ANC, ALC, and AMC levels with plasma drug levels.
- Ig and specific antibodies:
    - Changes from baseline in levels of total IgG, IgG subclasses, IgA, IgD, IgE and IgM.
- Optional bone marrow aspirates (analyzed centrally by a blinded reviewer):
    - Change from baseline in cellularity.
    - Change from baseline in frequency of apoptotic cells.
- Quality of life as assessed by the 36-item Short Form Survey, Life Quality Index, and HPV Impact Profile (if applicable),
- Qualitative patient interviews conducted in the Extension Phase via telephone by a third party (optional) (see Section 7.1.5.3).

5. STUDY ENROLLMENT AND WITHDRAWAL

5.1. Inclusion Criteria

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

1. Be at least 18 years of age.
2. Has signed the current approved informed consent form.
3. Has a genotype-confirmed mutation of *CXCR4*.
4. Agree to use contraception as follows:
   - For women of childbearing potential (WOCBP), agree to use highly effective contraceptive methods from Screening, through the study, and for at least 4 weeks after the last dose of study drug (see Section 7.4.1.1 for the definition of non-childbearing potential).
   - For males, agree to use a condom with any WOCBP sexual partner from Day 1 of study treatment, through the study, and at least 4 weeks after the last dose of study drug.
5. Be willing and able to comply with this protocol.
6. Has confirmed ANC ≤400/µL *or* ALC ≤650/µL *or* both, where confirmation applies to each cell type separately and requires meeting the criterion on at least 2 independent blood samples collected over up to 14 days.

5.2. Exclusion Criteria

Patients 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.
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 one or more of the following criteria:
   - A positive antibody test for hepatitis C virus, unless documented to have no detectable viral load on two independent samples.
   - A positive test for hepatitis B surface antigen.
5. Has, at Screening, safety laboratory tests meeting one or more of the following criteria:
   - Hemoglobin <8.0 g/dL.
   - Platelets <75,000/µL.

- Creatinine >2.0 x the ULN.
- Serum aspartate transaminase (AST) >2.5x ULN.
- Serum ALT >2.5x ULN.
- Total bilirubin >1.5x ULN (unless due to Gilbert's Syndrome, total bilirubin > 3.0x ULN and direct bilirubin > 1.5x ULN).

6. Has, within 2 months prior to Day 1, received Plerixafor (open-label or blinded) as treatment of WHIM Syndrome.
7. Has, within the 4 weeks prior to Day 1, had surgery requiring general anesthesia.
8. Has, within 2 weeks prior to Day 1, received any of the following treatments:
   - G-CSF or granulocyte macrophage-colony stimulating factor (GM-CSF).
   - Immunoglobulin – Intravenous or subcutaneous (unless deemed necessary by the treating physician and after agreement from the Sponsor).
   - Corticosteroids (>10 mg prednisone equivalent per day).
   - Investigational therapies should be discussed with the Medical Monitor.
9. Is currently taking or has, within 2 weeks prior to Day 1, received any medication that is a strong inhibitor or inducer of cytochrome P450 (CYP) and/or P-glycoprotein (see Sections 7.4.1.3 and 7.4.1.4).
10. Has, at the planned initiation of study drug, an uncontrolled and active infection (excluding warts) that has the potential to raise the ANC counts.
11. Has any other medical or personal condition that, in the opinion of the Investigator, may potentially compromise the safety or compliance of the patient, or may preclude the patient's successful completion of the clinical study.

Patients taking medications prohibited on the basis of CYP interactions (see Section 7.4.1.3), may, after discussion with the prescribing physician, be changed to a functionally equivalent, non-prohibited medication, and, after at least 2 weeks off the prohibited medication, reassessed for enrollment, including rescreening, if necessary.

5.3. Strategies for Recruitment and Retention

Following receipt of IRB/IEC approval, the Investigator may initiate patient recruitment (see Section 13.2). To reach an economically and socially diverse population, the study may be announced publicly, including on relevant Internet websites; prior to use, the form and content of such announcements will be submitted to the IRB/IEC for approval (see Section 13.2).

5.4. Participant Withdrawal or Termination

5.4.1. Reasons for Withdrawal or Termination

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

- *Treatment-limiting toxicity (TLT) event* – as defined in Section 5.7.
- *Completion* – Completed 24 weeks of treatment and End-of-Treatment (EOT) and End-of-Study (EOS) visit procedures (Week 25 [or at the time of study drug discontinuation] and 30 ±5 days after the last study drug dose, respectively).
- *Adverse Event, other than TLT* – 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 patient.
  - The patient's request, based on any AE.
- *Lost to Follow-Up* – The patient stopped coming for visits.
- *Study Termination* – by the Sponsor, for any reason.

5.4.2. Handling of Participant Withdrawals or Termination

When study treatment is discontinued for any reason, the EOT and EOS visits will be performed as specified (see Section 7). If a patient cannot be seen, attempts will be made to contact the patient by telephone to inquire about reasons for stopping participation and get updated information on any unresolved AEs.

5.5. Premature Termination or Suspension of Study

The Sponsor reserves the right to discontinue or suspend 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.

If the study is terminated prematurely or suspended, the Sponsor will promptly inform the participating Investigators and institutions, the regulatory authorities, and the IRB/IEC (see Section 13.2 for definition) of the termination or suspension and the reason(s) for the action.

5.6. Patient Restrictions during the Conduct of the Study

In the interest of their safety and to facilitate assessment of both safety and treatment effect, the patients participating 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 their Investigator or if required in an emergency.
- Not take any over-the-counter medications, except as instructed or approved by their Investigator.
- Not drink grapefruit juice or eat grapefruit.

5.7. Definition of Treatment-Limiting Toxicity

A TLT event for mavorixafor is defined as an AE that meets *both* of the following criteria:

a) Is assessed by the Investigator as possibly or probably related to mavorixafor (see Section 8.2.3).

b) Represents one of the following events (grading as defined by the NCI CTCAE, v4.03) (see Section 8.2.1):

- Is a Grade 3 or Grade 4 clinical event.
  - *Exception*: Grade 3 nausea, vomiting, or diarrhea lasting <48 hrs in patients who have received suboptimal medical management
- Is a confirmed Grade 3 or Grade 4 laboratory event.
  - Exception: Grade 3 electrolyte abnormalities that persist <72 hrs and do not require hospitalization.
  - Exception: Grade 3 AST/ALT increases that persist <5 days and with total bilirubin ≤1.5x ULN.
- Is one of the following, which are designated as critical TLT events:
  - AST/ALT increased >3x ULN (Grade 2) with total bilirubin increased >2x ULN in the absence of cholestasis.
  - Retinopathy – confirmed treatment-emergent retinopathy.
  - Platelets <50,000/mm^3 (Grade 3) with bleeding or <25,000/mm^3 (Grade 4).

5.8. Duration of Treatment

Patients are expected to receive treatment for 24 weeks in the initial Treatment Period or until the earliest of:

- TLT event – see Section 5.7.

- For any TLT event occurring during the first 4 weeks of treatment, study treatment will be discontinued permanently.
- For one of the critical TLT events (see Section 5.7) occurring after successful completion of 4 weeks of treatment, study treatment will be discontinued permanently.

Extension Phase (if applicable): Patients may continue participation in an open-label extension phase of the protocol and receive treatment with mavorixafor, with an adjusted schedule of assessments (see Section 7.3.1 for details). The first 2 patients' starting dose of 50 mg QD (see Section 2.2.3) and maximum dose of 150 mg QD was determined to be suboptimal. At the discretion of the Sponsor and with agreement from the Investigator(s) and Data Monitoring Committee, these patients may have their dose escalated and have additional in-residence or dense-sampling visits conducted during the Extension Phase. Additional in-resident or dense-sampling visits may also be conducted in the absence of dose escalation in order to collect additional data regarding a specific dose.

When study treatment is discontinued for any reason, the EOT and EOS visits will be performed as specified (see Table 1-1). If a patient cannot be seen, attempts will be made to contact the patient by telephone to inquire about reasons for stopping participation and get updated information on any unresolved AEs.

5.9. Number of Patients

The maximum exposures to mavorixafor, the investigational agent in this study, will be as follows:

- Maximum number of patients:
  - Initial Treatment Period and Extension Phase: Up to 15 adult patients (≥18 years of age).
- Maximum treatment duration:
  - Initial Treatment Period: Up to 24 weeks.
  - Extension Phase: Until commercial availability (if regionally applicable) or termination of study by Sponsor for any reason.

5.10. Treatment Assignment

In the initial Treatment Period and Extension Phase, all patients will be treated with mavorixafor on an open-label basis.

6. STUDY DRUG(S)

6.1. Study Drug(s) and Control Description

6.1.1. Acquisition

All study drug will be supplied by the Sponsor.

6.1.2. Formulation, Appearance, Packaging, and Labeling

All manufacture, packaging and labeling operations will be performed according to International Conference on Harmonisation (ICH) Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) guidelines.

Table 9: 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

Table 10: Formulation of Mavorixafor 100 mg Capsule

Name	Mavorixafor 100 mg Capsule
Active ingredient	Mavorixafor (X4P-001)
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

6.1.3. Product Storage

For product storage details, see Table 10.

6.1.4. Preparation

None.

6.1.5. Dosing and Administration

All patients will receive mavorixafor capsules (100 mg dose strength).

Patients will be instructed about both dosing schedule and requirements relating to food or drink near the time of dosing.

The first dose of study drug will be taken at the study center under the observation of study center personnel. Patients will be observed for at least 1-hour post-dose.

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

- Dosing should be at a consistent time each morning (± 2 hr).
- The interval between successive doses should not be <21 hours nor >27 hours. If the interval would be <16 hrs before the next scheduled dose time, the dose should be omitted and the usual schedule resumed at the next dose.

If there are any repeated compliance issues related to the study drug, the study team, and Medical Monitor must be consulted.

Restrictions relating to food. Absorption is impacted by food and patients will be instructed as follows:

- No food or drink (except water) for 1-hour pre-dose
- No food or drink (except water) for 2-hours post-dose.

Patients 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.

In the Extension Phase, all patients will receive mavorixafor; the dose will not exceed 400 mg daily. Dose-escalation may be continued during the Extension Period, if necessary, after prior approval from the Data Monitoring Committee, based on $AUC_{ANC/ALC}$ values, safety data, and review of clinical efficacy, up to a maximum dose of 400 mg daily.

6.1.6. Route of Administration

All study drug will be administered orally.

6.1.7. Starting Dose and Dose Escalation Schedule

In the initial Treatment Period, 2 patients were treated at the initial proposed starting dose of 50 mg QD; this dose was determined to be a suboptimal dose. All subsequent patients received mavorixafor at a starting dose of 100 mg QD or a higher dose with potential escalation based on $AUC_{ANC/ALC}$ values to a maximum total daily dose of 400 mg. Provision is made for dose interruption and discontinuation (see Section 6.1.8).

6.1.8. Dose Adjustments/Modifications/Delays

If a patient receiving mavorixafor successfully completes the first 4 weeks of treatment, and subsequently has a TLT event (other than those designated critical) (see Section 5.7), study

treatment may, with the agreement of the patient, the Investigator, and the Medical Monitor, be managed as follows:

- Mavorixafor will be held (dosing interrupted).
- If the event does *not* improve to Grade ≤1 within the next 14 days, mavorixafor will be discontinued.
- If the event improves to Grade ≤1 within 14 days of holding mavorixafor, the patient may resume mavorixafor at the same dose.
- If there are any further Grade >2 recurrences, study treatment will be discontinued.
- If patients are escalated to 400 mg QD and dose interruptions are required for AEs they may have their dose reduced to 300 mg QD at the discretion of the investigator.

If dosing is interrupted for an extended period, the study treatment may be discontinued.

6.1.9. Duration of Therapy

Patients are expected to receive treatment for 24 weeks in the initial Treatment Period or until development of a TLT (see Section 5.7).

6.1.10. Treatment Compliance

Treatment compliance will be monitored by 2 procedures.

- Patients will complete a daily diary to record the number of capsules taken. Diaries will be reviewed with the patient at each clinic visit.
- Mavorixafor will be dispensed in bottles, which will be examined visually at each clinic visit; non-destructive pill counts will be performed if indicated.

6.2. Study Drug Accountability Procedures

Mavorixafor 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 and appropriate GCP and GMP principles. This includes:

- 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 and providing acknowledgement of receipt.
- 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 containing the following information:

  - Identification of the patient to whom the study drug was dispensed.
  - Date(s) and quantity of the study drug dispensed to the patient.
  - Date(s) and quantity of the study drug returned by the patient at each study visit.
- Having all records and drug supplies available for inspection by the study monitor.

6.3. Disposition of Study Drug

At the completion of the study, the site must obtain written authorization from the Sponsor regarding the final disposition of any remaining mavorixafor; that disposition must be appropriately documented. Typical procedures for handling any remaining study drug include the following:

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

7. STUDY PROCEDURES AND SCHEDULE

7.1. Study Procedures/Evaluations

All patients 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.

7.1.1. Baseline and Safety Assessments

7.1.1.1. Enrollment Procedure

Patients assessed by the Investigator as eligible after completing Screening will have all screening data entered into a web-based Electronic Data Capture (EDC) system. The data will be reviewed by the Medical Monitor or designated study personnel 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 acknowledgement that the patient may initiate treatment as per protocol.

7.1.1.2. Genotyping

A blood sample will be collected during Screening and submitted to the central laboratory for sequencing of *CXCR4*. Patients are required to have a genotype-confirmed mutation of *CXCR4* consistent with WHIM syndrome to be eligible for the study.

7.1.1.3. Bone Marrow Aspiration (Optional)

For patients who provide explicit written informed consent (or assent with parental/legal guardian consent), bone marrow aspiration will be performed during Screening and at the EOT visit. This procedure is optional; agreement to this procedure is *not* required for study entry.

At Screening, patients must be off all treatment for WHIM for the intervals specified in Exclusion #5.

Smears will be graded in batches for cellularity and myelokathexis by a blinded hematopathologist. If sufficient material is available, samples will be analyzed for markers of neutrophil apoptosis and lymphocyte subpopulations.

7.1.1.4. Revaccination

At Week 12 in the initial Treatment Period, patients that have levels of antibody below pre-defined protective levels will be revaccinated with common childhood vaccines. Blood samples will be collected from patients after revaccination for assessment of total IgG, IgG subclasses, IgA, IgD, IgE and IgM, and for levels of selected specific antibodies to common vaccine antigens in serum.

During the Extension Phase, patients who have inadequate antibody responses to tetanus toxoid or HPV vaccine will be revaccinated one time with tetanus, diphtheria, and pertussis (TDaP) and

HPV 9-valent vaccine, recombinant (Gardasil®9). The vaccination regimen for Gardasil 9 will follow current recommendations from Centers for Disease Control for unvaccinated individuals (e.g., 3 doses at months 0, 2, and 6 for patients greater than age 14) and may be given to older patients regardless of age. Patients may receive doses of Gardasil 9 at their local physician's office provided details are transmitted to the investigator and recorded in source documentation. In the Extension Phase, patients with antibody levels below pre-defined protective levels will be revaccinated at the 6-month visits.

7.1.1.5. Vital Signs

Vital signs include heart rate, blood pressure (BP) and temperature. Where feasible, vital signs should be measured before blood is drawn and after the patient has been sitting or semi-reclined quietly for 5 minutes with the BP cuff in place on the non-dominant arm. BP and heart rate 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.

7.1.1.6. Physical Examination and Body Weight

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

Examination of the reproductive system will be performed if genital warts are reported by history or are reported as present at the time of the physical examination; or if symptoms or AEs related to the reproductive system are reported. The examination may be performed by the Investigator or delegated to a specialist.

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 (Screening) examination will be recorded as AEs (see Section 8).

7.1.1.7. Assessment of Warts

Warts on the hands and feet will be identified during Screening and at all scheduled visits. Lesions will be assessed by counting the number of warts on the hands and feet. Genital warts will be assessed by reported physician examination and patient-reported outcome of impact on psychosocial well-being.

Areas with warts identified during Screening will be monitored throughout the study; areas that develop new warts during the study will be monitored for the remainder of the study according to the time and events schedule.

Photographs of representative warts may be collected.

7.1.1.8. Ophthalmologic Examination

Ophthalmologic examination will be performed as scheduled and include the following elements: assessment of visual acuity (using Snellen examination), refraction, assessment of color vision, slit lamp examination, and retinal examination with photographs. All examination reports and photographs will be submitted to a central repository as soon as feasible after being performed to be reviewed for quality and completeness.

Retinal abnormalities noted at Screening will be discussed with the Medical Monitor. Examination by a second ophthalmologist may be requested to confirm the description of the findings and the adequacy of the photographs. Enrollment may proceed with the approval of the Medical Monitor.

Any patient reported to have treatment-emergent findings of retinopathy will be examined by a second ophthalmologist.

All examination reports and photographs may be reviewed by an independent, blinded ophthalmologist designated by the Sponsor.

7.1.1.9. Electrocardiogram (ECG)

Standard 12-lead ECG will be obtained after the patient has been semi-recumbent for ~10 minutes. The following ECG parameters will be recorded: ventricular rate, RR interval, PR interval, QRS interval, QT interval, QTc interval, and QTc method using Fridericia's formula: $QTc = QT/RR^{1/3}$.

7.1.2. Pharmacokinetic Assessments

For all patients receiving study drug, dense PK samples will be obtained during the 24-hour periods in-residence at the following time points:

- Time 0 (up to 15 minutes prior), 30 minutes, 60 minutes (each ±5 minutes) and 90 minutes, 2, 3, and 4 hours (each ±15 minutes), and 8, 12, 16, and 24 hours (each ±30 minutes).

Additional time point 0 samples (trough) will be collected at Day 1 and Weeks 9, 17 and 25.

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

PK data will be analyzed using descriptive statistics for AUC, C_{max}, and T_{max} by patient and dosage regimen over the preceding week (initial Treatment Period only).

In the Extension Phase, trough PK samples will be obtained at the 12-month visits; dense PK sampling will be optional. In addition, a single sample will be obtained for evaluation of

mavorixafor metabolites at the yearly visit (e.g., Month 12, 24, etc.), whichever occurs earliest for each patient after implementation of the v5.0 protocol amendment.

7.1.3. Biomarker Assessments (in PBMC)

Biomarker samples will be collected concurrent with time point 0 PK samples. Assessments may include samples analyzed by flow cytometry for subpopulations of peripheral blood mononuclear cells (PBMC). Candidate subsets are shown in Table 11.

Table 11: Candidate Subsets of Peripheral Blood Mononuclear Cells for Biomarker Analysis

Naïve T cells
Memory T cells
B cells
Transitional B cells
NK cells
Monocytes

Abbreviations: NK=natural killer.

These investigational assays will be performed by a central laboratory designated by the Sponsor; to maximize consistency, tests may be batched. For patients who consent to future research, a subset of PBMCs may be isolated, frozen, and stored for future research to better understand the leukocyte defect in patients 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.

7.1.4. Efficacy Assessments

7.1.4.1. WBC, ANC, ALC, and AMC for Calculation of TAT and 24-hour AUC_{ANC} and AUC_{ALC}

Patients are scheduled to be admitted to a research unit 3 times over each 24-week Treatment Period (Weeks 5, 13, and 21) and blood samples collected as follows:

- Time 0 (up to 15 minutes prior), 30 minutes, 60 minutes (each ±5 minutes), and 90 minutes, 2, 3, and 4 hours (each ±15 minutes), and 8, 12, 16, and 24 hours (each ±30 minutes).

Time point 0 represents time of oral dosing that morning (typically between 7 and 8 am), the sample will be drawn pre-dose.

The in-residence stays will be rescheduled in the event of recent infection, administration of antibiotics, or of rescue therapy with G-CSF or Ig prescribed for an acute infection. Patients should be free from active infections and washed-out from any rescue therapies (G-CSF, Ig, corticosteroids, epinephrine, or any other treatment that in the opinion of the investigator might

impact cell counts) for a period of at least two weeks before obtaining the first blood samples during an in-residence stay (provision is made for patients on prophylactic long-term Ig after initial approval from the Medical Monitor).

Whole blood samples will be sent to a central laboratory selected by the Sponsor, and WBC, ANC, ALC, and AMC will be determined by standard methods. The 24-hour AUCs will be calculated as detailed in Section 10.4.2.

The 24-hour AUC_{ANC} and AUC_{ALC} represent the primary assessment for determining dose escalation.

7.1.4.2. Antibodies and Immunoglobulins in Revaccinated Patients

Serum will be collected at Screening and analyzed for levels of total IgG, IgG subclasses, IgA, IgD, IgE and IgM, and for levels of specific antibodies to common vaccine antigens (Table 12). Samples will be collected subsequently to permit monitoring of patients with depressed Ig levels or sub-protective levels of specific antibodies.

Table 12: Common Vaccines That Elicit Protective Antibody by Age Range of Initial Administration

Birth to 6 years (bacteria)	Birth to 6 years (viruses)	Age 7 to 18 years
Tetanus toxoid *H. influenzae* type B polysaccharide	Measles, Rubella	Human papilloma virus

7.1.4.3. Research Blood

For patients who consent to future research, a subset of PBMCs may be isolated, frozen, and stored for future research to better understand the leukocyte defect in patients with WHIM and the immune response to mavorixafor. Additionally, any duplicate and unused stored blood or serum samples may be used for future research to better understand the effect of treatment on the immune response of patients with WHIM syndrome.

7.1.5. Assessments of Clinical Benefit

7.1.5.1. Investigator-reported Data

In the initial Treatment Period, investigators will report the following items via an EDC system:

- All concomitant medications, including antibiotics, as well as rescue therapies (e.g., G-CSF, Ig).
- Clinical diagnoses of infection, including supporting laboratory data and sufficient information to support CTCAE severity grading.
- Assessment of Warts
  - Number of warts will be assessed on the top and bottom of both hands and feet.

- Genital warts will be assessed by physician examination with description of the number of lesions and size of the largest lesion.

Photographs may be taken of selected warts.

In the Extension Phase, the investigator will continue to evaluate warts as in the initial Treatment Period.

7.1.5.2. Patient-reported Data

Prospective patient-reported data will be collected daily by automated telephone- or web-based system. These data will include:

- Daily monitoring of temperature.
- Participation in activities of daily living (e.g., work, school, household tasks).
- Unscheduled healthcare visits, including hospitalizations, for signs or symptoms of infection.
- Treatment for infection, including antibiotics.
- Unscheduled hospitalizations for other reasons.

Patients will complete validated Quality of Life Questionnaires (36-item Short Form Survey [SF-36] and Life Quality Index [LQI], and HPV Impact Profile [if applicable]) per schedule of events (see Appendix 18.2 and Appendix 18.3 for further details regarding these assessments).

7.1.5.3. Qualitative Patient Interview

All patients on the Extension Phase may be invited to participate in a patient interview conducted by an independent third party. The patient interview may be conducted via telephone at any point during the Extension Phase. The interviews will follow a Semi-Structured Interview Guide.

The purpose of the patient interview is to capture, directly from the patient, if they experienced a meaningful improvement from baseline. Specifically, the participants may be interviewed about their decision to enter the clinical study, the patient's expectations about a meaningful improvement in their condition, the changes they experienced during the clinical study, and their perception as to why they did or did not experience a meaningful improvement in their condition.

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, if needed. Qualitative data will be coded using ATLAS.ti software, which was designed for the systematic qualitative analysis of textual, graphical, audio, and vignette data. A qualitative coding dictionary will be developed for use in the analyses.

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

7.2. Laboratory Procedures/Evaluations

7.2.1. Clinical Laboratory Evaluations

7.2.1.1. Safety Laboratory Studies

The laboratory safety tests below will be performed as scheduled by a central laboratory facility. However, if the patient is not able to travel to the site for the schedule clinic visit due to extenuating circumstances, safety labs may be drawn and or processed by a local laboratory. The Investigator may order additional local laboratory tests consistent with their routine standard of care.

Table 13: Safety Laboratory Tests

Hematology Panel	
Hematocrit	WBC differential and absolute cell counts:
Hemoglobin	Basophils
Platelet count	Eosinophils
Red blood cell count	Lymphocytes
WBC count	Monocytes
	Neutrophils
Clinical Chemistry Panel	
Alanine aminotransferase	Inorganic phosphorus
Albumin	Lactate dehydrogenase
Alkaline phosphatase	Lipase
Amylase	Magnesium
Aspartate aminotransferase	Potassium
Bicarbonate	Sodium
Calcium	Total bilirubin**
Chloride	Total protein
Creatine kinase	Urea
Creatinine*	Uric acid
Glucose	
*Creatinine clearance will be calculated using the method of Cockcroft and Gault (Cockroft, Gault, 1976).	
** If the total bilirubin concentration is above 1.5 times the upper limit of normal, direct and indirect bilirubin should be differentiated.	
Pregnancy tests (WOCBP only)	
beta-human chorionic gonadotropin	
Follicle stimulating hormone	
Serologic tests (Screening only)	
HBsAg	Antibody to HCV

Abbreviations: HbsAg=hepatitis B virus surface antigen; HCV=hepatitis C virus; WBC=white blood cell; WOCBP=women of childbearing potential.

7.2.1.2. Reporting of Safety Laboratory Tests

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 8.1.5. Procedures for the analysis of laboratory data are described in Section 8.2.2.

7.2.1.2.1. Pregnancy Testing

All WOCBP will have a urine or serum pregnancy test done at the site at each office visit. Results must be obtained at the baseline visit prior to dosing on Day 1. A negative result is required to dispense study drug. The pregnancy test results will be maintained in the source documents.

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

7.2.1.3. Repeating Abnormal Laboratory Tests

Laboratory tests showing abnormal or exclusionary values at Screening may be repeated no more than once; 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 is given.

7.2.2. Other Assays or Procedures

None.

7.2.3. Specimen Preparation, Handling, and Storage

Laboratory samples are to be prepared, handled, and stored as instructed in the laboratory manual.

7.2.4. Specimen Shipment

Laboratory samples are to be shipped as instructed in the laboratory manual.

7.3. Study Schedule

The schedule of events for the initial Treatment Period is in Table 1-1. A brief overview of the study schedule is as follows:

- Genotyping and ANC and ALC for eligibility will be performed by a central laboratory to assure consistent data. See Table 1-1 for details regarding Screening assessments.
- Alternative treatments (e.g., G-CSF, GM-CSF, Ig, plerixafor, antibiotics) will be discontinued, as indicated in the exclusion criteria, prior to receiving treatment (see Section 5.2).

- Patients will be requested to consent explicitly to have optional bone marrow aspirates performed at Screening and the EOT visit. Agreement to these procedures will not be required for study entry.
- All patients will be monitored with regularly scheduled office visits, daily remote monitoring, and 3 in-residence periods for 24-hour collections for WBC, ANC, ALC, AMC, and, in the Treatment Period, PK.
- Patients with baseline antibody levels to standard vaccines that are below the levels recommended for protection will be offered the opportunity for repeat vaccination after at least 12 weeks' treatment.
- The EOT visit is scheduled for Week 24; the patient should continue taking study drug up to this visit. If treatment is terminated prematurely for any reason, the EOT visit will be performed as soon as possible after the decision to terminate.
- The EOS visit will be performed 30 days ±5 days after the last dose of study drug.
- Extension Phase (if regionally applicable): Patients may continue to receive treatment during an Extension Phase of the protocol (see Section 7.3.1 for details). Patients may be considered eligible for the Extension Phase after the EOT or EOS visit; informed consent will be completed before entry into the Extension Phase.

  Note: Home health visits are authorized if there are extenuating circumstances that would impede patients from coming to the study site for a scheduled visit. Requests for home health visits will be reviewed and approved by X4 on a case-by-case basis. Home health visits will be an option applicable for all study visits.

7.3.1. Extension Phase

The schedule of events for the Extension Phase is in Table 1-2. If regionally applicable, provision is made for patients who wish to continue participating in the study to continue receiving treatment with mavorixafor in an Extension Phase. With the agreement of the Investigator, patients will enter the Extension Phase of the study and receive study drug until it becomes available via an alternative mechanism (e.g., drug is commercially available, an expanded access program, etc.). At the discretion of the Sponsor and with agreement from the Investigator(s) and Data Monitoring Committee, patients may have their dose escalated and have additional in-residence or dense-sampling visits conducted during the Extension Phase. Additional in-resident or dense-sampling visits may also be conducted in the absence of dose escalation in order to collect additional data regarding a specific dose. The patient's participation in the extension phase will be complete when study treatment is discontinued and all Extension Phase Visits are complete.

The following procedures will apply during the Extension Phase:

1. Patients will have on-site office visits for the assessment of vital signs, safety laboratory tests, and pregnancy tests between annual office visits, at 6-month (±30 days) intervals.
2. Office visits every 12 months (±30 days), for standard safety assessments and the following (see Table 1-2 for the full Schedule of Events):
    - Assessment of warts
    - Ophthalmologic examination
    - Trough WBC, ANC, ALC, AMC, and PK sampling
    - ANC, ALC, and AMC sampling for TAT and AUC (optional)
    - PK dense sampling (optional)
    - Revaccination (see Section 7.1.1.4)
    - Serum Ig and specific antibodies
    - Biomarker sampling
    - Pharmacogenetic sampling and research blood draw (optional)
    - Quality of life questionnaires
3. Full safety reporting requirements will apply, as detailed in Section 8.4.
4. Follow-up for safety will be conducted as per routine standard of care.
5. An optional patient interview via telephone may be conducted during the Extension Phase by an external third party (see Section 7.1.5.3).
6. An EOS visit will be conducted 30 days ±5 days after the last dose of study drug.

If a patient has their dose escalated during the Extension Phase, additional in-residence or dense-sampling visits may be conducted after the patient has received the escalated dose for at least 2 weeks.

Additional optional in-resident or dense-sampling visits may also be conducted in the absence of dose escalation in order to collect additional data regarding a specific dose. Patients may decline these additional visits and still continue treatment in the Extension Phase.

7.4. Concomitant Medications, Treatments, and Procedures

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

Any concomitant medication used from time of screening through last study visit will be recorded in the eCRF, including dose, dosage regimen, and indication (reason for its prescription).

7.4.1. Precautionary Medications, Treatments, and Procedures

7.4.1.1. Non-childbearing Potential

A WOCBP is defined as any female patient 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 level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single follicle stimulating hormone measurement is insufficient, and patients will be required to use a highly effective method of contraception. Non-childbearing potential is defined as a female who meets either of the following criteria: Age ≥50 years and no menses for at least 1 year.

7.4.1.2. Highly Effective Birth Control (Contraception) Methods

A WOCBP 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 (e.g., 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 patient.
- Double barrier methods of contraception are acceptable, such as condoms with spermicide.

All WOCBP will undergo serum or urine pregnancy testing at every visit; a negative result is required to dispense study drug. WOCBP must notify the site if a menstrual cycle is missed. Patients who become pregnant will be discontinued from the study.

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.

7.4.1.3. Restrictions related to CYP Interactions

Mavorixafor is metabolized through, and interacts with, the CYP metabolic enzymes found in the hepatic and intestinal microsomes (see Section 2.2.2.3 for details).

Based on these observations, the following restrictions are placed on concomitant medications:

- Strong inhibitors and inducers of CYP3A4 are prohibited.
  - In the event the Investigator and Medical Monitor conclude that a strong inhibitor "must be used", the dose of mavorixafor will be modified as per Table 14:

Table 14: Dose Modification of Mavorixafor when Co-Administered with a Strong CYP3A4 Inhibitor

Current Dose	Reduced Dose
400 mg QD	300 mg QD
300 mg QD	200 mg QD
200 mg QD	100 mg QD
100 mg QD	Treatment Discontinued

Abbreviations: QD=once daily.

- Grapefruit juice, a variable inhibitor of CYP3A4, is prohibited.
- Moderate inhibitors and inducers of CYP3A4 are to be prescribed only with the approval of the Medical Monitor; additional monitoring of mavorixafor drug levels may be required.
- Substrates of CYP3A that have a narrow therapeutic index are prohibited.
- Sensitive CYP2D6 substrates should be avoided and other CYP2D6 substrates should be administered only with the approval of the Medical Monitor.

Appendix 18.4 provides a list of commonly prescribed drugs that are inhibitors or inducers of CYP3A4 and substrates of CYP2D6. Known strong inducers and inhibitors are indicated. This list of drugs may not be a complete list, consultation with the Medical Monitor is requested for any concerns about concomitant medication use.

7.4.1.4. Restrictions Related to P-gp inhibitors

The following P-gp inhibitors, which are not also CYP inhibitors, are prohibited: amiodarone, carvedilol, dronedarone, quercetin, quinidine, ranolazine, and verapamil. Appendix 18.4 provides a list of commonly prescribed drugs that are P-gp inhibitors.

7.4.2. Prohibited Medications, Treatments, and Procedures

The exclusion criteria specify treatments prohibited at the time of study entry (Section 5.2).

Patients who discontinue treatment prematurely and have completed the EOT visit, may receive available or investigational treatment for their disease at any time based on the judgment of their

physician. If such treatment is initiated prior to the EOS visit (scheduled for 30 days after last dose of study drug), this will be recorded in concomitant medications and considered in assessment of any new AEs.

7.4.3. Prophylactic Medications, Treatments, and Procedures

None.

7.4.4. Rescue Medications, Treatments, and Procedures

7.4.4.1. Treatment of Expected Adverse Events

Based on prior clinical experience (as detailed in Section 2.2.3), the following treatments are recommended for symptomatic relief of "red eye", "dry eye", nasal congestion (in some instances with nosebleed), diarrhea and facial pains, which may occur within 48 hours of initiation of treatment:

- Lubricant eye drops containing carboxymethylcellulose sodium (0.5%), such as Refresh™ Tears or Thera Tears
- Non-medicated saline nasal spray, such as Simply Saline™ Nasal Mist (Arm & Hammer) or Xlear Sinus Care Saline Nasal Spray
- Diarrhea should be managed according to institutional standard of care
- Acetaminophen (paracetamol) Therapy for Febrile Episodes Consistent with Acute, Severe, Bacterial Infections

7.4.4.2. Rescue Medications for the Treatment of Acute Infections

Patients with WHIM syndrome typically have severe neutropenia (ANC <500 cells/µL); however, in contrast to patients who have similar counts associated with impaired production, patients with WHIM syndrome rarely have acute, fatal bacterial infections. This is consistent with the observation that during acute infection, circulating WBC counts can increase, presumably reflecting cell mobilization and bone marrow release by other mechanisms. Administration of G-CSF will raise ANC toward the normal range, but has little, if any, effect on ALC [McDermott 2014] and patients on G-CSF may continue to experience infections despite well-conducted prophylaxis.

Nevertheless, in some patients 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 patients 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. Provision is also made for the use of Ig therapy if, in the opinion of the Investigator, the patient would benefit from this therapy. Application of these provision should be reported promptly to the Medical

Monitor. However, if an Investigator decides that a patient requires ongoing, regularly scheduled treatment with G-CSF, then the patient must be discontinued from the study.

Chronic use of Ig therapy is permitted if deemed necessary by the treating physician and after agreement from the Sponsor.

7.4.4.3. Therapy for Warts

Topical and systemic treatments for warts should be discontinued prior to Day 1 of treatment. If warts do not show an improvement from Baseline after receiving study drug for 12 weeks, patients will, in consultation with the Medical Monitor, have treatment with imiquimod applied to a subset of lesions.

In the Extension Phase, the use of imiquimod is permitted for the treatment of warts. Laser treatment, surgery and bleomycin injections are not permitted. Other treatments for warts should be discussed with the medical monitor.

7.4.5. Participant Access to Study Drug after Study Completion

Provision is made for patients that wish to continue participation in the study to receive open-label treatment with mavorixafor. Section 7.3.1 describes a treatment Extension Phase of the study. If regionally applicable, patients who complete study treatment will continue to receive study drug until it becomes available via an alternative mechanism (e.g., drug is commercially available, an expanded access program, etc.)

7.5. Appropriateness of Measurements

See Section 4.2.

8. ADVERSE EVENTS

8.1. Definitions

8.1.1. Adverse Events (AE)

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, and which 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 patient. Patients will be encouraged to report treatment-emergent AEs 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.

8.1.2. Serious Adverse Events

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 patient was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which 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 patient was enrolled in the study, provided that it did not deteriorate in an unexpected manner during the study (e.g., 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 patient 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.

8.1.3. 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 products" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

8.1.4. Suspected, Unexpected Serious Adverse Reaction

A suspected, unexpected serious adverse reaction (SUSAR) is defined as an SAE that meets both the following criteria with respect to study drug:

- Suspected — is assessed as related or possibly related to study drug (see Section 8.2.3);
- Unexpected — compared to the study drug-related AEs described in 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 8.2.1);

- The event is now characterized more specifically (e.g., an event of "interstitial nephritis" in a patient receiving an agent previously described as associated with "acute renal failure").

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

8.1.5. Clinical Laboratory Adverse Events

The Investigator will review the results of all Safety Laboratory tests (see Section 7.2.1.1) 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 patient'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 8.1.1 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 one or more of the following:

- Process noted in the medical history:
- Ongoing AE already recorded;
- Expected course of the primary disease under study.

8.2. Classification of Adverse Events

8.2.1. Severity

The intensity (synonym: severity) of clinical AEs (i.e., symptoms reported by the patient and/or signs observed by the Investigator) will be assessed by the Investigator using the NCI CTCAE (v4.03) 5-level grading system, available on-line (see http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf).

If the AE is not included in the NCI CTCAE, then the Investigator is to determine the intensity of the AE according to the following criteria:

- ***Mild (Grade 1):*** AE that disappears or is easily tolerated on continuation of study drug.
- ***Moderate (Grade 2)***: AE sufficiently discomforting to cause interference with usual work activities.
- ***Severe (Grade 3):*** AE that is incapacitating, with inability to work or perform daily activities.

- ***Life-Threatening (Grade 4):*** AE that is potentially life threatening.
- ***Death (Grade 5):*** Death related to AE.

8.2.2. Grading of Laboratory Safety Tests for Reporting and Analysis

Treatment-emergent abnormal laboratory results will be reported as AEs when assessed as "clinically significant" using the procedures and criteria detailed in Section 8.1.5.

For purposes of analyzing laboratory data, all laboratory results will be graded using NCI CTCAE v4.03 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.

8.2.3. Relationship to Study Drug

This determination is based on the Investigator's clinical judgment 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 patient's underlying disease or co-morbid 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 known actions or toxicity of the study drug;
- Whether the AE resolved or improved with decreasing the dose or stopping the study drug (i.e., dechallenge); or recurred or worsened with re-exposure to the drug (i.e., rechallenge).

The relationship between the study drug and the AE will be described using one of the following categories:

- **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 subjects clinical state or other agents and/or therapies.
- **Possibly related:** event may be explained by the administration of the investigational product or the subject's clinical state or other agents and/or therapies.
- **Unlikely related:** event can be fully explained by the subject'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 subject's clinical state or other agents and or therapies.

Related and possibly 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.

Investigators will be asked to assess the relationship of an event to mavorixafor, based on their judgment and experience.

8.2.4. Expectedness

AEs meeting the criteria in Section 8.1.4 are to be considered unexpected.

8.2.5. Date and Time of Onset

The date and time at which the event was first apparent. Table 15 summarizes the basis for reporting the date and time of onset for the different types of AEs.

Table 15: Reporting the Date and Time of Onset of AE for Different Types of Events

Type of Event	Examples	Source of Date and Time of Onset
Symptom	Headache, feverish, paresthesia	When first experienced by the patient
Sign (Finding)	Elevated BP, enlarged liver on physical exam	When first observed by the Investigator or other study staff
Laboratory / diagnostic result	Neutropenia, hyperglycemia, lesions on brain scan	When laboratory sample was obtained or diagnostic study performed

Abbreviations: AE=adverse event; BP=blood pressure.

The time of onset of symptoms may be appreciably earlier than the date and time the Investigator becomes aware of the event. Some events may be apparent to the patient and Investigator independently, and information from each may contribute to the final report. For example, a patient may report the onset of a rash two days before being seen by a physician who makes a diagnosis of herpes zoster based on appearance and laboratory confirmation. In that case, there is a single AE, with the date of onset based on the date of the initial observation by the patient and a specific description (herpes zoster) based on the clinical examination and tests.

8.2.6. Actions Taken for Management of AE

AEs will be followed and managed by the Investigator, including obtaining any supplemental studies needed to define the nature and/or cause of the event (e.g., laboratory tests, diagnostic procedures, consultation with other health care professionals).

For each AE, the Investigator will categorize as follows the actions taken to manage the AE:

- Concomitant medication — one or more medications (prescription or over-the-counter) were started or increased in dose; non-medication actions may also have been ordered.
- Other action — only non-medication action(s) were ordered as management of the AE (e.g., bed placed in Trendelenburg position, warm compresses applied to intravenous access site).
- No action — no actions were ordered for management of the AE.

8.2.7. Follow-up and Outcome of AEs

If possible, AEs will be followed until resolved (synonyms: recovered, recuperated, ended) either with or without sequelae, including for patients who prematurely discontinue study participation. For AEs that are assessed as not drug-related and are not resolved at the EOS visit, follow-up may be limited with the approval of the Medical Monitor.

The outcome of each event will be described using the following categories:

- Resolved without sequelae — the event resolved and patient returned to baseline;
- Resolved with sequelae — the event resolved but the patient is left with residual problems (e.g., functional deficits, pain);
- Resolving — at the last observation, the event was improving;
- Not Resolved — at the last observation, the event was unchanged;
- Death (Fatal) — to be used for the one AE which, in the judgment of the Investigator, was the primary cause of death;
- Unknown — there were no observations after the onset (initial observation or report) of the event.

Note: Resolving and Not Resolved may also be used for AEs that were unresolved at the time a patient died, but were *not* assessed as the primary cause of death.

8.2.8. Date and Time of Outcome

For each class of outcome as defined above, Table 16 indicates the date and time to be recorded. As discussed in detail for date / time of onset (see Section 8.2.5), determining the date / time an event resolved (ended) should reflect the type of event and the source of the information.

Table 16: Date and Time of Outcome for AE by Outcome Class

Outcome assigned to AE	Date and Time to be Recorded
Resolved (with or without sequelae)	Date and time event observed or reported as resolved
Death	Date and time of death
Resolving or Not Resolved	Date and time of last observation
Unknown	None (see definition above)

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

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

- From 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.

- 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 8.1.4) will be recorded.

8.4. Reporting Procedures

8.4.1. Adverse Event Reporting

Each patient must be carefully monitored for the development of any AEs. This information should be obtained in the form of non-leading questions (e.g., "How are you feeling?") and from signs and symptoms detected during each examination, observations of study personnel, and spontaneous reports from patients.

All AEs (serious and non-serious) spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures occurring within the time frame specified in Section 8.3 will be documented in the patient's source documents and recorded in the eCRF. Any clinically relevant (as determined by the Investigator) deterioration in laboratory assessments or other clinical findings is considered an AE and must be recorded in the patient's source documents and in the eCRF.

The AE term should be reported in standard medical terminology when possible. Also, when possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. For each AE, the investigator will evaluate and report the onset, resolution, intensity, causality, action taken, serious criteria (if applicable), and whether or not it caused the patient to discontinue the study.

8.4.2. 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.

8.4.2.1. Procedures for Reporting SAEs 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 items of information (any items not available should be explicitly noted):

- Protocol number, study site, patient number;
- Investigator's name, address, and contact information (phone, fax, email);
- Description of the event (i.e., date and time of onset, initial assessment, treatments and course);
- Current status of the patient 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 (e.g., laboratory tests), surgical procedures, and consultations
- More definitive outcome for events previously reported as ongoing or unknown outcome

8.4.2.2. Requirements for Expedited and Periodic Reporting of Adverse Events

SUSARs are required to be reported rapidly 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.

8.4.2.3. Notification of SAEs 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.

8.4.3. Events of Special Interest

None.

8.4.4. Reporting of Pregnancy

Pregnancies occurring in the patient or patient's partner while the patient is receiving study drug or within 1 month after the patient'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 8.4.2.

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

The Investigator will follow the patient / patient'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 (i.e., spontaneous abortion [any congenital anomaly detected in an aborted fetus is to 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 the in-utero exposure to the study drug should also be reported.

8.5. Study Halting Rules

Stopping Rules may be developed if unexpected SAEs with causal relationship to study drug, including delivery procedure, appear during the study.

The study also may be stopped based on a decision on the part of the Sponsor to suspend or discontinue development of study drug.

8.6. Safety Oversight

8.6.1. Procedures for Monitoring Risks

Table 17: Monitoring Procedures for Risks Identified in Prior Studies of Mavorixafor

Potential Risk	Clinical Monitoring and Risk Management Procedures
Patient monitoring and management to be conducted throughout the trial.	• The first dose of study drug will be administered by study personnel; the patients will be observed post-dose. • 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, physical examinations, and ophthalmologic examinations will be conducted. • Scheduled ECGs will be performed throughout the study. • Criteria for discontinuing treatment in individual patients due to pre-specified TLTs has been determined.

Potential Risk	Clinical Monitoring and Risk Management Procedures
Mavorixafor is primarily metabolized through CYP3A4 and is a possible time-dependent inhibitor of CYP3A4. Monitoring and management of con-medications should be conducted.	• Strong inhibitors and inducers of CYP3A4 and P-gp inducers are prohibited.[1] • If a strong inhibitor/inducer of CYP3A4 cannot be avoided, they are to be prescribed only with the approval of the Medical Monitor. • 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. • Substrates of CYP3A that have a narrow therapeutic index are prohibited.
Mavorixafor is a moderate inhibitor of CYP2D6. Monitoring and management of con-medications should be conducted.	• Avoid sensitive CYP2D6 substrates.[1] • Other CYP2D6 substrates should be administered only with the approval of the Medical Monitor.
Mavorixafor appears to be a weak substrate of P-gp.	• P-gp inhibitors are prohibited.[1]
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.[2]	Guidelines for the management of AEs: • Patients 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 patient safety will be shared with the Principal Investigator.
LFT abnormalities were observed in the animal model. Detailed information can be found in the IB.[3]	• All clinical studies with mavorixafor have well defined eligibility criteria. • Safety laboratory tests including monitoring of liver function will occur during the study.

Potential Risk	Clinical Monitoring and Risk Management Procedures
Eye anomalies were observed in one animal model using a different salt form than that being studied in this protocol. Detailed information can be found in the IB.[4]	• No retinal changes were observed in beagles treated for 13 weeks with either the free base or the PHB salt. • No retinal changes were observed in 9-month dog toxicology study. • The review of 194 clinical subjects found no retinal disorder, except for 1 patient in Study X4P-001-RCCA with Grade 1 age-related macular degeneration and Grade 1 retinal pigmentation at screening, and 1 patient in Study X4P-001-RCCA with Grade 1 retinal hemorrhage and Grade 1 retinal vein occlusion, both of which an ophthalmologist evaluated to be related to the patient's pre-existing conditions (diabetes mellitus and hypertension). • Central review of retinal images in 23 subjects including 3 patients exposed to mavorixafor more than 2 years showed no findings. • Patients on this study will have ongoing ophthalmology evaluations with retinal photographs.
Embryo-fetal toxicity was observed in the animal model of an approved CXCR4 antagonist, Mozobil (plerixafor).	• WOCBP who are heterosexually active with childbearing potential must agree to use an effective method of contraception, as detailed in Section 7.4.1, 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 7.4.1, 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 patients are excluded from study participation

Abbreviations: CYP=cytochrome P450; ECG=electrocardiogram; IB=Investigator Brochure; LFT=liver function test; P-gp=P-glycoprotein; PHB=p-hydroxybenzoate salt; TLT=treatment-limiting toxicity; WOCBP=women of childbearing potential.

1. A detailed listing of agents with potential for P-gp and CYP-related interaction is provided in Appendix 18.4.
2. See IB v6.0 Section 6.2.7, Table 6-1 for Reference Safety Information
3. The liver findings in beagles treated for 13 weeks with the PHB salt were greater than those observed with the free base drug. This (and all prior) clinical studies use only the free base drug.
4. The retinal changes were observed only in albino rats treated for 26 weeks with the PHB salt.

8.6.2. Data Review Committee

During the initial Treatment Phase, all available data will be reviewed by a DRC approximately every 12 weeks. The DRC will include participating Investigator(s), an independent physician with relevant experience in clinical research and/or immune deficiency diseases, the Medical Monitor, and a representative of the Sponsor. During the Extension Phase, the DRC will review data approximately every 6 months. A detailed DRC charter is available.

9. CLINICAL MONITORING

9.1. External Review of the Study Conduct at Participating Sites

All study-related materials at the site are subject to external review to ensure the safety of the patients, the integrity of the study data, and compliance with all applicable regulatory and oversight requirements.

There are several different classes of review:

- Monitoring — review by the Sponsor or authorized representatives, typically from the contract research organization coordinating the clinical conduct of the study. As detailed below, visits may be conducted before, during, and after the conduct of the study.
- Audits — systematic, independent review by the quality assurance department of the Sponsor or authorized representatives, potentially from an organization not involved in the clinical conduct of the study;
- Regulatory review — performed by representatives of regulatory authorities with responsibility for oversight of the study or approval of the investigational agent. These authorities may be from the country where the site is located or from another country.

Monitoring and auditing visits on behalf of the Sponsor will be scheduled with the Investigator in advance and will be conducted at a reasonable time. To facilitate these visits, the Investigator will assure that the following are available:

- Appropriate space, facilities and access to all source documents (including access to computerized records either electronically or as complete print outs).
- Consent/assent forms, eCRFs, SAE forms, and medical records for all screened and enrolled patients.
- Timely access to site personnel, including the Investigator, sub Investigator(s), and other study personnel on the day of the visit to resolve any questions that arise.

Regulatory authorities may visit and review the site and/or Investigator during or after the study and may or may not notify the Investigator or the Sponsor in advance. The Investigator will fully cooperate with regulatory audits conducted at a reasonable time in a reasonable manner. The Investigator will notify the Sponsor immediately of any contact by or communication from regulatory authorities regarding the study.

9.2. Study Monitoring Visits

9.2.1. Site Qualification and Initiation Visits

Before an investigational site can enter a patient into the study, a representative of X4 will visit the site to perform the following:

- Inspect the facilities (e.g., clinical and administrative areas, pharmacy, laboratory).
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, as well as the responsibilities of X4 and its representatives.
- Review the site trial master file (TMF), including documentation related to the protocol, the Investigator, and other study site personnel; correspondence to and from the IRB/IEC the Sponsor, and their representatives.
- Review the standard operating procedures and current practices relating to clinical and pharmacy activities, data handling, the IRB/IEC oversight and the informed consent process.

9.2.2. Interim Monitoring Visits

During the study, a clinical research associate from or representing X4 will visit 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 is being appropriately handled and accounted.
- Perform source data verification, including verifying the data in the eCRFs against the relevant source documents (see Section 11.3) and resolving any discrepancies noted.
- Record and report any protocol deviations.
- Confirm that AEs and SAEs have been properly documented on eCRFs; that any SAEs have been forwarded to X4; and that SAEs meeting criteria for reporting have been forwarded to the IRB/IEC.

Between visits the clinical research associate will be available as needed to provide information or support to the Investigator(s) or other staff.

9.2.3. Study Closeout Visit

The study will be considered complete when all of the following have occurred:

- All treated patients have completed all scheduled visits plus any unscheduled follow-up required by AEs;
- All eCRFs have been completed, submitted and all queries resolved;
- The study database has been locked.

- The Sponsor or designee will then conduct a study closeout visit, which may include, but is not limited to, the following:
- Review the site TMF to assure all required regulatory documents are current and complete.
- Resolve any open issues from prior monitoring, audit or inspection visits.
- Review the site's provisions for meeting the requirements for retention study records and original data source.
- Discuss possible future site audits.
- Review the Sponsor's publication policy.
- Confirm compliance with requirements for notifying the IRB/IEC of study events, including closure.
- Collect any unused study materials for either return to the Sponsor or disposal in a manner approved by the Sponsor.

10. STATISTICAL CONSIDERATIONS

10.1. Statistical and Analytical Plans

A detailed statistical analysis plan has been developed.

Reference to Baseline will be assumed to mean the observation immediately prior to the first dose of study treatment.

10.2. Statistical Hypotheses

Statistical methods for this Phase 2 study will be descriptive.

10.3. Analysis Datasets

Analysis populations will be defined as shown in Table 18. The Intent-to-Treat population is the primary population for the analysis of efficacy parameters. Additional 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 18: Definition of Analysis Populations

Population	Definition
Safety Population	All patients who received at least one dose of mavorixafor.
Intent-to-Treat Population	All patients who received at least one dose of mavorixafor.
Per Protocol Population	All patients in the Intent-to-Treat population without any major protocol violations (as defined in statistical analysis plan) and with at least 1 efficacy evaluation.

10.4. Description of Statistical Methods

10.4.1. General Approach

All data collected in this study will be documented using summary tables, figures, and/or patient data listings. For continuous variables, descriptive statistics (number (n), mean, median, standard deviation, minimum and maximum) will be presented. For categorical variables, frequencies and percentages will be presented. For time-to-event variables, percentages of patients experiencing that event will be presented and median time to event will be estimated using the Kaplan-Meier method. As appropriate, a 95% CI will be presented. Graphical displays will be presented, as appropriate.

10.4.1.1. Missing Data

Patients in the ITT population will be included in the primary endpoint analysis based on all available data. Patients with fewer than the required 3 AUC calculations for ANC or ALC, as

appropriate, will have the last available AUC carried forward for calculation of the mean of 3 AUC values post-treatment.

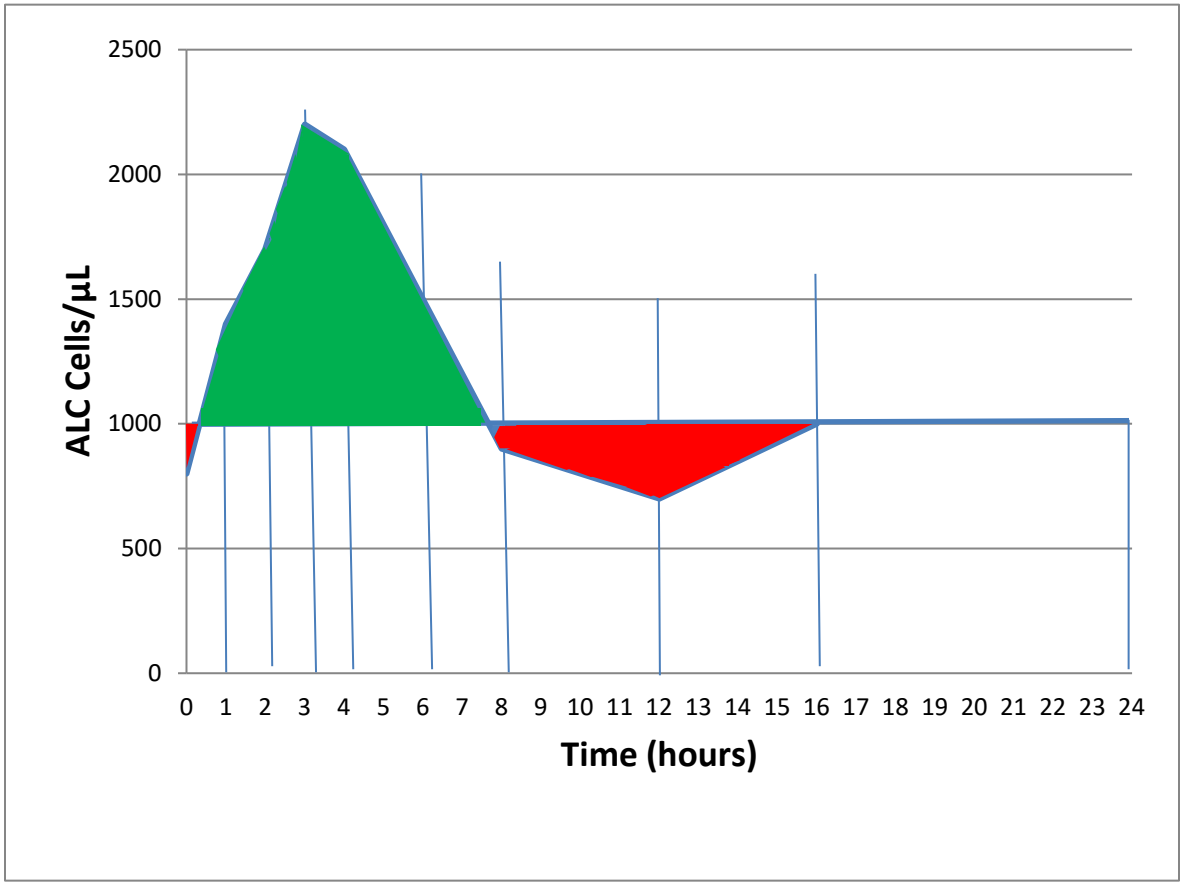
When tabulating AE data, partial dates will be handled as follows:

- 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 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 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.

10.4.2. Analysis of the Primary Efficacy Endpoints

The primary endpoint of this study is based on the ANC and ALC assessments collected during the in-residence stays and analyzed as AUC relative to pre-specified clinically meaningful thresholds of 600/μL and 1000/μL, respectively. The 24-hour AUC will be calculated using the trapezoidal method with area above threshold being positive, and area below threshold, negative. The results are referred to as threshold-adjusted AUC. Figure 3 illustrates the calculation of the 24-hr AUC for a hypothetical set of ALC data.

Figure 3: Calculation of 24-hr AUC for a Hypothetical Set of ALC Data



Abbreviations: ALC= absolute lymphocyte count; AUC=area under the curve.
Note: 24-hr AUC is the net sum of the interval areas.

To calculate the AUC above the clinically meaningful threshold for each in-residence stay, the area below the clinically meaningful threshold will be subtracted from the total AUC. Figure 3 illustrates the calculation of the AUC for ALC, where the red shaded area represents the area below the clinically meaningful threshold of 1000/µL, and the vertical blue lines represent the data collection time points. Patients with fewer than the required 3 AUC calculations for ANC or ALC, as appropriate, will have the last available AUC carried forward for calculation of the mean of 3 AUC values post-treatment.

10.4.3. Analysis of Exploratory Endpoints

The additional exploratory efficacy endpoints represent objectively defined, verifiable clinical outcomes. 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. Details of analyses of these endpoints will be provide in the statistical analysis plan.

10.4.4. Safety Analyses

The objective of safety and tolerability will be assessed by analysis of AEs and clinical laboratory parameters.

All AEs will be coded using the Medical Dictionary for Regulatory Activities coding system and displayed in tables and data listings using SOC and preferred term. Analyses will be performed for TEAE, 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 patients with:

- Any TEAE
- Frequent TEAEs (defined as TEAE with incidence ≥10%)
- AEs assessed as possibly or probably 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 patient incidence rates; therefore, in any tabulation, a patient contributes only once to the count for a given SOC and PT, regardless of the number of episodes.

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 v4.03 grades from baseline to worst value and from baseline to last value on treatment will be presented.

10.4.5. Adherence and Retention Analyses

A descriptive summary of patient adherence to treatment will be produced, to include duration of time on therapy, number of doses received, or discontinuation. This summary will account for dose modification for mavorixafor and summarize the number of patients included throughout each dosing stage.

10.4.6. Baseline Descriptive Statistics

Descriptive statistics will be used to summarize demographics and baseline characteristics. In addition, a summary will be presented for patient disposition, including number of patients enrolled, number completing the initial Treatment Period, and number of patients who entered the Extension Phase.

Medical history, medications used prior to treatment, and concomitant medications will be summarized.

10.4.7. Planned Interim Analyses

No interim analysis for the purposes of modifying the study is planned.

10.4.8. Multiple Comparison/Multiplicity

Not applicable.

10.4.9. Tabulation of Individual Response Data

The absolute values and change in ALC and ANC for each patient will be presented over time, using graphical methods that indicate all pre- and post-treatment values. In addition, cross-tabulation summary tables that present the number and proportion of patients with increases or decreases in ALC and ANC over time will be produced, for appropriate categories of change such as increments of $0.5x10^3/\mu L$.

10.5. Sample Size

Given the rarity of the disease under study as well as the known PK and PD profile of mavorixafor, albeit in populations other than WHIM syndrome, a traditional 3+3 dose escalation design was not selected. Alternatively, a small number of adult subjects (N= up to 15) will be treated with mavorixafor on an open-label basis. In the initial Treatment Period, safety data will be reviewed on an approximately every 12-week basis by the DRC. Based on subject' ANC and ALC results, the mavorixafor dose may be escalated to identify a dose for use in Phase 3. A sample size of up to 15 patients is considered adequate for the study objectives of assessing safety, tolerability, and preliminary efficacy for planning Phase 3.

11. SOURCE DOCUMENTS AND 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 patient and substantiate the integrity of the data collected during the study.

11.1. Medical Records

Medical records related to the patient's routine clinical care, including prior to or during the study:

- Information obtained from the patient's personal physicians or other third parties regarding the patient's medical history or prior physical condition.
- Medication prescription and administration records.
- Laboratory reports, including clinical pathology and diagnostic histologic pathology.
- Reports of imaging studies.
- Data and reports from automated instruments (e.g., vital signs).
- Medical records relating to scheduled and unscheduled clinical visits

11.2. Study-Specific Source Documents

Study-specific source documents include, but are not limited to, the following:

- The informed consent form, signed and dated by the patient.
- The site screening log.
- Any clinical reports noted above that are scheduled as part of the protocol and have been annotated to indicate the significance of any abnormal findings.
- Concomitant medication prescription and administration records.
- Records relating to scheduled and unscheduled study visits, including, but not limited to, results of examinations, observations relating to AEs, and concomitant medications.

11.3. Source Documents Requirements

The following document characteristics are essential to assuring data quality and are required of all documents generated by the Investigator and the study team during the course of the study.

- Be prepared at the time of the events or activities described (i.e., contemporaneously);
- Indicate both the date and time recorded;

- Identify the source of all recorded information (e.g., the patient, direct observations of the recorder, laboratory reports, external / historical sources).
- Text should be readable and unambiguous, including application of best medical record practices (e.g., minimal use of abbreviations; proper numerical, dose and posology formats).

Electronic health record systems must be compliant with current regulatory requirements for systems containing "protected health information", including, but not limited to:

- Security requirements for restricted access and electronic signatures
- Electronic timestamp
- Audit trails for any changes or amendment

Paper documents must meet the following requirements:

- Be written legibly in dark (preferably black) ink, including signature and date.
- Be signed (or initialed), with date and time, by the recorder. The site must maintain a formal log showing for all study personnel printed name, full signatures, and initials.
- In the event that any entry needs to be changed, a single line will be made through the original entry, the correct information entered (or referenced) on the same page, and the action initialed, dated, and (if appropriate) explained. The original entry must not be obscured or obliterated by multiple cross-out, correction fluid or overlay of other material.

Study-specific source document forms created by the site must be reviewed by the Sponsor prior to use.

11.4. Electronic Case Report Forms

The Sponsor will provide a regulatory-compliant EDC system for reporting study data to a central facility holding the study database. All study personnel will be trained on the system and each will have a unique login password and electronic signature.

The Investigator (or qualified sub-Investigator approved by the Sponsor) will review all eCRFs and indicate their concurrence by (electronic) signature.

12. QUALITY ASSURANCE AND QUALITY CONTROL

12.1. Study Monitoring

Monitoring and auditing procedures developed by the Sponsor or designee will be followed, in order to comply with ICH GCP guidelines, as described in Section 9.2.

12.2. Case Report Form Completion

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

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

12.3. Computerized Systems / Medical Records as Source Data

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.

12.4. 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 data were recorded, analyzed, and accurately reported according to the protocol, ICH GCP, and any applicable regulatory requirements.

The investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

12.5. 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.

13. ETHICS/PROTECTION OF HUMAN SUBJECTS

13.1. Ethical Standard

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.

ICH GCP Guideline E6 is available at:

http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf

13.2. Institutional Review Board/Independent Ethics Committee

The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of the patients. The study will only be conducted at study centers where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, informed consent, advertisements (if applicable), written information given to the patients (including diary cards), 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 patient 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 patients for the study. The protocol (and other amended study documents) must be re-approved 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.

13.3. Informed Consent Process

13.3.1. Consent/Assent and Other Informational Documents Provided to Participants

The Investigator(s) at each center will ensure that the patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Patients must also be notified that they are free to discontinue from the study at any time. The patient

should be given the opportunity to ask questions and allowed time to consider the information provided. This process should be recorded in the patient's source documentation.

An adult patient's signed and dated informed consent must be obtained before conducting any study procedures. A child patient's (aged <18 years) 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 patient's source documents.

For patients who consent to future research, a separate consent form will be signed for the collection and storage of additional blood samples. Subjects may also be asked to take part in optional pharmacogenetic research. Subjects who decline the pharmacogenetic research are eligible for the study if they meet all inclusion criteria and none of the exclusion criteria. The objective of the optional pharmacogenetic research is to assess how the genetic makeup of an individual affects his/her response to drugs, such as how CYP3A4*22 status may be associated with poor metabolism.

13.3.2. 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 patient, and this must be documented in the patient's source documents.

13.4. Participant and Data Confidentiality

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

14. DATA HANDLING AND RECORD KEEPING

14.1. Data Collection and Management Responsibilities

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.

14.2. Study Records Retention

The Investigator will maintain all study records according to ICH GCP and applicable regulatory requirement(s). Records will be retained for at least 2 years after the last marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirement(s). 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 e-mail and the notification confirmed in writing if a custodial change occurs.

14.3. Protocol Deviations

A protocol deviation is defined as an event in which the Investigator or site personnel did not conduct the study according to the Protocol, including compliance requirements and agreements. Guidelines for minor procedural variations (e.g., collection time of blood samples) will be agreed to and documented by the Investigator and the Sponsor prior to starting the study. Events conforming to those guidelines will not be considered deviations.

For protocol deviations relating to individual patients, 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 are not patient-specific (e.g., unauthorized use of an investigational agent outside the protocol, either human administration or laboratory use) will be reported to the Sponsor in writing and copies placed in the TMF.

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

14.4. Publication and Data Sharing Policy

X4 recognizes the importance of communicating the results of scientific studies, including clinical studies, and, therefore, encourages their publication in reputable scientific journals and presentation at seminars or conferences. X4 also has legitimate corporate and shareholder responsibilities, including, but not limited to, protecting confidential information about its proprietary products and obtaining patent protection for its intellectual property.

Therefore, the following procedures apply to any communication (including written, oral, or electronic; manuscript, abstract, other publication, or presentation) of results or information

arising from this study (including any ancillary studies involving study patients) to any third parties:

- The proposed communication will be prepared in collaboration with the Sponsor.
- The final proposed version must be submitted to X4 for review and comment at least 30 days prior to presentation, submission for publication or other dissemination.
- In the event X4 reasonably determines that a proposed communication contains confidential or patentable material, they may require either of the following:
  - The material be removed from the communication;
  - The communication be delayed for up to 60 additional days to permit filing the appropriate intellectual property protection.

These procedures apply regardless of whether the study is completed as planned or is terminated prematurely for any reason.

15. STUDY ADMINISTRATION

Key personnel, along with relevant contact information, are provided in the Study Manual.

16. CONFLICT OF INTEREST POLICY

The conflict of interest policy is addressed in the Clinical Trial Agreement.

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18. APPENDICES

18.1. Revision History and Sponsor Signature

The revision history is summarized in Table 19. Significant revisions made in each protocol version are provided in a separate Summary of Changes document.

Table 19: Protocol Revision History

Ver. No.	Date	Comment
1.0	01 June 2016	Initial submission to FDA
2.0	05 July 2016	Response to FDA review of IND submission; technical correction of Study Weeks in Schedules of Events and associated text
3.0	13 January 2017	Multiple changes for clarification, reduction in some laboratory assessments, removal of several assessments from Phase 3 Observation Period B1.
4.0: Never activated	20 March 2017	Response to VHP Grounds for Non-Acceptance submitted as a final draft. Never activated/signed-off.
4.1: US & Australia only	16 May 2017	Local changes for US & Australia (impacting the Phase 2 portion), including the Phase 2 dosing regimen and the addition of an extension phase.
4.2: Europe only	28 June 2017	Change in the primary endpoint, allowed use of immunoglobulin therapy and additional risk/benefit language.
4.3: US only	01 August 2017	Local changes for US allowing for additional dose escalation and “dense sampling” visits for Phase 2 patients and allowed use of immunoglobulin therapy.
4.4: Australia only (Never activated)	20 October 2017	Local changes for Australia to align the country specific protocol with protocol version 4.3 and allowing for additional dose escalation and “dense sampling” visits for Phase 2 patients and allowed use of immunoglobulin therapy.
4.5: US & Australia only	15 December 2017	Change to the dosing regimen, including a maximum daily dose of 400 mg QD
4.6: US & Australia only	02 April 2019	Removed Phase 3 component; add assessments to the Extension visits (ophthalmologic; ANC, ALC, and PK sampling; assessment of warts; Ig and antibodies; revaccination; biomarkers); added overall study schema, Schedule of Events for the Extension Phase, and table for estimated blood volumes in the Extension Phase; updated statistical methods to align with the SAP and eliminate redundancy; administrative changes; minor editorial changes (abbreviations, punctuation, grammar); administrative changes
5.0: US & Australia only	21 December 2020	Added TAT measurements for ANC, ALC, and AMC as an exploratory endpoint, updated interview language, reduced patient burden by decreasing Extension Phase office visit frequency, addition of home health visit language, additional consent proposed

	for collection of genetic samples for future PGX analysis, and removal of 25 mg capsule details.

Abbreviations: ALC=absolute lymphocyte count; AMC=absolute monocyte count; ANC=absolute neutrophil count; FDA=Food and Drug Administration; IND=Investigational New Drug Application; PGX=pharmacogenomics; PK=pharmacokinetics; QD=once daily; SAP=statistical analysis plan; TAT=time above threshold; US=United States; VHP=voluntary harmonization procedure.

This protocol Version 5.0 has been prepared and approved by the Sponsor.

[redacted]
X4 Pharmaceuticals, Inc.
[redacted]

[redacted] 07-Jan-2021

Signature Date

18.2. Quality of Life Assessment (SF-36)

Your Health and Well-Being

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one year ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

		Yes, limited a lot	Yes, limited a little	No, not limited at all
a	<u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b	<u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c	Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d	Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3
e	Climbing <u>one</u> flight of stairs	☐ 1	☐ 2	☐ 3
f	Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g	Walking <u>more than a mile</u>	☐ 1	☐ 2	☐ 3
h	Walking <u>several hundred yards</u>	☐ 1	☐ 2	☐ 3
i	Walking <u>one hundred yards</u>	☐ 1	☐ 2	☐ 3
j	Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

4. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the kind of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had difficulty performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the amount of time you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Accomplished less than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities less carefully than usual	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. During the <u>past 4 weeks</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. How much <u>bodily pain</u> have you had during the <u>past 4 weeks</u>?

None	Very mild	Mild	Moderate	Severe	Very severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. During the <u>past 4 weeks</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a	I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b	I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c	I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d	My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

18.3. LIFE QUALITY INDEX

Baseline LQI was not collected in this Phase 2 study, therefore LQI will not be followed.

18.4. Potential P-gp and CYP-Related Drug-Drug Interactions

Strong CYP3A inhibitor[1]	Strong CYP3A inducer[1]	Moderate CYP3A inhibitor[2]	Moderate CYP3A inducer[2]	CYP3A Substrates with Narrow Therapeutic Index	CYP2D6 sensitive substrate[1]	CYP2D6 moderate sensitive substrate[2]	P-gp inhibitors[1]
boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir and ritonavir, diltiazem, elvitegravir and ritonavir, grapefruit juice, idelalisib, indinavir, itraconazole, ketoconazole, lopinavir and ritonavir, mibefradil, nefazodone, nelfinavir, paritaprevir and ritonavir, ombitasvir and/or dasabuvir, posaconazole, saquinavir, telaprevir, telithromycin, tipranavir and ritonavir, troleandomycin, voriconazole	carbamazepine, enzalutamide, mitotane, phenytoin, rifampin (rifampicin), St. John's wort	amprenavir, aprepitant, atazanavir, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine (ciclosporin), darunavir and ritonavir, dronedarone, erythromycin, fluconazole, fluvoxamine, fosamprenavir, imatinib, tofisopam, verapamil	bosentan, efavirenz, etravirine, modafinil, nafcillin	alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimozide, quinidine, sirolimus, tacrolimus	atomoxetine, desipramine, dextromethorphan, eliglustat, nebivolol, nortriptyline, perphenazine, pimozide, thioridazine, tolterodine, venlafaxine	amitriptyline, encainide, imipramine, metoprolol, propafenone, propranolol, tramadol, trimipramine	amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir and ritonavir, quercetin, quinidine, ranolazine, ticagrelor, verapamil.

1 Prohibited.
2 Use with Medical Monitor approval only.
Note: This list of drugs may not be a complete list, consultation with the medical monitor is requested for any concerns about concomitant medication use.
Sources:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

http://labeling.pfizer.com/ShowLabeling.aspx?id=759

http://www.ema.europa.eu/ema/index.jsp?curl=/pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124