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 1/2 Trial of X4P-001 as Single Agent and in Combination with Axitinib in Patients with Advanced Renal Cell Carcinoma
Investigational Drug:	X4P-001
IND #:	124194
ClinicalTrials.gov ID:	NCT02667886
Sponsor:	X4 Pharmaceuticals, Inc. 955 Massachusetts Avenue, 4th Floor Cambridge, MA 02139
Protocol Number:	X4P-001-RCCA
Protocol Version, Date:	7.0, 08 June 2018
Replaces Version, Date:	6.0, 01 Feb 2017

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/Independent Ethics Committee (IRB/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.

Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with all of the instructions and procedures found in this protocol and to give access to all relevant data and records to X4 as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform X4 immediately that this request has been made.

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
ALT	Alanine amino-transferase
ANC	Absolute neutrophil count
AST	Aspartate transaminase
AUC	Area under the concentration-versus-time curve
BID	Twice daily
ccRCC	clear cell Renal Cell Carcinoma
CI	Confidence interval
C_{max}	Maximum concentration
$C_{min[12\ hr]}$	Minimum concentration at 12 hours
CNS	Central nervous system
CR	Complete response
CRA	Clinical Research Associate
CRO	Contract research organization
CS	Clinically significant
CT	Computed tomography
CV	Coefficient of variation
CXCL12	C-X-C chemokine ligand type 12 (also designated SDF-1)
CXCR4	C-X-C chemokine receptor type 4
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DLT	Dose-limiting toxicity
DCR	Disease Control Rate
DDI	Drug-drug interaction
DRC	Data Review Committee
EC	Effective concentration

Abbreviation	Explanation
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
E_{max}	Maximum exposure
EOS	End-of-study
EOT	End-of-treatment
FDA	Food and Drug Administration (U.S.)
FGFR	Fibroblast growth factor receptor
GCP	Good Clinical Practice
GI	Gastrointestinal
GMP	Good Manufacturing Practice
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIF-α	hypoxia-inducible factor1
HIV	Human immunodeficiency virus
HR	Heart rate
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
iRECIST	Modified RECIST 1.1 for immune based therapeutics
ITT	Intent-to-treat
IUD	Intrauterine device
LFT	Liver function tests
MDSC	Myeloid-derived suppressor cell
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MS/MS	Tandem mass spectrometry
MTD	Maximum tolerated dose

mTKI	Multi-tyrosine kinase inhibitor
mTOR	Mechanistic target of rapamycin
NA	Not applicable
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCS	Not clinically significant
NOAEL	No observed adverse effect level
ORR	Objective response rate
PBMC	Peripheral blood mononuclear cells
PD	Pharmacodynamics
PDGFR	Platelet-derived growth factor receptor
PFS	Progression-free survival
PHB	p-hydroxybenzoate
PlGF	Placental growth factor
PK	Pharmacokinetics
PO	Per Oral
PR	Partial response
PS	Performance Status
QD	Once daily
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RP-HPLC	Reversed-phase high performance liquid chromatography
RP2D	Recommended phase 2 dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Stable disease
SDF-1α	Stromal-derived-factor 1α (also designated CXCL12)
SOD	Sum of diameters
SUSAR	Suspected unexpected serious adverse reaction
T1/2	Half-life
T4	Thyroxin

TKI	Tyrosine kinase inhibitor
Tmax	Time to maximum concentration
TME	Tumor microenvironment
TMF	Trial master file
Treg	T regulatory
TSH	Thyroid stimulating hormone
TTP	Time to progression
ULN	Upper limit of normal
US	United States
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor

Abbreviation	Explanation
VHL	Von Hippel-Lindau syndrome
VL	Volume of distribution
WBC	White blood cell
WOCP	Women of childbearing potential
β-hCG	Beta-human chorionic gonadotropin

PROTOCOL SYNOPSIS

Study title	A Phase 1/2 Trial of X4P-001 as Single Agent and in Combination with Axitinib in Patients with Advanced Renal Cell Carcinoma
Study number	X4P-001-RCCA
Sponsor	X4 Pharmaceuticals, Inc. 955 Massachusetts Avenue, 4th Floor Cambridge, MA 02139
Phase	1 / 2
Study centers / countries	Multiple study centers globally
Planned study period	First patient enrolled: Q2 2016 Last patient enrolled: Q1 2018 Last patient last visit: Q1 2019 (anticipated)
Study objectives	The primary objective is: • To evaluate the safety and tolerability of escalating dose levels of X4P-001, both in combination with axitinib and as single agent, in patients with advanced clear cell Renal Cell Carcinoma (ccRCC). Secondary objectives are: • To assess the treatment effect (clinical activity) of X4P-001, both in combination with axitinib and as single agent, in patients with advanced ccRCC using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 [Eisenhauer 2009], including progression free survival (PFS). • To characterize the pharmacokinetics (PK) of escalating dose levels of X4P-001 administered orally. The exploratory objectives are: • To investigate associations between the treatment effect of X4P-001 (in combination with axitinib and as a single agent) and selected pharmacodynamic and disease-related biomarkers (e.g.,

	circulating CD34+ cells, plasma levels of soluble VEGF [vascular endothelial growth factor] receptor). • To assess the treatment effect (clinical activity) of X4P-001, both in combination with axitinib and as single agent, in patients with advanced ccRCC using modified Response Evaluation Criteria in Solid Tumors for immune-based therapeutics (iRECIST) [Seymour 2017].
Study design and plan	This study will be conducted in patients with advanced ccRCC and will comprise 3 parts. • **Part A (Phase 1)** will assess the safety and tolerability of escalating dose levels of X4P-001 in combination with axitinib, a TKI approved for use in this setting [Axitinib US prescribing information, 2014]. The X4P-001 dose level for the initial cohort is 200 mg twice daily (BID). Subsequent cohorts will be administered X4P-001 once daily (QD). The initial QD dose level will be 400 mg QD (representing the same total daily exposure as 200 mg BID), and then progressing to 600, 800, and 1200 mg. A safe maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D) will be identified in Part A. The RP2D may be the same as the MTD or may be lower (see Section 4.1.1). • **Part B (Phase 2)** is an expansion cohort assessing the safety, tolerability, and treatment effect of the RP2D of X4P-001 in combination with axitinib in approximately 45 patients. If the RP2D is determined before reaching the MTD, Part B may be initiated while Part A is ongoing (see Section 4.1.2). • **Part C** will assess the safety, tolerability, and treatment effect of X4P-001 as monotherapy in patients with advanced ccRCC and may be initiated after the MTD of X4P-001 with axitinib is defined in Part A. If that MTD was ≤800 mg QD, then the MTD as monotherapy will be defined by enrolling additional dose-escalation cohorts to receive X4P-001 as a single agent up to, but not exceeding, 1200 mg QD (see Section 4.1.3).
Planned number of patients	• Part A: Dose-escalation cohorts for X4P-001 in combination with axitinib; estimated to enroll approximately 15 patients. • Part B: Expansion cohort at the RP2D of X4P-001 in combination with axitinib; approximately 45 patients will be enrolled.

	• Part C: Dose-escalation (if needed after Part A) cohorts of X4P-001 as single agent (monotherapy); Expansion cohort of approximately 15 patients.
Schedule of visits and assessments	The overall study schedule is as follows: • Screening will be done within 28 days prior to Day 1 (the first dose of study drug). • Treatment is scheduled to be administered continuously; one cycle is 28 days. Missed doses will be considered skipped. • Assessments for treatment response (or disease progression) are scheduled for every 8 weeks (± 4 calendar days) starting from Cycle 1 Day 1 for 80 weeks (20 cycles) and then every 12 weeks thereafter. • The End-of-Treatment (EOT) visit will be performed within 6 days after the last dose of study drug or the decision to terminate treatment prematurely. • End-of-Study (EOS) visit, the final study event, will be performed 30 days (± 4 calendar days) after the last dose of study drug. In the event the EOT visit is delayed, the EOS visit will be performed at least 14 days after the EOT visit. **Safety Assessments:** Safety assessments include ongoing monitoring for clinical adverse events (AEs); and regularly scheduled measurement of vital signs; physical examinations; ophthalmologic examinations; laboratory tests (hematology and clinical chemistry); thyroid function tests (free thyroxin and thyroid stimulating hormone) (Parts A and B only); and electrocardiograms (ECG). Additional unscheduled assessments may be conducted at Investigator's discretion. ***Efficacy Assessments:*** Tumor Response assessments will be conducted every 8 weeks for 80 weeks (20 cycles) and then every 12 weeks thereafter, at EOT, and as indicated based on new signs, symptoms or laboratory findings. Disease status, time to progression, duration of response will be determined based on RESIST v1.1 criteria [Eisenhauer 2009]. Treatment decisions will be made by the Investigator incorporating the local radiology interpretation and consultation with the Medical Monitor. For data analysis, scans will be reviewed and interpreted by a blinded central review committee comprising

	up to 3 experienced radiologists. Tumor Response assessments may be explored by using modified Response Evaluation Criteria in Solid Tumors for immune-based therapeutics (iRECIST) [Seymour 2017]. Patients enrolled with a history or current evidence of central nervous system (CNS) disease should have brain imaging by magnetic resonance imaging (MRI) at baseline and, thereafter, as clinically indicated. **Pharmacokinetics** PK samples will be obtained on all patients in Part A and Part C, and at least 15 patients in Part B as follows: • Cycle 1 Day 1: pre-dose (-30 min); post-dose at 30, 60, 90 min (each ±5 min) and 2, 3, 4 hr (each ±15 min) • Cycle 1 Day 15: pre-dose (-10 min); post-dose at 30, 60, 90 min (each ±5 min) and 2, 3, 4, 8 hr (each ±15 min) • Cycle 2 Day 1 and Day 15: pre-dose (-10 min) In Part B, for patients who will not collect extensive PK samples on Cycle 1 Day 1 and Day 15, pre-dose (-10 min) samples will be collected on Cycle 1 Day 1, Cycle 1 Day 15, Cycle 2 Day 1, and Cycle 2 Day 15. All PK samples will be used to analyze X4P-001. PK samples collected in Part B may be used to analyze axitinib as well. These visits will be scheduled for early in the day and patients will be instructed to arrive at the clinic fasting and having not taken their morning dose of study drug(s). **Pharmacodynamics** Whole blood samples will be obtained concurrently with scheduled PK samples on Cycle 1 Day 1 and Cycle 1 Day 15 only (see above) for total white blood cell (WBC) counts and counts of circulating CD34+ positive cells. If sample yields permit, additional investigational immunomodulatory subsets may be analyzed. Pharmacodynamic samples will not be drawn at Cycle 2 Day 1 and Cycle 2 Day 15. **Biomarkers** Blood samples for biomarker assessment [serum and peripheral blood mononuclear cells (PBMC)] will be collected as scheduled for potential treatment- and tumor-related biomarkers that reflect the pharmacologic

	effects of CXCR4 antagonism on angiogenesis and immunomodulatory subsets of circulating PBMC. Additional investigational blood studies may be performed using the collected samples.
Diagnosis and main Inclusion criteria	Patients must meet all of the following criteria to be eligible for study participation: 1. Be at least 18 years of age. 2. Have signed the current approved informed consent form. 3. Have a histologically confirmed diagnosis of predominant ccRCC. 4. Have received at least one prior course of treatment for ccRCC (see Section 5.2. for specific exclusions). 5. Have on computed tomography (CT) imaging done within 28 days of Day 1 findings consistent with advanced ccRCC, including at least one extra-renal measurable target lesion meeting the criteria of RECIST v1.1 [Eisenhauer 2009]. 6. Agree to use contraception as follows: • For women of childbearing potential (WOCP, see Section 7.4.1.2 for definition), 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. • For males, agree to use a condom with any WOCP sexual partner from Day 1 of study treatment, through the study, and at least 4 weeks after the last dose of study drug. 7. For women of childbearing potential (WOCP), have a negative pregnancy test (serum or urine) on Day 1 prior to initiating study treatment. 8. Be willing and able to comply with this protocol.
Exclusion criteria	Patients with any of the following will be excluded from participation in the study: 1. Has life expectancy of less than 3 months. 2. Has performance status Grade >2 (Eastern Cooperative Oncology Group [ECOG] criteria). 3. Has New York Heart Association Class III or IV heart failure or uncontrolled hypertension (systolic blood pressure [SBP] ≥160 mm Hg; diastolic blood pressure [DBP] ≥100 mm Hg). 4. Has previously received X4P-001. 5. Parts A and B only: Has received a prior course of axitinib. Parts A and B only: Has received mechanistic target of rapamycin

	(mTOR) inhibitor(s) as their only prior treatment for ccRCC. 7. Has a prior history or current evidence of intracranial (CNS) metastatic RCC, *except* for ≤3 lesions treated by CyberKnife (or any type of radiation) or excisional surgery, clinically stable for at least 4 weeks, and without evidence of recurrence on MRI imaging at screening. 8. Has ongoing acute clinical AEs of National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Grade >1 resulting from prior cancer therapies (except alopecia, TKI-related hand-foot syndrome, or thyroid dysfunction). 9. Has had within the past 6 months the occurrence or persistence of one or more of the following medical conditions that could not be controlled with usual medical care (e.g., required emergency care or hospitalization): hypertension, angina, congestive heart failure, diabetes, seizure disorder. 10. Has had within the past 6 months the occurrence of one or more of the following events: myocardial infarction, cerebrovascular accident, deep vein thrombosis, pulmonary embolism, hemorrhage (CTCAE Grade 3 or 4), chronic liver disease (meeting criteria for Child-Pugh Class B or C), a second active malignancy (excluding malignancies that were treated curatively and have not recurred within 2 years prior to study treatment; completely resected basal cell and squamous cell skin cancers; any malignancy considered to be indolent and that has never required therapy; and completely resected carcinoma in situ of any type), organ transplantation. 11. Has had within the 4 weeks prior to initiation of study drug, or is expected to have during the study period, surgery requiring general anesthesia. 12. Has a known history of a positive serology or viral load for HIV or a known history of AIDS. 13. Has, at screening, serologic laboratory tests meeting one or more of the following criteria: • An indeterminate or positive test for antibody to hepatitis C virus (HCV), unless documented to have no detectable viral load on 2 independent samples. • A positive test for hepatitis B surface antigen (HBsAg). 14. Has, at screening, safety laboratory tests meeting one or more of the following criteria: • Hemoglobin <8.0 g/dL

	• Absolute neutrophil count (ANC) <1,500/μL • Platelets <75,000/μL • Creatinine >2.0x ULN • Serum aspartate transaminase (AST) >2.5x upper limit of normal (ULN) • Serum alanine transaminase (ALT) >2.5x ULN • AST and ALT >5x ULN for patients with liver metastasis • Total bilirubin >1.5x ULN (unless due to Gilbert's Syndrome, total bilirubin > 3.0x ULN and direct bilirubin > 1.5x ULN) 15. Has received other anti-cancer therapy within the following specified intervals prior to Day 1: • TKI within 2 weeks. • Radiation therapy within 2 weeks. • Bevacizumab within 4 weeks. • Other chemotherapy (e.g., mitomycin-C, nitrosourea) or immunotherapy (e.g., antibody, cytokine) within 4 weeks. • For investigational anti-cancer therapies, the interval will be determined in consultation with the Medical Monitor. 16. Has, within 2 weeks prior to Day 1, received a medication prohibited based on CYP3A4 interaction (see Section 7.4.1.1 for details). 17. Has, within 2 weeks prior to Day 1, received systemic corticosteroids exceeding prednisone 10 mg per day or equivalent; for other immunosuppressive agents, the exclusionary dose and duration will be determined in consultation with the Medical Monitor. 18. Is nursing. 19. Has, at the planned initiation of study drug, an uncontrolled infection. 20. 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
Investigational Medicinal Product: dose/mode of administration/dosing schedule	The investigational agent is X4P-001. X4P-001 will be provided as 100 mg capsules. XP4-001 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. • For first cohort in Part A, taken as 2 capsules (representing 200 mg) twice daily. The morning dose should be taken at a consistent time

	(±2 hr). The second daily dose should be taken 12 hr later (±3 hr). • For subsequent cohorts in Part A and for Parts B and C, taken as 4 to 12 capsules (representing 400 - 1200 mg) once daily in the morning at a consistent time (±2 hr). Manufacturing of a 200 mg capsule formulation is under development and may be introduced into the clinic when released. All patients enrolled in Parts A and B also will receive treatment with axitinib at 5 mg orally BID in addition to X4P-001 at the assigned dose level. Axitinib will be supplied as 5 mg tablets, with one tablet administered orally BID (continuous dosing).
Reference therapy: dose/mode of administration/dosing schedule	None.
Planned treatment duration per patient	Patients who do not experience a DLT in Cycle 1 (Parts A and C) and patients in Part B will remain on study treatment until they experience progression of disease, unacceptable toxicity, or other specified reason for discontinuation (Section 5.4.1). In Part A and Part C, patients who experience a DLT during Cycle 1 will be withdrawn from the study and will not receive further study treatment.
Safety and Efficacy Endpoints:	Safety endpoints are: • AEs • Clinical observations (e.g., vital signs, physical examination) • Laboratory tests, (e.g., clinical chemistry, hematology, and thyroid function tests [Part A and Part B only]) • ECGs • Ophthalmologic examination Treatment effect (tumor response) will be analyzed using RECIST v1.1 [Eisenhauer 2009] to determine the following efficacy endpoints: • Objective response rate (ORR) (Complete Response [CR] + Partial Response [PR]) • Time to objective response • Duration of objective response • Disease control rate (CR + PR + Stable Disease) • Time to progression • PFS • Treatment effect (tumor response) and efficacy endpoints may be explored using the iRECIST assessment [Seymour 2017].

Statistical methods (includes sample size calculation)	Sample Size: The **maximum** numbers of patients planned to be enrolled in Parts A and C are as follows: • Part A, Dose-escalation: up to 30 patients in total (up to 6 patients per dose level; 5 planned dose levels) • Part B, RP2D expansion cohort: approximately 45 patients will be enrolled; • Part C, Dose-escalation: up to 18 patients in total (up to 6 patients per single agent dose-escalation level; maximum 3 dose levels); • Part C, Single agent Expansion: maximum 15 patients Dose-escalation in Part A (and, if needed, in Part C) employs the standard 3+3 design. In Part B, approximately 45 patients will be enrolled and dosed with X4P-001 in the combination of axitinib to provide a preliminary assessment of both safety and anti-tumor activity. With 45 subjects at the RP2D, the two-sided 90% confidence interval width for any binary response rate (e.g., DLT or binary PD markers) will be approximately 0.24, assuming a 40% response rate. If a dose de-escalation occurs after the first 12 patients, the remaining 33 patients will be dosed at a lower dose level. With 33 patients, the confidence interval width will be approximately 0.28 for a binary response rate. Part C has an expansion cohort at or below the MTD to further assess the toxicity at that dose level. With 15 patients, there is a 79% chance of observing at least one AE with the true underlying rate of 10%, and a 54% chance of observing at least one AE with true underlying rate of 5%.
	Statistical Methods: The primary objective of the study is safety and tolerability. AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 16.0 (or later) and tabulated by event, grade, and relationship to study therapy. Laboratory results, vital signs, and ECG parameters will be summarized using descriptive statistics. Laboratory values will also be graded according to NCI CTCAE, Version 4.03, and summarized in shift tables. Dose-limiting toxicity (DLT) events will be summarized by dose level for Part A and identified in the listings. Safety observations will be analyzed using descriptive statistics and tabulation. No formal statistical comparisons are planned. All safety data will be presented in listings. Analysis of Tumor Response, ORR and Disease Control Rate (DCR) will be tabulated using best overall response, by dose level, incorporating 95% exact Clopper-Pearson confidence intervals (CI) for ORR and disease control rate. The analysis will be based on intent-to-treat (ITT) and Clinically Evaluable patient populations.

	Median time to objective response, TTP, PFS as well as the proportion of patients with PFS at 6 and 12 months (with 95% CI) will also be derived from Kaplan-Meier estimates. Duration of ORR will be summarized as median (with 95% CI) and interquartile range estimated using Kaplan- Meier method with corresponding 95% CIs. Tumor Response and endpoints listed above may also be explored by using may be explored using the modified Response Evaluation Criteria in Solid Tumours for immune-based therapeutics (iRECIST) [Seymour 2017]
Schedules of events:	The schedule of events and estimated blood volume collections are presented in Table 1-1 and Table 1-2. Each Cycle represents 28 days. Pre- and post-dose intervals are relative to the time of oral administration of X4P-001, designated 0 hr.

Table 1-1: Schedule of Events

Procedure[1]	Screening Visit[2]	Cycle 1		Cycle 2		Cycle 3		Cycle 4		Subsequent Odd-Numbered Cycles 5-19	Subsequent Even-Numbered Cycles 6-20	Repeats every 12 weeks[4]			EOT[5]	EOS[6]
		D1[3]	D15	D1	D15	D1	D15	D1	D15	D1	D1	Cycle 21 D1	Cycle 22 D1	Cycle 23 D1		
Informed Consent	X															
Inclusion/Exclusion Criteria	X															
Medical History	X															
History of Renal Cell Carcinoma	X															
Vital Signs[7]	X	X	X	X	X	X		X		X	X	X			X	X
Body weight & height[8]	X	X		X		X				X		X			X	X
ECOG PS	X					X				X		X			X	
Physical Examination	X	X		X		X				X		X			X	X
Ophthalmologic Examination[9]	X[10]			X		X		X		X		X			X	
12-Lead ECG	X	X	X[11]			X				X		X			X	X
Safety Laboratory Tests[12, 13]	X[14]	X	X	X	X	X	X	X	X	X	X	X			X	X
Serology	X[14]															
Pregnancy Test[13, 15]	X[14]	X[15]													X	X
Thyroid Function Test[13, 16]	X[14]	X		X		X		X		X		X			X	X
Blood Biomarker Collection[13, 17]		X		X		X		X		X		X			X	X
PK Collection[18]		X[19]	X[19]	X[20]	X[20]											
PD Collection[18]		X[19]	X[19]													
CT Imaging[21]	X					X				X		X			X[22]	
Administration of Study Drug(s) in clinic[23]		X	X	X	X											
Dispense eye drops and nasal spray[24]		X														
AE & Concomitant Med Monitoring[25]	X	X	X	X	X	X	X	X	X	X	X	X	X[26]	X[26]	X	X

1. The schedule is presented relative to Study Cycle, Day within Cycle, and Time of Dosing. The calendar day of the first administration of study drug is designated Day 1. Each Cycle represents 4 weeks (28 days). Pre- and post-dose intervals are relative to the time of oral administration, designated 0 hr.
2. Screening activities may be initiated up to 28 days prior to Day 1.
3. To allow for holidays and scheduling flexibility, on-treatment visits may be performed within ± 3 calendar days of the day indicated; ophthalmology exams and CT imaging within ± 4 calendar days.
4. For cycles >23, perform assessments as indicated for Cycle 21-23 every 12 weeks until EOT visit.
5. The EOT visit will be performed within 6 days after the last dose of study drug or the decision to terminate treatment prematurely.
6. The EOS visit is scheduled for 30 days (± 4 days) after the last dose of study drug. In the event the EOT visit is delayed, the EOS visit will be performed at least 14 days after the EOT visit.
7. Vital signs comprise heart rate, blood pressure, and temperature. For patients dosed in clinic on PK collection days, vital signs will be performed pre-dose.
8. Body height needs to be measured at screening only.
9. Ophthalmologic exam – see Section 7.1.1.5. for details. Note: an optometrist may complete the exam if all requirements can be met, including use of appropriate equipment to obtain the retinal photographs.
10. Screening ophthalmologic exam reports and retinal photos must be submitted to the sponsor at least 5 business days prior to Cycle 1 Day 1 to allow central review for eligibility
11. ECG should be performed at 2 hr (± 15 mins) post-dose
12. Safety laboratory tests – hematology and chemistry (see Section 7.2.1 for details).
13. Safety laboratory tests should be drawn and sent to central laboratory for analysis.
14. All laboratory tests required for screening will be performed by the central laboratory. Specimens should be submitted no more than 14 days prior to Day 1.
15. Women of child-bearing potential only (see Section 7.4.1.3). On Day 1, a urine or serum pregnancy test will be done at the site and the results obtained prior to dosing.
16. Thyroid Function Tests are performed for Parts A and B only; Section 7.2.1 for details.
17. Blood samples for tumor-related biomarkers; see Section 7.1.3.2 for details.
18. PK and PD samples will be collected for all patients in Part A and Part C, and for at least 15 patients in Part B.
19. PK and PD samples to be taken from 0-4 hr on Cycle 1 Day 1 and from 0-8 hr on Cycle 1 Day 15. See Section 7.1.2 and Section 7.1.3.1 for details of times for PK and PD dense sampling. For Part B subjects who do not complete PK/PD dense sampling (e.g. after the minimum 15 patients' samples are collected), a pre-dose PK sample will be collected at these visits.
20. PK sample is collected at Pre-dose only.
21. CT imaging of chest, abdomen, and pelvis; see Section 7.1.4.1 for details. Patients with history or current evidence of CNS disease should also have brain imaging by MRI.
22. CT imaging is not required at the EOT visit if performed within the previous 4 weeks and patient is being terminated for disease progression.
23. Study drugs will be self-administered by the patient daily, except at PK visits, when study drugs will be administered in the clinic.
24. See Section 7.4.4.1 for details.
25. Concomitant illnesses that worsen or illnesses with onset in screening period will be recorded as AEs (see Section 8).
26. Can be completed via telephone.

Table 1-2: Estimated Blood Volumes

Tests	MAX Vol (mL) per sample(s)	Screening[2] Visit	Cycle 1		Cycle 2		Cycle 3		Cycle 4		Odd-Numbered Cycles 5 through 19	Even-Numbered Cycles 6 through 20	Cycle 21 and every 3rd cycle until EOT[8]	EOT	EOS
			D1	D15	D1	D15	D1	D15	D1	D15					
Safety Laboratory	7	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetics	6		X[3]	X[4]	X[5]	X[5]									
Pharmacodynamic	6		X[3]	X[4]											
Blood Biomarker	11	-	X		X		X		X		X		X	X	X
Pregnancy test [6,7]		X												X	X
Serology[7]	2.5	X													
Total mL blood draw[1]		9.5	86	82.5	24	10.5	18	5	18	5	18	5	18	18	18

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 Cycle, Day within Cycle, and Time of Dosing. The calendar day of the first administration of study drug is designated Day 1. Each Cycle represents 4 weeks (28 days). Pre- and post-dose intervals are relative to the time of oral administration, designated 0 hr.
3. PK and PD samples taken at 7 different time points. See Section 7.1.2 and Section 7.1.3 for sampling times.
4. PK and PD samples taken at 8 different time points. See Section 7.1.2 and Section 7.1.3 for sampling times.
5. PK samples taken at pre-dose.
6. Pregnancy testing will be done on WOCP only.
7. Done at the central lab; extra blood volume is not required.
8. The samples are taken on Cycle 21, 24, 27, etc. (every 3 cycles) until EOT.

SCHEMATIC OF THE STUDY DESIGN

Figure 1-1 presents an overview of the design of Parts A, B, and C of the study.

Figure 1-1: Overview of Study Design

Part A X4P-001 with axitinib *Dose Escalation Cohort* X4P-001 planned dose levels: 200 mg BID; 400, 600, 800, 1200 mg QD, in combination with axitinib	**Part B** X4P-001 with axitinib *RP2D Dose-Expansion Study* Approximately 45 patients to receive: X4P-001 at RP2D in	**Part C** X4P-001 monotherapy *Dose Escalation and Expansion Cohort* If MTD with axitinib (Part A) is ≤800 mg QD, then additional monotherapy dose escalation cohorts may be enrolled to define the MTD of X4P-001 as single agent. Expansion Cohort: X4P-001 at or below MTD*

1. KEY ROLES

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2. INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1. Background Information

In ~75% of patients with sporadic clear-cell renal cell carcinoma (ccRCC) there is functional loss of the *VHL* gene, typically by mutation, but also silencing by hypermethylation. *VHL* encodes the von Hippel-Lindau tumor suppression protein which mediates proteolytic degradation of the hypoxia-inducible factor (HIF)-α [Turner 2002]. Loss of this function results in increased levels of HIF-α, increased expression of vascular endothelial growth factor (VEGF), tumor angiogenesis, and, ultimately, the hypervascularity characteristic of these malignancies. Multiple agents that block the activation of the VEGF pathway have been shown to improve outcomes, including:

- Tyrosine kinase inhibitors (TKIs), such as sunitinib, axitinib, sorafenib or pazopanib, that block the VEGF signaling pathway.
- Bevacizumab, a monoclonal antibody, that binds circulating VEGF and thus prevents the ligand from binding to the VEGF receptor.

Despite the demonstrated benefits of angiogenesis inhibitors in ccRCC, the approach is not curative. Although many patients respond initially, most of them experience relapse and progression. There is clear unmet need for agents that improve outcomes by preventing or delaying treatment resistance.

CXCR4 (C-X-C chemokine receptor type 4) is the receptor for CXCL12 (C-X-C chemokine ligand type 12; also referred to as SDF-1α, stromal-derived-factor 1α). CXCL12 has potent chemotactic activity for lymphocytes and MDSCs (myeloid-derived suppressor cells), and is important in homing of hematopoietic stem cells to the bone marrow. CXCR4 is also expressed and active on multiple types of human cancers, including ccRCC, ovarian cancer, and melanoma, and increased expression of CXCR4 on tumor cells has been associated with significantly decreased overall patient survival [Staller 2003; Sekiya 2012; Ejtesja, 2008; Maréchal 2009].

Multiple observations implicate the CXCL12/CXCR4 axis in contributing to the lack (or loss) of tumor responsiveness to angiogenesis inhibitors (also referred to as “angiogenic escape”). In animal cancer models interference with CXCR4 function has been demonstrated to disrupt the tumor microenvironment (TME) and unmask the tumor to immune attack by multiple mechanisms, including

- Eliminating tumor re-vascularization [Righi 2011; Kioi 2010].
- Decreasing the infiltration of MDSCs.

- Increasing the ratio of CD8+ T cells to T regulatory (Treg) cells [Righi 2011; Feig 2013; Fearon 2014].

These effects result in significantly decreased tumor burden and increased overall survival in xenograft, syngeneic, as well as transgenic, cancer models [Righi 2011; Feig 2013; Kioi 2010].

X4P-001 is a potent, orally bioavailable CXCR4 antagonist [Stone 2007], that has demonstrated activity in solid and liquid tumor models [Parameswaran 2011], and unpublished data] and has previously (under the designations AMD070 and AMD11070) been in Phase 1 and 2a studies involving a total of 71 healthy volunteers [Stone 2007; Cao 2008; Nyunt 2008] and human immunodeficiency virus (HIV)-infected patients [Moyle 2009; Study ACTG (DIAIDS) Protocol A5210]. These studies demonstrated the following:

- Oral administration of up to 400 mg twice daily (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 serious or severe treatment-related adverse events and no pattern of clinically significant laboratory changes.
- Pharmacodynamic activity, with dose- and concentration-related changes in circulating white blood cells (WBCs).
- High volume of distribution (V_L) suggesting high tissue penetrance.

We postulate that effective CXCR4 antagonism by X4P-001 would be of potential benefit in patients with advanced ccRCC and other cancers by multiple mechanisms:

- Decreased recruitment of MDSC, resulting in increased anti-tumor immune attack.
- Sustained decrease in neoangiogenesis and tumor vascular supply.
- Interference with the autocrine effect of increased expression by ccRCC of both CXCR4 and CXCL12, its only ligand, thereby, potentially reducing cancer cell metastasis.

This clinical study in patients with advanced ccRCC will evaluate X4P-001 both as a single agent (monotherapy) and also in combination with axitinib, a small molecule TKI approved for second-line treatment of patients with ccRCC. We hypothesize that the combination has the potential to further improve outcomes by reducing the angiogenic escape that typically occurs with TKI therapy.

2.2. Overview of X4P-001

X4P-001 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 and here X4P-001. Throughout the prior clinical development program, the drug product used was capsules containing 100 mg of the free base. The same formulation will be used in this protocol (see Section 6.1.2).

During the earlier clinical studies, a *p*-hydroxybenzoate (PHB) salt form of the drug (designated AMD11070PHB) was identified for future manufacturing and development purposes. Animal toxicology studies (13- and 26-week duration) conducted with AMD11070PHB demonstrated unexpected findings, including retinal changes in albino rats treated for 26 weeks and notable gastrointestinal (GI) 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 in this program, these observations were carefully considered in the safety monitoring plans for clinical studies of X4P‑001.

2.2.1. Prior Clinical Studies Conducted Using X4P-001

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 2-1 shows the protocol numbers, titles, and related publications; Table 2-2 summarizes the study populations, objectives, numbers, dose administered, and duration.

These studies demonstrated the following:

- Oral (PO) 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 X4P-001 is ~23 hours, supporting the use of QD dosing (see Investigator's Brochure).
- Pharmacodynamic activity, as assessed by increases in circulating WBC, was related to dose and duration of treatment.

Table 2-1: Prior Clinical Studies Conducted using X4P-001 – 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
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
A5210	Phase IB/IIA Dose-Finding Safety and Activity Study of AMD11070 (An Orally Administered CXCR4 Entry Inhibitor) in HIV-Infected Patients	(unpublished)

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

Table 2-2: Prior Clinical Studies Conducted using X4P-001 – 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, DDI 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

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 X4P-001

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 PO 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 half-life ($T_{1/2}$) was 22.9 hr, supporting the QD dosing regimen.

Steady-state PK parameters were similar in healthy volunteers (AMD-1002) and in HIV infected patients (A5210 and AMD-1001). The results (mean ± standard deviation) were derived from 26 subjects, including both healthy volunteers and HIV-infected subjects, who received X4P-001 at 200 mg BID for 8 to 10 days.

- AUC(0-12hr): 3735 ± 1755 ng·hr/mL
- Cmax: 1223 ± 600 ng/mL
- Minimum concentration (Cmin) at 12 hours: 74.3 ± 47.3 ng/mL
- Time to maximum concentration (Tmax): 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 X4P-001 200 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 X4P-001 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 X4P-001. 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 Based on CYP Metabolism

Two clinical studies (A5191, AMD-1002) were conducted to assess the potential for drug-drug interactions (DDI). Ritonavir (a strong CYP3A4 inhibitor, P-gp inhibitor) resulted in a modest increase in X4P-001 plasma concentrations [A5191, Cao et al., 2008]. The mean C_{max} and AUC of X4P-001 coadministered with the first dose of ritonavir were increased by 39% and 60%, respectively, compared to the administration of X4P-001 alone. Similar effects were seen after ritonavir had been administered twice daily for 14 days.

Study AMD-1002 assessed the effect of X4P-001 on metabolism of CYP3A4 and CYP2D6 substrates, using midazolam and dextromethorphan as substrates [Nyunt et al., 2008]. Administration of X4P-001 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.

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 et al., 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% confidence interval [CI], 1.95x to 2.11x).
- The estimated half maximal effective concentration (EC_{50}) was 39 ng/mL (95% CI, 28 to 50 ng/mL), which is below the observed steady-state $C_{min(12h)}$ for X4P-001 at 200 mg BID, the starting dose in the proposed oncology studies.

2.2.3. Clinical Safety Experience with X4P-001

2.2.3.1. Safety Experience – X4 Pharmaceuticals Clinical Development Program

As of July 05, 2017, the following studies have been initiated or completed:

- X4P-001-RCCA – the study detailed in this protocol.
- X4P-001-RCCB - a study adding X4P-001 to patients receiving nivolumab for treatment of advanced ccRCC.
- X4P-001-MELA – a phase 1b study of X4P-001 alone and in combination with pembrolizumab in patients with advanced melanoma.
- X4P-001-MKKA – a phase 2/3 randomized, double-blind, placebo-controlled trial of X4P-001 in patients with WHIM (Warts, Hypogammaglobulinemia, Infections and Myelokathexis) Syndrome
- X4P-001-REGA – a phase 1 study in healthy volunteers comparing 2 different dosing regimens: 200 mg BID versus 400 mg QD.

Please refer to the current Investigator's Brochure for more information related to X4P-001's clinical safety data.

2.2.3.2. Safety Experience – Prior Development Program

A total of 71 individuals were exposed to X4P-001 in 4 prior clinical studies. Across these 4 studies:

- The most common AEs across studies were mild to moderate GI events.
- There were no deaths and no discontinuations due to AEs. Two subjects discontinued for personal reasons after receiving 1 or 2 doses of X4P-001.
- There was one 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 liver function tests (LFTs) revealed no pattern of treatment-emergent LFT abnormalities suggesting a drug effect.

2.2.4. Treatment Effect of X4P-001 in Prior Clinical Studies

As of July 05, 2017, there are no efficacy data with X4P-001 to report in patients with malignancy (including ccRCC or melanoma).

2.2.5. Nonclinical Toxicity Studies of X4P-001

Pivotal nonclinical toxicity studies were conducted in rats and Beagle dogs with X4P-001 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 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 original development program of AMD11070 identified an alternative salt form of the drug substance for manufacturing purpose, PHB salt (designated AMD11070PHB). Toxicology studies of AMD11070PHB included unexpected findings of retinal degeneration in Albino rats treated for 26 weeks. This was not seen in Beagles administered either PHB or free base (X4P-

001) drug forms for up to 13 weeks. AMD11070PHB was never administered to humans and is not proposed for use in any clinical studies in this program.

2.3. Clinical Experience with Related Compounds

Mozobil® (plerixafor) is the only approved agent that blocks the CXCR4 receptor, which is an injectable drug with a very short half-life, and is approved in combination with granulocyte-colony stimulating factor (G-CSF) to mobilize hematopoietic stem cells (HSCs) to the peripheral blood for collection and subsequent autologous transplantation in patients with non-Hodgkin's lymphoma and multiple myeloma.

In tumor models in mice the drug has been administered by continuous infusion using subcutaneous osmotic reservoirs. The results of those nonclinical studies indicate that CXCR4 receptor blockade has an anti-tumor treatment effect and thereby support the hypothesis that an orally administered agent such as X4P-001 could have clinical benefit.

2.4. Rationale

Agents directed against the VEGF pathway have demonstrated clinical benefit in patients with advanced ccRCC. Targets of multi-tyrosine kinase inhibitors (mTKI) include vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR), and cytokine receptor (kit).

While these agents have demonstrated benefit in progression-free and overall survival, tumors typically develop resistance to therapy within 5-11 months [Wang 2011]. Consequently, strategies to improve or prolong the effects have been actively investigated, including dose-intensification, variations in the sequencing and scheduling of agents, and the use of more selective agents [Amato 2007; Houk 2010; Rini 2011a; Rini 2011b].

Animal studies of ccRCC xenografts implicate increased infiltration of MDSC as a central factor in acquired resistance to VEGF-targeted therapies [Panka 2013] as well as other anti-cancer therapies [Shojaei 2007; Zea 2005; Nagaraj 2007; Finke 2011]. MDSC trafficking into tumor tissue is regulated by chemokines, many of which (e.g. SDF-1/CXCL12) are produced in response to hypoxia in a HIF-dependent manner. Agents such as X4P-001 that directly block CXCL12/CXCR4 signaling should decrease MDSC trafficking and, thereby, prevent the emergence of resistance to mTKI. This approach would be expected to introduce comparatively little additional toxicity since CXCR4-targeted drugs do not induce cell-cycle arrest in normal proliferating cell populations and have been well tolerated in short-term (10-day) clinical studies [Moyle 2009]. This protocol is designed to test this hypothesis systematically by evaluating the effects of the CXCR4 inhibitor X4P-001 on MDSC trafficking and differentiation, tumor

vascularization, and disease progression in RCC in combination with axitinib, the most selective mTKI currently approved.

This protocol represents the first use of X4P-001 in patients with RCC.

3. OBJECTIVES AND PURPOSE

3.1. Primary Objective

The primary objective is:

- To evaluate the safety and tolerability of escalating dose levels of X4P-001, both in combination with axitinib and as single agent, in patients with advanced ccRCC.

3.2. Secondary Objectives

Secondary objectives are:

- To assess the treatment effect (clinical activity) of X4P-001, both in combination with axitinib and as single agent, in patients with advanced ccRCC using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 [Eisenhauer 2009], including progression free survival (PFS).
- To characterize the pharmacokinetics of escalating dose levels of X4P-001 administered orally.

3.3. Exploratory Objective

The exploratory objectives are:

- To investigate associations between the treatment effect of X4P-001 (in combination with axitinib and as a single agent) and selected pharmacodynamic and disease-related biomarkers (e.g., circulating CD34+ cells, plasma levels of soluble VEGFR).
- To assess the treatment effect (clinical activity) of X4P-001, both in combination with axitinib and as single agent, in patients with advanced ccRCC using modified Response Evaluation Criteria in Solid Tumors for immune-based therapeutics (iRECIST) [Seymour 2017].

4. STUDY DESIGN AND ENDPOINTS

4.1. Description of the Study Design

This study will be conducted in patients with advanced ccRCC and will comprise 3 parts.

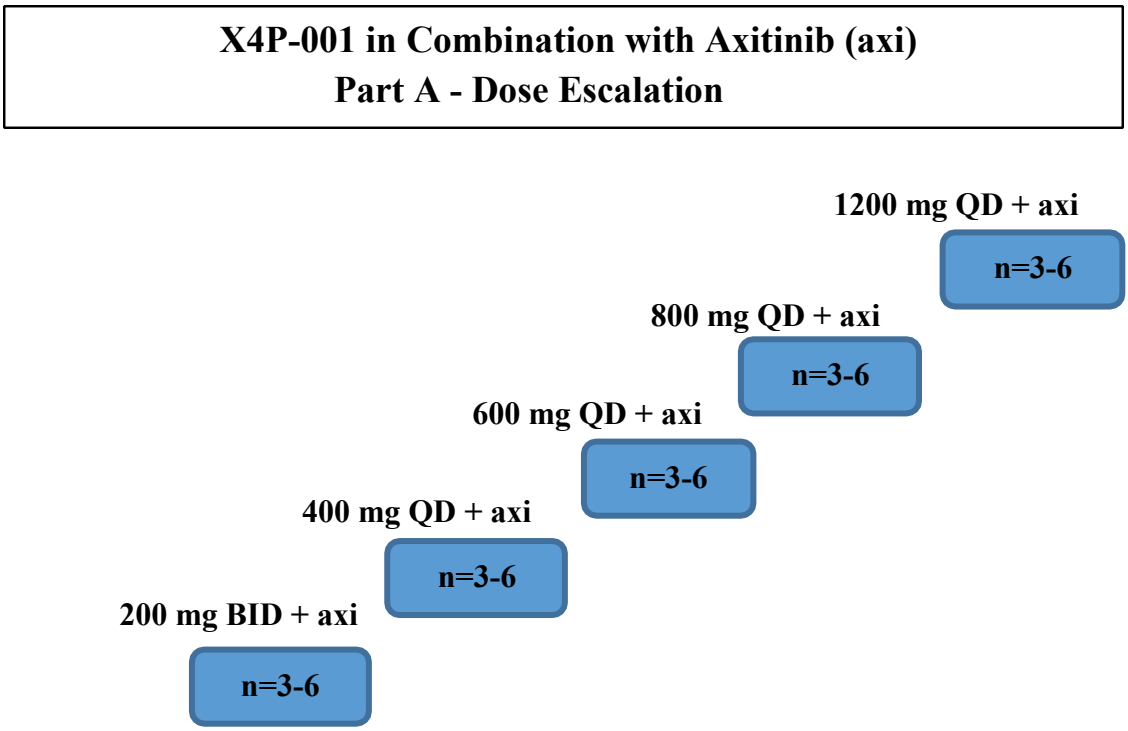
- **Part A (Phase 1)** will assess the safety and tolerability of escalating doses levels of X4P-001 in combination with axitinib, a TKI approved for use in this setting [Axitinib US prescribing information, 2014]. The X4P-001 dose level for the initial cohort is 200 mg BID. Subsequent cohorts will be administered X4P-001 QD. The initial QD dose level will be 400 mg QD (representing the same total daily exposure as 200 mg BID), and then progressing to 600, 800, and 1200 mg. A safe maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D) will be identified in Part A. The RP2D may be the same as the MTD or may be lower (see Section 4.1.1).
- **Part B (Phase 2)** is an expansion cohort assessing the safety, tolerability, and treatment effect of X4P-001 at RP2D in combination with axitinib in approximately 45 patients. If the RP2D is determined before the MTD is reached in Part A, Part B may be initiated while Part A is ongoing (see Section 4.1.2).
- **Part C** will assess the safety, tolerability, and treatment effect of X4P-001 as monotherapy in patients with advanced ccRCC and may be initiated after the MTD of X4P-001 with axitinib is defined in Part A. If that MTD was ≤800 mg QD, then the MTD as monotherapy will be defined by enrolling additional dose-escalation cohorts to receive X4P-001 as a single agent up to, but not exceeding, 1200 mg QD (see Section 4.1.3).

4.1.1. Part A (Phase 1): X4P-001 with Axitinib – Dose-escalation Cohorts

Part A will evaluate the safety and tolerability of X4P-001 at increasing dose levels –specifically, 200 mg orally BID, then 400, 600, 800, 1200 mg QD – in combination with axitinib (Figure 4-1). Axitinib is given at 5 mg orally BID in addition to X4P-001 at the assigned dose level. While proceeding with further dose escalation, additional patients may be enrolled at preceding dose levels that have been declared to be safe at a prior Data Review Committee (DRC) meeting to better understand the safety, tolerability and PK of X4P-001.

- Provision is made for a contingency cohort (escalation or de-escalation) receiving an additional dose level of X4P-001(e.g. 1000 mg QD) plus axitinib with the approval of the Data Review Committee (DRC; see Section 8.6.3).

Figure 4-1: Study Design for Part A



4.1.1.1. Dose Escalation Process

Dose-escalation will proceed using a standard "3+3" design with careful monitoring and review by the DRC. The review will include all available safety data. To facilitate standardizing the dose-escalation reviews across different cohorts, the focus will be on the observations at that dose level from the start of treatment (C1D1) through the visit scheduled for the beginning of C2D1 (Week 5). (Hereafter, this period will be referred to as "the first 4 weeks of treatment").

Each dose-escalation cohort is expected to enroll at least 3 patients, with a maximum of 6 patients.

- If 3 patients at the dose level complete the first 4 weeks of treatment without a DLT event, the DRC will conduct a dose-escalation review.
- If 1 patient at the dose level experiences a DLT event during the first 4 weeks of treatment, then enrollment at that dose level will continue to a total of 6 patients and the dose-escalation review will be done when all 6 patients have completed the first 4 weeks treatment.

- If 2 patients at a dose level experience DLT events during the first 4 weeks of treatment, then no further dosing will occur at that or higher dose levels.

The expected outcomes of the DRC review include:

- *Dose-escalation* – progression to the next planned dose level.
- *Continued enrollment at the dose level under review* (applicable only after 3 patients) – enroll up to 6 patients at the current dose level to obtain additional safety data for subsequent review.
- *No further dose-escalation cohorts* – at this time the DRC will indicate the dose level they consider represents the maximum tolerated dose (MTD) for X4P-001 in combination with axitinib.
- The MTD will be applicable for proceeding to Part C or RP2D is determined to proceed to Part B.

Replacement of Non-evaluable Patients. A maximum of 6 evaluable patients will be enrolled per dose-escalation cohort in Part A. An evaluable patient is defined as a patient who either (a) successfully completes 4 weeks treatment, receiving at least 75% of the assigned treatment (Section 6.1.9); or (b) experiences a dose-limiting toxicity (DLT) event in that period.

To assure that the required number of evaluable patients is available for DRC review, non-evaluable patients (i.e., those who discontinue treatment prior to completion of the C2D1 (Week 5) visit for reasons other than a DLT) may be replaced within a cohort; the replacement will be assigned the same dose level.

4.1.1.2. Treatment Cycle 2 and Beyond

Patients who do not experience a DLT in Cycle 1 will stay on study treatment. If during Cycle 2 or later treatment cycles, a patient experiences an unacceptable toxicity (defined with the same criteria of DLT for Cycle 1), then, based on the judgment of the Investigator, the patient may continue treatment per dose modification recommendations (Sections 6.1.7.1 and 6.1.7.2).

4.1.1.3. Definition of a Dose-Limiting Toxicity (DLT)

A DLT event is defined as an adverse event occurring in Cycle 1 (i.e., in the first 4 weeks of treatment) that meets *both* of the following criteria:

a) Is assessed by the Investigator as possibly or probably related to study drug (X4P-001) (see Section 8.2.2 for details).

b) Represents one of the following events (grading as defined by NCI CTCAE, Ver. 4.03) (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 (confirmatory sample to be submitted within 48 hrs of receiving initial lab report)
  - *Exception*: Grade 3 electrolyte events 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.
- Results, during the first 4 weeks of treatment, in the patient being unable to receive at least 75% of the intended dose (Section 6.1.9).
- Is one of the following, which are designated as *critical DLT events*
  - AST/ALT increased >3x ULN with Total Bilirubin increased >2x ULN in the absence of cholestasis.
  - Febrile neutropenia (Grade ≥3) — defined as ANC <1000/mm^3 with a single temperature of >38.3°C (101°F) *or* a sustained temperature of ≥38°C (100.4°F) for more than one hour.
  - Retinopathy – confirmed treatment-emergent retinopathy (see Section 7.1.1.5).

4.1.1.4. Definition of Maximum Tolerated Dose (MTD) and Recommended Phase 2 Dose (RP2D)

The MTD is the highest dose level meeting *both* of the following criteria:

- It is below the level at which 2 or more patients in a dose-escalation cohort experienced DLTs during the first 4 weeks of treatment;
- It is a dose level at which no more than 1 patient in a dose-escalation cohort experienced a DLT during the first 4 weeks of treatment.

The RP2D is defined as the dose which will be assigned in Part B based on Sponsor and DRC review of all available data of X4P-001, including safety and tolerability as well as PK, pharmacodynamic, and anti-tumor activity. The RP2D may be the same as the MTD or may be lower. The RP2D may not exceed the MTD.

4.1.2. Part B (Phase 2): An Expansion Cohort of the RP2D of X4P-001 in Combination with Axitinib

The goal of Part B is to assess the safety, tolerability, and treatment effect of X4P-001 at the RP2D dose level in approximately 45 patients with advanced ccRCC. If the RP2D is determined before the MTD is reached in Part A, Part B may be initiated while Part A is still ongoing.

Safety at the RP2D will be verified by monitoring DLTs as follows: if ≤ 4 DLTs are observed in the first 12 patients during the first 4 weeks of treatment, this RP2D dose will be considered safe to proceed for the remaining patients in this study. If 5 or more DLTs are observed in the first 12 patients during the first 4 weeks of treatment, the trial may continue with dose de-escalation after DRC review. The dose will be reduced at least one dose level lower, according to the dose levels presented in Figure 4-1. To further protect patient safety, if additional DLTs are observed anytime during the trial, dose de-escalation can be enforced based on DRC recommendation, or the trial can be stopped at the sponsor's discretion.

Patients in Part B will be followed for safety and tumor response per RECIST 1.1 guidance. Patients will remain on study treatment until experiencing disease progression, unacceptable toxicity, or other specified reasons for discontinuation (see Section 5.4.1). In addition, a subset of patients will have PK/PD evaluations performed (at least 15 patients).

4.1.3. Part C: X4P-001 as a Single Agent (Monotherapy)

The goal of Part C is to assess the safety, tolerability, and treatment effect of single agent X4P-001 in patients with advanced ccRCC. Part C may be initiated after the DRC determines the MTD for X4P-001 in combination with axitinib (i.e., may enroll in parallel with Part B); if enrollment for Part B closes before the Part C MTD is reached, the Sponsor may elect to terminate the study for administrative reasons.

The MTD of X4P-001 as single agent will be determined as follows:

- If the MTD in Part A using combination treatment with axitinib is 1200 mg QD, then that dose of X4P-001 will be used for the single agent expansion cohort. Higher doses will not be assessed.
- If the MTD in Part A using combination treatment with axitinib is ≤800 mg QD, then additional single agent, dose-escalation cohorts – that is, X4P-001 administered alone without axitinib – will be enrolled. The starting dose level will be one step above the MTD established in combination with axitinib in Part A; the maximum dose evaluated will be 1200 mg QD. Escalation will proceed as detailed for Part A; the same potential dose levels (Figure 4-1), the same "3+3" design, and the same dose-escalation review procedures will be applied (see Section 4.1.1).

Number of Patients. After establishing the MTD for single agent X4P-001, approximately 15 patients may be enrolled at that dose level as expansion cohort.

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

4.2.1. Rationale for the Study Design

The open-label study design is consistent with both the study objectives and current principles for the evaluation of investigational drugs in patients with advanced malignancy.

- Part A: The dose-escalation design with enrollment guided by safety experience and reviewed by a DRC serves to minimize the number of patients required and to assure patient safety is protected.
- Part B provides assessment of the safety and tolerability of X4P-001 in combination with axitinib at the RP2D dose level to guide further development of that regimen in the treatment of ccRCC and other malignancies. A DRC review of the initial 12 patients provides an additional safety assessment of the RP2D.
- Part C provides assessing X4P-001 as a single agent to guide further development of X4P-001 monotherapy in ccRCC and other malignancies.

4.2.2. Rationale for the Dose Regimen

Starting dose / Safety. The proposed starting dose (200 mg BID) is selected based on experience in prior clinical studies demonstrating that dose was (a) pharmacologically active (Section 2.2.2.4) and (b) generally safe and well-tolerated in 26 healthy volunteers and HIV-infected patients treated for 8 to 10 days (Section 2.2.3), with no treatment-related discontinuations and no pattern of significant laboratory abnormalities. See Section 2.2.5 for discussion of anticipated clinical exposure relative to findings seen in nonclinical studies.

Dosing interval. BID dosing is supported by clinical experience with BID dosing as detailed above. In the prior development program, 400 mg BID was generally safe and well tolerated for 3.5 days and the $T_{1/2}$ of X4P-001 is ~23hr. The once daily dosing regimen is easier and more reliable, particularly in patients with cancer, for whom avoiding food for two 3-hour periods each day may be difficult.

In consideration of the advantages of once daily dosing, provision is made for patients in the initial cohort administered X4P-001 at 200 mg BID to convert to 400 mg QD, contingent on the following:

- Successful DRC review of the 600 mg QD dose level with approval for further dose escalation.
- Request of the patient's Investigator and approval of the Medical Monitor.

Dose Escalation. Dose-escalation will proceed conservatively with increases never exceeding 1.5x the prior dose level (see Section 4.1.1). Conversion of the dose escalation program from BID to QD will be accomplished as follows:

- Following successful DRC review of the 200 mg BID cohort, once daily dosing regimens will be applied to subsequent cohorts.
- The first once daily cohort will be 400 mg QD, representing the same total daily dose as 200 mg BID.
- Dose escalation will then proceed through the planned daily doses, which will be administered as 600, 800, and 1200 mg QD, the last being the highest dose level that will be given.

4.3. Endpoints

4.3.1. Safety Endpoints

Safety endpoints are:

- AEs.
- Clinical observations (e.g., vital signs, physical examination).
- Laboratory tests, (e.g., clinical chemistry, hematology, and thyroid function tests [Part A and Part B only]).
- ECGs.
- Ophthalmologic examination

4.3.2. Efficacy Endpoints

Treatment effect (tumor response) will be analyzed using RECIST v1.1 [Eisenhauer 2009] to determine the following efficacy endpoints:

- Objective response rate (ORR) (Complete Response [CR] + Partial Response [PR])
- Time to objective response
- Duration of objective response
- Disease control rate (CR + PR + Stable Disease)
- Time to progression
- PFS

4.3.3. PK and PD Endpoints

PK samples will be collected from 0-4hr on Cycle 1 Day 1 (C1D1) and from 0-8 hr on C1D15. Pre-dose PK samples are also collection on C2D1 and C2D15.

White blood cell counts and counts of circulation CD34+ positive cells are PD samples.

4.3.4. Exploratory Endpoints

Exploratory endpoints are blood biomarkers, including serum biomarkers and PBMC, as well as tumor response assessed possibly using modified Response Evaluation Criteria in Solid Tumors for immune-based therapeutics (iRECIST) [Seymour 2017].

5. STUDY ENROLLMENT AND WITHDRAWAL

5.1. Inclusion Criteria

Patients must meet all of the following criteria to be eligible for study participation:

1. Be at least 18 years of age.
2. Have signed the current approved informed consent form.
3. Have a histologically confirmed diagnosis of predominant ccRCC.
4. Have received at least one prior course of treatment for ccRCC (see Section 5.2 for specific exclusions).
5. Have on computed tomography (CT) imaging done within 28 days of Day 1 findings consistent with advanced ccRCC, including at least one extra-renal measurable target lesion meeting the criteria of RECIST v1.1 [Eisenhauer 2009]. See Section 7.1.4.1 for details regarding specific imaging technology.
6. Agree to use contraception as follows:
   - For women of childbearing potential (WOCP, see Section 7.4.1.2 for definition) 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. Acceptable methods are described in Section 7.4.1.3
   - For males, agree to use a condom with any WOCP sexual partner from Day 1 of study treatment, through the study, and at least 4 weeks after the last dose of study drug.
7. For women of childbearing potential, have a negative pregnancy test (serum or urine) on Day 1 prior to initiating study treatment.
8. Be willing and able to comply with this protocol.

5.2. Exclusion Criteria

Patients meeting any of the following criteria are excluded from study participation:

1. Has life expectancy of less than 3 months.
2. Has performance status Grade >2 (Eastern Cooperative Oncology Group [ECOG] criteria).
3. Has New York Heart Association Class III or IV heart failure or uncontrolled hypertension (systolic blood pressure [SBP] ≥160 mm Hg; diastolic blood pressure [DBP] ≥100 mm Hg).
4. Has previously received X4P-001.
5. *Parts A and B only*: Has received a prior course of axitinib.
6. *Parts A and B only*: Has received mechanistic target of rapamycin (mTOR) inhibitor(s) as their only prior treatment for ccRCC.
7. Has a prior history or current evidence of intracranial (CNS) metastatic RCC, *except* for ≤3 lesions treated by CyberKnife (or any type of radiation) or excisional surgery, clinically stable for at least 4 weeks, and without evidence of recurrence on MRI imaging at screening.
8. Has ongoing acute clinical AEs of National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Grade >1 resulting from prior cancer therapies (except alopecia, TKI-related hand-foot syndrome, or thyroid dysfunction).
9. Has had within the past 6 months the occurrence or persistence of one or more of the following medical conditions that could not be controlled with usual medical care (e.g., required emergency care or hospitalization): hypertension, angina, congestive heart failure, diabetes, seizure disorder.
10. Has had within the past 6 months the occurrence of one or more of the following events: myocardial infarction, cerebrovascular accident, deep vein thrombosis, pulmonary embolism, hemorrhage (CTCAE Grade 3 or 4), chronic liver disease (meeting criteria for Child-Pugh Class B or C), a second active malignancy (excluding: malignancies that were treated curatively and have not recurred within 2 years prior to study treatment; completely resected basal cell and squamous cell skin cancers; any malignancy considered to be indolent and that has never required therapy; and completely resected carcinoma in situ of any type), organ transplantation.
11. Has had within the 4 weeks prior to initiation of study drug, or is expected to have during the study period, surgery requiring general anesthesia.
12. Has a known history of a positive serology or viral load for HIV or a known history of AIDS.
13. Has, at screening, serologic laboratory tests meeting one or more of the following criteria:

- An indeterminate or positive test for antibody to hepatitis C virus (HCV), unless documented to have no detectable viral load on 2 independent samples.
- A positive test for hepatitis B surface antigen (HBsAg).

14. Has, at screening, safety laboratory tests meeting one or more of the following criteria:
    - Hemoglobin <8.0 g/dL
    - Absolute neutrophil count (ANC) <1,500/µL
    - Platelets <75,000/µL
    - Creatinine >2.0x ULN
    - Serum aspartate transaminase (AST) >2.5x upper limit of normal (ULN)
    - Serum alanine transaminase (ALT) >2.5x ULN
    - AST and ALT >5x ULN for patients with liver metastasis
    - Total bilirubin >1.5x ULN (unless due to Gilbert's Syndrome, total bilirubin > 3.0x ULN and direct bilirubin > 1.5x ULN)
15. Has received other anti-cancer therapy within the following specified intervals prior to Day 1:
    - TKI within 2 weeks.
    - Radiation therapy within 2 weeks.
    - Bevacizumab within 4 weeks.
    - Other chemotherapy (e.g., mitomycin-C, nitrosourea) or immunotherapy (e.g., antibody, cytokine) within 4 weeks.
    - For investigational anti-cancer therapies, the interval will be determined in consultation with the Medical Monitor.
16. Has, within 2 weeks prior to Day 1, received a medication prohibited based on CYP3A4 interaction (see Section 7.4.1.1 for details).
17. Has, within 2 weeks prior to Day 1, received systemic corticosteroids exceeding prednisone 10 mg per day or equivalent; for other immunosuppressive agents, the exclusionary dose and duration will be determined in consultation with the Medical Monitor.
18. Is nursing.
19. Has, at the planned initiation of study drug, an uncontrolled infection.
20. 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 3A4 interactions (see Section

7.4.1.1), 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). 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).

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:

- *DLT event* – see Section 4.1.1.3.
  - For any DLT event occurring during the first 4 weeks of treatment, study treatment will be discontinued permanently.
  - For one of the critical DLT events (see Section 4.1.1.3) occurring after successful completion of 4 weeks of treatment, study treatment will be discontinued permanently.
  - For other unacceptable toxicity (defined with the same criteria of DLT for Cycle 1) occurring after successful completion of 4 weeks of treatment, provision is made for dose reduction (see Sections 6.1.7.1 and 6.1.7.2).
- *Disease progression* – Patients will be assessed at study entry and every 8 weeks for 80 weeks (20 cycles) and then every 12 weeks thereafter while on treatment; unscheduled assessments may be conducted in response to new clinical observations. Disease status will be classified according to RECIST v1.1 [Eisenhauer 2009] (see Section 7.1.4.2 for details).
  - Study treatment will be discontinued in patients who demonstrate disease progression. For patients who have radiological disease progression, but haven't experienced clinical progression/deterioration, the patient may stay on study if the Investigator considers that the patient may still derive benefit from this study and have consulted with Medical Monitor.

  Removal of the subject for clinical progression/deterioration will be at the discretion of the Investigator. The decision needs to be consulted with Medical Monitor.

- *Adverse Event, other than DLT* – 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.
- *Withdrawal of Consent* – The patient desired to withdraw from further participation in the study in the absence of a clinical issue. If the patient gave a reason for withdrawing (e.g., leaving area), it should be recorded in the eCRF.
- *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 End-of-Treatment (EOT) and End-of-Study (EOS) visits will be performed as specified. 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 terminate the study or particular study center at any time. If the Sponsor or Investigator discovers conditions arising during the study that suggest the study should be halted, then study termination can occur only after appropriate consultation between the Sponsor and Investigators. Conditions that may warrant study or study center termination include, but are not limited to:

- The discovery of any unexpected, significant, or unacceptable risk to the patients enrolled in the study.
- Failure of the Investigator to enter patients at an acceptable rate.
- Insufficient adherence to the protocol requirements.
- A decision on the part of the Sponsor to suspend or discontinue development of study drug.

Should the study be closed prematurely, all study materials (study drug, etc.) must be returned to the Sponsor or designee (or disposed of as directed by the Sponsor or designee).

6. STUDY DRUG(S)

6.1. Study Drug(s) and Control Description

6.1.1. Acquisition

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 ICH Good Manufacturing Practice (GMP) and Good Clinical Practice (GCP) guidelines.

Table 6-1: Physical and Chemical Properties of Active Ingredient (Drug Substance)

Name	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	X4P-001 is freely soluble in the pH range 3.0 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). X4P-001 is only slightly soluble in water.
Melting Point	111 °C

Table 6-2: Formulation of Drug Product

Name	X4P-001 100 mg or 200 mg Capsule
Active ingredient	X4P-001
Excipients	Microcrystalline cellulose, dibasic calcium phosphate dihydrate, croscarmellose sodium, sodium stearyl fumarate, colloidal silicon dioxide, sodium lauryl sulfate
How supplied	Refer to the Pharmacy Manual.
Storage	5°C ± 3°C; Protect from light and humidity
Administration	Oral

6.1.3. Product Storage and Stability

Refer to the Pharmacy Manual.

6.1.4. Preparation

None.

6.1.5. Dosing and Administration

6.1.5.1. X4P-001

X4P-001 at the assigned dose level is administered orally QD or BID. Patients will be instructed about both dosing schedule and requirements relating to food or drink near the time of dosing.

Dosing Schedule.

For BID dose, it is expected that the first daily dose will be taken in the morning and the second daily dose approximately 12 hours later using the following guidelines:

- Dosing should be at the same times each day ± 2 hr.
- The interval between successive doses should not be <9 hours nor >15 hours. It the interval would be >15 hrs, the dose should be omitted and the usual schedule resumed at the next dose.

For QD dose, it is expected that the daily dose will be taken as follows:

- The daily dose should be taken in the morning, at the same times each day ± 2 hr.
- The interval between successive doses should not be < 20 hrs.
- If the interval between successive doses is delayed to > 30 hrs, the dose should be omitted and the usual schedule resumed the next day.

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

- No food or drink (except water) for 1 hour before dosing
- No food or drink (except water) for 2 hours after dosing.

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.

6.1.5.2. Axitinib

Axitinib may be taken at the same time as X4P-001. Alternatively, since axitinib has been associated with GI AEs and its absorption is not altered by food (see current product label), patients may, with the approval of their Investigator, take the axitinib separately, following the same BID dosing schedule guidelines noted in Section 6.1.5.1.

Investigators should review and be familiar with the current US prescribing information for axitinib.

6.1.6. Route of Administration

X4P-001 will be administered PO.

6.1.6.1. Axitinib

Axitinib will be administered PO.

6.1.7. Dose Adjustments/Modifications/Delays

Treatment modifications should be implemented as described below. Any plan to deviate from the following guidelines in the interest of patient safety must be previously discussed with the Medical Monitor unless there is an urgent need for action. Investigators always have the option to discontinue study treatment based on their judgment of the patient's best interests. For dose modifications due to concomitant use of strong inhibitors and inducers of CYP3A4, see Section 7.4.1.1.

After dose modification, the reduced doses of X4P-001 and axitinib can be re-escalated to the initial assigned dose levels if treatment related AEs remain ≤ Grade 1 over 4 weeks.

A patient with a Grade 4 AE may resume treatment at the next lower dose level if the AE recovers to ≤ Grade 1 and, if in the opinion of the investigator and medical monitor, the patient can be monitored for recurrence of AE.

6.1.7.1. X4P-001 Administered in Combination with Axitinib (Part A and Part B)

1. Patients will be discontinued from this study if AEs (defined with the same criteria of critical DLT event; Section 4.1.1.3) occur and are considered to be related to X4P-001.

2. If a patient receiving X4P-001 in combination with axitinib successfully completes the first 4 weeks of treatment, and subsequently has a unacceptable toxicity (defined with the same criteria of DLT for Cycle 1, other than those designated critical)

a. And *the event is (possibly) related to both X4P-001 and axitinib*, study treatment may be managed as follows.

- Both X4P-001 and axitinib will be held (dosing interrupted). Note that the Schedules of Events are based on calendar days following the first dose and will not change.
- If the event does *not* improve to Grade ≤1 within the next 14 days, study treatment will be discontinued.
- If the event improves to Grade ≤1 within 14 days of holding study treatment, the patient may resume axitinib *alone at the next lower dose level* (see Section 6.1.7.3 for axitinib

dose adjustment guidelines).

  - If during the first 7 days on axitinib alone at the reduced dose, the event recurs or worsens to Grade >2, the dose modification procedure may be applied again, with the dose of axitinib being reduced one additional level.
  - If during the first 7 days on axitinib alone at the further reduced dose, the event recurs or worsens to Grade >2 again, study treatment will be discontinued.

- If after 7 days on axitinib alone at reduced dose, the event does not recur or worsen, then X4P-001 will be resumed at the next lower dose level (see Table 6-3).

b. And *the event is (possibly) related to X4P-001 and not related to axitinib*, study treatment may be managed as follows.
   - X4P-001 will be held (dosing interrupted) without dose modification of axitinib.
   - If the event does *not* improve to Grade ≤1 within the next 14 days, study treatment will be discontinued.
   - If the event improves to Grade ≤1 within 14 days of holding study treatment, the patient may resume X4P-001 at the next lower dose level (Table 6-3).
   - If the event recurs or worsens to Grade >2 at any time, the dose modification procedure may be applied again, with the dose of X4P-001 being reduced one additional level.
   - If there are any further Grade >2 recurrences, study treatment will be discontinued.

c. And *the event is (possibly) related to axitinib, but not X4P-001*, dose modification of axitinib is described in Section 6.1.7.3 without any dose change for X4P-001.

Table 6-3: Dose Modification Levels for X4P-001

Current Dose (mg)	200 BID	400 QD	600 QD	800 QD	1200 QD
Modified Dose (mg)	200 QD	200 QD	400 QD	600 QD	800 QD

6.1.7.2. X4P-001 Administered as a Single Agent (Part C)

If a patient receiving X4P-001 as single agent successfully completes the first 4 weeks of treatment, and subsequently has an unacceptable toxicity (defined with the same criteria of DLT for Cycle 1, other than those designated critical), study treatment may, with the agreement of the patient, the Investigator, and the Medical Monitor, be managed as follows.

- X4P-001 will be held (dosing interrupted).

- If the event does *not* improve to Grade ≤1 within the next 14 days, X4P-001 will be discontinued.
- If the event improves to Grade ≤1 within 14 days of holding X4P-001, the patient may resume X4P-001 as single agent *at the next lower dose level* (see Table 6-3).
- If the event recurs at Grade >2 *at any time* after resuming X4P-001, one (and only one) additional level of dose reduction may be implemented using the above procedure.
- If there are any further Grade >2 recurrences, study treatment will be discontinued.

6.1.7.3. Axitinib

Dose modifications of axitinib are recommended based on individual safety and tolerability and are permitted in this protocol. However, to minimize potential confounding of assessing concomitant X4P-001, the guidelines are adapted as follows.

- Axitinib dose increases
  - There will be no axitinib dose increases during the first 8 weeks of treatment.
  - Thereafter, dose increases may be made during the first week of a cycle after completion of all procedures scheduled for the visit that week, including AE and con med review, drug compliance, physical exam, and safety laboratory tests.
  - Dose increases will be done as recommended: Patients must have no AEs Grade >2 for at least 2 weeks, be normotensive, and not be receiving anti-hypertensives. Dose increases will proceed from 5 mg BID to 7 mg BID to a maximum of 10 mg BID.
- Axitinib dose decreases
  - These may be made at any time based on the Investigator's judgment and following the label recommendations – decreasing from 5 mg BID to 3 mg BID to 2 mg BID.
  - In the event of an unacceptable toxicity (defined with the same criteria of DLT for Cycle 1), dose reduction will be made as detailed above.

6.1.8. Duration of Therapy

Patients will remain on study treatment until disease progression, unacceptable toxicity, or other specified reasons for discontinuation (see Section 5.4).

6.1.9. Treatment Compliance

Treatment compliance will be monitored by 2 procedures.

- Patients will be provided with a treatment diary to record time and dose taken for both X4P-001 and axitinib, as well as time of last food prior to and after dosing X4P-001. Diaries will be reviewed with the patient at each clinic visit.
- Both X4P-001 and axitinib will be dispensed in bottles, which will be examined visually at each clinic visit; non-destructive pill counts will be performed if indicated.

For DLT evaluation, treatment compliance is required for both X4P-001 and axitinib during Cycle 1. The percentage of compliance is calculated using the following equation for doses taken at the intended dose level:

$$\%\,\text{Compliance} = \frac{\text{Number of X4P-001 or Axitinib doses actually taken}}{\text{Number of X4P-001 or Axitinib doses that should have been taken}} \times 100$$

6.2. Study Drug Accountability Procedures

Regulatory authorities require accounting of all investigational drug received by each study center. Records of drug disposition required include the date received by the center, date administered, quantity administered, and the patient to whom study drug was administered. The Investigator is responsible for the accountability of all used and unused study drug containers and unused study drug. For the Combination Cohort(s), the study center also will maintain records for the combination anticancer agent, including the date administered, quantity administered, and the patient to whom the agent was administered.

Each study center is to use a study drug accountability log to document study drug disposition. All items on this form are to be completed in full. The Sponsor's clinical research associate (CRA) is to approve the area where study drug is to be stored and accountability records are to be maintained.

The investigator identification number and patient initials (as allowed by local regulations) and identification number are to be recorded on each study drug accountability log. Each time study personnel dispense study drug for a patient, he or she is to record the date dispensed, amount of study drug dispensed, and his or her initials. Study personnel are to monitor the inventory of clinical supplies and maintain a count of all used and unused study drug. The CRA is to review study drug accountability records and remaining drug supplies during routine monitoring visits.

At the completion of the study, the site must obtain written authorization from the Sponsor regarding the final disposition of any remaining X4P-001; 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.

Supplies of axitinib that have been distributed to the patient should be returned to the study site and destroyed as per institutional procedures. Supplies of axitinib that have not been distributed may be returned to the Sponsor, destroyed, or used for clinical purposes in accordance with institutional procedures. The final disposition will be agreed to in writing between the Sponsor and the study site.

7. STUDY PROCEDURES AND SCHEDULE

7.1. Study Procedures/Evaluations

Written informed consent and, as applicable, assent will be obtained and the consent procedure recorded in source documentation before any other study-specific procedures are performed.

7.1.1. Baseline and Safety Assessments

7.1.1.1. Medical History

General Medical History

A complete medical history is to be documented during Screening, including relevant general medical and surgical history, current or past abnormalities or diseases of the following systems: allergic (including drug sensitivity), cardiovascular, dermatologic, endocrine/metabolic, gastrointestinal, gynecologic, hematologic/lymphatic, hepatic/biliary, immunologic, infectious, musculoskeletal, neurologic/psychiatric, renal, and respiratory.

The medical history should include all significant illnesses and hospitalizations that occurred in the past 6 months, whether active or resolved. Illnesses active at the time of informed consent will be recorded in the medical history.

History of Renal Cell Carcinoma (RCC)

Detailed history of the course of the patient's RCC will be recorded, including:

- Prior surgical procedures, diagnostic or therapeutic.
- Results (positive and negative) of prior tissue biopsies.
- Prior medical treatments (including supportive therapy) – agent, duration, best clinical response, adverse events related to treatment, and reason for discontinuation.
- Hospitalizations for clinically significant complications of the treatments or the

malignancy, e.g., systemic infections, bleeding.

7.1.1.2. Enrollment Procedure

All patients in this study will be treated open-label. To minimize the potential for patients being enrolled but not treated, patients will be enrolled (i.e., treatment assigned) as close as feasible to the scheduled date for first dose of study drug.

7.1.1.3. Vital Signs

Vital signs include heart rate (HR), SBP, DBP, and temperature. Where feasible, vital signs should be measured before blood is drawn and after the patient has been sitting comfortably for 5 minutes with the BP cuff in place on the non-dominant arm. BP and HR measurements will be taken first and 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.

7.1.1.4. Physical Examination, Body Weight, and Height

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

- For palpable lymph nodes, the location and maximal linear dimension will be recorded at each examination.
- Examination of the reproductive system, breast, and rectal will be performed if there are related symptoms, adverse events, or recent history; the exam 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).

7.1.1.5. Ophthalmologic Examination

Ophthalmologic examination will be performed as scheduled and include the following elements: assessment of visual acuity (using Snellen test or local equivalent in countries outside the U.S.), refraction (at screening only), 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 (see study operations manual for details). Note: an optometrist may complete the exam if all requirements can be met, including use of appropriate equipment to

obtain the retinal photographs.

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 may be examined by a second ophthalmologist.

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

7.1.1.6. ECOG Performance Status (PS)

The ECOG PS will be obtained by questioning the patient about their functional capabilities, according to the table below.

Table 7-1: ECOG PS Definitions

Grade	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

7.1.1.7. 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.

7.1.2. Pharmacokinetic Assessments

PK samples (i.e.: “PK dense sampling’) will be obtained on all patients in Part A and Part C and at least 15 patients in Part B as follows:

- Cycle 1 Day 1: pre-dose (-30 min); post-dose at 30, 60, 90 min (each ±5 min) and 2, 3, 4 hr (each ±15 min)
- Cycle 1 Day 15: pre-dose (-10 min); post-dose at 30, 60, 90 min (each ±5 min) and 2, 3, 4, 8 hr (each ±15 min)
- Cycle 2 Day 1 and Cycle 2 Day 15: pre-dose (-10 min)

These visits will be scheduled for early in the day and patients will be instructed to arrive at the clinic fasting and having not taken their morning dose of study drug(s).

At a minimum, all subjects in Part B should have pre-dose PK samples collected at the visits above (e.g. Cycle 1 Day 1, Cycle 1 Day 15, Cycle 2 Day 1, Cycle 2 Day 15) if subjects are not required to complete the PK dense sampling.

All samples will be analyzed for X4P-001 concentration and some samples in Part B may be analyzed to measure axitinib concentration using reversed-phase high performance liquid chromatography (RP-HPLC) with tandem mass spectrometry (MS/MS) detection.

7.1.3. Pharmacodynamic Assessments

Investigational biomarker and pharmacodynamic assays will be performed by a central laboratory designated by the Sponsor; to maximize consistency, tests may be batched. The clinical significance of these tests is unknown at this time, and the results will not be assessed by the Investigator.

7.1.3.1. Pharmacodynamics

Whole blood samples will be obtained concurrently with scheduled PK samples on Cycle 1 Day 1 and Cycle 1 Day 15 only (see above) for:

- WBC counts
- Counts of circulating CD34+ positive cells.

PD samples will be obtained on all patients in Part A and Part C and at least 15 patients in Part B.

If sample yields permit, additional investigational immunomodulatory subsets may be analyzed (Table 7-2). PD samples will not be drawn at Cycle 2 Day 1 and Cycle 2 Day 15.

7.1.3.2. Blood Biomarkers

Blood samples (serum and PBMC) will be collected as scheduled for potential treatment- and tumor-related biomarkers that reflect the pharmacologic effects of CXCR4 antagonism on angiogenesis and immunomodulatory subsets of circulating PBMC (Table 7-2). Additional investigational blood studies may be performed using the collected samples.

Table 7-2: Candidate Blood Biomarkers

Serum factors associated with angiogenesis [DePrimo 2007]	**Immunomodulatory subsets of circulating PBMC [Tarhini 2014]**
CXCL12	Treg lymphocytes
VEGF-A	Activated T cells
Soluble VEGFR-2 (sVEGFR-2)	MDSC
Placenta growth factor (PGF)	

7.1.4. Efficacy Assessments

7.1.4.1. Radiologic Assessment of ccRCC

Radiologic imaging of chest, abdomen and pelvis for assessing tumor status and treatment effect will be performed as indicated in the Schedules of Events. Interim assessments may be done at the request of the Investigator based on new findings. Patients enrolled with a history or current evidence of CNS disease will have brain imaging by magnetic resonance imaging (MRI) with contrast at baseline and, thereafter, as clinically indicated.

Imaging will be interpreted using RECIST v1.1 [Eisenhauer 2009] (see Section 7.1.4.2). The expected imaging technology is CT with slice thickness ≤5 mm and contrast. The use of alternative technologies (e.g., CT scan with slice thickness >5 mm or MRI) requires the approval of the Medical Monitor and must be performed in a manner consistent with RECIST. For each patient, the imaging modality should be consistent throughout the study. If there is a need to change modality (e.g., a patient cannot receive radiologic contrast), an alternative modality may be used with the approval of the Medical Monitor.

For clinical management during the study, imaging will be interpreted by the radiologist at the site and a written report provided. Patients who, in the judgment of the Investigator, have Progressive Disease, which is a protocol endpoint, will be reviewed with the Medical Monitor.

As soon as feasible after an imaging study is performed, the images (with indication of the modality used) will be submitted to a central repository to be reviewed for quality and for central reading; the written report will be submitted to the eCRF.

For endpoint analysis, after a patient completes the EOT visit, all imaging studies for that patient will be reviewed together and outcomes assigned by one or more radiologists designated by the Sponsor and experienced applying RECIST; they will be blinded to treatment allocation and clinical outcome.

7.1.4.2. Evaluation of Response to Treatment and Disease Status

Tumor response assessments will be conducted every 8 weeks (2 cycles) for 80 weeks (20 cycles) and then every 12 weeks thereafter, at EOT, and as indicated based on new signs, symptoms or laboratory findings. Disease status, time to progression, duration of response will be determined based on RECIST v1.1 [Eisenhauer 2009]. Treatment decisions will be made by the Investigator incorporating the local radiology interpretation and consultation with the Medical Monitor. For data analysis, scans will be reviewed and interpreted by a blinded central review committee comprising up to 3 experienced radiologists; see Section 7.1.4.1 for details.

Patients enrolled with a history or current evidence of CNS disease should have brain imaging by MRI at baseline and, thereafter, as clinically indicated.

The current (v1.1) RECIST provide a detailed process for using sequential CT imaging to classify tumor response [Eisenhauer 2009]. Key elements of the process are summarized below; details provided in the guideline [Eisenhauer 2009] remain determinative. NOTE: all specifications assume use of CT with slice thickness ≤5 mm. Modifications are required for other technologies [Eisenhauer 2009].

Definitions of key terminology:

- Measurable non-nodal lesions – ≥10 mm in longest diameter.
- Measurable nodal lesions – ≥15 mm in short axis
- Nonmeasurable lesions – lesions that are smaller, including those that cannot be measured.
- Measurable disease – presence of at least one measurable lesion. [NOTE: Entry into this study requires at least one measurable extra-renal lesion.]
- Target lesions – At baseline, a maximum of 5 measureable lesions, no more than 2 for any individual organ, should be identified, documented, and the appropriate diameter of each recorded. Lesions should be selected based on size, be representative of disease, and be suitable for reproducible repeat measurement. Target lesions may include measurable lymph nodes.
- The baseline sum of diameters (SOD) – The sum of the longest diameters for all non-nodal target lesions plus the sum of the short axis diameter for all nodal target lesions.
- Non-target lesions – All other lesions present at baseline, including pathologic nodes (defined as nodes >10 mm in short axis). These should be documented (quantitative measurements are not required) so that they can be classified on follow-up as present, absent, or unequivocal progression.
- New lesions – a new lesion should be unequivocal (e.g., not attributable to variation in technique); includes lesions in a location *not* scanned at baseline.
- Definitions of response criteria for target and non-target lesions are summarized in Table 7-3; these are integrated into an overall response assessment as summarized in Table 7-4.

Table 7-3: RECIST – Definitions of Response Categories for Target and Non-Target Lesions

Target Lesions	
Complete Response (CR)	(a) Disappearance of all non-nodal lesions, *and* (b) Absence of pathologic lymph nodes[1].
Partial Response (PR)	≥30% decrease from baseline in the SOD of the target lesions
Stable Disease (SD)	Persisting disease that does not meet criteria for either PR or PD
Progressive Disease (PD)	a) ≥20% increase in the SOD of the target lesions, compared to the smallest sum on study, which may be either at baseline *or* while on treatment; *and* (b) an absolute increase of ≥5 mm in the SOD.
Non-Target Lesions	
Complete Response (CR)	(a) Disappearance of all non-target lesions, *and* (b) Absence of pathologic lymph nodes[1].
Non-CR/non-PD	Persistence of one or more non-target lesions
Progressive Disease (PD)	*Unequivocal progression* of existing non-target lesions.

1. All lymph nodes, whether or not designated target or non-target lesions, have short axis diameter ≤10 mm

Table 7-4: RECIST – Overall Responses Based on Target Lesions, Nontarget Lesions, and New Lesions

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	
PR	Non-PD or not all evaluated	No	
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Non-evaluable
CR, PR, or SD	PD[a]	No	PD
PD	Any	Yes or no	
Any	Any	Yes	

1. "The designation of overall progression *solely* on the basis of change in non-target disease" in the face of CR, PR, or SD of target lesions is expected to be "extremely rare" [Eisenhauer 2009].

7.1.4.3. Exploratory Analysis of Efficacy Using iRECIST

Tumor Response assessments may be explored by using modified Response Evaluation Criteria in Solid Tumors for immune-based therapeutics (iRECIST) [Seymour 2017]. Details of this assessment will be defined in statistical analysis plan (SAP) and/or central imaging review documents.

7.2. Laboratory Procedures/Evaluations

7.2.1. Clinical Laboratory Evaluations

The laboratory safety tests below will be performed as scheduled by a central laboratory facility. The Investigator may order additional local laboratory tests consistent with their routine standard of care.

Table 7-5: Safety Laboratory Tests

Hematology Panel	
Hematocrit	WBC differential and absolute cell counts:
Hemoglobin	Basophils
Platelet count	Eosinophils
WBC	Lymphocytes
	Monocytes
	Neutrophils
Clinical Chemistry Panel	
ALT	Lipase
Albumin	Magnesium
Alkaline phosphatase	Potassium
Amylase	Total bilirubin**
AST	Total protein
Bicarbonate	Sodium
Calcium	Urea
Chloride	Uric acid
Creatine kinase	
Creatinine*	
Glucose	
Inorganic phosphorus	
*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.	
Thyroid Function Tests (Parts A and B only)	
Free thyroxin (Free T4)	Thyroid stimulating hormone (TSH)
Pregnancy tests (WOCP only)*	
beta-human chorionic gonadotropin	
*WOCP are required to take a pregnancy test if their period is late.	

Serologic tests (Screening only)	
HBsAg	Antibody to HCV

7.2.1.1. 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. 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 prepared, handled, and stored as instructed in the laboratory manual.

7.3. Study Schedule

The overall study schedule is as follows:

- Screening will be done within 28 days prior to Day 1 (the first dose of study drug). See Section 7.1.1.2 for details of the enrollment process.
- Laboratory tests required for screening will be performed with 14 days prior to Day 1.
- Treatment is scheduled to be administered continuously. Missed doses will be considered skipped.
- Assessments for treatment response (or disease progression) are scheduled every 8 weeks (± 4 calendar days) of treatment for 80 weeks (20 cycles) and every 12 weeks thereafter.

- The EOT visit is will be performed within 6 days after the last dose of study drug or the decision to terminate treatment prematurely.
- EOS visit, the final study event, will be performed 30 days after the last dose of study drug. In the event the EOT visit is delayed, the EOS visit will be performed at least 14 days after the EOT visit.

A detailed schedule of events is presented in Table 1-1.

7.4. Concomitant Medications, Treatments, and Procedures

Prior treatments for ccRCC will be recorded as detailed in Section 7.1.1.1.

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

7.4.1. Precautionary Medications, Treatments, and Procedures

7.4.1.1. Restrictions related to CYP Interactions

X4P-001 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. If a strong inhibitor or inducer cannot be avoided, the dose of X4P-001 can be reduced with approval of Medical Monitor.
- Grapefruit and/or starfruit products, variable inhibitors of CYP3A4, are prohibited.
- Moderate inhibitors and inducers of CYP3A4 are to be prescribed only with the approval of the Medical Monitor; additional monitoring of X4P-001 drug levels may be required.
- Sensitive CYP2D6 substrates should be avoided and other CYP2D6 substrates should be administered only with the approval of the Medical Monitor.

Appendix Section 18.2 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.

7.4.1.2. Non-childbearing Potential

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.
- Documented hysterectomy, bilateral tubal ligation, or bilateral oophorectomy.

7.4.1.3. Effective Birth Control (Contraception) Methods

Women of Childbearing Potential (WOCP) must use a highly effective method of contraception during the study and through 4 weeks after the last dose of study drug. Acceptable methods include:

- hormonal contraceptives when used with an additional barrier method (e.g., a male condom):
    - combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
        - oral
        - intravaginal
        - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation:
    - oral
    - injectable
    - implantable
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- bilateral tubal occlusion
- vasectomized partner who has received a medical assessment of surgical success (when the partner is the sole partner)
- sexual abstinence (when in agreement with the lifestyle and preference of the WOCP)

Males are required to use a condom with any WOCP sexual partner from Day 1 of study treatment, through the study, and at least 4 weeks after the last dose of study drug.

7.4.2. Prohibited Medications, Treatments, and Procedures

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

While patients are receiving study treatment, other treatments for ccRCC are prohibited. Patients who discontinue treatment prematurely and have completed the End-of-Treatment 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, this will be recorded in concomitant medications and considered in assessment of any new AE.

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), 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
- Non-medicated saline nasal spray, such as Simply Saline™ Nasal Mist (Arm & Hammer)
- Acetaminophen (Tylenol™)

7.4.5. Precautions Regarding Axitinib

Drug metabolism. Axitinib is metabolized primarily by CYP3A4 and 3A5 and to a lesser extent by CYP1A2 and CYP2C19. Co-administration of strong CYP3A4 inhibitors and inducers, and of grapefruit or starfruit products, is prohibited.

- The requirements detailed in Section 7.4.1.1 are consistent with this. Administration of X4P-001 caused only a modest increase in exposure to midazolam (also a CYP3A4 substrate).

Exclusions: Moderate to severe hepatic impairment; pregnancy.

- Both of these are also exclusions under this protocol.

Warnings and Precautions. The following events are listed: hypertension and hypertensive crisis; arterial thromboembolism; venous thromboembolism; hemorrhage; cardiac failure; gastrointestinal perforation; thyroid dysfunction; wound healing complications; reversible posterior leukoencephalopathy syndrome; proteinuria.

- None of these events was observed in prior studies using X4P-001. Recent uncontrolled hypertension, uncontrolled congestive heart failure, and thromboembolic events are all exclusions.

Elevation of liver enzymes. Grade 1 and 2 elevations of ALT (up to 5x ULN) were observed in ~20% of patients with advanced RCC treated with axitinib. The incidence of Grade 3/4 events was <1%.

- LFTs are being monitored closely in this protocol, and clinically significant abnormalities are explicitly defined (Section 4.1.1.3).

7.4.6. 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/starfruit.
- Use effective contraception as defined in Section 7.4.1.3.

7.5. Appropriateness of Measurements

Planned assessments are standard measurements for this type of study and are considered appropriate. Per regulatory guidance, demographic data, complete medical histories, including cancer treatment history, and Baseline disease status are to be documented for all patients at Baseline (FDA Guidance for Industry 2001).

AEs and SAEs are monitored in this study in accordance with International Conference on Harmonisation (ICH) GCP guidelines to ensure the safety of patients. Furthermore, additional safety assessments conducted during this study, including physical examinations, ECGs, vital signs assessments, and clinical laboratory tests, are widely used and generally recognized as reliable, accurate, and relevant. These tests and procedures also will be monitored in accordance with ICH GCP guidelines.

Tumor response and progression will be assessed using standard criteria for the assessment of disease response in solid tumors, RECIST, v1.1.

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 (SAE)

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 adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

8.1.4. Suspected, Unexpected Serious Adverse Reaction (SUSAR)

A 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 8.2.2);
- 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) and designate any results outside of the reference range as ***either*** of the following:

- Abnormal, not clinically significant (NCS)
- Abnormal, clinically significant (CS).

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 adverse event 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) five-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:*** the study drug is more likely the cause of the AE than other factors;
- ***Possibly related:*** there is a *reasonable* possibility that the study drug is the cause of the AE, including that the study drug and another factor(s) are equally likely as causes of the AE;
- ***Unlikely related:*** another factor is considered more likely the cause of the AE than the study drug;
- ***Not related:*** another factor is considered to be the cause of the AE.

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.

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 8-1 summarizes the basis for reporting the date and time of onset for the different types of AEs.

Table 8-1: 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 lab sample was obtained or diagnostic study performed

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 2 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).
- 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 8-2 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 8-2: 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 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

finding 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 outcome (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.

A ***narrative summary*** of the event will be reported within 2 days for death and life-threatening events and within 4 days for all other SAEs. The narrative summary will include specific information that will assist in understanding the event, e.g., relevant medical history, co-morbid conditions, physical exam, diagnostics, assessment, treatments (including concomitant medications), response to treatment, course, and outcome (if known).

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 IRB/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 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 Associated with X4P-001

Table 8-3 indicates specific procedures in this protocol for managing these previously identified risks.

Table 8-3: Monitoring Procedures for Risks Identified in Prior Studies of X4P-001 (AMD11070)

Prior Findings	Clinical Monitoring Procedures
X4P-001 is predominantly metabolized through CYP-3A4[a]	Avoid concomitant medications that are strong CYP3A4 inhibitors or inducers; If a strong inhibitor or inducer can not be avoided, the dose of X4P-001 can be reduced with approval of Medical Monitor.
X4P-001 is a moderate inhibitor of CYP-2D6[a]1	Avoid sensitive CYP2D6 substrates. Closely monitor other CYP2D6 substrates
Beagles, 13-week toxicology study with X4P-001 (free-base)[2] -- ALT: mild (1.4x–2.4x), exposure-related increases -- Total bilirubin: no increases in any animal -- Microscopic liver findings: multifocal necrosis (single cell) in 4 of 12 animals dosed at 35 or 70 mg/kg/d	Safety laboratory tests, including aspartate transaminase, alanine transaminase, total bilirubin, every 4 weeks during treatment.
Rats, 26-week toxicology study with AMD11070PHB (salt)[c3] -- retinal degeneration (20, 50, 100 mg/kg bid) -- retinal atrophy (100 mg/kg BID only)	An ophthalmology evaluation every 12 weeks: visual acuity assessment; color vision assessment; slit lamp exam; retinal examination with photographs.

1. A detailed listing of agents with potential for CYP-related interaction is provided in Appendix Section 18.2.
2. 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.
3. The retinal changes were observed only in albino rats treated for 26 weeks with the PHB salt. No retinal changes were observed in beagles treated for 13 weeks with either the free base or the PHB salt.

8.6.2. Additional Procedures for Monitoring Patient Safety

Additional procedures for patient safety are summarized below:

- The first dose of study drug will be administered by study personnel; in Part A, the patients will be observed over the next several hours while PK samples are obtained.
- Ongoing monitoring for adverse events.
- Regularly scheduled safety laboratory tests.
- Ongoing monitoring of all concomitant medications (prescription and over-the-counter) to avoid potential drug-drug-interactions mediated through alterations in CYP-metabolism.
- Detailed procedures for monitoring and review during dose-escalation, including:
  - Constitution of a DRC to make recommendations regarding dose-escalation and determination of the MTD (Section 8.6.3).
  - Definitions for DLT events (Section 4.1.1.3)
  - Definition for MTD (Section 4.1.1.4).
  - DRC will also review the data from the first 12 patients participating in Part B to confirm the safety of the RP2D selection (Section 4.1.2 and 8.6.3).
- Detailed provisions for management of study drug in individual patients based on safety, tolerability, and disease response. In brief, each enrolled patient is planned to receive study treatment until the earliest of:
  - *DLT event* – see Section 4.1.1.3.
  - *Disease progression* – based on CT imaging scan results or as prompted by new signs, symptoms, and laboratory findings, and classified according to RECIST v1.1 [Eisenhauer 2009](see Section 7.1.4.2 for details).

8.6.3. Data Review Committee (DRC)

Members of the DRC will have appropriate experience treating patients with advanced ccRCC and/or conducting early phase studies of investigational drugs and will include the following:

- An independent physician not otherwise involved with the study.
- The Medical Monitor for the study.
- Participating Investigator(s).

- A physician representative of the Sponsor.

The functions of the DRC are:

- Perform the dose-escalation review (see Section 4.1.1.3).
- Make specific recommendations for the progress of the study, including confirming the RP2D selection in Part B by planned safety review (see Section 4.1).
- Determine the MTD (see Section 4.1.1.4).

The DRC comprises experienced clinicians, who will make recommendations based on their judgment. In consideration of the dynamic nature of early phase studies, those recommendations may include alternative courses of action not anticipated here.

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 (CRO) 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 regards 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 CRA 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 CRA 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.
- 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 (SAP) will be developed. The SAP will define populations for analysis, outline all data handling conventions, including software, and specify additional statistical methods to be used for analysis of safety, efficacy and pharmacokinetics.

Consistent with the primary objective, the study design represents a pragmatic assessment of safety and tolerability across different dose levels of X4P-001 both in combination with axitinib and as single agent based upon clinical evaluations and laboratory tests. Secondary objectives relating to treatment effect are intended to guide further development of X4P-001 and aid in the design of appropriately controlled studies.

10.2. Statistical Hypotheses

Not applicable.

10.3. Analysis Datasets

Analyses will be performed using the following populations:

- Safety / Intent-to-Treat (ITT) Population — all patients who received at least one dose of study drug.
- PK – all patients who have at least one evaluable concentration.
- Clinically Evaluable Population –All patients who receive at least one dose of study medication, who have at least one valid post-baseline response (CR/PR/SD/PD), and have no major protocol deviations which will impact the efficacy assessment.

  The clinically evaluable population may be omitted from the final analysis if clinically evaluable and ITT population are similar and there are no clinically meaningful differences in outcomes between the 2 populations.

10.4. Description of Statistical Methods

10.4.1. General Approach

Study events will be recorded using the calendar date and (where applicable) the time to the nearest minute.

For purposes of post-study analysis (e.g., tables and listings), study days will be designated as follows:

- Day 1 is defined as the calendar day of the first dose of study drug.
- The days prior to Day 1 are designated Day –1, Day –2, etc; there is no Day 0.
- The days following the day of the first dose of study drug are designated Day 2, Day 3, etc.
- The day of each dose of study drug is indicated by adding the suffix "L", e.g., if the last dose is administered on Day 43, it will be displayed as "Day 43L".
- The days following the last administration of study drug are designated Day 1P, Day 2P, etc.

The times of events related to dosing of study drug will be designated as minutes or hours before or after the time of dosing, which is designated as t = 0 (zero). Thus, 15 minutes prior to dosing is t = –15 min; 2 hour after dosing is designated t = 2 h.

Missing and partial dates will be imputed. Full details will be given in the SAP.
Missing baseline data will be imputed with screening data where available. No further imputations of missing data will be made.

10.4.2. 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 into and completing each study part.

Medical history, medications used prior to treatment, and concomitant medications will be summarized by study part. Please refer to the SAP for details.

10.4.3. Analyses of Safety Endpoint

The primary objective of the study is safety and tolerability. AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 16.0 (or later) and tabulated by event, grade, and relationship to study therapy. Laboratory results, vital signs, and ECG parameters will be summarized using descriptive statistics. Laboratory values will also be graded according to

NCI CTCAE, Version 4.03, and summarized in shift tables. DLT events will be listed and summarized.

Safety observations will be analyzed using descriptive statistics and tabulation. No formal statistical comparisons are planned. All safety data will be presented in listings.

10.4.4. Analysis of the Efficacy Endpoint(s)

The secondary objective of treatment effect (tumor response) will be analyzed using RECIST v1.1 criteria [Eisenhauer 2009] as identified by the central review committee to determine the following metrics:

- ORR (CR + PR)
- Time to objective response
- Duration of objective response
- Disease control rate (CR+PR+ Stable Disease)
- Time to progression
- PFS

Analysis of Tumor response, ORR and Disease Control Rate (DCR) will be tabulated using Best overall response, by dose level, incorporating 95% exact Clopper-Pearson confidence intervals (CI) for ORR and disease control rate.. The analysis will be based on intent-to-treat (ITT) and Clinically Evaluable patient populations.

Duration of ORR will be summarized as median (with 95% CI) and interquartile range estimated using Kaplan-Meier method with corresponding 95% CIs.

Median time to objective response, TTP, PFS as well as the proportion of patients with PFS at 6 and 12 months (with 95% CI) will also be derived from Kaplan-Meier estimates.

Tumor Response and endpoints listed above may also be explored by using modified Response Evaluation Criteria in Solid Tumors for immune-based therapeutics (iRECIST) [Seymour 2017]. Details of the analysis plan will be defined in the SAP.

10.4.5. Planned Interim Analyses

There is no formal provision for an interim analysis in this early phase study.

10.4.6. Multiple Comparison/Multiplicity

Not applicable.

10.4.7. Tabulation of Individual Response Data

The individual response data will be provided in patient data listings and the details will be described in SAP.

10.4.8. Exploratory Analyses

The details of exploratory analyses will be described in SAP.

10.4.9. Pharmacokinetic Analyses

PK data will be analyzed (a) by patient and dose level using descriptive statistics for AUC, C_{max}, and T_{max}, and (b) across dose levels testing for dose proportionality of AUC and C_{max}.

10.5. Sample Size

The maximum numbers of patients planned to be enrolled in Parts A and C are as follows:

- Part A, Dose-escalation: 6 patients per dose level (5 planned dose levels)
- Part B, A RP2D expansion cohort: approximately 45 patients will be enrolled;
- Part C, Dose-escalation (to be done only if the MTD for X4P-001 from Part A (combination treatment) is ≤800 mg QD): up to 6 patients per single agent dose-escalation level (maximum 3 dose levels);
- Part C, Expansion: maximum 15 patients

Dose-escalation in Part A (and, if needed, in Part C) employs the standard 3+3 design. Table 10-1 presents the probability of escalation from a lower dose to the next higher dose, for true rates of DLT ranging from 10% to 90%. For example, if the true DLT rate were 0.20 (20%), then the chance of dose escalation would be 0.71 (71%).

Table 10-1: Relationship between Underlying DLT Rate and Probability of Dose Escalation

Underlying DLT Rate	10%	20%	30%	40%	50%	60%	70%	80%	90%
Probability of Dose Escalation	91%	71%	49%	31%	17%	8%	3%	1%	0.1%

In Part B, approximately 45 patients will be enrolled and dosed with X4P-001 in the combination of axitinib to provide a preliminary assessment of both safety and anti-tumor activity. With 45 subjects at the RP2D, the two-sided 90% confidence interval width for any binary response rate (e.g., DLT or binary PD markers) will be approximately 0.24, assuming a 40% response rate. If a dose de-escalation occurs after the first 12 patients, the remaining 33 patients will be dosed at a

lower dose level. With 33 patients, the confidence interval width will be approximately 0.28 for a binary response rate.

Safety at RP2D will be verified by monitoring DLTs as follows: if ≤ 4 DLTs are observed in the first 12 patients during the first 4 weeks of treatment, this RP2D dose will be considered safe to proceed for the remaining patients in this study. If 5 or more DLTs are observed in the first 12 patients during the first 4 weeks of treatment, the trial may continue with dose de-escalation after DRC review. The dose will be reduced at least one dose level lower, according to the dose levels presented in Figure 4-1. To further protect patient safety, if additional DLTs are observed anytime during the trial, dose de-escalation can be enforced based on DRC recommendation, or the trial can be stopped at the sponsor's discretion.

In Part C, dose-escalation (if needed after Part A) cohorts of X4P-001 as single agent (monotherapy) will employ the traditional 3+3 design. When the potential MTD is identified, an expansion cohort of approximately 15 patients will used to further assess MTD. With 15 subjects, there is a 79% chance of observing at least one AE with the true underlying rate of 10%, and a 54% chance of observing at least one AE with true underlying rate of 5%.

10.6. Measures to Minimize Bias

10.6.1. Enrollment/ Randomization/ Masking Procedures

No randomization or blinding methods will be employed in this study.

10.6.2. Evaluation of Success of Blinding

Not applicable.

10.6.3. Breaking the Study Blind/Participant Code

Not applicable.

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 (eCRFs)

The Sponsor will provide a regulatory-compliant electronic data capture (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:
https://www.fda.gov/downloads/drugs/guidances/ucm073122.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.

The patient'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.

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.

17. LITERATURE REFERENCES

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18. APPENDICES

18.1. Revision History and Sponsor Signature

The revision history is summarized in Table 18-1. Significant revisions made in each protocol version are provided in a separate Summary of Changes document.

Table 18-1: Protocol Revision History

Ver. No.	Date	Comment
1.0	7 Apr 2015	Initial release – submitted with IND
2.0	24 June 2015	Revised based on FDA Comments
3.0	9 Sep 2015	Technical corrections, including RECIST 1.1
4.0	3 Mar 2016	Updated safety experience; technical corrections
5.0	20 Jun 2016	Changed dose regimen from BID to QD, added clinical PK data supporting QD dosing, and updated sample size justification section.
6.0	01 Feb 2017	Change Part B study design
6.1	23 Feb 2017	South Korea specific amendment only. Fixed errors in Table 1-1 (schedule of events) and 1-2 (blood volumes table). Fixed typos in Section 7.4.1.3 & Section 10.4.3
6.2	08 March 2017	South Korea specific amendment only. Updated table on page 23
6.3	02 Nov 2017	South Korea specific amendment only. Updated information around using iRECIST criteria, modification of exclusion criterion #14, removal of unnecessary laboratory tests, and minor administrative changes
6.4	15 February 2018	South Korea specific amendment only. Updated schedule of procedures & correction to blood volume in table 1-2
7.0	08 June 2018	US specific amendment only. Updated information around using iRECIST criteria, modification of exclusion criterion #14, removal of unnecessary laboratory tests, and minor administrative changes. Updated study's planned analysis.

This protocol Version 7.0 has been prepared and approved by the Sponsor.

[redacted]
[redacted]
X4 Pharmaceuticals, Inc.

[redacted] June 08, 2018

Signature and Date

18.2. Potential CYP-Related Drug-Drug Interactions

Strong CYP3A inhibitor[1]	**Strong CYP3A inducer**[1]	**Moderate CYP3A inhibitor**[2]	**Moderate CYP3A inducer**[2]	**CYP2D6 sensitive substrate**[1]	**CYP2D6 moderate sensitive substrate**[2]
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, St. John's wort	amprenavir, aprepitant, atazanavir, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, darunavir and ritonavir, dronedarone, erythromycin, fluconazole, fluvoxamine, fosamprenavir, imatinib, tofisopam, verapamil	bosentan, efavirenz, etravirine, modafinil, nafcillin	atomoxetine, desipramine, dextromethorphan, eliglustat, nebivolol, nortriptyline, perphenazine, pimozide, thioridazine, tolterodine, venlafaxine	amitriptyline, encainide, imipramine, metoprolol, propafenone, propranolol, tramadol, trimipramine

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