A Phase 1 Open-Label, Dose-Finding Study Evaluating Safety and Pharmacokinetics of FPA144 in Patients with Advanced Solid Tumors

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Indication Studied:	Advanced Solid Tumors
Protocol Version:	5 – Amendment 5
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Supersedes:	*Version 4, Amendment 4, dated 29 March 2016*
Sponsor:	Five Prime Therapeutics, Inc. Two Corporate Drive South San Francisco, CA 94080-7047 Tel: + 1 415-365-5600
Responsible Medical Officer:	Helen L. Collins, MD Senior Vice President and Chief Medical Officer Five Prime Therapeutics, Inc.

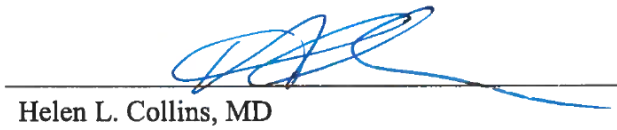
Protocol Approval Signature Page

Declaration of Sponsor

A Phase 1 Open-Label, Dose-Finding Study Evaluating Safety and Pharmacokinetics of FPA144 in Patients with Advanced Solid Tumors

The study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), the Declaration of Helsinki, and other applicable regulatory requirements. Essential study documents will be archived in accordance with applicable regulations.

This study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki, 1989, and the International Conference on Harmonization (ICH) guidelines on GCP.



30 May 2017

Helen L. Collins, MD
Senior Vice President and Chief Medical Officer
Five Prime Therapeutics, Inc.

Date

Declaration of the Investigator

A Phase 1 Open-Label, Dose-Finding Study Evaluating Safety and Pharmacokinetics of FPA144 in Patients with Advanced Solid Tumors

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes this study protocol, Investigator's Brochure (IB), electronic case report forms (eCRFs), and other scientific data.

The study will not be commenced without the prior written approval of a properly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC). No changes will be made to the study protocol without the prior written approval of the Sponsor and the IRB or IEC, except as necessary to eliminate an immediate hazard to the patients.

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

Principal Investigator's Signature	Date
Name (printed)	
Institution or Company Name	

Protocol Synopsis

Title: A Phase 1 Open-Label, Dose-Finding Study Evaluating Safety and Pharmacokinetics of FPA144 in Patients with Advanced Solid Tumors

Protocol Number: FPA144-001

Clinical Phase: 1

Sponsor: Five Prime Therapeutics, Inc.

Study Centers: Up to 35 study centers

Objectives:

Primary:

- To evaluate the safety profile of escalating doses of FPA144 in patients with advanced solid tumors, and to determine the MTD and RD (*Part 1A only*)
- To evaluate the safety profile of escalating doses of FPA144 in patients with advanced gastric or gastroesophageal cancer (*Part 1B only*), hereinafter referred collectively to as 'gastric cancer.'
- To evaluate the safety and tolerability of FPA144 administered intravenously every two weeks at the RD in patients with gastric cancer and other solid tumors, including transitional cell carcinoma of the genitourinary tract (hereinafter referred to as bladder cancer) (*Part 2 only*)

Secondary:

- To characterize the PK profile of single and multiple doses of intravenously administered FPA144 in gastric cancer patients and in other solid tumor patients, including bladder cancer
- To evaluate the safety and tolerability of longer term exposure to FPA144 administered intravenously every two weeks
- To evaluate the objective response rate (ORR) in patients with FGFR2b-selected gastric cancer and other solid tumors by tumor type, including FGFR2b-selected bladder cancer (*Part 2 only*)
- To evaluate duration of response in responding patients with FGFR2b-selected gastric cancer and other solid tumors by tumor type, including FGFR2b-selected bladder cancer (*Part 2 only*)
- To characterize the pharmacodynamic profile of FPA144 through an analysis of the immune cell infiltrate in pre-treatment and on-treatment tumor biopsies by tumor type (*Part 2 only)*

Objectives (Cont.):

Exploratory:

- To evaluate the stable disease rate and duration in patients with FGFR2b-selected gastric cancer and other solid tumors by tumor type, including FGFR2b-selected bladder cancer (*Part 2 only*)
- To assess progression-free survival (PFS) in patients with FGFR2b-selected gastric cancer and other solid tumors by tumor type, including FGFR2b-selected bladder cancer (*Part 2 only*)
- To explore the association between extent of FGFR2b overexpression and *FGFR2* amplification (or other molecular aberration, as applicable) in tumor tissue and clinical outcome by tumor type
- To characterize the pharmacodynamic profile of FPA144 through an analysis of exploratory biomarkers in pre-treatment and on-treatment tumor biopsies by tumor type (*Part 2 only)*

Study Design:

This is a three-part, open-label, safety, tolerability, and PK study of FPA144. Patients will be enrolled into either Part 1 (A or B), or Part 2 of the study, but not both Part 1 and 2.

After an initial screening period of up to 28 days (4 weeks), patients will be treated with FPA144 every 2 weeks in 28-day cycles. In Part 1A, each enrolled patient will be observed for 28 days for safety assessments and occurrence of dose-limiting toxicities (DLT Observation Period). Additional treatments may be administered every 2 weeks in 28 day cycles thereafter as clinically indicated (Extended Treatment Period).

In Part 1B, patients will be treated with FPA144 every 2 weeks in 28-day cycles at the current Part 1A DLT-cleared dose levels.

In Part 2, patients will be treated with FPA144 every 2 weeks in 28-day cycles at a recommended dose (RD) selected after assessment of data obtained in Parts 1A and 1B.

Part 1A: Dose-Escalation

Part 1A is a dose-escalation study in patients with any locally advanced or metastatic solid tumor or lymphoma for which standard therapies have been exhausted. Approximately 6 dose cohorts are anticipated, with a minimum of 3 patients enrolled in each cohort. The anticipated dose levels are:

Dose level 1: 0.3 mg/kg FPA144
Dose level 2: 1 mg/kg FPA144
Dose level 3: 3 mg/kg FPA144
Dose level 4: 6 mg/kg FPA144
Dose level 5: 10 mg/kg FPA144
Dose level 6: 15 mg/kg FPA144

Study Design (Cont.):

Review of safety and PK parameters may inform decisions to add cohorts with alternative dose levels or dose regimens (e.g. less frequent dosing) in order to reach an optimal target exposure.

All dose escalation decisions will be based on assessment of DLTs, overall safety, and tolerability and will be made after the last patient enrolled in each cohort has completed the first treatment cycle. Dose escalation decisions will be agreed upon by the Cohort Review Committee (CRC), consisting of the Sponsor and Investigators.

The maximum tolerated dose (MTD) is defined as the maximum dose at which < 33% of patients experience a DLT during Cycle 1 (Safety and PK Assessment Period). If a DLT is observed in 1 of 3 patients, then 3 additional patients will be enrolled at that same dose level. Dose escalation may continue until 2 of 3-6 patients treated at a dose level experience a DLT. The next lower dose will then be considered the MTD. Alternatively, an intermediate dose between the last cleared dose level and the dose level resulting in >33% DLTs may be explored before concluding that the MTD has been reached. Once the MTD or RD has been reached, 3-10 additional gastric cancer patients *may* be added prior to commencing Part 2, to further explore the safety and PK at this dose level.
The following algorithm will be used for Part 1A dose escalation decisions:

Number of Patients with DLTs	Action
0/3	Open next cohort
1/3	Enroll 3 more patients in same cohort
≥ 2/3	Stop enrollment. Enter 3 more patients at dose level below, if only 3 were previously entered
1/6	Open next cohort
≥ 2/6	Stop enrollment. Enter 3 more patients at dose level below, if only 3 were previously entered.

In the event no MTD is identified yet drug exposures exceed those deemed necessary based on nonclinical pharmacology data or the clinical PK profile, the Sponsor and Investigators may decide to discontinue dose escalation.

Part 1A: Optional Extended Treatment Period

On completion of Cycle 1 (Safety and PK Assessment Period), Part 1A patients may participate in an optional Extended Treatment Period, which begins on Day 1 of Cycle 2. FPA144 will be administered every 2 weeks in 4-

week cycles until disease progression, unacceptable toxicity, patient or physician request to discontinue, death, or termination of the study.

Study Design (Cont.):

Part 1B:

The purpose of Part 1B is to further assess safety and evaluate PK of FPA144 in gastric cancer patients prior to commencing Part 2. Clearance of some antibodies (e.g., bevacizumab and trastuzumab) has been shown to be more rapid in gastric cancer patients than in patients with other solid tumors (Han 2014, Cosson 2014). Enrolled patients may be gastric cancer patients whose tumors will be tested retrospectively, or those who are known to be FGFR2 gene-amplified or FGFR2b protein-overexpressed. In a staggered fashion with Part 1A dose escalation, patients in Part 1B will be enrolled one dose level below the current highest dose level cohort being studied in Part 1A. For example, if the current dose level in Part 1A being studied is 3 mg/kg, enrollment of Part 1B patients will be at the 1 mg/kg dose level; if the current dose level being studied in Part 1A is 6 mg/kg, enrollment of Part 1B patients will be at the 3 mg/kg dose level.

In Part 1B, approximately 3 patients may be enrolled at each dose level, with an election by the Sponsor and investigators to enroll up to 6 patients per dose cohort. Dose escalation may continue in Part 1B up to 15 mg/kg if no MTD in Part 1A is identified.

Part 2: Dose Expansion

Enrollment in Part 2 will begin when a recommended dose (RD) has been identified by the CRC, based on overall safety, tolerability, PK, and estimates of efficacious exposures extrapolated from nonclinical data. The RD may or may not be the same as the MTD identified in Part 1A. For example, if the MTD is not reached, or if exposure at the MTD is much higher than the level believed to be required for efficacy, or if data from Part 1B patients or subsequent cycles of treatment from both Parts 1 (A and B) provide additional insight on the safety profile, then the RD may be a different, though not higher, dose than the MTD.

Once the RD has been established, patients with gastric cancer, bladder cancer, or with other locally advanced, recurrent or metastatic solid tumor types will be enrolled in Part 2 of the study. Patients will be selected for enrollment in Part 2 based on FGFR2b expression, as determined by an accompanying validated laboratory test for the analysis of FGFR2b expression for each tumor type in which an assay is available.

Part 2 patients will be enrolled and treated to further characterize safety and preliminary efficacy in a selected cancer patient population with the greatest potential for clinical benefit from FPA144 treatment. Treatment may continue until disease progression, unacceptable toxicity, patient or physician decision to discontinue, death, or termination of the study.

Study Design (Cont.):

Two cohorts of patients with FGFR2b-selected tumors will enroll in Part 2, as follows:

- Cohort A: Approximately 20 patients with gastric cancer with strong FGFR2b overexpression
- Cohort F: Up to 30 patients with FGFR2b-selected non-gastric solid tumors, including patients with FGFR2b-selected bladder cancer. Enrollment of non-gastric tumor types will be contingent on the development of an accompanying validated laboratory test for the analysis of FGFR2b overexpression.

Based on Sponsor discretion, the following cohorts will be closed for enrollment in Part 2:

- Cohort B: Patients with FGFR2b overexpressing gastric cancer in the absence of *FGFR2* amplification
- Cohort C: Patients with gastric cancer without FGFR2b overexpression
- Cohort D: Patients with gastric cancer with moderate FGFR2b overexpression
- Cohort E: Patients with gastric cancer with low FGFR2b overexpression

Study Population:

Inclusion Criteria

Patients enrolling into Part 1(A or B) or Part 2 must meet ***all*** of the following inclusion criteria:

1. Understand and sign an Institutional Review Board/Independent Ethics Committee-approved informed consent form prior to any study-specific evaluation
2. Life expectancy of at least 3 months
3. ECOG performance status of 0 to 1
4. Age ≥18 years at the time the informed consent form is signed except for the patients in Taiwan, where the patient's age must be ≥ 20 at the time the informed consent form is signed.

Study Population (Cont.)

5. In sexually-active patients (i.e., females of child bearing potential, who have not undergone menopause as defined by 12 consecutive months of amenorrhea or had a permanent sterilization procedure and males, who have not had a permanent sterilization procedure), willingness to use 2 effective methods of contraception, of which one must be a physical barrier method (condom, diaphragm, or cervical/vault cap) until 6 months after the last dose of FPA144. Other effective forms of contraception are permanent sterilization (hysterectomy and/or bilateral oophorectomy, or bilateral tubal ligation with surgery, or vasectomy) at least 6 months prior to Screening. Female patients of childbearing potential must be on stable oral contraceptive therapy or intrauterine or implant device for at least 90 days prior to the study, or abstain from sexual intercourse as a way of living.
6. Adequate hematological and biological function, confirmed by the following laboratory values:
   a) Bone Marrow Function
      - ANC $\geq 1.5 \times 10^9$/L
      - Platelets $>100 \times 10^9$/L
      - Hemoglobin ≥9 g/dL
   b) Hepatic Function
      - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3 x upper limit of normal (ULN); if liver metastases, then ≤5 x ULN
      - Bilirubin ≤1.5 x ULN
   c) Renal Function
      - Serum creatinine ≤1.5 x ULN
7. Tumor tissue for determination of FGFR2b expression (***optional for Part 1A patients***)

Patients enrolling into **Part 1A (Dose-Escalation)** of the study must also meet the following inclusion criteria:

8. Histologically or cytologically confirmed solid tumor or lymphoma that is locally recurrent or metastatic and has progressed following standard treatment or is not appropriate for standard treatment
9. Measurable or Non-measurable disease

Study Population (Cont.)

Patients enrolling into **Part 1B** of the study must also meet the following inclusion criteria:

10. Histologically documented gastric or gastroesophageal cancer
11. Tumor tissue for prospective or retrospective determination of FGFR2b expression and *FGFR2* amplification
12. Locally recurrent or metastatic disease that has progressed following standard treatment or is not a candidate for standard treatment
13. Measurable disease as defined by RECIST version 1.1

Patients enrolling into **Part 2 (Dose-Expansion)** of the study must also meet the following inclusion criteria:

14. The following tumor types, by cohort:
    - Cohort 2A: Histologically documented gastric or gastroesophageal cancer with FGFR2b overexpression, as determined by an accompanying validated IHC assay
    - Cohort 2F: Histologically or cytologically confirmed bladder cancer including tumors of the renal pelvis, ureters, urinary bladder, or urethra, or other histologically or cytologically confirmed solid tumor types with FGFR2b overexpression, as determined by an accompanying validated laboratory test for the analysis of FGFR2b expression
15. Tumor tissue for prospective determination of FGFR2b overexpression and retrospective determination of *FGFR2* amplification and other molecular aberrations (as applicable)
16. Locally recurrent or metastatic disease that has progressed following standard treatment or is not appropriate for standard treatment
17. Measurable disease as defined by RECIST version 1.1

Exclusion Criteria

Patients enrolling into Part 1(A or B) or Part 2 will be excluded if any of the following criteria apply:

1. Untreated or symptomatic central nervous system (CNS) metastases. Patients with asymptomatic CNS metastases are eligible provided they have been clinically stable for at least 4 weeks and do not require intervention such as surgery, radiation or any corticosteroid therapy for management of symptoms related to CNS disease.

Study Population (Cont.)

2. Impaired cardiac function or clinically significant cardiac disease, including either of the following:
    - Unstable angina pectoris ≤6 months prior to first scheduled dose of FPA144
    - Acute myocardial infarction ≤6 months prior to first scheduled dose of FPA144
3. QTc segment >470 msec
4. Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness, or history of chronic hepatitis B or C.
5. Treatment with any anticancer therapy or participation in another therapeutic clinical study with investigational drugs ≤14 days (≤ 28 days for patients in Korea) prior to first dose of FPA144.
6. Ongoing acute adverse effects from prior treatment > NCI CTCAE Grade 1.
7. Retinal disease or a history of retinal disease or detachment or, in the ophthalmologist's opinion, increased risk for retinal detachment
8. Corneal defects, corneal ulcerations, keratitis, keratoconus, history of corneal transplant, or other known abnormalities of the cornea that may, in the opinion of an ophthalmologist, pose a risk with FPA144 treatment.
9. NSCLC patients with exon 19 or 21 EGFR mutation or ALK amplification who have not received an EGFR or ALK TKI, respectively (*Part 1A only*)
10. Gastric and breast cancer patients with HER2 over-expression who have not received anti-HER2 targeted therapy.
11. Major surgical procedures are not allowed ≤28 days prior to FPA144 administration. In all cases the patient must be sufficiently recovered and stable before treatment administration.

Study Population (Cont.)

12. Females who are pregnant or breastfeeding; women of childbearing potential must not be considering getting pregnant during the study.
13. Presence of any serious or unstable concomitant systemic disorder incompatible with the clinical study (e.g., substance abuse, psychiatric disturbance, or uncontrolled intercurrent illness including active infection, arterial thrombosis, and symptomatic pulmonary embolism)
14. Presence of any other condition that may increase the risk associated with study participation or may interfere with the interpretation of study results, and, in the opinion of the Investigator, would make the patient inappropriate for entry into the study.
15. Known allergy or hypersensitivity to components of the FPA144 formulation including polysorbate.
16. History of prior malignancy except:
    a) Curatively treated non-melanoma skin cancer or
    b) Solid tumor treated curatively more than 5 years previously without evidence of recurrence or
    c) History of other malignancy that in the Investigator's opinion would not affect the determination of study treatment effect.
17. In **Part 1B and 2 (Dose Expansion),** prior treatment with any selective inhibitor (e.g., AZD4547, BGJ398, JNJ-42756493, BAY1179470) of the FGF-FGFR pathway

No waivers of these inclusion or exclusion criteria will be granted.

Study Treatment:

FPA144 will be supplied in a sterile vial for dilution into an intravenous bag for administration by the study site.

In Part 1A, patients will receive 2 doses of FPA144, 2 weeks apart. If this is tolerated without disease progression by the end of the first cycle, patients will be eligible to continue on study in the Extended Treatment Period and receive FPA144 every 2 weeks until disease progression or other cause for study withdrawal.

Dose-Modification Criteria:

Dose reductions may be permitted for patients on treatment beyond the DLT period in Part 1A or any patient in Parts 1B or 2 upon discussion with and approval by the Sponsor.

Patients may miss up to 2 consecutive doses (up to 6 weeks between doses) for adverse or other events; omission of additional dosing longer than 6 weeks for adverse or other events will necessitate the patient's removal from the study unless allowed by the study Sponsor.

Intra-patient dose escalation above the starting dose for each patient in Part 1 (A and B) and Part 2 will not be permitted. If a patient's dose is decreased for a reason that is no longer relevant, dose escalation to the originally assigned dose may occur after discussion and approval by the Sponsor.

Concomitant Medications:

Supportive care (e.g., anti-emetics; analgesics for pain control) may be used at the Investigator's discretion and in accordance with institutional procedures. Hematopoietic stimulating agents may be used if indicated. Concomitant anticancer therapies of any kind are not permitted except chronic maintenance therapies, such as luteinizing hormone releasing hormone (LHRH)-modulating agents for breast or prostate cancer, which may be continued if the patient has been on these agents and 1) continued use is unlikely to result in additional reduction in tumor measurements and 2) is considered standard therapy for the patient.

Withdrawal Criteria:

A patient must be discontinued from protocol-prescribed therapy if any of the following apply:

- Consent withdrawal at the request of the patient or their legally authorized representative
- Progression of patient's disease. Patients who are receiving clinical benefit despite isolated disease progression may continue on study after discussion with Medical Monitor
- Any event that would pose an unacceptable safety risk to the patient
- A concurrent illness that would affect assessments of the clinical status to a significant degree and require discontinuation of therapy
- A positive pregnancy test at any time during the study
- At the specific request of the Sponsor or its authorized representative (e.g., if the study is terminated for reasons of patient safety)

Pharmacokinetic Assessments:

Patients enrolled in Parts 1A and 1B will have blood sampling for measurement of serum FPA144 concentration during Cycle 1 Days 1, 2, 4, and 8. In addition, blood samples will be collected both before and at the end of the infusion at Cycle 1 Day 15 and Cycles 2-5 Day 1 and every other cycle Day 1 starting from Cycle 5 as well as at the end of treatment.

For patients in Part 2, Cycle 1 blood samples will be collected on Cycle 1 Days 1 and 8. Blood samples will be collected on Cycle 1 Day 15 and Cycles 2-5 Day 1 and every other cycle Day 1 starting from Cycle 5 both before and at the end of each infusion as well as the end of treatment to explore the PK in enrolled patients.

Standard PK parameters will be determined based on serum FPA144 concentration-time data.

Immunogenicity:

All patients in the study will have blood samples collected prior to dosing on Day 1 of Cycles 1-5 and every over other cycle from Cycle 5 for measurement of anti-FPA144 antibodies.

Efficacy Assessments:	Efficacy measures will include tumor assessments consisting of clinical examination and appropriate imaging techniques, preferably computed tomography (CT) scans of the chest, abdomen, and pelvis with appropriate slice thickness per RECIST; other assessments (magnetic resonance imaging [MRI], X-ray, positron emission tomography (PET), and ultrasound) may be performed, if required. Tumor assessments will be performed at Screening, then every 6 weeks from the first dose, for 24 weeks, and then approximately every 12 weeks thereafter. Once an initial complete response (CR) or partial response (PR) is noted, confirmatory scans must be performed 4–6 weeks later.
Safety Assessments:	Safety measures will include AEs, hematology, clinical chemistry, urinalysis, vital signs, body weight, concomitant medications/procedures, ECOG performance status, targeted physical exams, ECGs, ophthalmology/retinal examinations, and FPA144 dose modifications.
Pharmacodynamic Assessments:	Tumor biopsies, mandatory as feasible, will be performed before treatment and **either** at 15 days **or** 29 days on-treatment for all patients in Part 2 (see Section 6.4). Feasibility at each timepoint will be assessed by the Investigator and should include a consideration of patient safety. Patients may also have an optional on-treatment biopsy upon documented tumor response and/or optional post-treatment biopsy upon documented tumor progression after discussion with the Sponsor.
Statistical Procedures:	The total enrollment planned for this study was approximately 70–210 patients. Based on the Sponsor decision to close a subset of cohorts in Part 2 (as described in Section 4.1), the planned patient enrollment will be approximately 100 patients. Approximately 20–30 patients will be enrolled into Part 1A. In Part 1B, up to 30 patients with gastric cancer will be enrolled. For Part 2, exploratory activity will be examined by enrollment of: • Cohort A: Approximately 30 patients with gastric cancer with strong FGFR2b overexpression defined as IHC 3+ ≥ 10% tumor membrane staining. • Cohort C: Approximately 10-30 patients with gastric cancer without FGFR2b overexpression (IHC 0). Expansion of this cohort to 30 patients will be contingent on Sponsor's decision to evaluate additional patients without FGFR2b overexpression as a basis for exploring patient selection based on FGFR2b expression.

Statistical Procedures (Cont.):

The following additional cohorts may be explored in Part 2 at the discretion of the Sponsor:

- Cohort D: Approximately 30 patients with gastric cancer with moderate FGFR2b overexpression defined as IHC 2+ ≥ 10% **and/or** IHC 3+ < 10% tumor membrane staining.%. Enrollment in this cohort will be contingent on Sponsor's decision to explore lower IHC score limits.
- Cohort E: Approximately 30 patients with gastric cancer with low FGFR2b overexpression defined as IHC 1+ **and/or** IHC 2+ < 10% tumor membrane staining.%. Enrollment in this cohort will be contingent on Sponsor's decision to explore lower IHC score limits.
- Cohort F: Approximately 30 patients with FGFR2b-selected non-gastric solid tumors, including patients with FGFR2b-selected bladder cancer. Enrollment of additional tumor types will be contingent on the development of an accompanying validated laboratory test for the analysis of FGFR2b overexpression.

List of Key Study Personnel

Sponsor:	Neyssa Marina, MD FivePrime Therapeutics, Inc. Two Corporate Drive South San Francisco, CA 94080-7047 + 1 650-745-9676 (office) + 1 650-996-0510 (mobile) + 1 415-365-5615 (fax) Helen Collins, MD FivePrime Therapeutics, Inc. Two Corporate Drive South San Francisco, CA 94080-7047 + 1 707-321-8168 (mobile) + 1 650-745-9633 (office) + 1 415-365-5615 (fax)
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List of Abbreviations and Definitions

ADA	Anti-drug antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
ALK	Anaplastic lymphoma kinase
ALT	Alanine transaminase
ANC	Absolute neutrophil count
ANOVA	Analysis of variance
APTT	Activated partial thromboplastin time
AST	Aspartate transaminase
β-HCG	Beta-human chorionic gonadotropin
BUN	Blood urea nitrogen
CBC	Complete blood count
C_{max}	Maximum serum concentration
C_{min}	Minimum serum concentration
CNS	Central nervous system
CO_2	Carbon dioxide (bicarbonate)
CR	Complete response
CRC	Cohort Review Committee
CRO	Contract research organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting toxicity
eCRF	Electronic case report form
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EOT	End of treatment
FDA	Food and Drug Administration
FGF	Fibroblast growth factor (subtypes, e.g., FGF-1, FGF-2)
FGFR	Fibroblast growth factor receptor (subtypes, e.g., *FGFR1*, *FGFR2*)
FISH	Fluorescence *in situ* hybridization
FRS2	FGF receptor substrate-2
GCP	Good Clinical Practice
GLP	Good Laboratory Practice

HER	Human epidermal growth factor receptor
HIV	Human immunodeficiency virus
HNSTD	Highest non-severely toxic dose
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IHC	Immunohistochemistry
IND	Investigational New Drug (application)
INR	International normalized ratio
IRB	Institutional Review Board
IV	Intravenous
LDH	Lactate dehydrogenase
LHRH	Luteinizing hormone-releasing hormone
MABEL	Minimal anticipated biologic effect level
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NOAEL	No observed adverse effect level
NSCLC	Non-small cell lung cancer
OCT	Ocular coherence tomography
ORR	Objective response rate
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression free survival
PK	Pharmacokinetics
PR	Partial response
PS	Performance status
PSA	Prostate-specific antigen
QTc	Corrected QT interval

RBC	Red blood cell
RD	Recommended dose
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RPE	Retinal pigmented epithelium
RVO	Retinal vein occlusion
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
$t_{1/2}$	Half-life
TKI	Tyrosine kinase inhibitor
ULN	Upper limit of normal
WBC	White blood cell

1. Introduction

1.1 Background

The role of the fibroblast growth factor (FGF)-FGF receptor (FGFR) pathway in cancer is well known. FGFs can stimulate the transformation and proliferation of tumor cells and stimulate angiogenesis. There are 22 known human FGFs with the expression of individual FGFs generally restricted to specific tissues, cell types, and/or developmental stage. Fibroblast growth factor signaling is mediated by a family of transmembrane tyrosine kinase receptors encoded by 4 distinct genes producing FGF receptor subtypes termed FGFR1–4 (Turner 2010).

The FGFR2 has two splicing variants, b and c. In general, FGFR2b is expressed in tissues of epithelial origin (e.g., stomach, skin) (Miki 1992). The major ligands signaling through FGFR2b are FGF7, FGF10 and FGF22. Alteration in signaling in the FGF/FGFR2 pathway (e.g. overexpression of FGFR2b protein or amplification of *FGFR2* gene) has been associated with gastric, breast, and other cancers, and appears to portend a worse prognosis (Wu 2013, Turner 2010). In fact, as early as 1990, subsets of patients with gastric cancer (~3-9%) and breast cancer (1–2%) were noted to have amplification of the *FGFR2* gene, which resides on chromosome 10q26. In gastric cancer, *FGFR2* amplification leads to high-level expression of the FGR2b receptor on the surface of the cells.

FPA144 is a humanized monoclonal antibody (IgG1 isotype) specific to the human FGFR2b receptor (NCBI reference sequence ID NP_001138385.1) that blocks FGF ligand binding to the receptor. This antibody is glycosylated, but is produced in a CHO cell line that lacks the *FUT8* gene (α1,6-Fucosyltransferase) and therefore lacks a core fucose in the polysaccharide portion of the antibody. The absence of the core fucose results in higher affinity for the Fc receptor

FcγRIIIa compared to the fucosylated molecule and potentially enhances immune cell-mediated tumor cell killing (Shinkawa 2003).

FPA144 inhibits FGF ligand-stimulated FGFR2b phosphorylation and cell proliferation in cell culture in FGFR2b overexpressing gastric and breast cancer cell lines. FPA144 also inhibits tumor growth in FGFR2b overexpressing gastric and breast xenograft models. In addition, FivePrime has demonstrated *in vitro* that FPA144 mediates antibody-dependent cell-mediated cytotoxicity (ADCC) in cells expressing FGFR2b. The 3 potential mechanisms of action of FPA144 include blocking ligand binding and downstream signaling, decreasing expression of the FGFR2b driver protein and enhancing ADCC.

As FPA144 is a targeted biologic, the clinical development of FPA144 will ultimately be in selected patients with alterations in the FGFR2b pathway that are most likely to respond to this novel agent. The tumor types most relevant to date include gastric and bladder cancer, as well as potentially breast, ovarian, and cholangiocarcinoma. Each of these cancers is in need of new therapeutic options. FPA144, a selective FGFR2b inhibitor, may offer benefit in patients with appropriately selected tumors, with an improved safety profile relative to less or non-targeted therapeutics.

1.2 Overview of the FGF/FGFR Pathway

FGF signaling is mediated by a family of transmembrane tyrosine kinase receptors encoded by four distinct genes producing four FGF receptor (FGFR) subtypes termed FGFR1–4. Splice variations lead to several receptor variants, including two predominant isoforms each of FGFR1–3 and one isoform of FGFR4. Many FGFs have high affinity binding to multiple FGF receptors and as such each FGF receptor has a characteristic binding profile.

The extracellular domains of the FGFRs contain 3 immunoglobulin (Ig)-like domains. The carboxyl-terminal segment of the third Ig domain of FGFR1–3 can be encoded by two different exons, designated IIIb and IIIc, leading to expression of two distinct proteins, FGFR2b and FGFR2c. This alternative splicing regulates both ligand specificity and tissue distribution. In the literature, FGFR2b is generally referred to as FGFR2IIIb, FGFR2b, or K-sam. FGFR2b expression is largely restricted to epithelial tissues, and this isoform has high affinity for the FGF ligands FGF7, FGF10, and FGF22, with lower affinity for FGF21, FGF1 and FGF3. Among FGF receptors, FGF7, FGF10, and FGF22 bind exclusively to FGFR2b (Zhang 2006).

FPA144 selectively targets the FGFR2b isoform. It does not bind to the FGFR2c receptor isoform or to any other FGFR.

1.3 The Role of FGFR2 in Normal Tissue Homeostasis and in Cancer

FGFR2 plays important roles in embryonic development and tissue repair. *FGFR2* knockout mice are embryonic lethal (Xu 1998). The role of FGFR2 in normal adult tissue homeostasis is less well defined but has been explored by a series of tissue-specific conditional knockouts (Grose 2007) and by expression of a dominant negative version of the FGFR2b receptor (Werner

1994). In rodents, the FGFR2b is known to be important for incisor stem cells and continued growth of incisors throughout life (Lin 2009, Parsa 2010), which is not relevant in humans. Other data suggest there is a degree of redundancy between the FGFR1 and FGFR2 pathways in the maintenance of the skin (Yang 2010), liver and central nervous system (Böhm 2010), suggesting a selective approach to blocking the FGFR2b pathway is preferable to therapeutics with broader FGFR pathway inhibition.

High levels of FGFR2 expression have been found in many advanced solid tumors including gastric and bladder cancer. Specifically, FGFR2b can be highly expressed on tumors either via amplification of the *FGFR2* gene or via transcriptional regulation of the FGFR2b isoform. Using a validated immunohistochemistry (IHC) assay to specifically detect FGFR2b expression in solid tumors, approximately 9% of gastric cancers and 10% of bladder cancers were observed to express a range of FGFR2b protein.

In patients with gastric cancer, 3–9% have amplification of the *FGFR2* gene, which resides on chromosome 10q26 (Hattori 1990, Turner 2010). This amplification is most often found in poorly differentiated gastric cancer samples, results in high levels of FGFR2b overexpression, and is correlated with a poor prognosis (Jung 2012). Interestingly, amplification of *FGFR2* is very rare in gastric tumors that overexpress or have amplification of the *HER2* gene (Deng 2012), as those pathways appear to be largely mutually exclusive. In addition to *FGFR2* amplification, there may be a subset of gastric cancer patients whose tumors overexpress FGFR2b in the absence of amplification; similar to patients with *FGFR2* amplification, these patients are thought to have a poor prognosis (Hattori 1996)..

Some other tumor types have also been found to have dysregulation of the FGFR2 signaling pathway. Similar to gastric cancer *FGFR2* amplification has been found in a small percentage of triple negative breast cancers (Turner 2010). FGFR2b protein overexpression has been found in ovarian cancer (Steele 2001), endometrial and lung cancers. In addition, *FGFR2* gene translocations have been identified in cholangiocarcinoma (Wu 2013). These tumors, selected for FGFR2b overexpression, may also be responsive to treatment with FPA144.

1.4 FPA144: An FGFR2b Specific Antibody

FPA144 is an antibody to the third Ig region of the FGFR2b receptor isoform, the region that is alternatively spliced and regulates ligand specificity. FPA144 recognizes only the b isoform of the FGFR2. The antibody has been glycoengineered for enhanced ADCC (Gemo 2014). When the antibody recognizes the FGFR2b receptor on the cell surface, it blocks ligand binding and downstream signaling including cell proliferation. Enhanced ADCC may increase tumor cell killing. Since FPA144 is specific for the FGFR2b receptor, it does not interfere with signaling of the other FGFs/ FGFRs, including FGFR2c. Additionally and in contrast to the FGFR TKIs, FPA144 does not inhibit FGF23 signaling. FGF23 is a ligand involved in calcium/phosphate metabolism. Thus, treatment with FPA144 is not expected to cause significant dose-limiting

hyperphosphatemia associated with the FGFR TKIs (Andre 2013, Brown 2005, Dienstmann 2014, Sequist 2014).

1.5 Nonclinical Studies with FPA144

There are three potential mechanisms of action of FPA144. It blocks ligand binding and downstream signaling, decreases expression of the FGFR2b driver protein and has enhanced ADCC. These mechanisms have been explored both *in vitro* and *in vivo*.

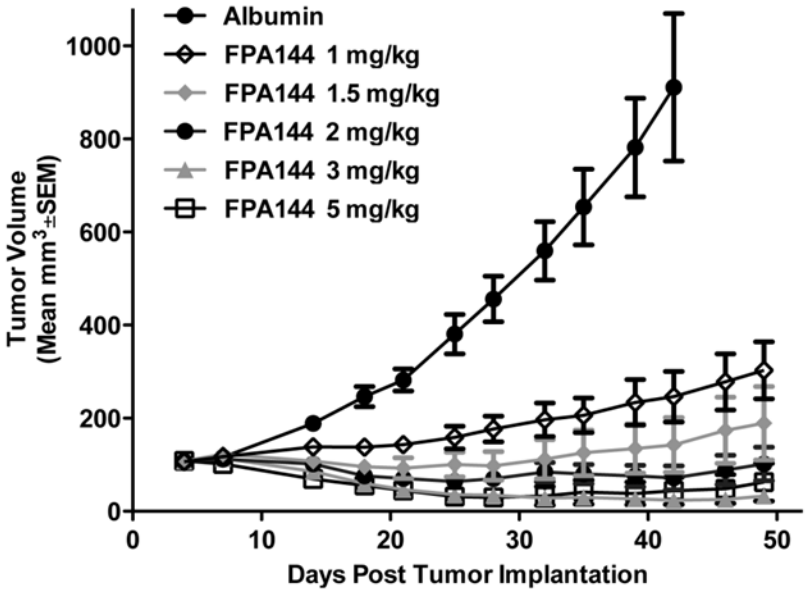
1.5.1 *In Vivo* Pharmacology

1.5.1.1 *In Vivo* Anti-Tumor Studies

FPA144 has been studied in a series of mouse xenograft models using human gastric and breast tumor cell lines that contain the *FGFR2* amplicon. These *FGFR2* amplified lines all express high levels of the FGFR2b protein and respond to FPA144 in a dose-dependent fashion. A dose response study (twice weekly dosing) was performed with the most sensitive model, a gastric cancer line, OCUM-2 (Figure 1). Mice were treated at the indicated concentrations of FPA144, and the tumor growth was compared to mice treated with albumin alone. Statistically significant tumor growth inhibition was seen at 0.3 mg/kg but not at 0.1 mg/kg, and tumor regression was seen at 1 mg/kg with complete tumor regression starting at doses of 1.5 mg/kg (2/15 animals), 2 mg/kg (1/15 animals), 3 mg/kg (5/15 animals), and 5 mg/kg (8/15 animals). In the SNU-16 gastric cancer model, tumor growth inhibition was seen at 1 mg/kg, while in the MFM-223 tumor-bearing mice, 5 mg/kg led to tumor stasis.

All of these tumor models require immunodeficient mice for tumor engraftment. Because these mice lack a fully functioning immune system, and because the mouse Fcγ receptor (the receptor on immune cells required for ADCC) has lower affinity for human antibodies than the human Fcγ receptor, ADCC is impaired in these models of FPA144 mediated tumor growth inhibition. Thus, in patients with FGFR2b overexpressing tumors, ADCC may further contribute to anti-tumor activity in the clinical setting.

Figure 1: Tumor Growth Inhibition in OCUM-2 Gastric Cancer Cell Line



Mechanistically, FPA144 blocks FGFR2b phosphorylation, downregulates the receptor and inhibits downstream signaling. The effect on downstream signaling was measured by examing phosphorylation of a protein that is directly phosphorylated by the FGFR2 protein, FGF receptor substrate-2 (FRS2). This has been demonstrated in the SNU-16 *FGFR2*-amplified gastric cancer xenograft model. In this experiment, mice were treated twice weekly with 10 mg/kg FPA144. When tumors had reached approximately 500 mm^3, the animals were sacrificed and protein levels in tumors were measured via Western Blotting. FPA144 treatment resulted in decreased FGFR phosphorylation, total receptor expression, and phosphorylation of the downstream signal transduction molecule, FRS2.

In contrast to the results with *FGFR2*-amplified gastric cancer models, FPA144 has minimal impact on xenograft models that are not *FGFR2* amplified or do not express the FGFR2b protein. Mice bearing NCI-87 gastric tumors, which do not express FGFR2b, were dosed intraperitoneally twice a week with FPA144 once the tumors reached approximately 100 mm^3. The tumor growth rate was indistinguishable between animals treated with either FPA144 (5 mg/kg) or control animals administered albumin.

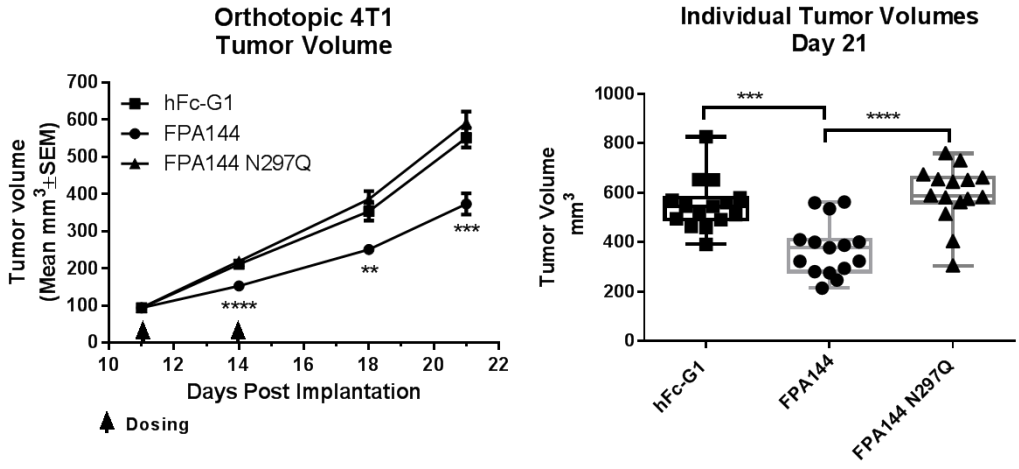
These results in models with different FGFR2b/FGFR2 profiles suggest that in the clinical setting, patients whose tumors overexpress FGFR2b may be more likely to respond to FPA144, highlighting the rationale for selecting patients whose tumors overexpress FGFR2b.

1.5.1.2 *In Vivo* ADCC Activity of FPA144

To understand the contribution of ADCC on FPA144 anti-tumor efficacy, a mutant antibody, FPA144 N297Q, which cannot bind Fc receptors, was compared to FPA144 in the syngeneic

4T1 model that expresses FGFR2b but to a lesser degree than amplified or overexpressed FGFR2b xenografts, such as OCUM-2M or SNU-16 xenograft tumors. 4T1 tumors were grown to a volume of approximately 100 mm3, then treated with FPA144, FPA144 N297Q, or the Fc fragment of human IgG1 (hFc-IgG1) as control. FPA144 decreased tumor burden vs hFc-IgG1 control while FPA144 N297Q showed no effect (Figure 2). These data support a role for ADCC activity through Fc receptor binding as a required mechanism for FPA144 efficacy in a model that expresses modest amounts of FGFR2b protein.

Figure 2: FPA144 but Not an ADCC-Deficient FGFR2b Antibody Leads to Tumor Suppression in a Syngeneic Tumor Model with Modest FGFR2b Expression



1.5.1.3 FPA144 Induces Tumor-Specific Innate and Adaptive Immune Profile Changes

To assess the effects of FPA144 on the tumor microenvironment, changes in infiltrating leukocytes post-FPA144 exposure were analyzed in 4T1 tumors. Once tumors reached approximately 150 mm^3, mice were treated with FPA144, FPA144 N297Q, or hFc-G1 Control on Day 0 and Day 3. Tumors were harvested for immunofluorescence or FACS analysis 24 hours after the second dose. FPA144 treatment leads to a recruitment of NK cells. In addition, PD-L1 expressing cells are increased within the tumor upon FPA144 treatment compared to either hFc-G1 control or FPA144N297Q mutant. Furthermore, an increase in CD3-positive T cells was observed within tumors treated with FPA144 and was not evident in mice treated with hFc-G1 Control or FPA144 N297Q groups, suggesting that these changes in the tumor microenvironment are dependent on both FGFR2b and Fc receptor engagement.

1.5.2 FPA144 Exposure Efficacy Relationships

To translate the efficacy results in animal models to patients with FGFR2b overexpressing gastric cancers, the relationship between FPA144 trough concentrations and efficacy in animal models was examined. Intraperitoneal FPA144 doses of 1 mg/kg twice weekly were associated

with tumor growth inhibition while greater efficacy depicted by tumor regression was noted at doses ≥3 mg/kg. A dose of 1 mg/kg in the mouse xenograft model led to steady state trough plasma concentrations of about 1 μg/ml, while 3 mg/kg resulted in significant tumor regression and trough plasma concentrations of 67–109 μg/mL. These data suggest that clinical dosing regimens resulting in steady state trough plasma concentrations of at least 1 μg/mL may be efficacious in patients with FGFR2b-associated gastric cancer.

1.5.3 Toxicology

Toxicology studies with FPA144 have been performed in rat and cynomolgus monkey. The studies performed have included pilot single dose pharmacokinetic/tolerability and repeat-dose studies as well as GLP repeat-dose studies. The longest of these studies involved intravenous (IV) administration of 13 weekly doses in rats and monkeys.

In pilot repeat-dose toxicology studies, rats and cynomolgus monkeys received 4 weekly IV doses of FPA144 up to 150 mg/kg. There were no changes in clinical signs and symptoms or clinical chemistry. The most significant findings from these repeat-dose pilot studies were microscopic findings in corneal epithelium. FPA144-treated animals displayed a dose-dependent "thinning" that represents both attenuation and reduction in the number of cells present in the corneal epithelium. In addition, microscopic changes in the retinal pigmented epithelium (RPE) in rat were noted that included RPE atrophy in one high-dose animal that received 4 weekly 150 mg/kg doses. Retinal changes were not observed in the 13-week GLP toxicology studies with a high dose of 100 mg/kg.

In the 13-week repeat-dose GLP toxicology studies, FPA144 was administered by IV at dose levels of 1, 5, or 100 mg/kg/dose to both rats and monkeys for 13 weekly doses.

In the rat, FPA144 resulted in adverse findings including: tooth (incisor) abnormalities (clinical, macroscopic, and microscopic findings) and body weight loss/lack of weight gain, which were most likely secondary to the tooth findings that necessitated early euthanasia at the 100 mg/kg/dose, ocular findings (ophthalmic and microscopic findings), and macroscopic and/or microscopic findings in the Harderian gland (not present in humans) and oral mucosa (hard palate) at 5 and 100 mg/kg/dose; and macroscopic and/or microscopic findings in the tongue at all dose levels. FGFR2 pathway signaling is known to play a critical role in maintaining the health of rat incisors but has not been found to be relevant in human dentition. FPA144-related, but non-adverse microscopic findings, were also noted in the mammary gland of animals at all dose levels. Administration of FPA144 also resulted in exacerbation of background microscopic findings in the prostate gland of males given 1, 5, and 100 mg/kg, the non-glandular stomach of animals given 5 and 100 mg/kg/dose, and the lung of animals given 100 mg/kg/dose. With the exception of FPA144-related effects on incisor teeth, some degree of recovery up to total recovery was evident for all findings at the end of recovery. The absence of FPA144-related findings in the eye (ophthalmic or microscopic findings), Harderian gland, mammary gland, and prostate gland at the end of the recovery period indicated complete reversibility of the findings in

these tissues. Since all findings in the 1 mg/kg/dose group were minimal, without clinical consequences, and recoverable, the highest, non-severely toxic dose (HNSTD) in rats was determined to be 1 mg/kg/dose when given weekly for 13 weeks. The lowest dose of 1 mg/kg/dose level was associated with mean C_{max} and AUC_{τ} (τ=168 hours) of 27.7 µg/mL and 789 h*µg/mL, respectively, for combined sexes on Day 85 of the dosing phase.

In the 13-week repeat-dose GLP toxicology study performed in cynomolgus monkeys, FPA144 was generally well tolerated. FPA144-related effects were limited to microscopic findings of corneal atrophy (slight to moderate) in animals given 5 and 100 mg/kg/dose and mammary gland atrophy (moderate to marked severity) in females from all dose groups. These findings in the cornea and mammary gland were not associated with clinical sequelae and were not observed at the end of the recovery phase, indicating complete recovery. Therefore, based on the lack of correlative clinical findings or changes (e.g., ophthalmic findings or clinical observations) and the demonstrated reversal during a recovery period, neither finding was considered adverse. The 100-mg/kg/dose level is considered below the severely toxic dose level in monkeys for the study. This represents a >300-fold safety factor over the proposed starting dose of 0.3 mg/kg. The highest dose of 100 mg/kg was associated with mean C_{max} and AUC_{τ} (τ=168 hours) values of 3266 µg/mL and 252787 h*µg/mL, respectively, for combined sexes on Day 85 of the dosing phase.

In addition to *in vivo* toxicology studies, a GLP-compliant tissue cross reactivity study has been performed to compare the binding of FPA144 to a panel of 36 tissues from rat, cynomolgus monkey, and human. In general the binding pattern of FPA144 was similar among the 3 species and agreed with literature reports on the expression of FGFR2b being epithelial-based.

Further details of the nonclinical program for FPA144 can be found in the Investigator's Brochure (IB), which contains comprehensive information on the investigational product.

1.6 Patient Selection

FPA144 is an antibody designed to recognize the FGFR2b receptor when expressed on tumors. FGFR2b may be highly expressed as a result of a molecular aberration of the *FGFR2* gene (e.g. amplification or translocation) or transcriptional regulation of the FGFR2b isoform. The current hypothesis is that the presence of FGFR2b is an important predictor of patients who may respond to FPA144 treatment. This is based on the preclinical observation that only tumors that overexpressed FGFR2b responded to FPA144 treatment in xenograft studies (described in Section 1.5.1). For this reason, during Part 2 of the clinical trial, patients will be selected according to the extent of FGFR2b overexpression using immunohistochemistry (IHC). In addition, clinical outcomes will be explored in FGFR2b-selected gastric and bladder cancer patients across a range of IHC-based selection criteria that take into account both the level of tumor membrane staining intensity and the percentage of the tumor sample positively stained. This will enable a better understanding of the relationship between the extent of FGFR2b expression and clinical outcomes in the setting of gastric and bladder cancer.

FivePrime has developed an anti-FGFR2b antibody for nonclinical use, whose sensitivity and specificity to detect FGFR2b by IHC has been optimized. Evaluation of tumor samples from 125 gastric cancer patients demonstrates high concordance between FISH positive (*FGFR2* amplified) tumors and FGFR2b IHC score of 3+ (Deshpande 2014). The relationship between FGFR2b expression and molecular aberrations of *FGFR2* in other tumor types are not well-established and are currently under preclinical investigation.

Thus in Part 1B and Part 2, samples from all patients will be assessed prospectively by IHC to determine the expression of FGFR2b. For gastric cancer patients, overexpression of FGFR2b will be defined as follows in Part 2:

- **Strong FGFR2b Overexpression:** defined as strong membranous staining of at least 10% of the tumor cells in a sample (scored as IHC 3+ ≥ 10%)

The two gastric cancer cohorts enrolling patients with moderate (Cohort D) and low (Cohort E) FGFR2b overexpression will be closed.

For patients with bladder cancer, overexpression of FGFR2b will be defined as follows in Part 2:

- **High FGFR2b Overexpression:** defined by the extent of membranous staining in tumor cells giving rise to an H-score of ≥ 20 in a sample

- **Low FGFR2b Overexpression:** defined by the extent of membranous staining in tumor cells giving rise to H-score of ≥ 10, but < 20 in a sample

The H-score is a method of assessing the extent of membranous immunoreactivity and is derived using the formula: 3 x the percentage of tumor cells with strong membranous staining (3+) + 2 x the percentage of tumor cells with moderate membranous staining (2+) + percentage of tumor cells with weak membranous staining (1+), giving a range of 0 to 300.

For other FGFR2b-selected tumor types outside of gastric and bladder cancer, criteria for defining FGFR2b overexpression will be determined upon availability of a validated assay for each individual tumor type in question. Criteria for determining FGFR2b overexpression will be based on preclinical data and may differ between tumor types.

For determining *FGFR2* gene amplification by FISH, samples submitted for Part1B will be analyzed either prospectively or retrospectively, while samples submitted for Part 2 will be analyzed retrospectively. For this study, a tumor will be considered *FGFR2* gene amplified if the ratio of the *FGFR2* probe to the centromeric probe (CEN10) is ≥2 in ≥10% of the cells, or there are small clusters of amplification in which the ratio cannot be determined (Su 2014).

A total of 8 patients with gastric cancer with or without FGFR2b overexpressing tumors and with or without *FGFR2* amplification were enrolled in Part 1B (which is closed to enrollment). Two cohorts of patients with FGFR2b-selected tumors will continue enrolling in Part 2. Cohort A will

enroll approximately 20 patients with gastric cancer with strong FGFR2b overexpression. Cohort F will enroll up to 30 patients for FGFR2b-selected solid tumors outside of gastric cancer, including patients with FGFR2b-selected bladder cancer. Enrollment of additional tumor types in this cohort will be contingent on the development of an accompanying validated laboratory test for the analysis of FGFR2b overexpression. Cohort B, which was defined as the cohort of patients with tumors with FGFR2b overexpression in the absence of *FGFR2* amplification, was closed for enrollment due to the absence of eligible patients (unpublished internal FivePrime data). In addition, Cohort C, planned to enroll patients with gastric cancer without FGFR2b overexpression (IHC score of 0), will be closed. Cohort D, which was defined as the cohort of patients with gastric cancer with moderate FGFR2b overexpression, and Cohort E, which was defined as the cohort of patients with gastric cancer with low FGFR2b overexpression, will also be closed to enrollment.

1.7 Clinical Experience with FPA144

This study was initiated in December 2014 and is the first-in-human assessment of the safety, tolerability and PK profile of FPA144. Dose escalation has been completed in patients with solid tumors (Part 1A) and gastric cancer (Part 1B) and the dose expansion phase (Part 2) is currently enrolling patients with FGFR2b-selected gastric and bladder cancer in this study.

Prior to completing Part 1A in November 2015, 19 patients with a variety of solid tumors were enrolled. Of these 19 patients, 18 completed at least one cycle and were evaluable for dose limiting toxicity. FPA144 was well tolerated in doses up to 15 mg/kg in patients with advanced solid tumors. There were no DLTs observed during dose-escalation and a MTD was not reached. Based on an assessment of safety, tolerability, and PK, a RD of 15 mg/kg was selected.

In parallel to Part 1A, escalating doses of FPA144 were also evaluated in gastric cancer patients in Part 1B. In Part 1B, a total of 8 gastric cancer patients were enrolled. One patient received FPA144 at 3 mg/kg, one patient at 6 mg/kg, and six patients at 10 mg/kg. Out of the 8 enrolled, 6 met both the criteria for FGFR2b overexpression by IHC and *FGFR2* amplification by FISH.

As of the latest data cut-off (October 28, 2016), a total of 53 patients across Part 1 (27 patients) and Part 2 (26 patients) have enrolled in the study and received at least 1 dose of FPA144. Of the 53 patients, 35 patients had gastric cancer and 18 patients were identified as having gastric cancer that was FGFR2b^{+} high (IHC 3+ intensity in ≥ 10% of tumor cells). Of those 18 patients, 6 patients were enrolled in the Part 1B dose escalation and 12 patients in the Part 2 dose expansion Cohort A. In addition, 4 patients with gastric cancer with low FGFR2b overexpression have been enrolled into Cohort E and 10 patients with gastric cancer (IHC 0 – 2) have been enrolled into Cohort C in Part 2.

Safety and tolerability of FPA144 is supported by experience from a total of 53 patients from the Phase 1 study (FPA144-001) who have received at least 1 dose of FPA144. As of October 28, 2016, AEs have been reported in 48 of 53 patients (90.5%). Twenty-nine of the 53

(54.7%) patients reported an AE that was deemed by the Investigator to be drug related. Of the drug-related AEs, none were Grade 4, and 4 events were Grade 3: an infusion reaction in 1 patient, an aspartate transaminase (AST) elevation and alkaline phosphatase increase in 1 patient, nausea in 1 patient, and a transient decrease in neutrophil count in 1 patient which resolved without dose interruption or modification. No patient permanently discontinued treatment due to a treatment-related AE. Overall, 1 patient discontinued treatment due to an AE of E.Coli sepsis that was considered unrelated to study treatment. Treatment-related serious adverse events (SAEs) were reported in 2 patients: 1 patient had a Grade 3 infusion reaction and 1 patient had a Grade 2 corneal ulcer, both at the 15 mg/kg dose level. The patient with the infusion reaction was subsequently able to receive drug after pre-medication, while the patient with the corneal ulcer resumed drug after temporarily holding study drug and receiving treatment with antibiotic drops.

As discussed in Section 1.5.3, the pre-clinical animal toxicity studies supported a need for comprehensive ophthalmologic examinations. As of the October 28, 2016 cut off, there have been no reported adverse events (AEs) of any grade related to the retina. Ocular adverse events have been reported in 13 patients. There was 1 reported SAE of Grade 2 corneal ulcer which was symptomatic and resolved with topical antibiotic treatment and FPA144 dosing interruption. The patient missed 1 dose of FPA144 and was subsequently able to resume dosing. Other treatment-emergent Grade 2 AEs that fall under the System/Organ/Class of eye disorders were 1 patient each with dry eye, increased lacrimation, and blepharitis. The remaining eye disorder AEs were all Grade 1. After October 28, 2016, an event of Grade 2 limbic stem cell deficiency was reported by the investigator as related to study drug. The event was unexpected and considered medically important per the Sponsor and thus reported. The main symptom of the limbic stem cell deficiency, blurred vision, improved symptomatically after stopping FPA144. The slit lamp exams remain abnormal approximately 2 months after discontinuation of treatment with FPA144.

Evidence of early efficacy in the FGFR2b^{+} high gastric and gastroesophageal junction (GEJ) cancer patient population is supported by a confirmed response rate (per Response Evaluation Criteria in Solid Tumors [RECIST] 1.1) of 22.2% in 18 patients in the target patient population with a duration of response of 15.9 weeks (95% CI 9.7, 20.0 weeks) and a median progression-free survival of 14 weeks (95% CI 8.0, 21.6 weeks).

While the data are preliminary and potentially subject to change, it supports continued investigation of FPA144 in FGFR2b-selected gastric cancer.

In addition, in Part 1A, a response was seen in a 75 year-old man with recurrent urinary bladder cancer. He is being treated with 3 mg/kg FPA144 and has had complete radiographic and metabolic regression of the lymph nodes that were his evaluable sites of disease. This is a complete response by RECIST v1.1, based on the original size of lymph nodes and subsequent response to treatment. This supports the further exploration of the potential for FPA144 therapy in additional cancer settings, including urothelial bladder cancer.

1.8 FPA144 Starting Dose Justification

A starting dose of 0.3 mg/kg every 2 weeks is planned for this initial single agent Phase 1 trial based on several approaches to identifying an appropriate starting dose for this cancer patient population:

1) In mouse pharmacology studies using xenograft responses, the minimal anticipated biologic effect level (MABEL) was determined to be 0.3 mg/kg when dosed twice a week. No anti-tumor effects were observed at 0.1 mg/kg on the same schedule. Thus, 0.3 mg/kg may represent a minimally effective dose in patients.
2) In the monkey, the no adverse event level (NOAEL) is ≥100 mg/kg in the 13-week GLP toxicology program. The monkey is likely the more relevant species based on more similar FGFR biology between man and cynomolgus monkey. In rats, many of the observations in the toxicology study appear to be a consequence of the documented dependence of rat incisor growth on FGFR2 signaling (Lin 2009) that is not relevant for human use.
3) In the rat study, adverse findings were found at the 1 mg/kg dose level based on the observation of minimal, microscopic subepithelial fibrosis in the tongue in 1/30 animals. This lesion was deemed only partially reversible in the recovery group based on findings in 1/10 recovery animals. In the higher dose groups, there was obvious ongoing recovery of these findings in the tongue. While this finding could set the NOAEL at <1 mg/kg in the rat, FivePrime believes a determination that this lesion was adverse is conservative since these lesions are very infrequent and minimal in nature and were not associated with clinical sequelae or overt signs of toxicity such as weight loss or reduced food consumption at the 1 mg/kg dose level.
4) No lesions in the tongue were observed in the monkey study even at the highest dose level of 100 mg/kg/dose.
5) The mRNA expression pattern of FGFR2b in adult human tissues is very low in the tongue.
6) Such lesions will be monitored in the clinic by oral examination.

1.9 Risk-Benefit Assessment

This overview is not intended to replace the complete information presented in the FPA144 IB. Investigators participating in this study are required to review the FPA144 IB before administering the antibody.

FPA144 is being developed for testing in FGFR2b overexpressed tumors given the sensitivity of these tumors in nonclinical studies to FPA144 treatment. This first in human study is currently ongoing in the US, Korea, and Taiwan and aims to assess the safety, tolerability and PK profile of FPA144. Prior to this study, there have been no other trials of FPA144 or other antibodies specifically targeting FGFR2b to provide guidance with regard to potential risks or benefits of FPA144. As of the last data cut-off (October 28, 2016), the number and nature of drug-related adverse events have been limited, with no patients discontinuing the study for drug-related

toxicity (outlined in detail in Section 1.7). Therefore, specific inhibition of a potentially important target in a subset of gastric cancer or other solid tumor patients may be accomplished with limited toxicity.

Ongoing clinical studies with FGFR TKIs may provide additional insight into the safety and anti-tumor activity associated with targeting the FGF signaling pathway.

AZD4547 is a selective inhibitor of FGFR 1, 2 and 3 that has been evaluated in an ongoing Phase 1 trial with expansion in patients with *FGFR 1* or *2* amplified tumors. A dose range of 20-200 mg *bid* was evaluated with dose limiting toxicities of increased liver enzymes, stomatitis, renal failure, hyperphosphatemia and mucositis. At the expansion dose of 80 mg *bid*, adverse events included hyperphosphatemia, dry skin and mucous membranes, and retinal pigmented epithelium (RPE) detachment. A partial response was reported in a non-small cell lung cancer patient with *FGFR1* amplification (Andre 2013).

BGJ398 is a pan-FGFR inhibitor at low nanomolar concentrations in early Phase 2 development. In Phase 1, the dose-limiting toxicities included Grade 3 aminotransferases and hyperphosphatemia and Grade 1 corneal toxicity. At the MTD of 125 mg/day, hyperphosphatemia occurred in 78% of patients, stomatitis (37%), alopecia (32%), decreased appetite (32%), and fatigue (22%) and were generally mild. Anti-tumor activity, characterized as regressions and unconfirmed and confirmed partial responses, was observed in patients with activating mutations of *FGFR1*, *FGFR2* and *FGFR3* in several different tumor types (Sequist 2014).

JNJ-42756493 is also a small molecule pan-FGFR inhibitor that is undergoing evaluation in a Phase 1 trial. No dose limiting toxicities were reported across the dose range reported. The most common adverse events (AEs) were hyperphosphatemia (57%), asthenia (46%), dry mouth (32%), abdominal pain (29%), diarrhea (25%), vomiting (25%), decreased appetite (21%), and constipation (21%). Tumor response occurred in a bladder cancer patient with an FGFR3-TACC translocation (Dienstmann 2014).

Hyperphosphatemia is an expected result from inhibition of FGF23, given its role in phosphate homeostasis. FGF23 signaling occurs via FGFR1c and FGFR4, neither of which is inhibited by FPA144. Hyperphosphatemia has not been seen in toxicology studies with FPA144 treatment of up to 13 weeks in duration. Although hyperphosphatemia is not an expected effect of treatment with FPA144, serum phosphate levels will be monitored throughout the study. No abnormal serum phosphate levels have been reported in any patients who received FPA144 to date.

Based on the nonclinical studies with FPA144 and the FGFR2 pathway literature, the adverse events of interest for safety monitoring include those involving mammary glands, oropharynx and ocular toxicity, particularly potential changes in corneal epithelium. No AEs related to mammary glands have been reported thus far on FPA144-001. As of the data cutoff of October 28, 2016, 13 patients have reported ocular adverse events. Only 1 event, a Grade 2 corneal ulcer,

required treatment and follow-up from an ophthalmologist. The event was unexpected and considered medically important per the Investigator and reported. The corneal ulcer resolved after holding study drug, after which the patient continued FPA144 administration. After the data cutoff, an event of Grade 2 limbic stem cell deficiency was reported by an Investigator as related to study drug. The event was unexpected and considered medically important per the Sponsor and reported. The main symptom of the limbic stem cell deficiency, blurred vision, improved symptomatically after stopping FPA144. The slit lamp exams remain abnormal approximately 2 months after discontinuation of treatment with FPA144. In addition, one event of grade 1 dry mouth was reported in a patient during cycle 6 of FPA144 given at 3 mg/kg.

In addition to the study design (dose escalation) and eligibility criteria that exclude patients with significant organ dysfunction, the following precautions will be taken.

Patients found to have certain ocular abnormalities during screening will be excluded. Ophthalmology examinations will be performed during the course of the study to monitor potential ocular effects.

Potential oral abnormalities will be evaluated by serial physical examinations.

Patients will be closely monitored for infusion-related reactions. The infusion length may be increased at the Investigator's discretion based on occurrence of infusion-related reactions, such as changes in vital signs, nausea, vomiting, or other constitutional symptoms or allergic reactions occurring during infusion or up to 2 hours after cessation of the infusion. For subsequent infusions, patients may be pre-medicated with antiemetics, steroids, or antihistamines at the discretion of the Investigator. The treatment will be administered according to the institution's standard practice. Epinephrine for subcutaneous injection, diphenhydramine for IV injection, and any other medications and resuscitation equipment for emergency management of anaphylactic reactions must be available in the room where the infusions are being performed. To date, four events of infusion-related reaction have been reported across three patients [one grade 1 event reported in a patient receiving FPA144 at 10 mg/kg, one grade 2 event in a patient receiving 10 mg/kg, and two events (grade 3 and 2) reported in a patient receiving 15 mg/kg] The grade 3 infusion-related event was unexpected and considered medically important per the Investigator and reported.

In summary, FGF signaling pathways appear to be valid targets for clinical investigation in human cancer based on preclinical models as well as Phase 1 clinical investigations demonstrating anti-tumor activity with broad FGFR targeted agents. Pre-clinical data support specific targeting of FGFR2b in tumors with overexpression of the receptor and non-clinical toxicology evaluation has demonstrated that potentially effective doses may be safely administered.

However, as this is the first clinical study of FPA144, the safety profile in humans has not been established, and unanticipated side effects may occur. Cautious dose escalation with close monitoring of safety is planned in this study in order to limit the risk to patients.

2. Study Objectives and Endpoints

2.1 Primary Objectives

- To evaluate the safety profile of escalating doses of FPA144 in patients with advanced solid tumors, and to determine the MTD and RD *(Part 1A only)*
- To evaluate the safety profile of escalating doses of FPA144 in patients with advanced gastric cancer (*Part 1B only)*
- To evaluate the safety and tolerability of FPA144 administered intravenously every two weeks at the RD in patients with gastric cancer and other solid tumors, including bladder cancer (*Part 2 only*)

2.2 Secondary Objectives

- To characterize the PK profile of single and multiple doses of intravenously administered FPA144 in patients with gastric cancer and in other solid tumors, including bladder cancer
- To evaluate the safety and tolerability of longer term exposure to FPA144 administered intravenously every two weeks
- To evaluate the objective response rate (ORR) in patients with FGFR2b-selected gastric cancer and other solid tumors by tumor type, including FGFR2b-selected bladder cancer (*Part 2 only*)
- To evaluate duration of response in responding patients with FGFR2b-selected gastric cancer and other solid tumors by tumor type, including FGFR2b-selected bladder cancer (*Part 2 only*)
- To characterize the pharmacodynamic profile of FPA144 through an analysis of the immune cell infiltrate in pre-treatment and on-treatment tumor biopsies by tumor type (*Part 2 only*)

2.3 Exploratory Objectives

- To evaluate the stable disease rate and duration in patients with FGFR2b-selected gastric cancer and other solid tumors by tumor type, including FGFR2b-selected bladder cancer (*Part 2 only*)
- To assess progression-free survival (PFS) in patients with FGFR2b-selected gastric cancer and other solid tumors by tumor type, including FGFR2b-selected bladder cancer (*Part 2 only*)
- To explore the association between extent of FGFR2b overexpression and *FGFR2* amplification (or other molecular aberrations, as applicable) in tumor tissue and clinical outcome by tumor type

- To characterize the pharmacodynamic profile of FPA144 through an analysis of exploratory biomarkers in pre-treatment and on-treatment tumor biopsies by tumor type (*Part 2 only)*

2.4 Primary Study Endpoints

- The incidence of Grade 3 and Grade 4 adverse events (AEs) and clinical laboratory abnormalities defined as dose-limiting toxicities (DLTs) (*Part 1 only*)
- The incidence of AEs and clinical laboratory abnormalities (*Parts 1B and 2 only*)

2.5 Secondary Endpoints

- PK parameters
- The incidence of AEs, clinical laboratory abnormalities, retinal findings, and ECG abnormalities
- Objective response per RECIST v1.1
- Duration of response per RECIST v1.1
- Levels of immune cell infiltrate in pre-treatment and on-treatment tumor biopsy samples

2.6 Exploratory Endpoints

- Stable disease ≥6 weeks per RECIST v1.1
- Occurrence of disease progression per RECIST v1.1 or death
- Identified FGFR2b protein overexpression and *FGFR2* amplification (or other molecular aberrations, as applicable) in tumor tissue and response by RECIST v1.1
- Analysis of exploratory biomarkers in pre-treatment and on-treatment tumor biopsy samples

3. Overall Design and Plan of the Study

3.1 Overview

This is a three-part, open-label, safety, tolerability, and PK study of FPA144. Patients will be enrolled into either Part 1(A or B) or Part 2 of the study, but not both.

Enrolled patients will be treated in 28-day cycles. Each cycle will consist of 2 doses: on Day 1 and Day 15.

3.1.1 Screening Period

All patients will undergo screening assessments within 4 weeks prior to the first dose of FPA144, with the exception that FGFR2b overexpression may be determined by the central laboratory at any time prior to enrollment in the study (*Part 1B and Part 2 patients*).

Tumor tissue for FGFR2b expression analysis will be submitted for Part 1A patients if available for retrospective analysis, and is mandatory for all patients enrolling in Part 1B and Part 2 of the study. In Part 1B, 8 patients with gastric cancer were enrolled, whose tumor tissue was analyzed for FGFR2b expression and *FGFR2* amplification. In Part 2, approximately 40 patients with gastric cancer will be enrolled based on prospective IHC analysis of FGFR2b expression. In addition, up to 30 patients with FGFR2b-selected non-gastric solid tumors (including patients with FGFR2b-selected bladder cancer for which a validated IHC assay is available) will be enrolled based on prospective FGFR2b analysis. Additional non-gastric solid tumor types, aside from bladder cancer, can be enrolled only upon availability of an accompanying validated laboratory test for the analysis of FGFR2b expression.

Study-procedure-related AEs that occur after signing of the informed consent form and before administration of the first FPA144 dose will be collected during this period.

3.1.2 Part 1A (Dose Escalation)

Part 1A is a dose escalation in patients with any solid tumor or lymphoma who, in the opinion of the Investigator, may benefit from treatment with FPA144. Dose escalation will continue until either the MTD or maximum feasible dose is reached, with a minimum of three patients enrolled in each cohort. The anticipated dose levels are:

- Dose level 1: 0.3 mg/kg
- Dose level 2: 1 mg/kg
- Dose level 3: 3 mg/kg
- Dose level 4: 6 mg/kg
- Dose level 5: 10 mg/kg
- Dose level 6: 15 mg/kg

All dose escalation decisions will be based on assessment of DLTs, overall safety, and tolerability and will be made after the last patient enrolled in each cohort has completed the first treatment cycle. Dose escalation decisions will be agreed upon between the Investigators and the Sponsor's Medical Monitor. Prior to initiating each new dose level or expanding an existing dose level, a safety teleconference will be held wherein Investigators and Sponsor's Medical Monitor review patient data, including, but not limited to, demographics, FPA144 dosing, concomitant medications, hematology and serum chemistry, and AEs; and confer and document agreement that dose escalation or expanding an existing dose level is considered appropriate. If the Sponsor and Investigators collectively agree that following review of safety and pharmacokinetic data, that a different dose escalation scheme should be used than the one outlined, this will be permitted. Review of safety and PK parameters may inform decisions to add cohorts with alternative dose levels or dose regimens (e.g., less frequent dosing) in order to reach an optimal target exposure.

The following algorithm will be used for dose escalation decisions:

Table 1: Dose-Escalation Considerations

Number of patients with DLT at a Given Dose Level	Dose Escalation Decision Rule
0/3	Escalation will occur to the next higher dose cohort
1/3	Enroll three more in same cohort
≥ 2/3	Stop enrollment. Enter three more patients at dose level below, if only 3 were previously entered
1/6	Open next cohort
≥ 2/6	Stop enrollment. Enter three more patients at a dose level below, if only 3 were previously entered

The MTD is defined as the highest dose associated with DLTs in less than 33% of patients receiving FPA144 administered on Days 1 and 15 of a 28-day cycle. This will normally be the dose recommended for further study (RD); however, based on review of safety and PK data, the RD could be lower than the MTD. If the MTD is not reached, and the highest evaluated FPA144 dose is well tolerated, the data will be reviewed to assess whether further dose escalations are warranted. The protocol will be amended if additional dose escalation is considered appropriate.

If the MTD is not reached during Part 1A, or subsequent cycles of treatment in Part 1A provide additional insight on the safety profile, an RD may be selected based on overall tolerability, safety, and PK.

If a patient does not receive 2 doses and does not complete the safety and PK assessment in Cycle 1 for reasons other than toxicity (e.g., disease progression or withdrawal of consent), then an additional patient will be enrolled into the cohort so that the cohort has at least three patients evaluable for tolerability through Cycle 1. All such discussions and decisions will be documented as part of the dose escalation decision-making process.

Intra-patient dose escalation above the starting dose for each patient will not be permitted for patients in Part 1 (A and B) and Part 2. If a patient's dose is decreased for a reason that is no longer relevant, dose escalation to the originally assigned dose may occur after discussion and approval by the Sponsor.

On completion of Cycle 1 (Safety and PK Assessment Period), Part 1A patients may participate in an optional Treatment-Extension Period, which begins on Day 1 of Cycle 2. FPA144 will be administered once every 2 weeks until disease progression, unacceptable toxicity, patient or physician decision to discontinue, death, or termination of the study (as defined in Section 9.11), assuming no limitations with availability of drug supply, or other issues that may preclude the Sponsor from providing FPA144.

Enrollment into Part 1A is complete. A total of 19 patients with solid tumors were enrolled into Part 1A before its closure in November of 2015.

3.1.3 Part 1B

The purpose of Part 1B is to further assess safety and evaluate PK of FPA144 in gastric cancer patients, prior to commencing Part 2. Clearance of some antibodies (e.g., bevacizumab and trastuzumab) has been shown to be more rapid in gastric cancer patients than in patients with other solid tumors. Enrolled patients may be those with *FGFR2* amplification or FGFR2b overexpression, or gastric cancer patients whose tumors will be tested retrospectively.

In a staggered fashion with Part 1A dose escalation, patients in Part 1B will be enrolled at one dose level below the current highest dose level cohort being studied in Part 1A. For example, if the current dose level being studied is at 3 mg/kg for Part 1A, enrollment of Part 1B patients will be at the 1 mg/kg dose level. If the current dose level being studied in Part 1A is 6 mg/kg, enrollment of Part 1B patients will be at the 3 mg/kg dose level.

In Part 1B, approximately 3 gastric cancer patients may be enrolled at a dose level, starting one dose level below the current Part 1A dose. The Sponsor and Investigators may elect to enroll up to an additional 3 patients per dose cohort, based on prospective analysis of tumor tissue with FGFR2b overexpression as determined by IHC, in the presence or absence of *FGFR2* amplification, as determined by FISH. Enrollment in Part 1B may not replicate every dose level explored in Part 1A. Dose escalation may continue in Part 1B up to 15 mg/kg if no MTD is identified in Part 1A.

Enrollment into Part 1B is complete. A total of 8 patients with gastric cancer were enrolled into Part 1B prior to its closure in November of 2015.

3.1.4 Part 2 (Dose Expansion)

Part 2 will evaluate the recommended dose of FPA144 in patients with FGFR2b-selected gastric and bladder cancer or with other locally advanced or metastatic solid tumors. Patients will be selected for enrollment in Part 2 based on FGFR2b expression, as determined by a validated laboratory test for the analysis of FGFR2b expression for each tumor type.

Enrollment into Part 2 of the study will begin when the MTD or RD has been determined from Part 1 of the study. Patients in Part 2 will be assessed for tolerability, safety, and efficacy.

3.2 Procedures

Patients will undergo safety evaluations (DLTs and other AEs, vital signs, ECGs, clinical laboratory tests), determination of ECOG performance status [PS], and physical and ophthalmologic examinations. Additionally, blood samples will be collected for PK analyses and for exploratory PD assessment in all patients. For all patients enrolled in Part 2, biopsy at the primary tumor site or metastatic site is mandatory, as feasible, at Screening (at least 24 hours

prior to Cycle 1 Day 1 dosing) and at **either** Day 15 (within 7 days prior to Cycle 1 Day 15 and at least 24 hours prior to dosing) **or** at Day 29 (within 7 days prior to Cycle 2 Day 1 and at least 24 hours prior to dosing). Feasibility at each timepoint will be assessed by the Investigator and should include a consideration of patient safety.

Tumor assessments will be performed at Screening (within 4 weeks prior to first dose), then every 6 weeks from the first dose, for 24 weeks, and every 12 weeks thereafter. Once an initial complete response (CR) or partial response (PR) is noted, confirmatory scans must be performed 4–6 weeks later. A tumor assessment should also be performed at the End-of-Study visit unless already performed within the previous 6 weeks or if tumor progression was previously determined. Response will be evaluated using RECIST v1.1. Subsequent tumor assessments will be performed using the same technique used to evaluate baseline tumor measurements. It is assumed that tumor assessments will be performed by CT unless clinical circumstances warrant the use of another methodology, in which case prior written approval must be obtained from the Sponsor.

Safety will be assessed by monitoring AEs and changes in physical examinations (including oral and ophthalmologic assessments), weight, vital signs, 12-lead ECGs, and laboratory measurements. Assessment of AEs will follow the guidelines provided in the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE), version 4.03. Blood samples will also be drawn at scheduled time points during the study for determination of drug plasma concentration, and anti-drug antibodies (ADAs) (i.e., antibody response to FPA144).

Patients enrolled in Part 1(A and B) or Part 2 of the study may continue treatment with FPA144 in 28-day cycles until disease progression, intolerable toxicity, patient or physician decision to discontinue, death, or termination of the study. Responding patients who discontinue treatment while still in response (CR, PR or SD) should get follow-up scans at 12-week intervals to determine the duration of response, unless other anticancer therapy is started.

All patients should return to the clinic for end-of-treatment (EOT) assessments irrespective of whether a patient is withdrawn or withdraws at a planned visit or mid-cycle.

During Part 1(A and B) and Part 2, AEs will be assessed as outlined in Section 6.2.1.1 below.

3.2.1 Ophthalmologic Monitoring

At Screening, prior to Cycle 2 Day 1, and at the EOT visit, each patient will undergo a comprehensive ophthalmologic examination, with particular focus on the cornea and retina. Comprehensive ophthalmologic exams are to include fundoscopic and slit lamp exam, ocular coherence tomography (OCT), visual acuity, and review of ocular and visual symptoms.

Additionally, slit lamp examinations (with completion of fluorescein staining form) will be performed every 6 weeks after Cycle 2 Day 1 (prior to Cycle 3 Day 15, Cycle 5 Day 1, and Cycle 6 Day 15), and then every 12 weeks after Cycle 6 Day 15. Slit lamp examinations will

continue every 6–8 weeks if a patient has any persistent corneal findings. OCT is not required at these time points.

The comprehensive ophthalmologic exam will also be repeated at any point if the patient develops new visual or ocular symptoms or reports changes in visual acuity.

3.2.2 Tumor Analysis for Patient Selection

A third party laboratory in the United States will perform the FGFR2b expression and *FGFR2* amplification analysis using validated IHC and FISH assays.

Tumor tissue for FGFR2b expression and *FGFR2* amplification is optional for patients enrolling into Part 1A, and analysis may occur retrospectively.

Patients in Part 1B and Part 2 of this study must consent to tumor tissue analysis and will have their tumor tissue sent to a third party laboratory in the United States for FGFR2b expression and *FGFR2* amplification analysis. Patients may consent to tumor tissue analysis prior to consenting to enrollment in the treatment portion of this study. It is the responsibility of each Investigator to obtain an adequate tumor specimen for analysis of FGFR2b overexpression for enrollment into Part 1B and 2. Tumor slide or tumor block specimen processing, labeling, and shipping instructions are detailed in the Lab Manual that will be distributed with the specimen collection kit. For Part 1B, the first 3 gastric cancer patients enrolling into a dose cohort may have their tumor tissue analyzed retrospectively, then additional gastric cancer patients may be enrolled into that cohort if tumor tissue analysis shows FGFR2b overexpression, in the presence or absence of *FGFR2* amplification. For Part 2, once tumor specimens are received, analysis will be performed as efficiently as possible (typically within 7 calendar days of receipt), and results will be communicated back to the Investigator or designee.

For gastric cancer samples analyzed using IHC, strong FGFR2b overexpression will be defined as strong membranous staining of at least 10% of the tumor cells in a sample (scored as IHC 3+ $\geq$ 10%). For bladder cancer samples analyzed using IHC, high FGFR2b overexpression will be defined by the extent of membranous staining in tumor cells giving rise to H-score of $\geq$ 20 in a sample. Low FGFR2b overexpression will be defined by the extent of membranous staining in tumor cells giving rise to H-score of $\geq$ 10, but $<$ 20 in a sample. For other FGFR2b-selected non-gastric tumor types, criteria for defining FGFR2b overexpression will be determined upon availability of a validated IHC assay for each additional tumor type in question. A cohort may be closed for at any time according to the Sponsor's discretion.

Samples submitted for Part1B will be subjected to both IHC and FISH analysis (prospective or retrospectively). For Part 2, all samples from enrolled patients will be subjected to FISH retrospectively to determine *FGFR2* gene amplification (or other molecular aberrations, as relevant). For this study, a tumor will be considered *FGFR2* gene amplified if the ratio of the *FGFR2* probe to the centromeric probe (CEN10) is $\geq$2 in $\geq$10% of the cells, or if there are small clusters of amplification in which the ratio cannot be determined.

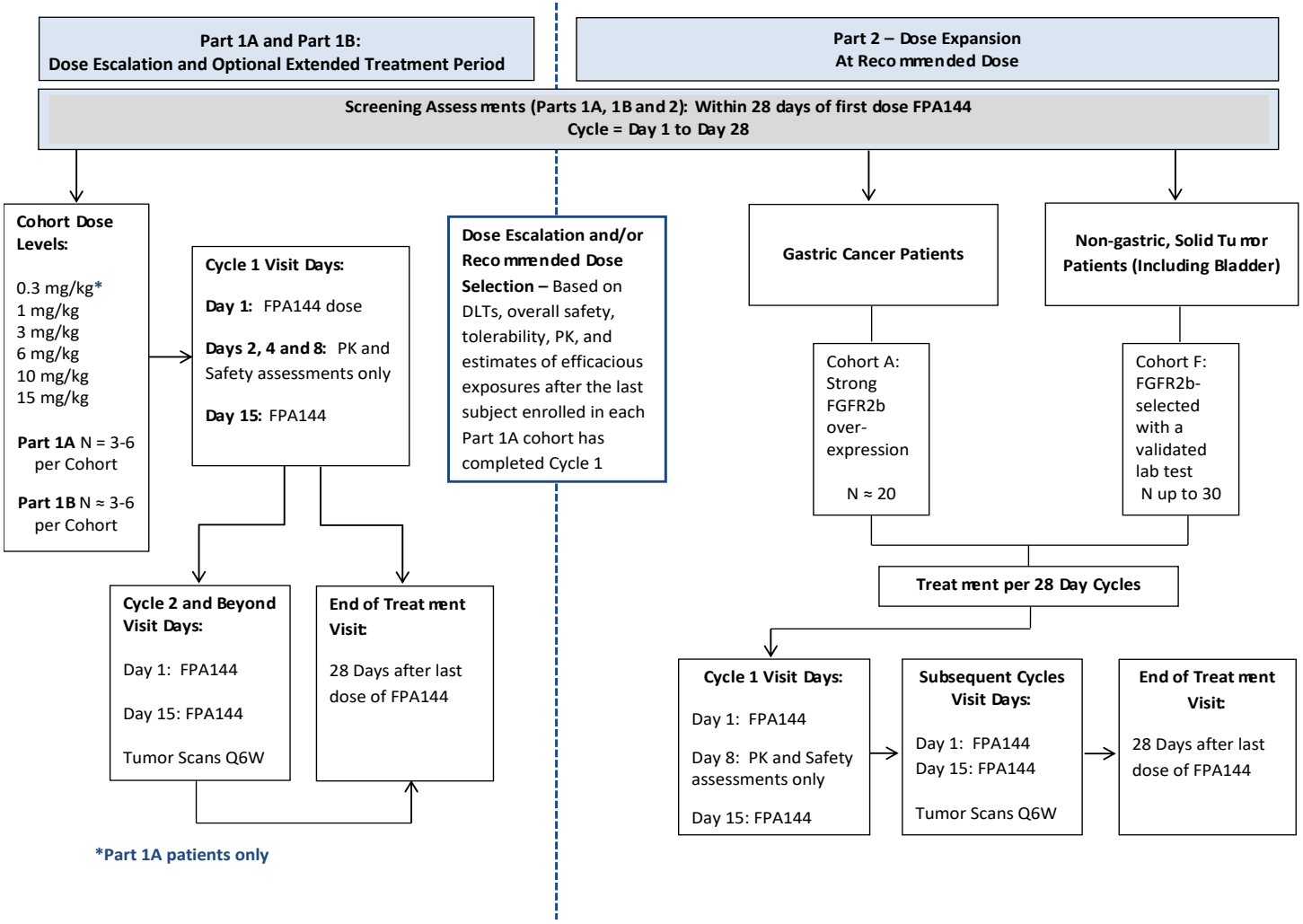
3.2.3 Optional Exploratory Archival Tumor Tissue Analysis

Patients enrolled into the study (Part 1A, Part 1B, or Part 2) may elect to consent to exploratory analyses of available archival tissue samples. This exploratory analysis is distinct from the FGFR2b expression and *FGFR2* amplification analyses prescribed for patient selection in Section 3.2.2, and therefore necessitates the availability of additional archival tissue outside of that required for patient selection. The objective of this optional exploratory tumor tissue analysis is to explore the mechanism of action of FPA144 through a more thorough examination of FGFR2b signaling and immune status in the tumor. Specifically, the presence of FGFR2b fusions or mutations, the expression levels of FGFR2b and FGFR pathway genes, as well as immune cell gene signatures will be explored.

For patients who consent to the optional exploratory tumor analysis, participation is contingent upon the availability of adequate archival tumor specimens (a minimum of 1 paraffin embedded block or, in cases where a block is unavailable, approximately 10 unstained slides) and is permitted only after discussion and approval by the Sponsor. Patients may consent to exploratory tumor tissue analysis at any time after enrollment onto the treatment portion of the study. Tumor slide or tumor block specimen processing, labeling, and shipping instructions will be provided by the Sponsor upon request. Third party laboratories in the United States will perform the exploratory analyses, which will include, but are not limited to multiplex immunofluorescence, RNA sequencing, and whole exome Next Generation Sequencing (NGS).

3.3 Study Schema

Figure 3: Study Schema



3.4 Rationale for the Study Design

This is an open-label study to assess the safety, PK, PD, and preliminary efficacy of FPA144 in patients with solid tumors. The study will comprise three parts: a dose escalation portion in unselected solid tumor patients (Part 1A), a dose escalation portion in patients with gastric cancer (Part 1B), and a dose expansion portion in patients with gastric cancer and other FGFR2b-selected solid tumors, including bladder cancer (Part 2).

The 3+3 dose escalation design is standard for early stage trials of novel anticancer treatments. Dose expansion in gastric cancer and other FGFR2b-selected solid tumor patients will allow for a more thorough investigation of the safety, PK, and biological effects of FPA144 in the target population for future trials.

4. Study Eligibility and Withdrawal Criteria

4.1 Planned Number of Patients and Study Centers

Part 1A (Dose Escalation): A total of 19 patients with locally advanced or metastatic solid tumors were enrolled.

Part 1B: A total of 8 patients with gastric cancer with or without FGFR2b overexpression, in the presence or absence of *FGFR2* amplification, were enrolled.

Enrollment in Part 1(A and B) is closed as the RD for Part 2 has been determined.

Part 2 (Dose Expansion): Part 2 is open for enrollment into the following cohorts:

- Cohort A: Approximately 20 patients with gastric cancer with strong FGFR2b overexpression.
- Cohort F: Up to 30 patients with FGFR2b-selected non-gastric solid tumors (including bladder cancer for which an accompanying validated IHC assay is available). Enrollment of additional tumor types will be contingent on the development of an accompanying validated laboratory test for the analysis of FGFR2b overexpression.

The following cohorts will be closed for enrollment in Part 2:

- Cohort B: Patients with gastric cancer with FGFR2b overexpression without FGFR2 amplification
- Cohort C: Patients with gastric cancer without FGFR2b overexpression
- Cohort D: Patients with gastric cancer with moderate FGFR2b overexpression
- Cohort E: Patients with gastric cancer with low FGFR2b overexpression

The study will be conducted at up to 35 investigational centers globally.

4.2 Inclusion Criteria for Study Participation

Patients enrolling into Part 1(A and B) or Part 2 must meet ***all*** of the following inclusion criteria:

1. Understand and sign an Institutional Review Board/Independent Ethics Committee-approved informed consent form prior to any study-specific evaluation
2. Life expectancy of at least 3 months
3. ECOG performance status of 0 to 1
4. Age ≥18 years at the time the informed consent form is signed except for the patients in Taiwan, where the patient's age must be ≥ 20 at the time the informed consent form is signed
5. In sexually-active patients (i.e., females of childbearing potential, who have not undergone menopause as defined by 12 consecutive months of amenorrhea or had a permanent sterilization procedure and males, who have not had a permanent sterilization procedure), willingness to use 2 effective methods of contraception, of which one must be a physical barrier method (condom, diaphragm, or cervical/vault cap) until 6 months after the last dose of FPA144. Other effective forms of contraception are permanent sterilization (hysterectomy and/or bilateral oophorectomy, or bilateral tubal ligation with surgery, or vasectomy) at least 6 months prior to Screening. Female patients of childbearing potential must be on stable oral contraceptive therapy or intrauterine or implant device for at least 90 days prior to the study, or abstain from sexual intercourse as a way of living
6. Adequate hematological and biological function, confirmed by the following laboratory values:
   a) Bone marrow function
      - ANC ≥1.5 x 10^9/L
      - Platelets >100 x 10^9/L
      - Hemoglobin ≥9 g/dL
   b) Hepatic function
      - AST and ALT ≤3 x upper limit of normal (ULN); if liver metastases, then ≤5 x ULN
      - Bilirubin ≤1.5 x ULN
   c) Renal function
      - Serum creatinine ≤1.5 x ULN
7. Tumor tissue, must be available for determination of FGFR2b overexpression (***optional for Part 1A patients***)

4.2.1 Part 1A (Dose-Escalation)

Patients enrolling in this portion of the study must also meet the following inclusion criteria:

8. Histologically or cytologically confirmed solid tumor or lymphoma that is locally recurrent or metastatic and has progressed following standard treatment or is not appropriate for standard treatment
9. Measurable or non-measurable disease

4.2.2 Part 1B

Patients enrolling in this portion of the study must also meet the following inclusion criteria:

10. Histologically documented gastric or gastroesophageal cancer
11. Tumor tissue for prospective or retrospective determination of FGFR2b expression and *FGFR2* amplification
12. Locally recurrent or metastatic disease that has progressed on or following standard treatment, or is not a candidate for standard treatment
13. Measurable disease as defined by RECIST version 1.1

4.2.3 Part 2 (Dose-Expansion)

Patients enrolling in this portion of the study must also meet the following inclusion criteria:

14. The following tumor types, by cohort:
    - Cohort 2A: Histologically documented gastric or gastroesophageal cancer with FGFR2b overexpression, as determined by an accompanying, validated IHC assay
    - Cohort 2F: Histologically or cytologically confirmed bladder cancer (including tumors of the renal pelvis, ureters, urinary bladder, or urethra), or other histologically or cytologically confirmed solid tumor types with FGFR2b overexpression, as determined by an accompanying validated laboratory test for the analysis of FGFR2b expression
15. Tumor tissue for prospective determination of FGFR2b expression and retrospective determination of *FGFR2* amplification and other molecular aberrations (as applicable)
16. Locally recurrent or metastatic disease that has progressed on or following standard treatment, or is not a candidate for standard treatment
17. Measurable disease as defined by RECIST version 1.1

Exclusion Criteria for Study Participation

Patients enrolling into Part 1(A and B) or Part 2 will be excluded if any of the following criteria apply:

1. Untreated or symptomatic central nervous system (CNS) metastases. Patients with asymptomatic CNS metastases are eligible provided they have been clinically stable for at least 4 weeks and do not require intervention such as surgery, radiation, or any corticosteroid therapy for management of symptoms related to CNS disease

2. Impaired cardiac function or clinically significant cardiac disease, including either of the following:
   a) Unstable angina pectoris ≤6 months prior to first scheduled dose of FPA144
   b) Acute myocardial infarction ≤6 months prior to first scheduled dose of FPA144
3. QTc segment >470 msec
4. Known HIV or AIDS-related illness, or history of chronic hepatitis B or C
5. Treatment with any anticancer therapy or participation in another therapeutic clinical study with investigational drugs ≤14 days (≤28 days for patients in Korea) prior to first dose of FPA144
6. Ongoing acute adverse effects from such treatment > NCI CTCAE Grade 1
7. Retinal disease or a history of retinal disease or detachment or, in the ophthalmologist's opinion, at increased risk for retinal detachment
8. Corneal defects, corneal ulcerations, keratitis, keratoconus, history of corneal transplant, or other known abnormalities of the cornea that may, in the opinion of an ophthalmologist, pose a risk with FPA144 treatment
9. NSCLC patients with exon 19 or 21 EGFR mutation or ALK amplification who have not received an EGFR or ALK TKI, respectively (*Part 1A only*)
10. Gastric and breast cancer patients with HER2 overexpression who have not received anti-HER2 targeted therapy
11. Major surgical procedures are not allowed ≤28 days prior to FPA144 administration. In all cases, the patient must be sufficiently recovered and stable before treatment administration
12. Females who are pregnant or breastfeeding; women of childbearing potential must not be considering getting pregnant during the study
13. Presence of any serious or unstable concomitant systemic disorder incompatible with the clinical study (e.g., substance abuse, psychiatric disturbance, or uncontrolled intercurrent illness including active infection, arterial thrombosis, and symptomatic pulmonary embolism)
14. Presence of any other condition that may increase the risk associated with study participation or may interfere with the interpretation of study results, and, in the opinion of the Investigator, would make the patient inappropriate for entry into the study
15. Known allergy or hypersensitivity to components of the FPA144 formulation including polysorbate
16. History of prior malignancy except:
    a) Curatively treated non-melanoma skin cancer or

b) Solid tumor treated curatively more than 5 years previously without evidence of recurrence or

c) History of other malignancy that in the Investigator's opinion would not affect the determination of study treatment effect

4.2.4 Additional Part 1B and Part 2 (Dose Expansion) Exclusion Criteria

17. Prior treatment with any selective inhibitor (e.g., AZD4547, BGJ398, JNJ-42756493, BAY1179470) of the FGF-FGFR pathway

No waivers of these inclusion or exclusion criteria will be permitted.

4.3 Patient Withdrawal and Replacement

The patient has the right to stop treatment or to withdraw from the study at any time. Patients may continue to repeat cycles of FPA144 treatment until at least one of the following criteria applies:

- Consent withdrawal at the patient's request or at the request of their legally authorized representative
- Progression of patient's underlying disease. Patients who are receiving clinical benefit despite isolated disease progression may continue on study after discussion with Medical Monitor
- Any event that would pose an unacceptable safety risk to the patient
- An intercurrent illness that would affect assessments of the clinical status to a significant degree and require discontinuation of therapy
- A positive pregnancy test at any time during the study
- At the specific request of the Sponsor or its authorized representative (for example, if the study is terminated for reasons of patient safety)

The date and reason for cessation of FPA144 will be documented, and the Investigator must make every effort to perform the EOT procedures. Patients will be followed for 28 days after the last dose of FPA144 for safety; those with ongoing SAEs will be followed until either resolution or stabilization.

Data from patients who discontinue prematurely will remain part of the study database. Withdrawn patients at a given dose level may be replaced at the discretion of the Sponsor.

4.4 Patient Identification and Enrollment

Patients must be able to provide written informed consent and meet all inclusion criteria and none of the exclusion criteria. No waivers of inclusion or exclusion criteria will be granted by the Investigator and Sponsor or its designee for any patient enrolled in the study. Before enrolling a patient, all eligibility criteria must be satisfied. Patients who qualify for Part 1A of the study will

be enrolled into the first available cohort. In Part 1B, approximately 3 gastric cancer patients may be enrolled at each dose level, starting one dose level below the current Part 1A dose. The Sponsor and Investigators may elect to enroll up to an additional 3 patients per dose level whose tumors overexpress FGFR2b. In Part 2, approximately 20 patients with gastric cancer with strong FGFR2b overexpression (IHC 3+ ≥ 10%, Cohort A) will be enrolled. A cohort of patients with FGFR2b-selected non-gastric solid tumors will also be enrolled in Part 2 (Cohort F), including FGFR2b-selected bladder cancer which has an accompanying validated IHC assay. Patients with additional tumor types may be enrolled, contingent on the development of an accompanying validated laboratory test for the analysis of FGFR2b expression.

The Investigator may repeat qualifying lab tests and vitals/ECGs prior to enrollment if a non-qualifying finding is considered an error or an acute finding is likely to meet eligibility criteria on repeat testing.

4.5 Pre-Study Screening (Part 1B and Part 2)

Potential Part 1B and Part 2 patients may elect to consent to tumor tissue analysis at any time prior to full assessment of eligibility for enrollment to have their tumor tissue sent to a third party laboratory in the United States for FGFR2b expression and *FGFR2* amplification analysis. Approximately 10 unstained slides or formalin-fixed, paraffin-embedded tumor tissue must be available for determination of FGFR2b overexpression. For Part 2, once a potential study patient's tumor is known to overexpress FGFR2b, the patient may be given the opportunity to consent to full study participation and will undergo screening to ensure the eligibility criteria are met. The tumor tissue analysis may be done at any time prior to enrollment in the study, if patients have:

- Confirmed diagnosis of either gastric or gastroesophageal cancer, bladder cancer or other locally advanced or metastatic non-gastric solid tumor with an accompanying validated laboratory test for the analysis of FGFR2b expression
- Age ≥ 18 years
- Performance status (PS) ≤1 on the ECOG Performance Status Scale (see Appendix 3) or Investigator's opinion that PS will have recovered to this level by the time of enrollment
- The patient will have signed and dated the Institutional Review Board/Ethics Committee-approved consent document prior to any protocol-specific screening procedures being performed

Note: Patients should not undergo any study-related procedures until full study consent has been obtained.

5. Study Drug

5.1 Identity

FPA144 drug product is a sterile aqueous solution supplied in single-use glass vials. The composition of the drug product contains 20 mg/mL active ingredient, 20 mM L-histidine, 270 mM sucrose, 0.01% polysorbate 20 at pH 6.0. The container-closure system consists of a 10 mL Type I borosilicate tubing glass vial, a 20 mm bromobutyl rubber stopper, and a 20 mm flip-off seal. The final drug product will be provided as refrigerated liquid 5ml fill in ISO 6R vials, which is diluted for administration per instructions provided in a separate Pharmacy Manual.

5.2 Administration

FPA144 will be administered only to patients in this study using procedures described in this protocol.

The dose of FPA144 is based on body weight at Cycle 1 Day 1 and adjusted if the patient's weight changes > 10% from Cycle 1 Day 1.

A pharmacist (or other responsible person) will prepare the solution for administration. After calculating the number of vials, based on the patient's weight, the study drug product will be diluted in a 0.9% sodium chloride solution. Prepared FPA144 should be administered ≤8 hours after preparation (ambient temperature). FPA144 will be administered under medical supervision over approximately 30-minute IV infusion via a peripheral vein or central venous catheter. The IV administration set for FPA144 infusion must contain a 0.22-µm in-line filter or a 0.22-µm syringe filter.

Infusion of FPA144 must be stopped, reduced, interrupted, or discontinued per Section 5.4.6. If a patient experiences an infusion reaction, the patient's vital signs (temperature, blood pressure, pulse, and respiration rate) should be monitored during the infusion as well as every 30 minutes after the infusion for a minimum of 2 hours and until resolution of the infusion reaction.

Further instructions on drug preparation and administration are in the Pharmacy Manual.

5.3 Packaging, Labeling, and Storage

Study drug will be packaged as a 5 ml fill in ISO 6R vials by the Sponsor (or designee) according to all local legal requirements. Study drug will be labeled in accordance with applicable regulatory requirements.

All study drug supplies must be stored refrigerated at 2°– 8°C in accordance with the manufacturer's instructions as provided in the Pharmacy Manual. Until dispensed to patients, the study drug will be stored in a securely locked area, accessible to authorized personnel only.

5.4 Starting Dose and Dose Modifications

The starting dose level of FPA144 and subsequent dose escalations between cohorts in Parts 1A and 1B are described in Section 3.1.2. The dose of FPA144 in Part 2, the expansion phase of the study, will be determined by evaluation of the data from Part 1A of the study.

5.4.1 Dose Escalation of FPA144 between Cohorts (Part 1A)

Dose escalation to the next cohort will only start after the preceding dose cohort has completed the DLT period. Twenty-eight days (DLT period) of safety data must be available on at least 3 safety-evaluable patients prior to a potential dose-escalation decision by the CRC. In the event that a patient in a cohort is lacking adequate safety data (e.g., due to early withdrawal from study or poor compliance with the protocol), an additional patient will be enrolled to the cohort.

Dose escalation in each successive dose cohort will proceed in a stepwise fashion. All relevant safety information for the first cohort or the preceding dose cohort will be reviewed by the CRC (see Section 9.9).

During dosing, the CRC may decide to stop dosing a patient or the complete cohort for safety reasons.

Dose escalation is planned to continue until dose-limiting toxicities occur in 2 or more patients in a cohort. The decision to discontinue dose escalation will be made jointly by the Sponsor and Investigator(s) based on reaching MTD or a dose level that achieves target serum concentration of FPA144.

Once the MTD or RD has been reached, 3-10 additional gastric cancer patients *may* be added prior to commencing Part 2, to further explore the safety and PK at this dose level.

The dose escalation decision rules are summarized in Table 2.

Table 2: Decision Criteria for Escalation

Number of Patients with DLTs	Action
0/3	Open next cohort
1/3	Enroll 3 more in same cohort
≥2/3	Stop enrollment. Enter three more patients at dose level below, if only 3 were previously entered
1/6	Open next cohort
≥2/6	Stop enrollment. Enter three more patients at dose level below, if only 3 were previously entered

5.4.2 Dose Escalation of FPA144 (Part 1B)

In a staggered fashion with Part 1A dose escalation, patients in Part 1B will be enrolled at one dose level below the current highest dose level cohort being studied in Part 1A. For example, if the current dose level in Part 1A being studied is 3 mg/kg, enrollment of Part 1B patients will be at the 1 mg/kg dose level; if the current dose level being studied in Part 1A is 6 mg/kg, enrollment of Part 1B patients will be at the 3 mg/kg dose level.

During dosing, the CRC may decide to stop dosing a patient or the complete cohort for safety reasons. Dose escalation may continue in Part 1B up to 15 mg/kg if no MTD in Part 1A is identified.

5.4.2.1 Maximum Tolerated Dose

The MTD is defined as the highest dose associated with DLTs in Cycle 1 in less than 33% of patients receiving FPA144 administered on Day 1 and Day 15 of a planned 28-day cycle.

If the MTD is not reached during Part 1A or subsequent cycles of treatment in Part 1 provide additional insight regarding the safety profile, an RD may be selected depending on overall tolerability, PK, and estimates of efficacious exposures extrapolated from ongoing clinical evaluations.

Alternatively, the protocol may be amended to explore higher dose levels of FPA144.

5.4.2.2 Toxicity at Lowest Dose Level

If the MTD is unexpectedly exceeded at the first dose level of FPA144 (0.3 mg/kg), then decisions on how to proceed will be based on safety, tolerability, and PK data; and will be agreed on between the Investigators and Sponsor's Medical Monitor.

5.4.3 Dose Escalation within a Cohort

In Part 1 (A and B), intra-patient dose escalation will not be permitted.

In Part 2, patients will be treated at the RD as determined from Part 1 (A and B), and dose escalation will not be allowed.

5.4.4 Dose-Limiting Toxicity

DLTs are defined as any of the following events that occur during the first cycle of treatment and are assessed by the Investigator as related to FPA144. As applicable, events will be classified according to the NCI CTCAE (Version 4.03).

- Absolute neutrophil count (ANC) $<0.5 \times 10^9$/L >5 days duration or febrile neutropenia (i.e., fever >38.3°C with ANC $<1.0 \times 10^9$/L).
- Platelets $<25 \times 10^9$/L or platelets $<50 \times 10^9$/L with bleeding requiring medical intervention
- Prolonged (>7 days) Grade 3 thrombocytopenia

- Grade 4 anemia (i.e., life-threatening consequences; urgent intervention indicated)
- Any Grade 2 or greater ophthalmologic AE that does not resolve within 7 days
- AST/ALT >3 x ULN ***and concurrent*** total bilirubin >2 x ULN.
- Any non-hematological AE CTCAE Grade 3 or greater (except nausea, vomiting, and diarrhea if well controlled by systemic medication). Grade 3 or 4 lab values that are not of clinical significance per Investigator and Sponsor agreement will not be considered DLTs.

Part 1A patients who experience a DLT are not required to discontinue study participation in FPA144-001.

5.4.5 Dose Modification Criteria

Dose reductions may be permitted for patients on treatment beyond the DLT period (in Part 1A) or any patient in Parts 1B or 2 per the guidelines outlined in Table 3 and Table 4 for non-ocular and ocular-related (defined as related to the cornea and retina) toxicities, respectively. If dose reductions or interruptions that do not fall within these guidelines are being considered by the Investigator, these will require discussion with and approval by the Sponsor.

Table 3: Dose Modification Guidelines (Non-corneal Toxicity)

Toxicity Grade	FPA144 Dose	Dose Schedule
1	Continue 100% of dose	No delay or missed dose required
2	Continue 100% of dose	No delay or missed dose required
3	Continue 75–100% of starting dose following recovery to Baseline or Grade 1	Up to 2 missed doses allowed without Sponsor approval to continue
4	Continue 50–75% of starting dose following recovery to Baseline or Grade 1	Up to 2 missed doses allowed without Sponsor approval to continue

Table 4: Dose Modification Guidelines for FPA144-related Corneal Toxicity

FPA144/IP-related Toxicity Grade	Dose Schedule	New FPA144 Dose
Grade 1	**No Delay**	**100%**
Grade 2	**Delay dosing, see ophthalmologist and treat with topical (ophthalmologic) antibiotics**	**If recovery to baseline or Grade 1 within 28 days, may resume at 100% dose**
Grade 2 which does not return to baseline within 28 days **Any Grade 3 or Grade 4**	**Permanently discontinue dosing of FPA144**	**N/A**

Any patient who reports pain or irritation of the eye or change in vision should be evaluated by an ophthalmologist.

Patients may miss up to 2 consecutive doses (up to 6 weeks between doses) for adverse or other events and may resume the study drug if the event returns to Baseline or ≤ Grade 1 within 6 weeks of treatment interruption. Omission of additional dosing longer than 6 weeks for adverse events will necessitate the patient's discontinuation from the study unless allowed by the Sponsor. Patients may miss doses in the course of participation in the study, including missed doses for scheduled vacations or other personal reasons as needed, but not more than 2 doses sequentially.

There is a ±3-day window for the scheduled dosing visits. Patients should not have 2 consecutive doses of FPA144 within 7 days. The first dose of each cycle is considered Day 1 of each Cycle, Cycles will repeat every 28 days unless there is a treatment delay. For patients who cannot receive Day 15 treatment by Day 21, patients should skip Day 15 treatment of that cycle and resume Day 1 treatment of the next cycle. Patients can have treatment delay of Day 1 of the subsequent Cycle as long as the Day 1 treatment is within 6 weeks of the last treatment.

Intra-patient dose escalation above the starting dose for each patient will not be permitted for patients in Part 1 (A and B) and Part 2. If a patient's dose is decreased for a reason that is no longer relevant, dose escalation to the originally assigned dose may occur after discussion and approval by the Sponsor.

5.4.6 Dose Interruptions during Study Drug Infusion

Infusion of FPA144 must be stopped if any AE ≥ Grade 3 occurs during the infusion. If bronchospasm or dyspnea occurs in a patient during infusion, the infusion should be stopped.

In addition, at the Investigator's discretion, the infusion rate may be reduced or stopped if a less severe AE (Grade 1 or 2) occurs during the infusion. If a Grade 3 or less severe AE resolves within 4 hours, the infusion may be restarted at half the previous rate. If the same AE appears again with the same severity at any time during the restarted infusion, the infusion should be discontinued, and no further dosing of study drug will occur without consultation with the Sponsor or Sponsor's designee.

If a patient experiences an infusion reaction, the patient's vital signs (temperature, blood pressure, pulse, and respiration rate) should be monitored during the infusion, as well as every 30 minutes after the infusion for a minimum of 2 hours and until resolution of the infusion reaction.

5.5 Blinding and Breaking the Blind

Blinding and breaking the blind are not applicable as this is an open-label study.

5.6 Drug Accountability

The Investigator or appropriately qualified staff is responsible for maintaining accurate study drug accountability records throughout the study.

The Investigator is responsible for returning all unused study drug to the Sponsor (or designee), and must verify that no remaining supplies are in the Investigator's possession. The study site is permitted to destroy used or partially used study drug vials according to the site policy once Sponsor approval of their documented destruction procedure has been obtained. On completion of the study, the number of FPA144 vials shipped, destroyed, and returned must be reconciled.

5.7 Investigational Product Compliance

Only qualified trained site personnel may administer FPA144. Pharmacy personnel trained in the study requirements will monitor compliance with the treatment assignments. FPA144 will be infused over approximately 30 minutes via a peripheral vein or central venous catheter by a trained healthcare professional. Records of study medication administered (date, time, and dose administered relative to time of preparation) will be recorded on the patient's electronic case report form (eCRF).

5.8 Concomitant Medication and Treatment

All concomitant medications including herbal and other non-traditional remedies are to be captured on the eCRF. The following parameters will be collected: generic name, route of administration, start date, stop date, dosage and frequency, and indication. Any changes in the dosage or regimen of a concomitant medication also must be recorded on the eCRF.

At Screening, patients will be asked what medications they have taken during the previous 30 days. At each subsequent study visit, patients will be asked about any changes in concomitant medications since the previous visit.

Throughout the study, Investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care ***except*** for the following:

- Concomitant anticancer therapy including chemotherapy, radiation therapy, targeted therapies, and other experimental drugs. Chronic maintenance therapies, such as LHRH-modulating agents for breast or prostate cancer, may be continued if the patient has been on these agents and 1) continued use is unlikely to result in additional reduction in tumor measurements and 2) is considered standard therapy for the patient

If a patient uses a prohibited medication or undergoes tumor resection, the Sponsor should be consulted for a decision on whether the patient should be withdrawn from the study (see Section 7.2.11).

Patients may initiate or continue pain medications as dictated by standard clinical practice. Transfusions are permitted as needed.

No routine premedication will be administered for the initial FPA144 dose. If a patient develops nausea, vomiting, or other infusion-related AEs, he/she may be pre-medicated with antiemetics, steroids, or antihistamines prior to subsequent infusions of FPA144 at the discretion of the Investigator. The treatment will be administered according to the institution's standard practice, and should be captured on the patient's eCRF.

6. Parameters and Methods of Assessment

Safety of FPA144 will be assessed by monitoring AEs and changes in physical examinations (including weight and ophthalmologic findings), vital signs, 12-lead ECGs, and clinical laboratory measurements. Blood samples will be evaluated for immunogenicity. In Part 2, pharmacodynamic assessments will be conducted on tumor biopsy samples acquired at Screening and **either** at 15 days **or** 29 days on-treatment (see Section 6.4). Patients in Part 2 may also have an optional on-treatment biopsy upon documented tumor response and/or optional post-treatment biopsy upon documented tumor progression after discussion with the Sponsor.

6.1 Tumor Response Parameters

Tumor assessments will be performed at Screening (within 28 days prior to first dose), then every 6 weeks from the first dose, for 24 weeks, and then every 12 weeks thereafter. Tumor assessments should be completed within 1 week prior to start of the dose when re-imaging is scheduled. All patients should have tumor response parameters assessed at the EOT visit unless a tumor assessment has been performed within the previous 6 weeks.

Response will be evaluated using RECIST v1.1 for measurable disease (*required for Part 2*). A response (complete or partial) to treatment must be confirmed 4–6 weeks later. Subsequent tumor assessments will be performed using the same physical, biomarker, or radiological parameter(s) used to measure the tumor at baseline.

Progressive disease is defined as the appearance of one or more of the following as described in RECIST v1.1 (Eisenhauer 2009):

- For patients with measurable disease, at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
- Unequivocal progression of currently or previously non-measurable lesions
- The appearance of one or more new lesions
- Development of clinical signs or symptoms which, in the opinion of the Investigator, indicate clinically significant disease progression

***Note*:** Tumor assessments performed as part of the patient's standard of care within 28 days (4 weeks) of the first dose of FPA144 do not need to be repeated during screening.

6.2 Safety Parameters

6.2.1 Adverse Events

6.2.1.1 Collection of Adverse Events

Any new symptoms, injury or worsening of symptoms that occur following signing of the informed consent form (ICF) but prior to first infusion (Cycle 1 Day 1) will be considered pretreatment events and reported on the Medical History page of the eCRF, unless they directly correlate to a study-related procedure. Adverse event reporting will continue until completion of the End-of-Treatment visit or until 28 days after the last dose of study drug. Serious AEs occurring after the end of the study should be reported to the Sponsor by the Investigator if the Investigator considers a causal relationship with the study drug.

Serious AEs should always be recorded on the AE eCRF page.

SAEs and new AEs that are not SAEs will be collected until 28 days after the last dose of FPA144 (or withdrawal of consent). If a new SAE comes to the attention of the Investigator after the final visit, information regarding the SAE should be collected and reported only if assessed as possibly or probably related by the Investigator.

6.2.1.2 Definitions

An AE is any untoward medical occurrence that occurs in a patient 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 finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the product.

All AEs including intercurrent illnesses that occur during the study, from the time of study drug administration, will be documented on the eCRF. Concomitant illnesses, which existed prior to the day of the first study infusion, will not be considered AEs unless they worsen by at least 1 grade during the treatment period. Intensity (severity) grade will be defined according to the NCI-CTCAE, version 4.03. Pre-existing conditions will be recorded on the Medical History eCRF.

A treatment-emergent AE will be defined as an AE that begins or worsens in severity after at least 1 dose of study drug has been administered.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, will not be reported as an AE, but the procedure and/or therapeutic treatment should be recorded on the appropriate eCRF. The medical condition for which the procedure was performed must be reported as an AE (or as part of the patient's medical history, if appropriate). Disease progression is an endpoint and not an AE or SAE.

6.2.1.3 Assessment of Adverse Events

Each AE will be assessed by the Investigator with regard to the following categories:

6.2.1.3.1 Seriousness

An SAE is defined as any untoward medical occurrence that at any dose:

- Results in death. Death may occur as a result of the underlying disease process. All events other than progression of underlying disease that result in death during the reporting period up to 28 days following the last dose of FPA144 must be treated as an SAE and reported as such.
- Is life-threatening (patient is at immediate risk of death from the event as it occurred).
- Requires inpatient hospitalization (formal admission to a hospital for medical reasons) or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.

Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Medical and scientific judgment should be exercised in deciding whether a case is serious and whether expedited reporting is appropriate.

Hospitalization for an event solely related to disease progression is not considered an SAE. Hospitalization for an elective or planned procedure to treat a pre-existing condition is not considered an SAE unless it results in one of the outcomes listed above.

6.2.1.3.2 Intensity

Investigators need to assess the severity of AEs according to the guidelines provided in NCI-CTCAE, version 4.03.

CTCAE v 4.03 Severity Grades are:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated; mild AE
- Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living; moderate AE
- Grade 3: Severe or medically significant but non immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living; severe AE
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Fatal AE

If the AE is not specified in the CTCAE or the study protocol, the grading of severity will be assessed as mild (Grade 1), moderate (Grade 2), severe (Grade 3), life-threatening (Grade 4), or death due to the AE (Grade 5) using the following definitions:

- Mild: The patient is aware of the event or symptom, but the event or symptom is easily tolerated.
- Moderate: The patient experiences sufficient discomfort to interfere with or reduce his or her usual level of activity.
- Severe: Significant impairment of functioning: the patient is unable to carry out usual activities.
- Very severe (life-threatening): The patient's life is at risk from the event.

6.2.1.3.3 Causality

The Investigator will assess the causality/relationship between the study drug and the AE and record that assessment on the eCRF.

The most likely cause of an SAE (e.g., disease under treatment, concomitant disease, concomitant medication, other) will be indicated on the eCRF with details of the concomitant disease or medication or other cause.

The causal relationship of the AE to study drug will be described in terms of:

- Probably related. The AE:
  - Follows a reasonable temporal sequence from administration of the study drug.
  - Could not be reasonably explained by the patient's clinical state, environmental or toxic factors, or other therapies administered to the patient.
  - Disappears or decreases on cessation or reduction in dose of the study drug.
  - Follows a known pattern of response to the study drug.
  - Reappears or worsens on re-challenge.
- Possibly related. The AE:
  - Follows a reasonable temporal sequence from administration of the study drug
  - Could be reasonably explained by the patient's clinical state, environmental or toxic factors, or other therapies administered to the patient.
  - Follows a known pattern of response to the study drug.
- Unlikely related. The AE:
  - Does not follow a reasonable temporal sequence from administration of the study drug.
  - Could be reasonably explained by the patient's clinical state, environmental or toxic factors, or other therapies administered to the patient.
  - Does not follow a known pattern of response to the study drug.
  - Does not reappear or worsen on re-challenge.
- Not related:
  - The AE does not meet the above criteria.
  - There is sufficient information that the etiology of the AE is not related to the study drug.
  - The AE that, after consideration, is clearly due to extraneous causes (diseases, environment, etc.), which should be specified, if known.

The relatedness for SAEs will also be assessed and documented on the SAE form.

6.2.1.3.4 Outcome and Action Taken

The Investigator will record the action taken and outcome for each AE according to the following criteria:

- Action Taken
  - None
  - Dose reduced
  - Administration of FPA144 temporarily interrupted

  - Administration of FPA144 delayed
  - Administration of FPA144 permanently discontinued
  - Unknown
- Outcome
  - Recovered
  - Recovered with sequelae
  - Ongoing
  - Death
  - Unknown/Lost to follow-up

6.2.1.4 Recording Adverse Events

Any new symptoms or injury or worsening of symptoms that occur following signing of the ICF, but prior to the first infusion (Cycle 1 Day 1), will be considered pretreatment events and reported on the Medical History page of the eCRF, unless they directly correlate to a study-related procedure. New or worsening symptoms or injury related to study-related procedures that occur before Day 1 will be reported as adverse events. Otherwise, adverse event reporting will begin on Cycle 1, Day 1 (day of first infusion) and continue until completion of the End-of-Study visit or until 4 weeks (28 days) after the last dose of study drug. Serious AEs occurring after the end of the study should be reported to the Sponsor by the Investigator if the Investigator considers there is a causal relationship with the study drug.

All AEs, regardless of the relationship to study drug, will be recorded on the eCRF. This includes potential end-organ toxicity, e.g., renal (proteinuria), hepatic, and cardiovascular (increased blood pressure) effects, and effects on wound healing. All AE reports should contain a brief description of the event, date and time of onset, date and time of resolution, intensity, treatment required, relationship to study drug, action taken with the study drug, outcome, and whether the event is classified as serious.

Abnormal laboratory findings that are not considered clinically significant will be recorded only on the laboratory eCRF pages and not on the AE pages. Abnormal laboratory results that are considered clinically significant in the Investigator's opinion are also to be recorded on the AE page of the eCRF. Relationship (reasonable causal relationship) to drug therapy and counter measures undertaken will be noted on the eCRF.

6.2.1.5 Reporting Serious Adverse Events

Any SAEs, whether or not considered related to treatment with FPA144, must be reported, by the Investigator, to the Sponsor or Sponsor's designee within 24 hours of the Investigator becoming aware of the event and will be recorded on both the SAE form and AE page of the eCRF. Additional SAE information including medications or other therapeutic measures used to treat

the event, action taken with the study drug due to the event, and outcome/resolution of the event will be recorded on the SAE form. Forms for reporting SAEs will be provided to the study sites.

A copy of SAE forms must be faxed **within 24 hours** to the attention of the INC Pharmacovigilance Safety Specialist:

INC Research Safety and Pharmacoviligance
Fax number: 1-877-464-7787
Email: INCDrugSafety@INCResearch.com

The Investigator should not wait to receive additional information to fully document the event before notification of a SAE, though additional information may be requested. The minimum information that is required for an initial SAE report is as follows:

- Patient number
- Investigator name and site number
- Event term
- Event onset date
- Serious criteria
- Relationship to study drug

As applicable, information from relevant laboratory results, hospital case records, and autopsy reports should be obtained.

The Investigator and Sponsor will review each SAE report and evaluate the seriousness and causal relationship of the event to study treatment. In the event of a disagreement about causality, the greater level of assessment will be used. In addition, the Sponsor will evaluate the expectedness according to the FPA144 Investigator's Brochure. Based on the Investigator and Sponsor's assessment of the event, a decision will be made concerning the need for further action.

The Sponsor or its designee is responsible for submitting reports of AEs associated with the use of the drug that are both serious and unexpected to FDA, according to 21 Code of Federal Regulations (CFR) 312.32, and to other regulatory authorities, according to national law and/or local regulations. All Investigators participating in ongoing clinical studies with the study medication will receive copies of these reports for prompt submission to their Institutional Review Board (IRB) or Independent Ethics Committee (IEC).

The Sponsor or its designee will submit all safety updates and periodic reports to the regulatory authorities as required by applicable regulatory requirements.

6.2.1.6 Follow-up of Adverse Events

All AEs experienced by a study patient, irrespective of the suspected causality, will be monitored until the event has resolved or stabilized, any abnormal laboratory values have returned to baseline or stabilized at a level acceptable to the Investigator and Medical Monitor, there is a satisfactory explanation for the changes observed, or the patient is lost to follow-up.

6.2.1.7 Pregnancy

Pregnancy tests should be performed for any patient of childbearing potential, as noted in Appendix 1. In the event of suspected pregnancy, the pregnancy test should be repeated. Patients who become pregnant during the study must discontinue study treatment immediately.

INC Research Pharmacovigilance must be notified of any patient that becomes pregnant while participating in this study. Although pregnancy is not an AE, all pregnancies must be followed to conclusion to determine their outcome. It is the responsibility of the Investigator or designee to report any pregnancy in a patient that occurs during the study by completing the Pregnancy Reporting Form. Please contact the study monitor to receive the Pregnancy Reporting Form on learning of a pregnancy.

Notification of the pregnancy including the anticipated date of birth should be submitted on a Pregnancy Reporting Form within 24 hours of awareness and reported using the same procedure as described for reporting SAEs (Section 6.2.1.5). If the pregnancy is to be terminated, the anticipated date of termination should be provided.

6.2.1.7.1 Follow-up in the Event of a Pregnancy

The patient will be asked to provide information on the outcome of the pregnancy, including premature termination should the case arise. Spontaneous miscarriages and congenital abnormalities will be reported as SAEs. Information on the status of the mother and child will be forwarded to INC Research Pharmacovigilance and the Sponsor. Generally, follow-up will be in accordance with regulatory guidance and at least 6 to 8 weeks after the estimated delivery date. Any premature termination of the pregnancy will be reported as an SAE.

6.2.2 Laboratory Parameters

Laboratory assessments will be performed locally at each study site's laboratory by means of their established methods. Before starting the study, the Investigator will provide the Sponsor (or designee) with a list of the normal ranges and units of measurement.

Blood samples should be taken using standard venipuncture techniques. The following laboratory parameters (Table 5) will be determined in accordance with the Schedule of Assessments (Appendix 1):

Table 5: Laboratory Assessments

Hematology:

Complete blood cell (CBC) with differential:

- white blood cells (WBC)
- ANC
- neutrophils (%)
- eosinophils (%)
- basophils (%)
- lymphocytes (%)
- monocytes (%)
- platelets
- hemoglobin
- hematocrit
- red blood cells (RBC)
- RBC indices:
  - mean corpuscular volume (MCV)
  - mean corpuscular hemoglobin (MCH)
  - mean corpuscular hemoglobin concentration (MCHC)

Urinalysis:

Dipstick (appearance, color, pH, specific gravity, ketones, protein, glucose, bilirubin, nitrite, urobilinogen, and occult blood)

If dipstick is positive (2+ or greater) for blood or protein, perform a microscopic examination.

Clinical chemistry:

- Albumin
- alkaline phosphatase
- ALT (SGPT)
- AST (SGOT)
- blood urea nitrogen (BUN)
- calcium
- chloride
- carbon dioxide (CO_2 [bicarbonate])
- creatinine
- direct bilirubin
- globulin
- glucose
- lactate dehydrogenase (LDH)
- phosphate
- potassium
- sodium
- total bilirubin
- total cholesterol
- total protein
- uric acid

Other chemistry tests:

Magnesium

Coagulation:

- INR
- APTT

Serum pregnancy test:

In females of childbearing potential only.

Tumor Markers

If a patient is being followed with a tumor marker (e.g., CA-125, PSA or other), the tumor marker should be obtained prior to the start of each cycle

Abnormal laboratory results that lead to a change in patient treatment management (e.g., dose delay, requirement for additional medication or monitoring) are considered clinically significant for the purposes of this study and will be recorded on the AE page of the eCRF. Values meeting SAE criteria must be reported as SAEs.

The Investigator's determination of relationship of the AE to drug therapy and counter measures undertaken will be documented and noted on the eCRF.

6.2.3 Vital Signs

Vital signs will include sitting blood pressure, pulse, and body temperature. All vital signs will be obtained after the patient has been resting for at least 5 minutes. Vital signs will be performed in accordance with the Schedule of Assessments (Appendix 1).

6.2.4 Electrocardiograms

Twelve-lead ECGs will be performed in accordance with the Schedule of Assessments (Appendix 1). The Investigator must review the ECG, document this review in the source documents, and record any clinically significant changes that occur during the study as an AE in the eCRF.

6.2.5 Pregnancy

Pregnancy is an exclusion criterion and women of childbearing potential must not be considering getting pregnant during the study. A negative serum pregnancy test fewer than 5 days prior to first dosing with FPA144 treatment is mandatory. Patients of reproductive potential (males and females) must practice 2 effective contraception methods (per Section 4.2) during the study and for 6 months after last treatment.

6.2.6 Physical and Ophthalmologic Examinations

Physical and ophthalmologic examinations will be performed in accordance with the Schedule of Assessments.

A complete physical examination including height and weight will be performed at Screening. Limited physical examinations should be conducted per the Schedule of Assessments (Appendix 1) and include examination of the oropharynx. The examination should also include a description and measurement of visible or palpable lesions. Examination of the genitourinary and gastrointestinal body systems may be excluded.

Comprehensive ophthalmologic exams will be performed during Screening, prior to Cycle 2 Day 1, and at the EOT visit. These comprehensive evaluations should include slit-lamp examination, optical coherence tomography, visual acuity, determination of intraocular pressure, completion of fluorescein staining score form, and review of ocular/visual symptoms. When performing the ocular exam by the Ophthalmologist, the following should be noted:

- IOP can be done by Tonopen or Applanation but should be done before dilation.
- Confrontation VF is adequate.
- OCT should include the macula.
- Corneal staining and scoring should be done before dilation and before the IOP check as both may disrupt corneal integrity.

Additionally, slit lamp exams (including completion of fluorescein staining form) without OCT will be performed by an ophthalmologist every 6 weeks after Cycle 2 Day 1 (prior to Cycle 3 Day 15, Cycle 5 Day 1, and Cycle 6 Day 15), and every 12 weeks starting at Cycle 6 Day 15. Slit lamp exams will continue every 6–8 weeks if a patient has any persistent corneal findings.

Comprehensive ophthalmologic exams will be performed any other time when the patient complains of photophobia, changes in vision, or eye pain, or other ocular or visual complaints.

6.2.7 Immunogenicity

Immunogenicity, defined as an immune response to FPA144, will be assessed by measurement of total anti-FPA144 antibodies from all patients. Immunogenicity testing will consist of screening, confirmation, and titration. Additional characterization of a confirmed anti-FPA144 antibody response may be considered.

Samples for immunogenicity assessment will be drawn from each patient at the time points outlined in Appendix 1 and Appendix 2). Samples for immunogenicity testing will be collected and processed according to the instruction provided in the Laboratory Manual.

6.2.8 Optional Test for FCGR Polymorphisms

Blood samples will be collected prior to the first dose (Cycle 1 Day 1) from all patients (Part 1 and Part 2) consenting to test for polymorphisms that frequently occur in Fc-gamma receptors, such as *FCGR2A* and *FCGR3A*. These genes express Fc gamma receptors on white blood cells that are an integral part of the ADCC pathway, which is an anticipated mechanism of action of FPA144. The data will be collected for a retrospective analysis at the completion of the study to correlate patient response to FPA144. These biomarker tests are considered exploratory.

6.2.9 Exploratory Blood Based Biomarker Analysis for Patients in Part 2

Blood (approximately 20 ml) for analyses of circulating tumor DNA and other exploratory blood-based biomarkers will be collected from all patients enrolled in Part 2. These samples will be collected as outlined in Appendix 2.

This is an exploratory biomarker study to determine whether patients with *FGFR2* molecular aberrations (e.g. amplification) can be identified by analyzing tumor DNA present in the circulation, and whether response or resistance to FPA144 can be measured. Additional analyses may explore the feasibility of alternative liquid-based biopsy approaches (e.g. using circulating tumor cells or exosomal RNA). Data will be analyzed retrospectively.

6.2.10 ECOG Performance Status

ECOG performance status will be assessed at Screening, at Day 1 Cycle 2 and subsequent cycles, and at the EOT visit in all patients (Appendix 1).

6.3 Pharmacokinetic Parameters

Blood samples to determine serum FPA144 concentration will be collected as outlined in Appendix 1 and Appendix 2. Patients enrolled in Part 1A and Part 1B will have blood sampling during Cycle 1 Days 1, 2, 4, and 8. In addition, blood samples will be collected before and at the end of the infusion at Cycle 1 Day 15 and Day 1 of Cycles 2 - 5 and every other Cycle Day 1 starting from Cycle 5 (i.e. Cycle 5 Day 1, Cycle 7 Day 1, Cycle 9 Day 1, etc.), as well as the End of Treatment visit.

Patients enrolled in Part 2 will have blood sampling during Cycle 1 Days 1 and 8. Blood samples will also be collected pre-dose and at the end of each infusion on Cycle 1 Day 15 and Day 1 of Cycles 2 – 5 and every other Cycle Day 1 starting from Cycle 5 (i.e. Cycle 5 Day 1, Cycle 7 Day 1, Cycle 9 Day 1, etc.), as well as the EOT visit.

These samples will be collected and processed according to the instructions provided in a separate Laboratory Manual.

6.4 Tumor Biopsy in Part 2

Biopsy at the primary tumor site or metastatic site is mandatory as feasible at:

- Screening (at least 24 hours prior to dosing)

And either:

- 15 days on-treatment (within 7 days prior to Cycle 1 Day 15 and at least 24 hours prior to dosing)

Or

- 29 days on-treatment (within 7 days prior to Cycle 2 Day 1 and at least 24 hours prior to dosing).

Feasibility at each timepoint will be determined by the Investigator and should include a consideration of patient safety. If the Investigator assesses that a biopsy is not feasible, then this determination must be recorded in the source documents. Patients may also have on-treatment biopsy upon documented tumor response and post-treatment biopsy upon documented tumor progression after discussion with the Sponsor.

Biopsied lesions may become inflamed, bleed, or change dimensions, which could result in inaccurate tumor measurements. Therefore, it is strongly recommended not to use the biopsied lesion as a target lesion when assessing the response by RECIST v 1.1 criteria.

These biopsy samples should be excisional, incisional or core needle. Fine needle aspirates or other cytology specimens are insufficient for downstream biomarker analyses. Tumor tissue specimens in the form of a paraffin embedded block or unstained slides will be submitted for central IHC assessment.

Tumor biopsy samples are being collected to evaluate the pharmacodynamic effect of FPA144 on the tumor microenvironment. These samples may also undergo RNA sequencing to determine the effect of FPA144 on gene expression pathways as well as identified gene expression signatures associated with response or resistance to response. These analyses may help predict future response to treatment.

These biopsy samples will be obtained before treatment and on-treatment to examine immune infiltrates and expression of selected tumor markers. An optional biopsy may be obtained of tumors that have responded and/or progressed on or after treatment to understand mechanisms of resistance.

Tumor biopsy samples may be assessed for the expression of immune or disease-related genes and/or proteins, as well as for the presence of immune cell populations using a variety of methodologies including but not limited to IHC, qRT-PCR, genetic mutation detection, and fluorescent *in situ* hybridization (FISH). Other methods of tumor biomarker expression are being evaluated.

7. Study Conduct

7.1 Overview of Patient Assessments

After an initial screening period of up to 28 days (4 weeks), patients will be treated with FPA144 every 2 weeks (± 3 days) in 28-day cycles, and FPA144 will be administered as a 30-minute infusion. All time points of assessments should be completed in the timeframe stated. Assessments performed prior to the patient signing the informed consent are acceptable only if confirmed to have been standard of care.

The schedule of detailed patient assessments is shown in Appendix 1 and Appendix 2. Instructions for the sampling and processing of PK and immunogenicity data are described in a separate, protocol-specific laboratory manual.

7.2 Study Assessments and Procedures by Visit

7.2.1 Pre-Study Period *(Parts 1B and 2)*

Study eligibility for Part 1B and Part 2 includes analysis of either archived or recently obtained tumor tissue for evaluation of FGFR2b overexpression and *FGFR2* amplification. Potential patients may elect to consent for this tumor tissue analysis by a third party laboratory in the United States at any time prior to enrollment into the study.

In Part 1B, approximately 3 gastric cancer patients may be enrolled at each dose level, whose tumor tissue may be tested retrospectively. The Sponsor and Investigators may elect to enroll up to an additional 3 patients per dose level whose tumors overexpress FGFR2b.

In Part 2, those patients whose tumors are documented to have FGFR2b overexpression will subsequently be given the opportunity to consent to full study participation, and will undergo in-clinic screening to ensure the eligibility criteria are met.

7.2.2 Screening Period (Day –28 to Day 0)

Written, signed informed consent must be collected prior to any study-specific procedures. Patients who have fully consented to participation in the study will undergo screening assessments within 28 days (4 weeks) prior to administration of the first infusion of FPA144 (unless otherwise stated). To determine if the patient meets all the inclusion criteria and does not violate the exclusion criteria, the following procedures will be performed:

- Tumor tissue for central FGFR2b expression testing

  ***Note*:** This requirement is mandatory for Part 1B and Part 2 of the study, and may be done at any time prior to enrollment. Tumor tissue analysis for Part 1B may be done prospectively or retrospectively. Tumor tissue analysis will be encouraged for patients enrolled in Part 1A, for retrospective analysis. *FGFR2* amplification testing may be performed either prospectively or retrospectively for patients in Part 1B, but will only be performed retrospectively for patients enrolled in Part 2.

- Complete medical and disease history

- Demographic and baseline characteristics
- Vital signs (sitting blood pressure, pulse, respiration, and body temperature [°C] after 5 minutes rest)
- Complete physical examination, including weight, and height
- Comprehensive ophthalmologic exams including fundoscopic and slit lamp exam, ocular coherence tomography (OCT), determination of intraocular pressure, visual acuity, completion of fluorescein staining score form, and review of ocular/visual symptoms.
- ECOG performance status evaluation
- 12-lead ECG (required at screening, and if clinically indicated during the study)
- Document prior and concurrent medications
- Hematology (hemoglobin, hematocrit, white blood cell [WBC] and differential [with ANC], and platelet count). Blood will be analyzed by a local laboratory
- Serum chemistry (total protein, albumin, creatinine, BUN or urea, uric acid, total bilirubin, alkaline phosphatase (ALP), ALT, AST, lactate dehydrogenase (LDH), glucose, globulin, phosphate, calcium, sodium, potassium, magnesium, chloride, carbon dioxide (CO2 [bicarbonate]), total cholesterol, creatinine, and direct bilirubin. Blood will be analyzed by a local laboratory
- Urinalysis (includes dipstick for protein, glucose, blood, pH, and ketones)
- Serum pregnancy test (beta-human chorionic gonadotropin [β-HCG]), ≤5 days prior to Cycle 1 Day 1, for women of childbearing potential
- Radiological imaging/tumor assessments: Tumor assessments should consist of clinical examination and appropriate imaging techniques (preferably CT scans with appropriate slice thickness per RECIST v1.1); other assessments (MRI, X-ray, PET, and ultrasound) may be performed if required. The same methods used to detect lesions at baseline are to be used to follow the same lesions throughout the clinical study. CT assessments are to be performed within 28 days prior to the first infusion of FPA144. Radiological assessments performed as part of the patient's standard of care within 28 days of the first study infusion do not need to be repeated if the documentation of results is provided and is adequate for an assessment.
- Mandatory as feasible biopsy collection (at least 24 hours prior to dosing) for patients enrolled in Part 2

  ***Note*:** A protocol-specific Patient Enrollment Number Assignment Form must be submitted to the Sponsor (or designee) to confirm patient eligibility prior to initiation of study treatment and assignment of a patient enrollment number.

7.2.3 Treatment Allocation (Dosing Assignment)

This is an open-label study. Enrollment numbers will be faxed or emailed to the Investigator (or designee). The Sponsor or designee will maintain records of the number of patients treated

within a specific cohort and will determine to which treatment cohort newly enrolled patients will be assigned.

7.2.4 Cycle 1, Day 1 *(Parts 1A, 1B, and 2)*

The following procedures will be performed:

- Prior to FPA144 infusion (within ≤ 72 hours unless otherwise stated):
  - Verification of eligibility
  - Update medical and disease history to capture any changes from screening
  - AE reporting, if applicable, and review of concomitant medications
  - Vital signs (sitting blood pressure, pulse, respiration, and body temperature [°C] after 5 minutes rest)
  - Limited physical examination including weight and oral exam
  - Clinical safety labs (hematology results must be available prior to dosing)
  - Serum ß-hCG (evaluated by local laboratories) will be performed ≤5 days prior to the first dose of FPA144 only on women of childbearing potential
  - Urinalysis
  - Blood sample for immunogenicity testing ≤4 hours prior to dosing of FPA144
  - Blood sample for PK ≤4 hours prior to dosing of FPA144
  - Optional blood sample for FCGR polymorphism testing
  - Blood-based biomarker sample collection in all patients enrolled in Part 2 as outlined in Appendix 2
- Study drug administration:
  - Administer FPA144, by IV infusion over approximately 30 minutes
- Post FPA144 administration:
  - Post-dose Vital signs (sitting heart rate, blood pressure, respiration, and body temperature [°C] after 5 minutes rest) at the following time points relative to the start of the infusion:
    - 0.5 hours (within 5 minutes after end of infusion), + 1 hour (±5 minutes), 2 hours (±5 minutes), and 4 hours (±5 minutes) from start of infusion.
  - AE reporting and review of concomitant medications, if applicable
  - PK sample collection, at the following time points *relative to the start of the infusion*:
    - **Part 1A:** 0.5 hours (within 5 minutes after end of infusion), + 1 hour (±5 minutes), 2 hours (±5 minutes), 4 hours (±5 minutes), and 8 hours (±5 minutes) from start of infusion.

- **Part 1B:** 0.5 hours (within 5 minutes after end of infusion), + 1 hour (±5 minutes), and 4 hours (±5 minutes) from start of infusion.
- **Part 2**: PK sample collection at 0.5 hours (within 5 minutes after end of infusion), + 1 hour (±5 minutes), and 4 hours (±5 minutes) from start of infusion as outlined in Appendix 2.

7.2.5 Cycle 1, Day 2 (*Part 1A and B only*)

- Vital signs (sitting heart rate, blood pressure, respiration and body temperature)
- PK sample collection at the following time point:
  - 24 hours (±1 hour) from start of infusion on Day 1
- AE reporting, if applicable, and review of concomitant medications

7.2.6 Cycle 1, Day 4 (*Part 1A and 1B only*)

- Vital signs (sitting heart rate, blood pressure, respiration and body temperature)
- PK sample collection at the following time point:
  - 72 hours (+24 hour) from start of infusion on Day 1
- AE reporting, if applicable, and review of concomitant medications

7.2.7 Cycle 1, Day 8 *(Parts 1A, 1B and 2)*

Study patients will return to the study center on Day 8 (± 2 days). No treatment will be administered.

The following assessments will be completed:

- Vital signs (sitting blood pressure, pulse, respiration, and body temperature [°C] after 5 minutes rest)
- Limited physical examination including oral exam
- Clinical safety labs
- Blood sample for PK
- AE reporting, if applicable, and review of concomitant medications

7.2.8 Cycle 1, Day 15 *(Parts 1A, B, and 2)*

Study patients will return to the study center on Day 15 and the following assessments will be completed.

- Prior to FPA144 infusion (within ≤ 72 hours unless otherwise stated):
  - Vital signs (sitting blood pressure, heart rate, respiration, and body temperature [°C] after 5 minutes rest)

  - Limited physical examination including weight and oral exam
  - Clinical safety labs (hematology results must be available prior to dosing)
  - Blood sample for PK, ≤4 hours prior to dosing of FPA144
  - AE reporting, if applicable, and review of concomitant medications
  - Mandatory as feasible biopsy collection for patients enrolled in Part 2 only, at **either:**
  - 15 days on-treatment (within 7 days prior to Cycle 1 Day 15 and at least 24 hour prior to dosing)

    Or
  - 29 days on-treatment (within 7 days prior to Cycle 2 Day 1 and at least 24 hour prior to dosing).

- Study drug administration:
  - Administer FPA144, by IV infusion over 30 minutes
- Post FPA144 administration:
  - PK sample collection at 0.5 hours (within 5 minutes after end of infusion)
  - Post-dose Vital signs (sitting heart rate, blood pressure, respiration, and body temperature [°C] after 5 minutes rest) at the following time points relative to the start of the infusion:
    - 0.5 hours (within 5 minutes after end of infusion) and + 1 hour (±5 minutes)
  - AE reporting, if applicable, and review of concomitant medications

7.2.9 End of Cycle 1 *(Part 1A only)*

For Part 1A patients, if at the end of Cycle 1 the Investigator determines that the patient may benefit from continued dosing with FPA144, entry into the Extended Treatment Period may be offered.

- If the patient is continuing onto the Extended Treatment Period (Cycle 2), proceed to procedures outlined in Section 7.2.10.
- If the patient does not qualify to receive further doses of FPA144, the patient will undergo procedures in an EOT visit (see Section 7.2.11).

7.2.10 Part 1A Extended Treatment/Part 1B and Part 2 Cycle 2 and Subsequent Cycles

Part 1A Extended Treatment may begin on Cycle 2, Day 1. Dosing will be discontinued if the patient experiences either disease progression or unacceptable toxicity.

At each infusion visit, patients are to remain at the study site after each administration of FPA144 until completion of all post-dose assessments for safety monitoring. The following assessments will be performed at each visit unless otherwise noted:

7.2.10.1 Cycle 2 and Subsequent Cycles, Day 1 and Day 15 *(Parts 1A, 1B, and 2)*

- Prior to each infusion of study drug:
  - Vital signs (sitting heart rate, blood pressure, respiration, and body temperature [°C] after 5 minutes rest)
  - Limited physical examination including oral exam
  - Weight on Day 1 of each Cycle (after Cycle 1, dose will be recalculated only if weight has changed >10% from Cycle 1, Day 1)
  - Comprehensive ophthalmologic exams including fundoscopic and slit lamp exam, ocular coherence tomography (OCT), visual acuity, completion of fluorescein staining score form, determination of intraocular pressure, and review of ocular/visual symptoms prior to Cycle 2 Day 1only
  - Slit lamp exams (including completion of fluorescein staining form) without OCT every 6 weeks through Cycle 6, Day 15 (prior to Cycle 3, Day 15; Cycle 5, Day 1; Cycle 6, Day 15), and every 12 weeks starting at Cycle 6, Day 15. Continue every 6–8 weeks if the patient has any persistent corneal findings

    ***Note*:** Refer for additional comprehensive ophthalmologic evaluation at any time if patient complains of photophobia, vision changes, or eye pain
  - ECOG performance status evaluation (Cycle 2 Day 1, then Day 1 of every subsequent Cycle)
  - Clinical safety labs (hematology results must be obtained prior to dosing)
  - Blood sample for PK (≤4 hours pre-dose)
  - Day 1 Cycles 2-5 and starting at Cycle 5, blood samples will only be collected every other Cycle on Day 1 (Cycle 5, 7, and 9 etc…)
  - Blood sample for immunogenicity (≤4 hours pre-dose).
  - Day 1 Cycles 2-5 and starting at Cycle 5, blood samples will only be collected on Day 1 of every other Cycle (Cycles 5, 7, and 9 etc…)
  - Urinalysis Day 1 of each Cycle
  - Tumor assessment using the same physical or radiologic parameter(s) used to evaluate baseline tumor measurements are to be done every 6 weeks from the first dose for 24 weeks (within 7 days prior to the start of Cycle 2 Day 15, Cycle 4 Day 1, Cycle 5 Day 15, Cycle 7 Day 1), then approximately every 12 weeks thereafter.
  - Mandatory as feasible biopsy collection for patients enrolled in Part 2 only, at **either:**
  - 15 days on-treatment (within 7 days prior to Cycle 1 Day 15 and at least 24 hour prior to dosing)

    Or

  - 29 days on-treatment (within 7 days prior to Cycle 2 Day 1 and at least 24 hour prior to dosing).
  - Optional biopsy (after discussion with the Sponsor) for consenting patients enrolled in Part 2 who responded to treatment (within 14 days post tumor assessment)
  - Optional exploratory archival tumor tissue analysis for consenting patients enrolled in Part 2
  - Blood-based biomarker sample collection every 6 weeks from the first dose for 24 weeks (prior to Cycle 2 Day 15, Cycle 4 Day 1, Cycle 5 Day 15, Cycle 7 Day 1), and then approximately every 12 weeks thereafter from patients enrolled in Part 2 as outlined in Appendix 2
  - AE reporting, if applicable, and review of concomitant medications
- Study drug administration:
  - Administer FPA144, by IV infusion over 30 minutes
- Post study drug administration:
  - Post-dose vital signs (sitting heart rate, blood pressure, respiration, and body temperature [°C] after 5 minutes rest) at the following time points relative to the start of the infusion:
    - 0.5 hours (after the end of infusion) and +1 hour (±5 minutes)
  - PK sample collection at 0.5 hours (from start of infusion, within 5 minutes after end of infusion)
    - Day 1 Cycles 2-5 and starting at Cycle 5, blood samples will only be collected on Day 1 of every other Cycle (Cycle 5, 7, and 9 etc…)
  - AE reporting, if applicable, and review of concomitant medication

7.2.11 End-of-Treatment Visit or Early Termination

Patients will return to the study center approximately 28 (± 3) days after their last infusion of FPA144, or in the event a patient discontinues prematurely from the study.

The following assessments will be performed at the EOT visit:

- Vital signs (sitting pulse, blood pressure, respiration, and body temperature [°C] after 5 minutes rest)
- 12-lead ECG
- Limited physical examination including oral exam
- ECOG performance status evaluation

- Comprehensive ophthalmologic exams including fundoscopic and slit lamp exam, ocular coherence tomography (OCT), visual acuity, intraocular pressure, completion of fluorescein staining score form, and review of ocular/visual symptoms if at least 6 weeks since the previous ophthalmologic exams.
- Clinical safety labs
- Blood sample for PK
- Blood sample for immunogenicity
- Serum ß-hCG (evaluated by local laboratories) in women of child-bearing potential
- Blood- based biomarker sample collection from patients enrolled in Part 2 as outlined in Appendix 2
- Urinalysis
- Tumor assessment using the same physical or radiologic parameter used to evaluate baseline tumor measurements. (*This scan can be omitted if the last scan was performed <6 weeks prior to EOT visit or if tumor progression was previously determined.*
- Optional biopsy (after discussion with the Sponsor) for consenting patients enrolled in Part 2 who progressed, (28 [±7] days, post last infusion of FPA144 visit only)
- AE reporting, if applicable, and review of concomitant medications

8. Statistical Methods

Before database lock, a separate statistical analysis plan (SAP) will be finalized, providing detailed methods for the analyses outlined below.

Any deviations from the planned analyses will be described and justified in the final integrated study report.

8.1 Study Patients

8.1.1 Disposition of Patients

The number and percentage of patients entering and completing each phase (e.g., Screening, Cycle 1, and Extended Treatment Period) of the study will be presented. Reasons for withdrawal will also be summarized.

8.1.2 Protocol Deviations

A summary of the number and percentage of patients with major protocol deviations by type of deviation will be provided. Deviations will be defined in the SAP prior to database lock.

8.1.3 Analysis Populations

The following analysis populations are defined for the study:

- Safety Population—all patients who have received any portion of at least one dose of FPA144.
- DLT-Evaluable Population—all patients enrolled into Part 1A of the study who received at least 2 doses of FPA144 and completed Cycle 1 of treatment, or who experienced a DLT in Cycle 1.
- PK-Evaluable Population—all patients who have received at least one dose of FPA144 and have had adequate PK assessments drawn for determination of the PK profile. Adequacy will be determined on a case-by-case basis and will be assessed prior to analysis of the blood samples.
- Efficacy-Evaluable Population—all patients who met eligibility criteria, received at least

  1 dose of FPA144, have measurable tumor lesions at baseline, and have at least

  1 post-Baseline disease assessment.

8.2 General Considerations

Data collected in this study will be presented using summary tables and patient data listings. Continuous variables will be summarized using descriptive statistics, specifically the mean, median, standard deviation (SD), minimum, and maximum. Categorical variables will be summarized by frequencies and percentages.

The statistical and analytical plans presented below summarize the more complete plans to be detailed in the statistical analysis plan (SAP). A change to the data analysis methods described in the protocol will require a protocol amendment only if it alters a principal feature of the protocol. The SAP will be finalized prior to database lock. Any changes to the methods described in the final SAP will be described and justified in the clinical study report.

8.3 Demographics, Baseline Characteristics, and Concomitant Medications

Demographic data, medical history, concomitant disease, and concomitant medication will be summarized by cohort and overall. To determine whether the criteria for study conduct are met, corresponding tables and listings will be provided. These will include a description of patients who did not meet the eligibility criteria, an assessment of protocol violations, study drug accountability, and other data that may impact the general conduct of the study.

Baseline characteristics will be summarized for the safety population. Patients who died or withdrew before treatment started or do not complete the required safety observations will be described and evaluated separately.

8.4 Treatment Compliance

Treatment administration will be summarized by cohort including dose administration, dose modifications or delays, cumulative dose, average dose, number of infusions, and the duration of therapy.

8.5 Analyses of Tumor Response

Patients will be classified according to their best overall tumor response (complete response [CR], partial response [PR], stable disease [SD], or progressive disease [PD]). Frequencies, proportions, and exact 95% CI of patients, when appropriate, stratified by their best overall tumor response will be calculated. Patients with a best overall tumor response of CR or PR with duration of at least 4 weeks (28 days) will be further classified as having an objective tumor response. Listing of patients with an objective tumor response will be presented.

Duration of response will be calculated as the number of days from the first documentation of overall response (CR or PR) to the first documentation of disease progression or death, whichever comes first. Patients who are alive and progression-free at the time of data analysis will be censored at the time of their last assessment for tumor response.

Duration of stable disease will be calculated from Cycle 1, Day 1.

8.6 Safety Analyses

Safety analyses will be performed separately within both parts of the study and for all patients combined. Data from all patients that receive any portion of at least 1 dose of FPA144 will be included in the safety analyses. AEs, clinical laboratory information, vital signs, ECOG performance status, body weight, ECGs, results of ophthalmology/retinal exams, and concomitant medications/procedures will be tabulated and summarized.

AEs will be summarized overall and with separate summaries for serious AEs, AEs leading to discontinuation, AEs leading to death, and NCI CTCAE Version 4.03 Grade 3 or higher AEs.

Body weight and vital signs will be summarized descriptively (N, mean, standard deviation, median, minimum, and maximum). ECOG will be summarized categorically and descriptively.

Shift tables displaying patient counts and percentages classified by baseline grade and maximum grade on treatment will be provided for laboratory data by cohort and overall. A marked laboratory change is defined as a shift from a baseline Grade 0 to Grade 3 (non-hematologic) or Grade 4 (hematologic) on treatment, or a shift from a baseline Grade 1 to Grade 4 on treatment. The number and percentage of patients with marked laboratory changes will be tabulated by cohort and overall.

8.7 Efficacy Analysis

Efficacy analyses will be descriptive. The overall response rate will be summarized with frequencies and percentages. The duration of response for CR and PR patients will be summarized with descriptive statistics (N, mean, standard deviation, median, minimum, and maximum) as well as categorically. Response and duration of response will be determined using RECIST v1.1. Kaplan-Meier methodology will be used to summarize duration of response and PFS.

8.8 Pharmacokinetic Analyses

Individual and mean (±SD) serum FPA144 concentration-time data will be tabulated and plotted by dose level. FPA144 PK parameters will be estimated from the serum study drug concentration-time data using a non-compartmental analysis (NCA) method with intravenous infusion input. Alternative methods may be considered. Estimated individual and mean (±SD) PK parameters will be tabulated and summarized by dose level. Other descriptive statistics might be reported for serum FPA144 concentration-time data and estimated PK parameters. Dose proportionality, study drug accumulation, and attainment of steady state will be evaluated as data allow.

The impact of immunogenicity on FPA144 exposure will be assessed.

8.9 Interim Analyses

No formal interim analysis of efficacy is planned. For Part 2 Cohorts A, C, D, E and F, an interim analysis of response may be performed to determine adequate efficacy.

Safety data will be reviewed on a routine basis by the Sponsor and CRO's Medical Monitors. In Part 1 (A and B), the Medical Monitors and Investigator(s) will review safety data from each dose cohort prior to dose escalation or de-escalation. Adverse event data from the extended treatment period will be presented to the Medical Monitors when available.

In addition, interim safety reviews will be conducted by an external Data Safety Monitoring Board (DSMB) on a regular basis throughout the treatment phase in Part 2. If warranted from these reviews, the DSMB may request additional safety data or recommend modification of study conduct as outlined in the DSMB Charter.

8.10 Determination of Sample Size

Three patients per dose group, with a sample size increase to 6 in the case of DLT, is generally accepted as adequate to determine the safety of escalating doses of novel oncologic drugs. If a DLT is observed in 1 of 3 patients, then 3 additional patients will be enrolled at that same dose level. Dose escalation will continue until 2 of 3–6 patients treated at a dose level experience a DLT. The maximum tolerated dose (MTD) is defined as the maximum dose at which < 33% of patients experience a DLT during Cycle 1. After the MTD is determined, additional gastric cancer patients may be recruited at that dose level to further characterize the safety, PK, pharmacodynamics, and preliminary efficacy of FPA144.

In Part 1B, up to 30 patients with gastric cancer with or without FGFR2b overexpression, in the presence or absence of *FGFR2* amplification may be enrolled to explore preliminary long-term safety and PK.

In each of the Part 2 gastric cancer cohorts (Cohorts A, C, D, and E), approximately 30 gastric cancer patients with ranges of FGFR2b overexpression scores (IHC 3+ ≥ 10%; IHC 0; IHC 2+ ≥

10% tumor membrane staining **and/or** IHC 3+ < 10%; IHC 1+ **and/or** IHC 2+ < 10%) will be enrolled and treated to further characterize safety and preliminary efficacy. For each cohort, a response rate of ≥ 20% would be considered clinically meaningful. To ensure adequate efficacy, an interim analysis may be performed (with the assumption that a response rate of ≤ 5% would be of no interest in the first stage). Assuming a significance level of 5% and 80% power (Table 5), the required sample size is 29 evaluable patients per cohort. The Sponsor may choose to suspend enrollment if no confirmed response (CR or PR) is observed after the first 10 evaluable patients have either received at least 4 cycles of therapy or have had disease progression, as it is unlikely the response rate would be 20% or more. If a full cohort of 30 patients is enrolled for a group, the precision of the 95% confidence interval for the response rate is within 18%.

Table 6: Parameters of Simon's 2-stage Design

Targeted Response Rate	Response Rate of No Interest	Overall Sample Size	Sample Size at Stage I	Responses to go to Stage II	Number of Overall Responses
20%	5%	29	10	≥ 1	≥ 4

For Part 2 Cohort F, enrollment of patients with non-gastric solid tumors, including FGFR2b-selected bladder cancer, will be guided by the same 2-stage design used for cohorts A, C, D, and E for each tumor type.

However, the Sponsor may choose to close enrollment of a cohort at any time (Section 9.11). Based on Sponsor decision to close a subset of cohorts in Part 2 (as described in Section 4.1), the planned patient enrollment will be approximately 100 patients.

9. Ethical, Legal, and Administrative Aspects

9.1 Data Quality Assurance

The Sponsor (or designee) may conduct a site visit prior to study initiation at a site to verify the qualifications of each Investigator, inspect the site facilities, and inform the Investigator of responsibilities and for ensuring study compliance and procedures for adequate and correct documentation.

The Investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other pertinent data for each study patient. All information recorded on the eCRFs for this study must be consistent with the patients' source documentation (i.e., medical records).

9.2 Electronic Case Report Forms and Source Documentation

All data obtained during this study should be entered into the eCRFs promptly. All source documents from which eCRF entries are derived should be placed in the patient's medical records. eCRF fields for which source documents will typically be needed include laboratory assessments, physical exam reports, nursing notes, ECG recordings, hospital records, computed tomography (CT) scans, X-rays, and/or magnetic resonance imaging (MRI) reports.

The eCRFs for each patient will be checked against source documents at the study site by the site monitor.

Instances of missing or uninterpretable data will be discussed with the Investigator for resolution.

9.3 Access to Source Data

During the study, a monitor will perform routine site visits to review protocol compliance, compare eCRFs and individual patient's medical records, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. eCRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained.

In accordance with ICH GCP guidelines, the Investigator must ensure provision of sufficient time, reasonable space, and adequate qualified personnel for the monitoring visits. The visits are for the purpose of verifying adherence to the study protocol and the completeness, consistency, and accuracy of data entered on the eCRF and other documents. Moreover, regulatory authorities, IRBs, IECs, and/or the Sponsor's Quality Assurance group may wish to carry out such source data checks and/or on-site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality. The Investigator assures that the Sponsor and/or Sponsor's designee will receive the necessary support to complete these activities.

All participating centers should take particular care in ensuring that original imaging source data (CT images, MRI images, echo images, etc.) are maintained and accessible for monitoring, and that these original source data are then archived on a long-term basis in compliance with ICH GCP Section 8. These images must be stored in a secure location until the Sponsor or Sponsor's designee authorizes their destruction, and must be retrievable by study patient number in the event of an audit.

9.4 Data Processing

The Data Management Plan, to be developed during the initiation phase of the study, will include specifications for consistency and plausibility checks on data and will also include data-handling rules for obvious data errors. All processes for data processing and query handling will be described in the Data Management Plan.

9.5 Archiving Study Records

The study site will maintain a study file, which should contain, at minimum, the Investigator's Brochure, the protocol and any amendments, the protocol for tissue sampling, drug accountability records, correspondence with the IEC/IRB and the Sponsor (or designee), and other study-related documents.

The Investigator agrees to keep records and those documents that include (but are not limited to) the identification of all participating patients, medical records, study-specific source documents, source worksheets, all original signed and dated ICFs, copies of all eCRFs, query responses, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities and Five Prime Therapeutics or its designees.

The Investigator shall retain records required to be maintained for a period of 5 years following the date a marketing application in an ICH region is approved for the drug for the indication for which it is being investigated or, if no application is to be filed or if the application is not approved for such indication, until at least 5 years after the investigation is discontinued. However, these documents should be retained for a longer period if required by the applicable regulatory requirement(s) or if needed by the Sponsor. In addition, the Investigator must make provision for the patients' medical records to be kept for the same period of time.

No data should be destroyed without the agreement of Five Prime Therapeutics. Should the Investigator wish to assign the study records to another party or move them to another location, Five Prime Therapeutics must be notified in writing of the new responsible person and/or the new location.

Patients' medical records and other original data will be archived in accordance with the archiving regulations or facilities of the investigational site.

9.6 Good Clinical Practice

The procedures set out in this study protocol are designed to ensure that the Sponsor and Investigator abide by GCP guidelines of the ICH and the Declaration of Helsinki (1989). The study also will be carried out in compliance with local legal requirements.

9.7 Informed Consent

All information about the clinical study, including the patient information and the ICF, is prepared and used for the protection of the human rights of the patient according to ICH GCP guidelines and the Declaration of Helsinki.

The ICF, prepared by the Investigator with the assistance of the sponsor, must be approved along with the study protocol by the IEC/IRB and be acceptable to the sponsor before each patient is enrolled on the study, written informed consent will be obtained according to the regulatory and legal requirements. A copy of the signed ICF will be retained by the patient and the original will be filed in the Investigator's site file, unless otherwise agreed. The Investigator will not undertake any investigation specifically required only for the clinical study until valid consent has been obtained. The terms of the consent and when it was obtained must be documented in the source documents and in the eCRF.

If a protocol amendment is required, the informed consent form may need to be revised to reflect the changes to the protocol. If the consent form is revised, it must be reviewed and approved by the appropriate IRB/IEC, and signed by all patients subsequently enrolled in the study as well as those currently enrolled in the study.

9.8 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IRB/IEC, in accordance with local legal requirements. The Sponsor, Sponsor's agents, and Investigator must ensure that all ethical and legal requirements have been met before the first patient is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB/IEC approval prior to implementation (if appropriate). Following approval, the protocol amendment will be submitted to the investigational new drug (IND) application under which the study is being conducted.

All amendments will be distributed to all protocol recipients, with appropriate instructions. Administrative changes (not affecting the patient benefit/risk ratio) may be made without the need for a formal amendment. Administrative changes will be distributed to the Investigator and others as appropriate.

9.9 Cohort Review Committee

The CRC will assess safety of the study, Part 1 (A and B) and Part 2, on a regular basis. The CRC will consist of representatives from the Sponsor, CRO, as well as one or more designated Investigators from actively participating sites in which FPA144 is being evaluated.

9.10 Duration of the Study

For any individual patient, the minimum duration of the study will be approximately 3 months. This includes up to 28 days for screening, and 1 month on study including 4 weeks (28 days) of post-treatment follow-up. Patients who are considered to be benefitting from FPA144 treatment may continue on study until disease progression.

9.11 Premature Termination of the Study or Cohorts

If the Investigator, Sponsor, or Medical Monitor becomes aware of conditions or events that suggest a possible hazard to patients if the study continues, the study may be terminated. The study may also be terminated early at the Sponsor's discretion in the absence of such a finding.

Conditions that may warrant termination include, but are not limited to:

- Discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study
- Failure to enroll patients at an acceptable rate
- Decision on the part of the Sponsor to suspend or discontinue development of the drug

Individual study cohorts may be closed at any time according to the Sponsor's discretion.

9.12 Confidentiality

All study findings and documents will be regarded as confidential. The Investigator and members of his/her research team must not disclose such information without prior written approval from the Sponsor.

The anonymity of participating patients must be maintained. Patients will be identified on eCRFs and other documents submitted to the Sponsor or Sponsor's designee by their patient number, initials, and/or birth date. Study patients are not to be identified by name, and any information sent to the Sponsor or Sponsor's designee should have patient identifiers redacted, and replaced with patient ID. Documents that include the name of the patient (e.g., the signed informed consent) must be maintained in confidence by the Investigator. The Investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study center to any third party or otherwise into the public domain.

9.13 Other Ethical and Regulatory Issues

If a significant safety issue is identified, either from an individual case report or review of aggregate data, then the Sponsor will issue prompt notification to applicable regulatory

authorities and Investigators. Investigators will then notify local IRB/IECs as deemed appropriate based on individual IRB/ IEC policy.

A significant safety issue is one that has a significant impact on the course of the clinical trial or program (including the potential for suspension of the trial program or amendments to protocols) or warrants immediate update of informed consent.

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11. Appendices

The following appendices are provided for this protocol.

Appendix 1: Schedule of Assessments–Dose Escalation and Dose Expansion Cohorts

	Screening	Parts 1A, 1B and 2 Cycle 1					Part 1A/Part 1B/Part 2 Cycle 2 and Subsequent Cycles			End of Treatment[b]
	Day –28 to Day 0	**Day 1**	**Day 2**	**Day 4**	**Day 8**	**Day 15**	**Day 1**	**Day 15**	**Other**	
Procedure[a]	Week 0	Week 1	Week 1	Week 1	Week 2	Week 3	≥Week 4			
Informed Consent	X[z]									
Review/Confirm Eligibility Criteria	X	X								
Medical/Oncology History	X	X								
Tumor Tissue Collection[c]	X									
Optional Archival Tumor Tissue Collection[d]									X	
Demography/Baseline Characteristics	X									
Physical Examination[e, f]	X	X			X	X	X	X		X
ECOG Performance Status	X						X[n]			X
Vital Signs[g]	X	X[g]	X	X	X	X[g]	X[g]	X[g]		X
12-lead ECG[h]	X								X[i]	X
Comprehensive Ophthalmologic Exam[t]	X						X[t]		X[i]	X
Slit Lamp Exam[u]							X	X	X[i]	
Clinical Safety laboratory sampling[j, k]	X	X			X	X	X	X		X
Serum Pregnancy Test[l]	X	X								X
Urinalysis[m]	X	X					X		X[i]	X
Radiological/Tumor Scans[o]	X						X[p]	X[p]	X[p]	X[q]
Biopsy[y]	X					X	X		X	X
Immunogenicity Sampling[v]		X					X			X
Optional collection for FCGR Polymorphism[w]		X								
Blood-based biomarker sample collection[x]		X							X	X
PK Samples		X[r]	X[r]	X[r]	X[r]	X[r]	X[r]			X[r]
FPA144 Dose		X				X	X	X		
Adverse Events[s] and Prior/Concomitant Meds	X	X ——— X								

a	Unless specified, procedure is to be completed within ± 72 hours of scheduled time point and to be synchronized with administration day of FPA144 infusion.
b	End of Treatment (EOT) assessments should be performed 28 (±3) days following the last dose of FPA144.
c	Tumor tissue from archival or newly obtained material will be submitted for Part 1A patients (optional, if available), and is required for enrollment in Part 2. Refer to the Laboratory Manual for sample handling instructions.
d	For patients who consent to the optional exploratory tumor analysis, participation is contingent on the availability of adequate archival tumor specimens (distinct from those provided for patient selection) and is permitted only after discussion and approval by the Sponsor.
e	Complete physical exam and height will be measured at Screening only. Limited physical examinations should be conducted, including examination of the oropharynx, thereafter.
f	After Cycle 1, dose will be recalculated at each infusion visit only if weight has changed >10% from Cycle 1, Day 1.
g	Vital signs (blood pressure, pulse, respiration, and temperature) are to be measured on Cycle 1 Day 1 at the following time points: pre-dose, and 0.5, 1, 2, and 4 hours, from the start of infusion. On subsequent dosing days, pre-dose and at 0.5 and 1 hour from start of infusion.
h	With patient resting for 5 minutes prior to recording.
i	If clinically indicated at any time.
j	Includes hemoglobin, hematocrit, WBC and differential (with ANC), and platelet count. Blood will be analyzed by a local laboratory and must be reviewed by the Investigator prior to dosing with FPA144.
k	CBC with differential, platelets, hemoglobin, hematocrit, RBC, and RBC indices. Blood chemistry including magnesium. Hematology, blood chemistry, and urinalysis test results must be obtained within 72 hours of dosing to confirm eligibility. On FPA144 dosing days, hematology, blood chemistry to be performed but only hematology results are required prior to dosing. Coagulation samples need to be obtained at Cycle 1 through Cycle 4 only, unless clinically indicated.
l	Serum ß-hCG (evaluated by local laboratories) will be performed only on women of childbearing potential ≤ 5 days prior to the first dose of FPA144 and at EOT.
m	Includes dipstick for protein, glucose, blood, pH, and ketones. If dipstick findings are abnormal, then a microscopic evaluation will be performed to assess the abnormal findings.
n	ECOG Performance Status will be assessed at Day 1 Cycle 2 and Day 1 of subsequent cycles until the End of Treatment visit.
o	Tumor assessments should consist of clinical examination and appropriate imaging techniques (preferably CT scans with appropriate slice thickness per RECIST); other assessments (MRI, X-ray, PET, and ultrasound) may be performed if required. The same methods used to detect lesions at baseline are to be used to follow the same lesions throughout the clinical study. Screening tumor scan must be within 4 weeks of the start of treatment on Day 1.
p	Tumor scans to be performed at Screening (within 4 weeks of Cycle 1 Day 1) and within 7 days prior to the start of Cycle 2 Day 15, Cycle 4 Day 1, Cycle 5 Day 15, Cycle 7 Day 1, and then approximately every 12 weeks. If initial CR or PR is noted, confirmatory scans must be performed 4–6 weeks later.
q	This scan can be omitted if the last scan was performed < 6 weeks prior to EOT visit or if tumor progression was previously determined.
r	**For Part 1A Cycle 1 Day 1 to Day 8:** PK samples to be collected within 4 hours prior to dosing of FPA144 and at the following time points relative to the start of the infusion: 0.5 hours (within 5 minutes after end of infusion), +1 hour (±5 minutes), 2 hours (±5 minutes), 4 hours (±5 minutes), 8 hours (±5 minutes), 24 hours (Day 2, ±1 hour), 72 hours (Day 4, +24 hour) and 168 hours (Day 8) from start of infusion. **For Part 1B Cycle 1 Day 1 to Day 8:** PK samples to be collected within 4 hours prior to dosing of FPA144 and at the following time points relative to the start of the infusion: 0.5 hours (within 5 minutes after end of infusion), +1 hour (±5 minutes), 4 hours (±5 minutes), 24 hours (Day 2, ±1 hour), 72 hours (Day 4, +24 hour) and 168 hours (Day 8) from start of infusion. **Part 2 Cycle 1 Day 1 to Day 8:** PK samples to be collected within 4 hours prior to dosing of FPA144 and at 0.5 hours (within 5 minutes after end of infusion), +1 hour (±5 minutes), 4 hours (±5 minutes), and 168 hours (Day 8, ± 2 days) from the start of infusion. **For Parts 1 (A & B) and 2 Cycle 1 Day 15 and Cycles 2-5 Day 1 and every other cycle Day 1 starting from Cycle 5:** PK samples to be collected ≤4 hours ***prior*** to dosing of FPA144 and 0.5 hours (within 5 minutes after the end of infusion). Refer to the Laboratory Manual for detailed sample handling instructions.
s	AE collection begins following signing of the ICF for Screening. Events reported prior to the first infusion will be considered pretreatment events and reported on the Medical History page of the eCRF, unless they directly correlate to a study-related procedure. Adverse event reporting will continue until completion of the EOT visit or until 28 days after the last dose of study drug.

t	Prior to Cycle 2 Day 1 only comprehensive ophthalmologic evaluations should include fundoscopic and slit lamp exam, OCT, visual acuity, and review of symptoms. The comprehensive ophthalmologic exam will be repeated at any point if changes in visual acuity or visual symptoms are reported by patients.
u	Slit lamp exams (including completion of fluorescein staining form) without OCT every 6 weeks through Cycle 6 Day 15 (prior to Cycle 3, Day 15; Cycle 5, Day 1; Cycle 6, Day 15), and then every 12 weeks after Cycle 6 Day 15. Slit lamp exams will continue every 6–8 weeks if the patient has any persistent corneal findings.
v	Blood samples to be collected prior to dosing on Day 1 of Cycles 1-5and every other cycle starting from cycle 5 for measurement of anti-FPA144 antibodies.
w	FCGR polymorphism testing sample must both be collected prior to first dose
x	Blood-based biomarker sample will be collected from Part 2 patients prior to dosing on Cycle 1 Day 1 and then every 6 weeks from the first dose for 24 weeks (prior to Cycle 2 Day 15, Cycle 4 Day 1, Cycle 5 Day 15, Cycle 7 Day 1), and then approximately every 12 weeks thereafter as outlined in Appendix 2.
y	Biopsy at primary tumor or metastatic tumor site will be collected at screening [at least 24 hours prior to dosing] and **either** at 15 days on-treatment [within 7 days prior to Cycle 1 Day 15 and at least 24 hours prior to dosing] **or** at 29 days on-treatment [within 7 days prior to Cycle 2 Day 1 and at least 24 hours prior to dosing]. After consultation with the Sponsor, patients who have documented response may receive another biopsy within 28 (±7) days post tumor assessment and/or patients who have progression may receive another biopsy at the End-of–Treatment visit. The post-response and post-progression biopsies are optional.
z	Written, signed informed consent must be collected prior to any study-specific procedures. The most recent IRB/EC approved ICF must be signed.

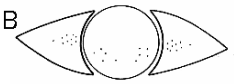
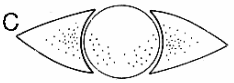
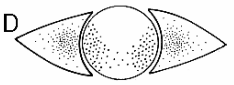
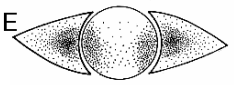
Appendix 2: Study Flowchart for Pharmacokinetic, Immunogenicity, and Pharmacodynamic Blood Sample Collections for Part 2

Study Cycle	Study Day	Time Point	Type of Sample
Cycle 1	Day 1 (First Dose)	≤ 4 hours Prior to infusion	FPA144 PK (serum)
			ADA (serum)
			Blood-based Biomarker (whole blood)
			FCGR Polymorphism (optional; whole blood)
		5 minutes after end of infusion	FPA144 PK (serum)
		1 hour after end of infusion (± 5 minutes)	FPA144 PK (serum)
		4 hours after end of infusion (±5 minutes)	FPA144 PK (serum)
	Day 8	168 hours after infusion (±2 days)	FPA144 PK (serum)
	Day 15 (Second Dose)	≤ 4 hours Prior to infusion	FPA144 PK (serum)
		5 minutes after end of infusion	FPA144 PK (serum)
Cycle 2 thru Cycle 5	Day 1 (First Dose)	≤ 4 hours Prior to infusion	FPA144 PK (serum)
			ADA (serum)
			Blood-based Biomarker at Cycle 4 only (whole blood)
		5 minutes after end of infusion	FPA144 PK (serum)
	Day 15 (Second Dose)	≤ 4 hours Prior to infusion	Blood-based Biomarker at Cycle 2 and 5 only (whole blood)
Cycle 7 and Subsequent Cycles	Day 1 (First Dose)	≤ 4 hours Prior to infusion	FPA144 PK at odd cycles only (serum)
			ADA at odd cycles only (serum)
			Blood-based Biomarker at Cycle 7 and then every 12 weeks thereafter (whole blood)
		5 minutes after end of infusion	FPA144 PK at odd cycles only (serum)
End of Treatment Follow-up	Visit Date	During Visit	FPA144 PK (serum)
			ADA (serum)
			Blood-based Biomarker (whole blood)

Appendix 3: ECOG Performance Status

Grade	Performance Status Criteria
0	Fully active, able to carry on all pre-disease activities without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light sedentary nature (light housework, 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.

Appendix 4: Fluorescein Stain Grading Systems

<table>
<tr><td>DEWS</td><td>DRY EYE: DIAGNOSTIC TEST TEMPLATE</td><td></td></tr>
<tr><td>RAPPORTEUR</td><td>A.J.Bron</td><td>21st Oct 2004</td></tr>
<tr><td>TEST</td><td>Grading staining: Oxford Schema</td><td></td></tr>
<tr><td>TO DIAGNOSE</td><td>The scheme is used to estimate surface damage in dry eye.</td><td>REFERENCES</td></tr>
<tr><td>VERSION of TEST</td><td>[V 1]</td><td></td></tr>
<tr><td>DESCRIPTION</td><td>Surface damage to the exposed eye, assessed by staining, is graded against standard charts.</td><td></td></tr>
<tr><td>NATURE of STUDY</td><td>N. A.</td><td></td></tr>
<tr><td>CONDUCT of TESTS</td><td>Grading Schema:
Staining is represented by punctate dots on a series of panels (A-E). Staining ranges from 0-5 for each panel and 0-15 for the total exposed inter-palpebral conjunctiva and cornea. The dots are ordered on a log scale
<table>
<tr><th>PANEL</th><th>GRADE</th><th>CRITERIA</th></tr>
<tr><td>A  </td><td>0</td><td>Equal to or less than panel A</td></tr>
<tr><td>B  </td><td>I</td><td>Equal to or less than panel B, greater than A</td></tr>
<tr><td>C  </td><td>II</td><td>Equal to or less than panel C, greater than B</td></tr>
<tr><td>D  </td><td>III</td><td>Equal to or less than panel D, greater than C</td></tr>
<tr><td>E  </td><td>IV</td><td>Equal to or less than panel E, greater than D</td></tr>
<tr><td>>E</td><td>V</td><td>Greater than panel E</td></tr>
</table>
Conduct of Test:
• Dye is instilled.
• Slit-lamp is set (eg.16 magnification with x10 oculars with Haag-Streit).
• Cornea: The upper eyelid is lifted slightly to grade the whole corneal surface,
• Conjunctiva: To grade the temporal zone, the subject looks nasally; to grade the nasal zone the subject looks temporally.
• (The upper and lower conjunctiva can also be</td><td>Bron Evans Smith 2003.</td></tr>
</table>

Appendix 4: Fluorescein Stain Grading Systems (Cont.)

	graded). **Selection of dyes:** A list dyes and filters can be found in the original paper. With fluorescein, staining must be graded as quickly as possible after instillation, since the dye then diffuses rapidly into the tissue and its high luminosity blurring the stain margin. Staining after rose bengal or lissamine green, persists at high contrast and may therefore be observed for a considerable period. This is convenient for both grading and photography. **Fluorescein sodium** **1. Quantified drop instillation** eg 2 µl of 2 % sterile fluorescein instilled into each conjunctival sac with a micro-pipette (using a sterile tip). In very dry eye, larger volumes risk the possibility of inadequate dilution into the fluorescent range. **2. Unquantified instillation – impregnated paper strips** This is a convenient approach in the clinic using the following method of application: • A single drop of unit dose saline is instilled onto a fluorescein-impregnated strip. • When the drop has saturated the impregnated tip, the excess is shaken into a waste bin with a sharp flick. • The right lower lid is then pulled down and the strip is tapped onto the lower tarsal conjunctiva. A similar procedure is carried out on the left. If too large a volume is delivered then the concentration in the tear film will be too high, and the tear film and staining pattern will be non-fluorescent. **3.Timing** The fluorescein break-up time (FBUT) is usually performed prior to grading. Since fluorescein diffuses rapidly into tissues, punctate staining blurs after a short period. It is therefore essential to assess staining rapidly, in sequence, in the right and then the left eye, so that the staining patterns observed are equally crisp. If it is intended to photograph the staining pattern for grading, then photography should follow immediately after each instillation. **Exciter and Barrier Filters** The absorption peak of fluorescein sodium occurs between 465 - 490 nm and the emission peak between 520 - 530 nm A suggested filter pair for detection of fluorescein staining is a yellow, Kodak Wratten 12 barrier filter (transmitting above 495 nm) or an orange Wratten 15 filter (transmitting above 510 nm) in combination with a blue Wratten 47 or 47A exciter filter. The 47A shows greater transmittance than the Wratten 47 over the absorption range. The 'cobalt' filter of many slit-lamps is suitable to use with a Wratten 12 or 15	

Appendix 4: Fluorescein Stain Grading Systems (Cont.)

	barrier. Where more light is required for photographic purposes, narrow band-pass, interference filters can be used. The use of both exciter and barrier filters allows both the cornea and conjunctiva to be assessed using a single stain. This is a major advantage in clinical trials where it is otherwise customary to employ fluorescein to grade corneal staining and rose bengal or lissamine green to grade conjunctival staining. **Disadvantages of Fluorescein Staining** Blurred pattern if reading is delayed. Delay in photographing fluorescein staining results in blurred images of the staining pattern. **Rose Bengal** The intensity of rose bengal staining is dose dependent. If drop size or concentration is reduced to minimize stinging, the amount of staining is also reduced. Use of impregnated strips will give weaker staining than use of a full drop of 1% solution. Best results are achieved with, eg. 25 µl 1%, instilled into the conjunctival sac. Because rose bengal stings, instillation is best preceded by a topical anesthetic. **Instillation Technique** 1) eg. A drop of Proxymetacaine is instilled into the conjunctival sac followed, after recovery, by; 2) A drop of rose bengal 1.0%. This is instilled onto the upper bulbar conjunctiva with the upper lid retracted and the patient looking down. 3) Since both anaesthetic and drop may stimulate reflex tearing, the test should follow measurement of the FBUT and of the Schirmer test. (Conjunctival staining due to insertion of the Schirmer paper can usually be distinguished from that due to dry eye disease). Both eyes may be stained prior to grading, since there is no risk of the staining pattern in the first eye being obscured by the time the second eye is graded. The cited paper gives advice about avoidance of overspill. **Visibility** Rose bengal staining on the conjunctiva shows up well against the sclera and may be enhanced using a red-free (green) light source. Corneal staining may show up well against a blue iris, but is difficult to see against a dark brown iris. **Phototoxicity** Photo-activation of rose bengal by sunlight increases post-instillation symptoms, especially in severe dry eye with heavy staining. This post-instillation pain can be minimised	

Appendix 4: Fluorescein Stain Grading Systems (Cont.)

<table>
<tr><td></td><td>by liberal irrigation with normal saline at the end of the test.

Lissamine green stains the eye in a similar manner to rose bengal but is as well tolerated as fluorescein. Visibility and dose-dependency are the same as rose bengal and staining is persistant so that photography need not be performed immediately after instillation.
Lissamine green is available as impregnated strips or may be ordered as a pre-prepared solution. A 25 µl 1% drop will give more intense staining. Because the drop is well tolerated, no anaesthetic is required.

Visibility
As with rose bengal, lissamine green staining is easily visible on the conjunctiva. On the cornea, staining is seen well against a light blue iris background but is poorly visible against a dark brown iris background. For both rose bengal and lissamine green, because the dyes are poorly seen within the tear film, the dye in the tear film does not obscure the staining pattern. Also, since both dyes do not diffuse into the substantia propria of the conjunctiva, the staining pattern is retained for longer.

Visibility of staining may be enhanced using a white light source and a red barrier filter, to give a black pattern on a red ground. A suitable filter is a Hoya 25A, or a Kodak Wratten 92.</td><td></td></tr>
<tr><td>Web Video</td><td>Not available</td><td></td></tr>
<tr><td>Materials:</td><td>Oxford Grading Charts - available from A J Bron anthony.bron@eye.ox.ac.uk</td><td></td></tr>
<tr><td>Standardization</td><td>Nil additional</td><td></td></tr>
<tr><td>Variations of technique</td><td></td><td></td></tr>
<tr><td>Diagnostic value</td><td>No stats supplied.</td><td></td></tr>
<tr><td>Repeatability</td><td>A small intra-interobserver study was carried out in 1986 and was presented but not published:

Intra-observer study: This study asked two trained ophthalmologists to grade a series of standard slides, showing corneal and conjunctival fluorescein staining, on 2 separate occasions. [note: -this study is only relevant to grading photographic records not patients.]

Intra-observer κ for grading photographs of staining, using the Oxford scheme. Two observers.
<table><tr><td></td><td>Cornea</td><td>Conjunctiva</td></tr><tr><td>Observer 1</td><td>0.86</td><td>0.69</td></tr><tr><td>Observer 2</td><td>0.65</td><td>0.83</td></tr></table>
Not that values are in the good to excellent range.

Inter-observer study: In this study, the same 2 observers</td><td>Hardman Lea et al. 1986 AER abstract.</td></tr>
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Appendix 4: Fluorescein Stain Grading Systems (Cont.)

<table>
<tr><td></td><td>graded fluorescein staining (blue exciter; yellow filter) in 13 dry eye patients at an interval within 2-3 weeks.

Inter-observer κ for grading patients with dry eye, using the Oxford scheme. Two observers. Fluorescein; bengal rose
<table><tr><td>Observer 1 v 2</td><td>Cornea</td><td>Conjunctiva</td></tr><tr><td>Fluorescein</td><td>0.88</td><td>0.48</td></tr><tr><td>Bengal rose</td><td>0.87</td><td>0.54</td></tr></table>
It is of interest that observations are in the excellent category for cornea, with either stain and in the fair category for conjunctiva.</td><td></td></tr>
<tr><td>Sensitivity</td><td>(true positives) [-]</td><td></td></tr>
<tr><td>Specificity</td><td>(100 – false positives) [-]</td><td></td></tr>
</table>

References:

Bron A, Evans VE, Smith JA. (2003). Grading of corneal and conjunctival staining in the context of other dry eye tests. *Cornea* 22(7): 640-50.