FIGHT: A Phase 2 Randomized, Double-Blind, Controlled Study Evaluating FPA144 and Modified FOLFOX6 in Patients with Previously Untreated Advanced Gastric and Gastroesophageal Cancer: Phase 2 Preceded by Dose-Finding in Phase 1

Protocol Number:	FPA144-004
Investigational Product:	FPA144
IND Number:	117701
Development Phase:	Phase 1/2
Indication Studied:	Advanced Gastric and Gastroesophageal Cancer
Protocol Version:	Amendment 4
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Sponsor:	Five Prime Therapeutics, Inc. 111 Oyster Point Boulevard South San Francisco, CA 94080 Tel: + 1 415-365-5600
Responsible Medical Officer:	[redacted], MD Chief Medical Officer Five Prime Therapeutics, Inc. 111 Oyster Point Boulevard South San Francisco, CA 94080

Confidential

NCT Number: NCT03694522
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for the purposes of posting on clinicaltrials.gov

Protocol Approval Signature Page

Declaration of Sponsor

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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.

DocuSigned by:
[redacted]
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10Mar2021

[redacted], MD
Chief Medical Officer
Five Prime Therapeutics, Inc.

Date

Declaration of the Investigator

FIGHT: A Phase 2 Randomized, Double-Blind, Controlled Study Evaluating FPA144 and Modified FOLFOX6 in Patients with Previously Untreated Advanced Gastric and Gastroesophageal Cancer: Phase 2 Preceded by Dose-Finding in Phase 1

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 confirm that I have read the above-mentioned protocol/protocol amendments and its attachments. I agree to conduct the described trial in compliance with all stipulations of the protocol, applicable laws, regulations and ICH E6 Guideline for Good Clinical Practice (GCP).

_____ _____

Principal Investigator's Signature Date

_____

Name (printed)

_____

Institution or Company Name

Protocol Synopsis

Title:	**FIGHT: A Phase 2 Randomized, Double-Blind, Controlled Study Evaluating FPA144 and Modified FOLFOX6 in Patients with Previously Untreated Advanced Gastric and Gastroesophageal Cancer: Phase 2 Preceded by Dose-Finding in Phase 1**
Protocol Number:	FPA144-004
Clinical Phase:	1/2
Sponsor:	Five Prime Therapeutics, Inc.
Study Centers:	Up to approximately 190 global study centers
Phase 1 Objectives:	**Primary** To determine the recommended dose (RD) of FPA144 combined with a fixed dose of 5-fluorouracil (5-FU), leucovorin, and oxaliplatin (mFOLFOX6) (hereinafter referred to as FPA144 + mFOLFOX6) in patients with advanced gastrointestinal (GI) tumors **Secondary** • To evaluate the safety and tolerability of FPA144 + mFOLFOX6 in patients with GI tumors • To characterize the pharmacokinetic (PK) profile of FPA144 + mFOLFOX6 in patients with GI tumors • To characterize the immunogenicity of FPA144 **Exploratory** [redacted]
Phase 2 Objectives:	**Primary** To compare investigator-assessed progression-free survival (PFS) in patients with fibroblast growth factor receptor 2 (FGFR2)-selected gastric or gastroesophageal cancer (GC) treated with FPA144 + mFOLFOX6, to those treated with placebo combined with mFOLFOX6 (hereafter referred to as placebo + mFOLFOX6) **Secondary** To compare the following in patients with FGFR2-selected GC treated with FPA144 + mFOLFOX6 to those treated with placebo + mFOLFOX6: • Overall survival (OS) • Investigator-assessed objective response rate (ORR) • Safety and tolerability

Exploratory

To compare the following in patients with FGFR2-selected GC treated with FPA144 + mFOLFOX6 to those treated with placebo + mFOLFOX6:

- Duration of response (DOR)
- Patient-reported outcomes (PROs) and quality of life (QOL) outcomes until investigator-assessed disease progression
- To explore the association between FGFR2 status (in tumor tissue and/or blood) with clinical outcome
- To explore the concordance between FGFR2b overexpression in tumor tissue and *FGFR2* gene amplification in blood

To characterize the following:

- PK profile of FPA144 + mFOLFOX6 in patients with FGFR2-selected GC
- Immunogenicity of FPA144

Phase 1 Endpoints:

Primary

The incidence of Grade 2 or higher adverse events (AEs) assessed as related to FPA144 by the investigator and the incidence of clinical laboratory abnormalities defined as dose-limiting toxicities (DLTs)

Secondary

- The incidence of AEs, clinical laboratory abnormalities, corneal and retinal findings, and electrocardiogram (ECG) abnormalities
- PK parameters of FPA144, such as area under serum concentration-time curve (AUC), maximum serum concentration (C_{max}), trough serum concentration (C_{trough}), clearance (CL), terminal half-life ($t_{1/2}$), volume of distribution, the time to achieve steady state, dose-linearity, and accumulation ratio
- Incidence of treatment-emergent anti-FPA144 antibody response

Exploratory

[redacted]

Phase 2 Endpoints:

Primary

Investigator-assessed progression-free survival (PFS), defined as time from randomization until the date of disease progression based on investigator assessment (using Response Evaluation Criteria in Solid Tumors version 1.1 [RECIST v1.1]) or death from any cause, whichever comes first

Secondary

- Overall survival (OS), defined as time from randomization until death from any cause
- Objective response rate (ORR), defined as the proportion of patients with partial or complete response based on investigator assessment of tumor lesions per RECIST v1.1
- Incidence of AEs, clinical laboratory abnormalities, corneal and retinal findings, and ECG abnormalities

Exploratory

- DOR limited to patients who are responders to treatment, as determined by the investigator per RECIST v1.1, and defined as the time of first response to progression or death from any cause, whichever comes first
- Change from baseline in functional outcomes as measured by EuroQOL-5D-5L (EQ-5D-5L) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Version 3.0 (EORTC QLQ-C30)
- The correlation between identified FGFR2 status in tumor tissue and/or circulating tumor DNA (ctDNA) blood assay, as determined by immunohistochemistry (IHC) and blood-based molecular diagnostic assay, with OS, PFS, and ORR per RECIST v1.1
- The correlation between identified FGFR2b overexpression in tumor tissue by IHC and *FGFR2* gene amplification as determined by ctDNA blood assay
- Pharmacokinetic (PK) parameters, C_{max} and C_{trough} of FPA144 in combination with mFOLFOX6
- Incidence of treatment-emergent anti-FPA144 antibody response

Investigational Product

FPA144 drug product is supplied for intravenous (IV) administration as a sterile, aqueous, colorless to slightly yellowish, pyrogen-free 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, and 0.01% (w/v) polysorbate 20 at pH 6.0.

mFOLFOX6: Leucovorin (or levo-leucovorin), 5-FU, and oxaliplatin will be obtained from Sponsor-approved commercial sources at each participating site. Management (ie, handling, storage, administration, and disposal) of these products will be in accordance with the relevant local guidelines. For countries where the Sponsor is required to provide all study drugs, including standard-of-care drugs, the Sponsor will provide leucovorin, 5-FU, and oxaliplatin from a commercial supply that is clinically labeled in accordance with relevant local guidelines. For further

details, refer to the manufacturer's prescribing information for the respective chemotherapies and the study Pharmacy Manual.

Placebo (only used in Phase 2) will match the FPA144 drug product. It will be supplied for IV administration as a sterile, aqueous, colorless to slightly yellowish, pyrogen-free solution supplied in single-use vials. The composition of matching placebo contains 20 mM L-histidine, 270 mM sucrose, and 0.01% (w/v) polysorbate 20 at pH 6.0.

Administration of Study Treatment is outlined below.

Study Design

This is a double-blind, randomized, controlled, multicenter Phase 1/2 study to evaluate the safety, tolerability, efficacy, and PK of FPA144 + mFOLFOX6 versus placebo + mFOLFOX6.

This study includes a Phase 1 safety run-in portion and a Phase 2 portion. Patients may enroll in either Phase 1 or Phase 2, but may not enroll in both phases of the study.

The Phase 1 safety run-in is an open-label dose-escalation of FPA144 + mFOLFOX6 in patients with GI tumors (not FGFR2-selected).

The Phase 2 part of this study was initially designed as a Phase 3 study in the front-line setting evaluating bemarituzumab (FPA144) with SOC chemotherapy. The study initiated following promising monotherapy activity of bemarituzumab in the Phase 1 study conducted in late-line gastric cancer. The Phase 3 statistical design assumed the incidence of FGFR2b positivity in front-line gastric cancer to be ~10%. However, over the conduct of the study, the true incidence has been 30%. Additionally 2 methods of testing for FGFR2b status, IHC and ctDNA, were utilized to identify eligible patients and the expectation was that the majority of positive tumors would be identified by both tests. In actuality, the vast majority of tumors have been identified by IHC alone, leading to a question of adequate study power. The study design has been modified in consideration of these factors.

The Phase 2 portion of the study (to follow the Phase 1 safety run-in) is a global, randomized, double-blind, controlled, study to evaluate the efficacy of FPA144 + mFOLFOX6 versus placebo + mFOLFOX6 in patients with FGFR2-selected GC (as determined by prospective IHC demonstrating FGFR2b overexpression and/or a ctDNA blood assay demonstrating *FGFR2* gene amplification).

FGFR2 Expression Requirements (Pre-Screening):

- Required provision of tissue and blood sample for FGFR2 positive status by 1 of these testing methods for enrollment in Phase 2: Provision of archival (or fresh biopsy if archival tissue is not available) for pre-screening FGFR2b overexpression testing by IHC is required; provision of a blood sample is also required for pre-screening by ctDNA for FGFR2 amplification.

- Results of the centralized FGFR2 testing may take approximately 2 weeks; patients are permitted to receive up to 1 dose of mFOLFOX6 during this interim time period (pre-screening) at the discretion of the investigator. This 1 dose of chemotherapy is not a requirement of the study and is not considered part of this clinical study.

Screening Period:

Pre-screening allows for collection of blood and tissue to determine FGFR2 positivity using ctDNA and IHC assays. Once a patient is confirmed to have a positive result based on central testing, the screening period initiates, allowing for evaluation of all other eligibility criteria.

All study assessments are outlined in the Schedules of Assessments in Protocol Appendix 2 and Appendix 3.

Phase 1 Safety Run-in

Dose Escalation Design

The Phase 1; after a maximum 28-day screening period, eligible patients will initiate study treatment.

In Phase 1, dose cohorts are planned at proposed doses beginning at an FPA144 dose level of 6 mg/kg per dose, and enrollment will depend on safety and tolerability. Phase 1 will include a standard 3+3 dose escalation design (Cohort 1), and rolling-6 design (Cohort 2, 1a, and 1b), until the RD of FPA144 to be administered in combination with mFOLFOX6 in Phase 2 is determined. A minimum of 2 dosing cohorts of FPA144 combined with mFOLFOX6 will be included in Phase 1.

Proposed FPA144 Dose Levels

The proposed FPA144 dose levels for dose escalation are as follows:

- Cohort 1: 6 mg/kg FPA144 once every 2 weeks (Q2W)
- Cohort 2: 15 mg/kg FPA144 Q2W with 1 dose of FPA144 7.5 mg/kg on Day 8 (Cycle 1 only)
- Cohort 1a (if needed, eg, if the Cohort 2 dose level or schedule is not tolerated): 15 mg/kg FPA144 Q2W
- Cohort 1b (if needed, eg, if Cohort 2 and 1a dose levels or schedules are not tolerated): Dose level lower than Cohort 1a, but higher than Cohort 1 to achieve tolerability with optimal target exposure.

Dose-Limiting Toxicity Observation

Patients will be observed for a 28-day DLT period, starting on the first day (Cycle 1 Day 1 [C1D1]) of treatment with FPA144 and mFOLFOX6, for safety assessments, PK, and occurrence of DLTs. If the first dose cohort (6 mg/kg) clears the 28-day DLT period, the second dose cohort (15 mg/kg Q2W with 1 dose of 7.5 mg/kg on Day 8 [Cycle 1 only]) will be tested in a rolling-6 design and will enroll 6 patients to explore the safety and efficacy at this dose level. Subsequent cohorts will also be

enrolled as a rolling 6 design and will only be enrolled if Cohort 2 is deemed intolerable.

Dose-Limiting Toxicity Definitions

DLTs during Phase 1 are defined as any of the following events considered by the investigator to be related to study drug:

- Absolute neutrophil count (ANC) $< 0.5 \times 10^9$/L > 5 days' duration or febrile neutropenia (ie, ANC $< 1.0 \times 10^9$/L with a single temperature of > 38.3°C, or fever ≥ 38°C for more than 1 hour). Use of granulocyte-colony stimulating factor (G-CSF) is permitted in accordance with institutional standards
- Platelets $< 25 \times 10^9$/L
- Platelets $< 50 \times 10^9$/L with bleeding requiring medical intervention
- Platelets $< 50 \times 10^9$/L (> 3 days)
- Grade 4 anemia (ie, life-threatening consequences; urgent intervention indicated)
- Any Grade 2-3 ophthalmologic AE that does not resolve within 7 days
- Any Grade 4 ophthalmologic AE
- Any Grade 4 laboratory value
- Any Grade 3 laboratory values that are not of clinical significance according to investigator and Sponsor agreement if they do not resolve within 72 hours
- Aspartate aminotransferase/alanine aminotransferase (AST/ALT) ≥ 3× upper limit of normal (ULN) and concurrent total bilirubin ≥ 2× ULN not related to liver involvement with cancer
- Any non-hematological AE Grade 3 or greater (except nausea, vomiting, and diarrhea)
- Grade 3 nausea, vomiting or diarrhea that does not resolve with supportive care in 72 hours
- Grade 4 nausea, vomiting or diarrhea

Algorithm for Dose Escalation Decisions

The following algorithm will be used for dose escalation decisions in Phase 1:

Number of Patients with DLTs	Dose Escalation Decision
0/3	Open next cohort
1/3	Enroll 3 more patients in same cohort
≥ 2/3	Stop enrollment. If Cohort 1, then the study will be stopped.
1/6	Open next cohort
≥ 2/6	Stop enrollment at that level. If at Cohort 1, the study will end. If at Cohort 2 or Cohort 1a, then Cohorts 1a or Cohort 1b will open respectively and 6 patients will be enrolled.

After the 28-day DLT period, mFOLFOX6 or FPA144 may be dose adjusted (held or reduced) based on the toxicity experienced according to Section 5.1.3.4 and Section 5.2.3.1.

Determination of a Recommended Dose for Phase 2

The RD of FPA144 for Phase 2 will be identified by the Cohort Review Committee (CRC) based on an evaluation of all available safety, tolerability, and PK data and will not exceed 15 mg/kg administered IV Q2W with 1 dose of 7.5 mg/kg on Day 8 of Cycle 1 only. Based on the totality of the data, the chosen RD of FPA144 will be a dose that is not anticipated to lead to a decrease in the dose intensity of mFOLFOX6 to be administered. Cohort 1a will not be opened for enrollment unless the Cohort 2 dose level is not tolerated. Identifying a maximum tolerated dose (MTD), therefore is not a requirement of this study and the recommended dose (RD) may be lower than the MTD.

The MTD is defined as the maximum dose at which < 33% of patients experience a DLT during the DLT period. If a DLT is observed in 1 of 3 patients in Cohort 1, then 3 additional patients will be enrolled at that dose level. Dose escalation may continue until 2 of 3 to 6 patients treated at a dose level experience a DLT. The next lower dose will then be considered the MTD.

No additional doses of FPA144 or more than 2 doses of mFOLFOX6 should be administered during the 28-day DLT period. The doses of FPA144 and mFOLFOX6 on Day 1 of Cycle 2 do not need to be synchronized. For example, if mFOLFOX6 is delayed due to an AE that is deemed related only to mFOLFOX6 and not to FPA144, FPA144 should be administered as scheduled for Cycles 1 and 2 regardless of delays in the mFOLFOX6 dosing schedule.

Phase 2

Phase 2 Dose

Based on an assessment of overall safety, tolerability, and PK of FPA144 in combination with mFOLFOX6 by the CRC, the dose of 15 mg/kg Q2W with an additional dose of 7.5 mg/kg on Cycle 1 Day 8 will be used for the Phase 2 portion of the trial.

Global, Randomized, Double-Blind, Controlled Design

Enrollment in Phase 2 will begin when an RD for FPA144 has been identified by the CRC, which will not exceed the highest dose level evaluated and tolerated in Phase 1. Opening the Phase 2 portion of the study for enrollment will be at the discretion of the Sponsor.

The Phase 2 screening period will be up to 28 days; after a maximum 28-day screening period, eligible patients will initiate randomized study treatment.

Phase 2 will include 2 treatment arms:

- Arm 1: FPA144 combined with mFOLFOX6, administered Q2W
- Arm 2: Placebo combined with mFOLFOX6, administered Q2W

In Phase 2, patients must initiate first administration of study treatment within 3 days of enrollment.

Dosing

Administration of Study Treatment

Phase 1 (Open Label, FPA144 + mFOLFOX6)

FPA144 administration is outlined in Section 5.1.2 of the protocol; guidance for dose modification is provided in Section 5.1.3.

FPA144 will be administered over approximately 30 minutes (± 10 minutes) Q2W (± 3 days) on Day 1 of each 2-week cycle. FPA144 will be administered prior to mFOLFOX6 chemotherapy. Patients treated in Cohort 2 (only) will receive 1 additional dose of FPA144 on Day 8 of Cycle 1 (mFOLFOX6 will not be administered on this day).

mFOLFOX6 administration is outlined in Section 5.2 of the protocol; guidance for dose modification is provided in Section 5.2.3.1.

mFOLFOX6 will be administered Q2W beginning on C1D1 and will be administered at least 30 minutes after the end of the infusion of FPA144.

Leucovorin (or levo-leucovorin), 5-FU, and oxaliplatin will be administered in accordance with the relevant local guidelines and summary of product characteristics (SmPCs). For further details, refer to the manufacturer's prescribing information for the respective chemotherapies and the study Pharmacy Manual.

Instructions for mFOLFOX6 administration include the following:

On Day 1 of each cycle (at least 30 minutes after FPA144/placebo):

- Oxaliplatin 85 mg/m^2 IV infusion over 120 minutes

- Leucovorin 400 mg/m^2 IV infusion over 120 minutes, can be administered concurrently with oxaliplatin if using a Y connector, (if not using a Y connector, administer drugs sequentially)
    - If leucovorin is unavailable, 200 mg/m^2 levo-leucovorin may be used. Study treatment may be administered without either agent in the event that both are unavailable. Leucovorin (or levo-leucovorin) may be given at either the protocol-recommended doses or as deemed appropriate by the investigator in accordance with institutional standard of care
- Immediately after oxaliplatin and leucovorin, 5 FU 400 mg/m^2 bolus over approximately 5 minutes
- Immediately after the 5-FU bolus, 5-FU 2400 mg/m^2 as a continuous IV infusion over approximately 48 hours

Premedication for mFOLFOX6 may be used at the discretion of the investigator based on the local standard of care.

Phase 2 (Double-Blind, Randomized, Controlled)

Patients in Phase 2 will be randomized to receive FPA144 + mFOLFOX6 (Arm 1) or placebo + mFOLFOX6 (Arm 2). FPA144 will be prepared and administered as in Phase 1, and the dosing and schedule of FPA144 will be 15 mg/kg Q2W with an additional dose of 7.5 mg/kg on Cycle 1 Day 8 (determined in Phase 1).

mFOLFOX6 will be administered as described for Phase 1: Q2W beginning at least 30 minutes after the end of the infusion of FPA144/placebo. For further details, refer to the manufacturer's prescribing information for the respective chemotherapies and to the study Pharmacy Manual.

Dose Modification, Duration, and Discontinuation

Dose Delays and Modifications

In the event a cycle of mFOLFOX6 is delayed due to chemotherapy-related toxicity during the first 3 cycles of treatment (42 days), FPA144/ placebo should be administered on schedule (± 3 days). After the first 3 cycles, FPA144/placebo may be delayed up to 7 days to be synchronized with administered mFOLFOX6.

Duration of Dosing

There is no protocol-mandated maximum number of doses for FPA144/placebo or mFOLFOX6.

In Phase 1, upon completion of the DLT period (starting with Cycle 3), patients may continue receiving FPA144 in combination with mFOLFOX6. Ongoing administration of the mFOLFOX6 regimen beyond the DLT period will be according to the schedule noted in Section 5.1.2 with any modifications as noted in Section 5.2.3.1.

In both study phases, FPA144 or placebo dosing will continue Q2W until investigator-assessed disease progression, unacceptable toxicity, or until the patient meets any of the other protocol-specified withdrawal criteria (refer to Section 4.5).

Discontinuation

Patients who discontinue all study treatment (all components of FPA144 + mFOLFOX6 and placebo + mFOLFOX6) for any reason other than consent withdrawal will undergo an EOT safety follow-up visit approximately 28 days after the last dose of the last administered component of treatment (oxaliplatin, leucovorin, 5-FU, or FPA144). In addition, patients in Phase 2 will continue to undergo tumor assessments according to the protocol schedule until investigator-assessed disease progression or the initiation of additional anticancer therapy, at which point they will enter a long term follow up (LTFU) period to assess survival.

Discontinuation of any component of the study treatment (mFOLFOX6, a component of mFOLFOX6, or FPA144/placebo) for any reason other than disease progression or any of the other protocol-specified withdrawal criteria does not mandate discontinuation of other components. The exception is the permanent discontinuation of 5-FU for any reason, which requires discontinuation of oxaliplatin and leucovorin.

Study Duration

The duration of study for an individual patient includes Screening (up to 28 days), treatment and an EOT visit approximately 28 days after the last dose. Since all patients are eligible to be treated until disease progression, the actual treatment duration for each individual patient will vary depending on the time to progression.

In addition, patients enrolled in Phase 2 will be followed for subsequent anticancer therapy and survival. LTFU for survival will be performed approximately every 3 months (± 1 month) after the EOT visit until up to 24 months after the last patient is enrolled in the study, or until death, loss to follow up, withdrawal of consent, or study termination by the Sponsor (whichever occurs first).

Number of Patients

The total number of patients planned for enrollment in this study is approximately 167.

- **Phase 1** will enroll approximately 9 to 21 patients depending on incidence of DLTs; this allows for evaluation of safety, PK, and pharmacodynamics at 1 or more dose levels.
- **Phase 2** will enroll approximately 155 patients with FGFR2b overexpression and/or FGFR2 gene amplification. Patients will be randomized 1:1 to receive FPA144 at the RD in combination with mFOLFOX6 versus placebo in combination with mFOLFOX6

Patient Replacements

Phase 1

To be evaluable in Phase 1, patients must have received 2 doses of FPA144 (except for Cohort 2 [must have received 3 doses of FPA144]) and 2 doses of mFOLFOX6 (regardless of cohort). All patients deemed unevaluable must be replaced, unless the reason they didn't receive the required minimum amount of therapy was due to an FPA144-related DLT. The replaced patient may continue on study at the investigator's discretion and after discussion with the Sponsor.

Phase 2

Patients are not replaced. All enrolled patients are deemed evaluable for the endpoint of survival.

Eligibility Criteria

Inclusion Criteria for Phase 1 and Phase 2 (criteria may not be sequentially numbered due to data management convention)

Patients enrolling in either Phase 1 or Phase 2 of the study must meet ***all*** of the following inclusion criteria:

1) Disease that is unresectable, locally advanced, or metastatic (not amenable to curative therapy)
2) Understand and sign an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved ICF prior to any study-specific evaluation
3) Life expectancy of at least 3 months in the opinion of the investigator
4) Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1
5) Age ≥ 18 years at the time the ICF is signed
6) In sexually active patients (women of child bearing potential [WOCBP] and males), willingness to use 2 effective methods of contraception, of which 1 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 include:
    - Permanent sterilization (hysterectomy and/or bilateral oophorectomy, or bilateral tubal ligation with surgery, or vasectomy) at least 6 months prior to screening
    - WOCBP who are 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
7) Adequate hematological and biological function, confirmed by the following laboratory values within 96 hours prior to enrollment:

Bone Marrow Function

- ANC ≥ 1.5 × 10^9/L
- Platelets ≥ 100 × 10^9/L
- Hemoglobin ≥ 9 g/dL

Hepatic Function

- AST and ALT < 3 × ULN; if liver metastases, then < 5 × ULN
- Bilirubin < 1.5 × ULN except in patients with Gilbert's disease

Renal Function

- Calculated creatinine clearance (CrCl) using Cockcroft Gault formula ≥ 50 mL/min *or* estimated glomerular filtrate rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula ≥ 50 mL/min (refer to Appendix 1)

8) International normalized ratio (INR), or prothrombin time (PT) < 1.5 × the ULN except for patients receiving anticoagulation therapy who must be on a stable dose of warfarin for 6 weeks prior to enrollment

9) Measurable or non-measurable, but evaluable disease using RECIST v1.1

Additional Inclusion Criteria for Phase 1 Only

Patients enrolling in **Phase 1** of the study must also meet the following inclusion criteria:

10) Histologically or cytologically confirmed GI malignancy for which mFOLFOX6 is considered an appropriate treatment (eg, GC, colorectal carcinoma, pancreatic adenocarcinoma)

11) Patient must be a candidate to receive at least 2 doses of mFOLFOX6 chemotherapy

Additional Inclusion Criteria for Phase 2 Only

Patients enrolling in **Phase 2** of the study must also meet the following inclusion criteria:

14) Histologically documented gastric or gastroesophageal junction adenocarcinoma (not amenable to curative therapy)

15) Radiographic imaging of the chest, abdomen and pelvis (computed tomography [CT] preferred, magnetic resonance imaging [MRI] acceptable) performed within 28 days (+3 days) of treatment (C1D1)

16) FGFR2b overexpression as determined by a centrally performed IHC tissue test and/or *FGFR2* gene amplification as determined by a centrally performed ctDNA blood-based assay

17) Patient must be a candidate for mFOLFOX6 chemotherapy

18) No prior chemotherapy for metastatic or unresectable disease (except a maximum of 1 dose of mFOLFOX6 administered while waiting for results of FGFR2 testing during the pre-screening period)

19) If prior adjuvant or neo-adjuvant therapy (chemotherapy and/or chemoradiation) has been received, more than 6 months must have elapsed between the end of adjuvant therapy and the confirmation of radiographic disease progression

Exclusion Criteria for Phase 1 and Phase 2

Patients enrolling in either Phase 1 or Phase 2 will be excluded if *any* of the following criteria apply:

1) Untreated or symptomatic central nervous system (CNS) metastases (CNS imaging not required). 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 any of the following (Criteria a through g):

   a) Unstable angina pectoris ≤ 6 months prior to enrollment

   b) Acute myocardial infarction ≤ 6 months prior to enrollment

   c) New York Heart Association class II-IV congestive heart failure

   d) Uncontrolled hypertension (as defined as ≥ 160/90 despite optimal medical management)

   e) Uncontrolled cardiac arrhythmias requiring anti-arrhythmic therapy other than beta blockers or digoxin

   f) Active coronary artery disease

   g) Fridericia's correction formula (QTcF) ≥ 480

3) Peripheral sensory neuropathy ≥ Common Terminology Criteria for Adverse Events (CTCAE) Grade 2

4) Active infection requiring systemic treatment or any uncontrolled infection ≤ 14 days prior to enrollment

5) Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness, or known active or chronic hepatitis B or C infection

6) History of interstitial lung disease (eg, pneumonitis or pulmonary fibrosis)

7) Evidence or history of bleeding diathesis or coagulopathy

8) Radiotherapy ≤ 28 days of enrollment. Patients must be recovered from all acute radiotherapy-related toxicities. No radiopharmaceuticals (strontium, samarium) within 8 weeks of enrollment
9) Prior treatment with any selective inhibitor (eg, AZD4547, BGJ398, JNJ-42756493, BAY1179470) of the FGF-FGFR pathway
10) Ongoing adverse effects from prior systemic treatment > NCI CTCAE Grade 1 (with the exception of Grade 2 alopecia and anemia)
11) Participation in another therapeutic clinical study or receiving any investigational agent within 28 days of enrollment or during this clinical study
12) Corneal defects, corneal ulcerations, keratitis, keratoconus, history of corneal transplant, or other known abnormalities of the cornea that may pose an increased risk of developing a corneal ulcer
13) Known positivity for human epidermal growth factor receptor 2 (HER2) (as defined by a positive IHC test of 3+ or IHC of 2+ with positive FISH)
14) Major surgical procedures not permitted ≤ 28 days prior to enrollment. Surgery requiring local/epidural anesthesia must be completed at least 72 hours before enrollment. In all cases, the patient must be sufficiently recovered and stable before treatment administration.
15) Women who are pregnant or breastfeeding (unless the patient is willing to interrupt breastfeeding during study treatment administration and then resume 6 months after study discontinuation); WOCBP must not consider getting pregnant during the study
16) 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 arterial thrombosis, and symptomatic pulmonary embolism)
17) 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 in the study
18) Known allergy, hypersensitivity or contraindication to components of the FPA144 formulation including polysorbate or to platinum-containing medications, 5-FU, or leucovorin
19) History of prior malignancy, except (Criteria a through f):
    a) Curatively treated non-melanoma skin malignancy
    b) Cervical cancer *in situ*

c) Curatively treated Stage I uterine cancer

d) Curatively treated ductal or lobular breast carcinoma in situ and not currently receiving any systemic therapy

e) Localized prostate cancer that has been treated surgically with curative intent and presumed cured

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

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

Pharmacokinetic Assessments: Blood samples will be collected to measure serum levels of FPA144 at the time points outlined in Appendix 6 for Phase 1. Blood samples will be collected to measure levels of FPA144 at the time points outlined in Appendix 7 for Phase 2. PK parameters will be estimated using non-compartmental analysis, though compartmental analysis may be employed if appropriate. Serum concentration-time data from FPA144-004 will be pooled with data from other studies for integrated population PK analysis and exposure-response relationship assessment.

Immunogenicity Assessments: For all enrolled patients in Phase 1 and Phase 2, blood samples will be collected for anti-FPA144 antibodies at the time points specified in Appendix 6 and Appendix 7, respectively.

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 determination of the antidrug antibody (ADA) concentration. Additional characterization of a confirmed anti-FPA144 antibody response will be conducted.

Efficacy Assessments: During Phase 2, tumor response assessment will be performed by the investigator per RECIST v1.1 guidelines. All radiology images will be analyzed by the investigator and this assessment will be used in the determination of progression.

Efficacy measures will include tumor assessments consisting of clinical examination and appropriate imaging techniques, preferably CT scans of the chest, abdomen, and pelvis with appropriate slice thickness per RECIST v1.1 guidelines. Alternatively, MRI is also acceptable at the discretion of the investigator. Scans will be done during the screening window (within 28 +3 days of C1D1). A scan performed prior to Screening as part of standard of care, performed no greater than 28 days (+3 days) prior to treatment (C1D1) is acceptable. Scans will be performed every 8 weeks (± 7 days) from C1D1 until 12 months from C1D1 and then every 12 weeks (± 14 days) thereafter.

Safety Assessments:

Safety measures will include AEs, hematology, clinical chemistry, urinalysis, vital signs, body weight, concomitant medications/procedures, ECOG performance status, targeted physical examinations, ECGs, and ophthalmology examinations in both Phase 1 and Phase 2. Safety measures will also include evaluation for DLTs in Phase 1 only.

In Phase 2, an independent Data Monitoring Committee (DMC) will evaluate safety including AEs and serious adverse events (SAEs) on a regular basis throughout the treatment phase.

Pharmaco-dynamic Assessments:

Phase 1

Tumor tissue provided for evaluation of FGFR2 status, if available, will be retrospectively analysed for FGFR2b overexpression using IHC.

Blood samples provided for evaluation of FGFR2 status will be collected prior to the first dose of study treatment and analysed retrospectively for *FGFR2* gene amplification using a ctDNA blood assay.

[redacted] will be collected longitudinally according to Appendix 5.

No pharmacodynamic assessments will be performed during Phase 2.

Statistical Procedures:

Power and Sample Size

This Phase 2 study is designed to assess the hazard ratio (HR) of PFS for FPA144 + mFOLFOX6 compared with placebo + mFOLFOX6. It is planned to observe 84 PFS events in order to achieve 71% power to detect an HR of 0.67 for PFS, at the 1-sided alpha of 0.1. Assuming an exponential distribution, this corresponds approximately to an 50% increase in median PFS (e.g. from 5 months to 7.5 months). Statistical significance (at 1-sided alpha of 0.1) for PFS will occur with an observed HR=0.756, corresponding approximately to a 32.3% increase in observed median PFS (e.g. from 5 months to 6.6 months).

One hundred fifty-five patients have been randomized (1:1) during 13 months of accrual. It is projected to observe 84 PFS events with approximately 11 additional months of follow-up.

There is no planned interim analysis for this study.***Statistical Methods***

In Phase 1, all analyses will be descriptive and will be presented by dose cohort and cumulative as appropriate. Descriptive statistics will include number of observations, mean, standard deviation, median, range, and inter-quartile range for continuous variables, and the number and percent for categorical variables; 95% confidence intervals (CIs) will be presented where appropriate. Additionally, incidence of treatment-emergent adverse

events (TEAEs) leading to dosing reductions or dose discontinuation will be tabulated and summarized.

In Phase 2, efficacy and tolerability will be evaluated and presented by treatment arm (Arm 1, FPA144 + mFOLFOX6; Arm 2, placebo + mFOLFOX6).

Eligible patients will be stratified by:

- Geographic region
- Prior treatment status (*de novo* versus adjuvant/neo-adjuvant)
- Administration of a single dose of mFOLFOX6 prior to enrollment (yes or no)

In Phase 2, the primary efficacy analysis is the comparison of PFS between the treatment arms. The primary endpoint, PFS, is defined as time from randomization until the date of radiological disease progression based on investigator assessment (using Response Evaluation Criteria in Solid Tumors version 1.1 [RECIST v1.1]) or death from any cause, whichever comes first. The secondary efficacy endpoints include OS and ORR.

The analysis of PFS will be performed using the intent-to-treat (ITT) population and will be conducted using a stratified log-rank test. The stratification factors will be the same used to stratify the randomization schedule as documented in the interactive voice and web response system (IXRS).

The median PFS and the associated 95% CI for each treatment arm will be estimated using the Kaplan-Meier method. The hazard ratio (HR= $\lambda_{FPA144+mFOLFOX6}/ \lambda_{placebo+mFOLFOX6}$) will be estimated using a Cox regression model with treatment group as the only main effect and stratifying by the same stratification factors as were used for the stratified log-rank test. An unstratified HR will also be presented.

Analyses of secondary endpoints OS and ORR will be conducted hierarchically. The formal hypotheses regarding effects on OS and ORR will be tested hierarchically at a one-sided level of 0.1. The OS will be tested first and if it is significant, the ORR will be tested next. The family-wise type I error rate of testing primary and secondary endpoints will be in a control by employing this gate-keeping testing procedure at a one-sided level of 0.1.

Overall survival will be analyzed in a similar manner as for PFS.

The analysis of ORR will be performed based on the ITT population. In the analysis of ORR, patients without postbaseline adequate tumor assessments will be counted as non-responders. Formal hypothesis testing of ORR will be performed using the stratified Cochran-Mantel-Haenszel test at a one-sided level of 0.1. The stratification factors will be the same used to stratify the randomization schedule as documented in the IXRS.

Safety Analysis

All AEs will be coded using the Medical Dictionary for Regulatory Activities Version 20.1 (MedDRA v 20.1). The investigator will classify the severity of AEs using the CTCAE v 4.03 in Phase 1 and v 5.0 in Phase 2. A TEAE is defined as any event with an onset date on or after date of first dose of study treatment, or any event present before treatment that worsens after treatment.

Clinical laboratory data will be summarized by the type of laboratory test. The number and percentage of patients who experience abnormal (ie, outside of reference ranges) and/or clinically significant abnormal laboratories after study treatment administration will be presented for each clinical laboratory measurement. For each clinical laboratory measurement, descriptive statistics will be provided for baseline and all subsequent posttreatment scheduled visits. Changes from baseline to the posttreatment visits will also be provided. Descriptive statistics of vital signs will also be provided in a similar manner. In addition, shift from baseline in CTCAE grade (where applicable) and by high/low flags (where CTCAE grades are not defined) will be presented in a similar manner.

Safety Analyses in Phase 1

Safety analyses will be performed for patients included in the safety population. The incidence of DLTs, incidence of TEAEs, clinical laboratory abnormalities (eg, shift table), vital signs, corneal and retinal findings, and ECGs will be tabulated and summarized by dose level. Additionally, incidence of TEAEs leading to dosing reduction or dose discontinuation of FPA144 or any component of mFOLFOX6 will be tabulated and summarized.

Safety Analyses in Phase 2

The analyses of safety will include all patients who receive any study treatment (FPA144 + mFOLFOX6 or placebo + mFOLFOX6) throughout the study and will provide posttreatment safety information. The incidence of TEAEs, clinical laboratory abnormalities, vital signs, corneal and retinal findings, and ECGs will be tabulated and summarized by treatment group.

No formal comparisons of safety endpoints are planned.

PK Analysis and Immunogenicity

Individual and mean (± SD) serum FPA144 concentration-time data will be tabulated and plotted by dose level. PK parameters will be tabulated and summarized by dose level when appropriate and applicable. The impact of immunogenicity on FPA144 exposure will be assessed, tabulated, and summarized by dose level as data allow. Integrated population PK analysis and exposure-response relationship assessment will be presented in a separate report.

List of Key Study Personnel

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List of Abbreviations and Definitions

Abbreviation	Definition
ADCC	antibody-dependent cell-mediated cytotoxicity
ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
AIDS	acquired immunodeficiency syndrome
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under serum concentration-time curve
AUC_{τ}	AUC over the dose interval τ
β-hCG	β-human chorionic gonadotropin
BP	blood pressure
C1D1	Cycle 1 Day 1
CDC	complement-dependent cytotoxicity
CFR	Code of Federal Regulations
CHO	Chinese hamster ovary
CI	confidence interval
CL	total clearance
C_{max}	maximum observed serum concentration
CNS	central nervous system
CRC	Cohort Review Committee
CrCl	creatinine clearance
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report forms
ELISA	enzyme linked immunosorbent assay
EORTC	European Organization for Research and Treatment of Cancer

Abbreviation	Definition
EOS	end of study
EOT	end of treatment
EQ-5D-5L	EuroQOL-5D-5L
EU	European Union
5-FU	5-fluorouracil
FDA	Food and Drug Administration
FGF	fibroblast growth factor
FGFR	fibroblast growth factor receptor
FISH	fluorescent in situ hybridization
FP	5-FU/cisplatin
FRS2	FGF receptor substrate-2
GC	gastric or gastroesophageal cancer
GCP	Good Clinical Practices
G-CSF	granulocyte-colony stimulating factor
GEJ	gastroesophageal junction
GI	gastrointestinal
GLP	GLP Good Laboratory Practices
HER2	human epidermal growth factor receptor 2 also known as ERBB2
hFc-G1	Fc fragment of human IgG1
HIV	human immunodeficiency virus
HNSTD	highest, non-severely toxic dose
HR	hazard ratio
HR	heart rate
HR	hazard ratio
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IgG1	humanized monoclonal antibody
IHC	immunohistochemistry
IND	investigational new drug (application)
INR	international normalized ratio
IOP	intra-ocular pressure
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous
IXRS	interactive voice and Web response system

Abbreviation	Definition
LTFU	long term follow up
MedDRA	Medical Dictionary for Regulatory Activities
mFOLFOX6	modified FOLFOX (infusional 5-FU, leucovorin, and oxaliplatin)
mOS	median OS
mPFS	median progression free survival
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCBI	National Center for Biotechnology Information
NCI	National Cancer Institute
NK	natural killer
OCT	ocular coherence tomography
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell(s)
PFS	progression-free survival
PK	pharmacokinetic(s)
PRO	patient reported outcomes
Q2W	once every 2 weeks
QLQ	quality of life questionnaire
QLQ-C30	Quality of Life Questionnaire Version 3.0
QOL	quality of life
QTcF	Fridericia's correction formula
RD	recommended dose
RECIST	Response Evaluation Criteria in Solid Tumors
ROW	Rest of World
RPE	retinal pigment epithelium
RR	respiratory rate
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SEM	standard error of the mean
SmPCs	summaries of product characteristics
$t_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
ULN	upper limit of normal
US	United States

Abbreviation	Definition
VAS	visual analogue scale
VEGF	vascular endothelial growth factor
WOCBP	women of childbearing potential

1.0 INTRODUCTION

1.1 General Gastric Cancer

Gastric or gastroesophageal cancer (GC), including gastroesophageal junction (GEJ) cancer, represents the fourth most common cancer worldwide (Kamangar 2006) and is a highly lethal disease, with 5-year overall survival (OS) rates below 30% in the United States (US) regardless of stage (National Cancer Institute 2015). Though intensive multimodal therapy for locoregional disease improves survival (The GASTRIC Group 2010, Waddell 2014) it does not cure most patients and chemotherapy for metastatic disease provides only short-term benefits (Wagner 2006, Waddell 2014). First-line chemotherapy used in patients with metastatic or recurrent disease consists of a fluoropyrimidine (5-fluorouracil [5-FU] or capecitabine) with a platinum agent (usually oxaliplatin or cisplatin) (Al-Batran 2008, Kang 2009). This treatment prolongs survival by 6 months compared to best supportive care (Wagner 2006), but the benefits are only short-term with a median OS (mOS) of 9 to 10 months and a progression-free survival (PFS) of 5 to 5.6 months (Kang 2009, Waddell 2014).

1.2 Targeted Agents

It is important to identify new treatments with acceptable toxicities for this patient population. Recent studies have identified important pathways involved in GC development. The availability of targeted agents has led to the development of strategies incorporating these agents in the therapy for patients with such a poor prognosis. Recently ramucirumab (a monoclonal antibody targeting the vascular endothelial growth factor [VEGF] pathway) was approved for treatment in patients with GC who progressed following first line treatment (Wilke 2014). OS for patients treated with ramucirumab with paclitaxel was 9.6 months compared to 7.4 months with paclitaxel and placebo.

One well established pathway is the human epithelial growth factor receptor 2 (HER-2 also known as ERBB2) (Gravalos 2008, Hofmann 2008). HER-2 overexpression has been identified in 9 to 38% of GCs depending on histology and tumor location (Gravalos 2008). The availability of trastuzumab, a monoclonal antibody targeting HER-2, led to the development of a randomized trial in newly diagnosed GC patients whose tumors overexpressed HER-2. About 22% of screened patients were HER-2 positive and the combination of standard chemotherapy with trastuzumab resulted in a median OS of 13.8 months compared to 11.1 months for patients treated with standard chemotherapy (Bang 2010). Based on these results, this has become standard care for patients overexpressing HER-2.

In spite of these improvements, the majority of GC patients succumb to their disease, and there are few treatment options following progression after first-line chemotherapy. Recently anti-PD1 therapies have been approved for treatment of later line GC in Japan and the United States. In September 2017, Japanese Ministry of Health, Labor and Welfare approved the PD1 inhibitor nivolumab (Opdivo®) for the treatment of unresectable advanced or recurrent gastric cancer which has progressed after chemotherapy. This approval was based on the Phase 3 study

ATTRACTION-2 (ONO-4538-12), in which Opdivo® significantly reduced patients' risk of death by 37% (HR 0.63 [95% CI: 0.51-0.78, p<0.0001]) when compared to placebo (Kang 2017). Additionally, in September 2017, the United States Food and Drug Administration (FDA) granted accelerated approval to pembrolizumab (KEYTRUDA®) (Fuchs 2017) for patients with recurrent locally advanced or metastatic, gastric or gastroesophageal junction adenocarcinoma whose tumors express PD-L1. Patients must have had disease progression on or after 2 or more prior systemic therapies, including fluoropyrimidine- and platinum-containing chemotherapy and, if appropriate, HER2/neu-targeted therapy. Pembrolizumab approval was based on data from 143 patients with tumors expressing PD-L1 and who were either microsatellite stable (MSS) or had unknown microsatellite instable (MSI) or mismatch repair deficient (dMMR) status, who demonstrated an objective response rate (ORR) of 13.3% (95% CI: 8.2, 20.0) and a duration of response (DOR) ranging from 2.8+ to 19.4+ months. The majority of patients, however, do not respond to anti-PD1 therapy and other late line therapies such as ramucirumab with or without paclitaxel, and irinotecan improve the mPFS by less than 2 months (Thuss-Patience 2011, Ford 2014, Fuchs 2014). Therefore, continued evaluation of agents that can target the mutations present in GC is imperative.

Amplification of fibroblast growth factor receptor 2 (FGFR2) has recently been identified as having prognostic importance in patients with GC (Jung 2012, Matsumoto 2012, Su 2014, Seo 2016). Patients with *FGFR2* gene amplification appear to have a worse prognosis (Su 2014, Seo 2016), suggesting that inhibition of FGFR2 may be an important target (Jung 2012, Matsumoto 2012). FPA144 is a humanized monoclonal antibody specific to the human FGFR2b receptor that blocks fibroblast growth factor (FGF) binding to the receptor. Evaluation of this agent in patients with GC whose tumors have alterations of FGFR2 would be an important strategy to improve the prognosis for these patients.

1.3 FPA144

1.3.1 Background

The role of the 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. FGF 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 2 splicing variants, b and c. In general, FGFR2b is expressed in tissues of epithelial origin (eg, stomach, skin) (Miki 1992). The major ligands signaling through FGFR2b are FGF7, FGF10 and FGF22. Alteration in signaling in the FGF/FGFR2 pathway (eg, overexpression of FGFR2 protein or amplification of *FGFR2* gene) has been associated with gastric, breast, and other cancers, and appears to portend a worse prognosis (Turner 2010, Wu 2013). As early as 1990, subsets of patients with GC (approximately 3 to 9%) and breast cancer (1 to 2%) were noted to have amplification of the *FGFR2* gene, which resides on

chromosome 10q26 (Hattori 1990, Turner 2010). In GC, *FGFR2* gene amplification leads to high-level expression of the FGFR2b receptor on the surface of the cells.

1.3.2 FPA144, an Fibroblast Growth Factor Receptor 2-Specific Antibody

FPA144 is a humanized monoclonal antibody (IgG1 isotype) specific to the human FGFR2b receptor (National Cancer Institute 2015) that blocks FGF ligand binding to the receptor. FPA144 is directed against the third Ig region of the FGFR2b receptor isoform, the region that is alternatively spliced and regulates ligand specificity. This antibody is glycosylated but is produced in a Chinese hamster ovary (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). The antibody has thus been glycoengineered for enhanced antibody-dependent cell-mediated cytotoxicity (ADCC) (Gemo 2014). 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. The 3 potential mechanisms of action of FPA144 thus include blocking ligand binding and downstream signaling, decreasing expression of the FGFR2b driver protein, and enhancing ADCC.

FPA144 can produce complete and durable tumor growth inhibition in FGFR2b-overexpressing and *FGFR2* gene-amplified GC xenografts in immune-compromised mice where FGFR2b is considered a driver of tumor growth (Gemo 2014). In addition, FPA144 demonstrates recruitment of natural killer (NK) cells and concomitant tumor growth inhibition in the 4T1 syngeneic tumor model with modest expression of FGFR2b (Powers 2016). These data suggest that ADCC may be efficacious in patients without *FGFR2* gene amplification with moderate FGFR2b overexpression, and that ADCC activity may be a major contributor to the mechanism of action in these patients.

Additionally, since FPA144 is specific for the FGFR2b receptor, it does not interfere with signaling of the other FGFs/ FGFRs, including FGFR2c. In contrast to the FGFR tyrosine kinase inhibitors (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 the dose-limiting hyperphosphatemia associated with the FGFR TKIs (Brown 2005, Andre 2013, Dienstmann 2014, Sequist 2014).

As FPA144 is a targeted biologic, the clinical development of FPA144 will ultimately be in selected patients with alterations in the FGFR2 pathway that are most likely to respond to this novel agent. The tumor types most relevant to date include gastric, bladder, and possibly cholangiocarcinoma. Each of these cancers needs new therapeutic options. The FPA144-004 study is designed to evaluate the efficacy, safety, and PK of FPA144 in combination with modified FOLFOX (infusional 5-FU, leucovorin, and oxaliplatin) (mFOLFOX6) chemotherapy

treatment. Patients with gastrointestinal (GI) tumors will be enrolled in a Phase 1 safety run in, while the Phase 2 will enroll GC patients specifically selected for FGFR2 expression and/or *FGFR2* gene amplification (FGFR2 selected) who are eligible for first-line mFOLFOX6 chemotherapy.

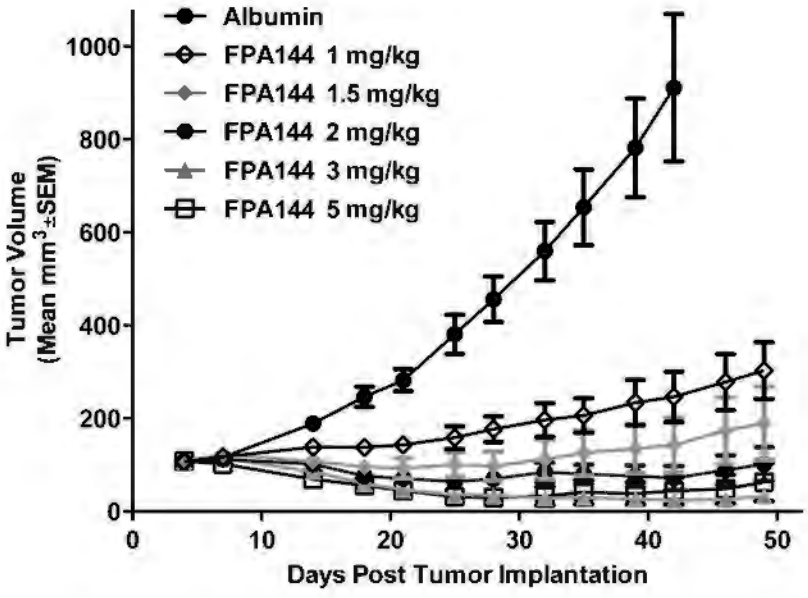
1.3.3 Nonclinical Studies with FPA144

The 3 mechanisms of action of FPA144 described above have been explored both in vitro and in vivo.

1.3.3.1 In Vivo Pharmacology

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 GC 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 GC 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.

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



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 FGFR2 overexpressing tumors, ADCC may further contribute to antitumor activity in the clinical setting. To understand the contribution of Fc receptor engagement and ADCC on FPA144 antitumor efficacy, a mutant antibody was engineered that cannot bind Fc receptors, thereby rendering it incapable of promoting ADCC. The syngeneic 4T1 model of breast cancer was employed in immune competent mice that express 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 mm^3, sorted into groups of equivalent tumor volume, then treated bi-weekly with FPA144, the ADCC-deficient FGFR2b antibody, or the Fc fragment of human IgG1 (hFc-G1) as control. FPA144 decreased tumor burden by 30% versus hFc-G1 control (p=0.001) while the mutant antibody showed no effect. 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.

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 GC 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 GC 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.

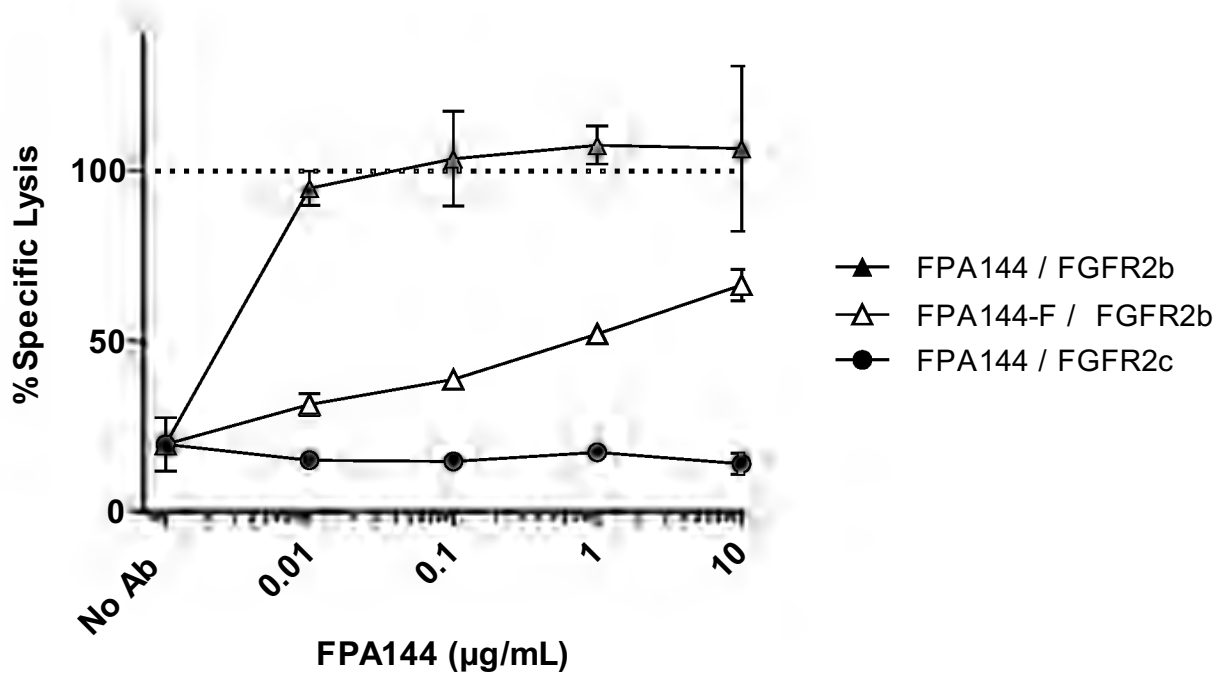
1.3.3.2 Analysis of Immune Effector Functions of FPA144

Some therapeutic antibodies containing IgG1 Fc are capable of recruiting immune effector function, specifically ADCC and complement-dependent cellular toxicity. Once antibodies of the IgG1 isotype bind to their target on tumor cells, immune cells which express the Fc gamma receptor IIIa (FcγRIIIa), especially NK cells and macrophages, are recruited to the tumor cells and promote cell death in a process known as ADCC. FPA144 is specifically engineered for enhanced ADCC. This antibody lacks a core fucose in the polysaccharide portion of the antibody, and the lack of fucose results in higher affinity of FPA144 for FcγRIIIa compared to

the fucosylated molecule and potentially enhanced immune cell mediated tumor cell killing. In some in vitro studies, including ADCC assays, and in vivo studies, including toxicology studies, the fucosylated form of FPA144 (FPA144-F) was compared to the afucosylated form (FPA144).

FPA144 was compared to FPA144-F for in vitro ADCC activity. The target cell in the assay was an engineered cell line that expresses the full-length human FGFR2b described as Ba/F3 FGFR2b, and the effector cells were peripheral blood mononuclear cells (PBMCs) obtained fresh from individual human donors. As a negative control, FPA144 was also tested using a target cell line that was engineered to express the FGFR2c variant of the receptor (Ba/F3 FGFR2c cells), to which FPA144 does not bind. The data are shown in Figure 2. FPA144 and FPA144-F both showed ADCC activity, but the degree to which FPA144 killed the target cells was substantially greater than what was measured for FPA144-F. As expected, FPA144 showed no ADCC activity in the negative control.

Figure 2: *In Vitro* ADCC Activity of FPA144



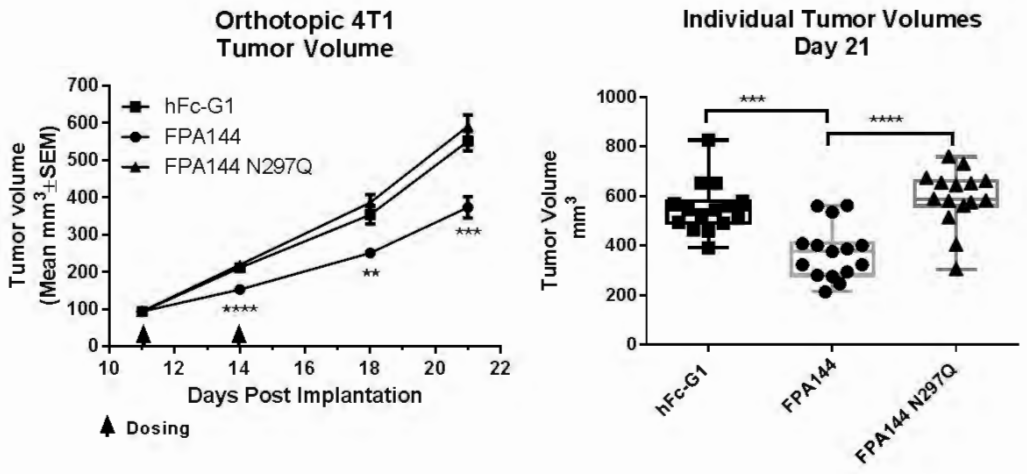
Abbreviations: ADCC = antibody-dependent cell-mediated cytotoxicity; FGFR = fibroblast growth factor receptor; No Ab = no antibody.

The ability of FPA144 to mediate complement-dependent cytotoxicity (CDC) of 4 gastric cell lines with high FGFR2b was tested using previously published methods (Li 2009, Zhao 2010). No CDC was observed under any conditions tested, although positive controls (rituximab tested with RAMOS and RAJI cells) did induce CDC (these data not shown).

1.3.3.2.1 In vivo Antibody-Dependent Cell-Mediated Cytotoxicity Activity of FPA144

To understand the contribution of ADCC on FPA144 antitumor 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 hFc-IgG1 as control. FPA144 decreased tumor burden versus hFc-IgG1 control while FPA144 N297Q showed no effect (Figure 3). 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 3: FPA144, but not an ADCC-Deficient FGFR2b Antibody Leads to Tumor Suppression in a Syngeneic Tumor Model with Modest FGFR2b Expression



1.3.3.3 FPA144 Exposure Efficacy Relationships

To translate the efficacy results in animal models to cancer patients, 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 to 109 µg/mL.

1.3.4 Toxicology

Toxicology studies with FPA144 have been performed in rat and cynomolgus monkey. The studies performed have included pilot single dose PK/tolerability and repeat-dose studies as well as Good Laboratory Practices (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 pigment epithelium (RPE) in rat were noted that included RPE atrophy in 1 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 maximum observed serum concentration (C_{max}) and area under serum concentration-time curve (AUC) over the dose interval τ (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 (eg, 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 3,266 µg/mL and 252,787 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.

Additional details of the nonclinical program for FPA144 are provided in the Investigator's Brochure (IB), which contains comprehensive information on the investigational product.

1.3.5 Clinical Experience with FPA144

Please refer to the bemarituzumab Investigator's Brochure for updated results of the clinical experience with FPA144.

FPA144 underwent evaluation in 2 Phase 1 dose escalation studies. The first Phase 1, first-in-human study, FPA144-001, entitled "A Phase 1 Open-Label, Dose-Finding Study Evaluating Safety and Pharmacokinetics of FPA144 in Patients with Advanced Solid Tumors" started in December 2014 and was conducted in the US, South Korea, and Taiwan. This open-label study assessed the safety, pharmacokinetics (PK), and preliminary efficacy of FPA144 monotherapy in patients with solid tumors. The study was comprised of 3 parts: a dose escalation portion in unselected solid tumor patients (Part 1A), a dose escalation portion in GC patients (Part 1B), and a dose expansion portion for patients with FGFR2b-selected tumors including FGFR2b-selected GC, and FGFR2b-selected bladder cancer (Part 2).

Two parallel dose escalations were performed: Part 1A enrolled patients with solid tumors (19 patients), and Part 1B enrolled patients with GC (8 patients) to evaluate early evidence of efficacy and PKs to support the RD for the dose expansion cohort. FPA144 was well tolerated in doses up to 15 mg/kg administered every 2 weeks (Q2W) in patients with advanced solid tumors. There were no dose-limiting toxicities (DLTs) observed during dose-escalation and a maximum

tolerated dose (MTD) was not reached. Based on an assessment of safety, tolerability, and PK, an RD of 15 mg/kg administered Q2W was selected.

As of 20 March 2017, a total of 64 patients across the dose escalation (Parts 1A and 1B: 27 patients) and the dose expansion (Part 2: 37 patients) enrolled in the study and 60 received at least 1 dose of FPA144. Of these 64 patients, 41 patients had GC and 21 of those were identified as having GC with strong FGFR2b overexpression (or FGFR2b$^+$ high, defined as IHC 3+ intensity in ≥ 10% of tumor cells). Of those 21 patients, 6 patients were enrolled in the Part 1B dose escalation and 15 patients in the Part 2 dose expansion (Cohort A). In addition, 4 GC patients with low FGFR2b overexpression (or FGFR2b$^+$ low, defined as IHC 2+ intensity in < 10% of tumor cells or any immunohistochemistry (IHC) 1+ staining) have been enrolled in Cohort E and 10 GC patients (IHC 0–2) have been enrolled in Cohort C in Part 2 (dose expansion).

Safety and tolerability of FPA144 is supported by a total of 64 patients from the Phase 1 study (FPA144-001) who have received at least 1 dose of FPA144.

Safety data from 64 patients enrolled in FPA144-001 including 37 patients treated at 15 mg/kg administered Q2W (expansion dose) are described here. Adverse events (AEs) have been reported in 58 of 64 patients (90.6%). Thirty-two of the 64 patients reported an AE that was deemed by the investigator to be drug related. Of the drug-related AEs, none were Grade 4 or 5. There were 6 Grade 3 events: an infusion reaction in 1 patient, an aspartate aminotransferase (AST) elevation and alkaline phosphatase increase in 1 patient, nausea in 2 patients and a transient decrease in neutrophil count (which resolved without dose interruption or modification) in 1 patient. Three patients discontinued treatment due to an AE. One for E. coli sepsis, a second for cancer pain, both considered unrelated to study treatment and a third patient (post data cut) with limbic stem cell deficiency after approximately 14 months of therapy, considered related to study treatment also discontinued treatment. All other patients discontinued treatment as a result of disease progression. Treatment-related serious adverse events (SAEs) were reported in 3 patients: 1 patient (15 mg/kg) with the Grade 3 infusion reaction, 1 patient (15 mg/kg) with the Grade 2 corneal ulcer, and 1 patient (10 mg/kg) with the Grade 2 limbic stem cell deficiency (post data cut). In all 3 patients with treatment-related SAEs, the events resolved. The patient with the infusion reaction resumed drug administration after premedication and a reduced dose. The patient with the Grade 2 corneal ulcer temporarily interrupted FPA144 and received ophthalmic drugs with resolution of the event. The patient with the Grade 2 limbic stem cell deficiency discontinued study treatment and her symptoms and signs resolved after approximately 3 months.

Additional development of FPA144 for the treatment of GC includes an ex-US, non-US investigational new drug (IND) study, FPA144-002, entitled “A Phase 1 Open-Label, Dose-Finding Study of FPA144 in Japanese Patients with Advanced Gastric or Gastroesophageal Cancer.” This dose escalation study was designed to assess the PK and safety of single agent

FPA144 and identified the RD for single agent FPA144 in Japanese patients. No DLTs were reported in the FPA144-004 study.

Please reference the bemarituzumab investigator's brochure for an updated review of the ocular events that have occurred in clinical studies with FPA144. As discussed in Section 1.3.4, preclinical animal toxicity studies support a need for comprehensive ophthalmologic examinations. The comprehensive ophthalmologic examinations in the Phase 1 study (FPA144-001) includedd fundoscopic and slit lamp examination, ocular coherence tomography (OCT), visual acuity, and review of ocular and visual symptoms at screening, prior to the third dose, and at the end of treatment (EOT) visit. Slit lamp examinations (with completion of fluorescein staining score form), were conducted at regular intervals for all patients.

Twenty-three of 79 (29%) patients treated with FPA144 monotherapy in study FPA144-001 reported ocular adverse events. The most common ocular events ($\geq$ 5%) were dry eye (14 patients [18%]) and increased lacrimation (5 patients [6%]). Among these patients, 3 events, a Grade 2 ulcerative keratitis, a Grade 2 limbic stem cell deficiency, and a Grade 2 corneal dystrophy, required treatment and follow-up from an ophthalmologist.

In the phase 1 part of study FPA144-004, two events of punctate keratitis and one each of corneal abrasion, corneal disorder and limbal stem cell deficiency were reported. As of October 29, 2019, 18 of 134 (13%) patients treated in the phase 2 part of the FPA144-004 study had reported ocular adverse events involving the cornea or retina. Eight patients experienced keratitis (grade 1 (1); grade 2 (5), grade 3 (2)), three patients experienced punctate keratitis (grade 1; grade 2; grade 3 (1 each)), two experienced limbal stem cell deficiency (grade 3), two patients experienced retinal hemorrhage (grade 1), two patients experienced ulcerative keratitis (grade 2 (1); grade 3 (1)),one patient each experienced corneal erosion (grade 1), corneal infiltrate (grade 1) and xerophthalmia (grade 2). The retinal hemorrhages were asymptomatic incidental findings during comprehensive ophthalmologic evaluation and did not preclude ongoing treatment with FPA144/placebo. The study drug/placebo was withdrawn in eight patients (2 patients with keratitis, 1 patient each with corneal infiltrates, corneal ulcer, eye disorder, dry eye, ulcerative keratitis, xerophthalmia) and was delayed in four patients (2 cases of keratitis, and one patient each with superficial punctate lentitis both eyes and punctate epithelial erosion).

Evidence of early efficacy in the FGFR2b^{+} high gastric and GEJ cancer patient population is supported by a confirmed response rate (using Response Evaluation Criteria in Solid Tumors version 1.1 [RECIST v1.1]) of 19.0% [5.4-41.9%]) in 21 patients in the target patient population with a duration of response (DOR) of 15.4 weeks (95% confidence interval [CI] 9.1, 19.1 weeks) and a median PFS of 11 weeks (95% CI 5.7, 20.6 weeks).

FPA144 serum concentration was measured by a validated enzyme linked immunosorbent assay (ELISA) (refer to the FPA144 IB). FPA144 demonstrated nonlinear clearance (CL) from 0.3 mg/kg to 1 mg/kg and close to linear CL from 1 mg/kg to 15 mg/kg in patients with solid

tumors including GCs tested in Parts 1A and 1B, suggesting target-mediated CL. The estimated half-life ($t_{1/2}$) ranged from 6.01 to 11.7 days across cohorts, which supports every 2-week dosing. As derived from the mouse efficacy study using the OCUM2 *FGFR2*-amplified GC xenograft model, 60 µg/ml was selected as target trough serum concentration at steady state ($C_{trough\ ss}$). Based on the PK data in combination with safety data and evidence of efficacious activity from Part 1 of the clinical study, the 15 mg/kg Q2W dose was selected to test in the Part 2 expansion cohorts as this dose level was expected to achieve target $C_{trough\ ss}$ of ≥ 60 µg/mL. Limited PK data in Part 2 from a total of 18 GC patients dosed at 15 mg/kg Q2W, including 8 patients with high FGFR2b overexpression (Cohort A) and 10 patients without FGFR2b overexpression defined as IHC 0 (Cohort C), suggested that a dose of 15 mg/kg Q2W will achieve $C_{trough\ ss}$ target of ≥ 60 µg/mL (refer to the FPA144 IB) in approximately 70% of patients at Day 28. PK modeling suggests that the addition of a single dose of 7.5 mg/kg administered on Day 8 of the first cycle allows at least 90% of patients to achieve the target trough of ≥ 60 ug/ml at Day 15, without significantly increasing the C_{max}.

1.4 Rationale for mFOLFOX6

Chemotherapy for advanced GC prolongs survival and improves symptoms (Wagner 2006, Al-Batran 2008, Kang 2009, Okines 2009, Waddell 2014). The combination of a platinum agent with a fluoropyrimidine has become a frequently used combination (Kang 2009) and in a recent meta-analysis has been identified as superior to single agent treatment and best supportive care (Wagner 2006). Although there is no single standard globally accepted first line reference chemotherapeutic regimen for advanced GC, the combination of a fluoropyrimidine (5-FU, capecitabine or S1) and a platinum agent (cisplatin or oxaliplatin) is an accepted standard of care in both Western and Asian countries (Wagner 2006, Al-Batran 2008, Keam 2008, Kang 2009, Okines 2009).

The antitumor treatment effect of fluorouracil derivatives (5FU, capecitabine) are believed to result from inhibiting the enzyme thymidylate synthase (TS). (Ulrich 2000, Pullarkat 2001, Chen 2003). Leucovorin, also known as folinic acid, causes a biochemical modulation of 5-FU enhances the treatment effect of 5-FU in patients with GC (Kim 2003).

Oxaliplatin is a cisplatin analog that functions through its ability to form DACH-platinum adducts and block deoxyribonucleic acid (DNA) replications. Oxaliplatin exhibits additive or synergistic properties when combined with 5-FU and has proven to be effective even when treating 5-FU resistant cell lines or cell lines resistant to cisplatin (Kim 2003, Keam 2008).

In a randomized Phase 3 trial comparing 5-FU/LV/oxaliplatin with 5-FU/LV/cisplatin (FLP) in the treatment of 220 patients with GC reported a statistically insignificant improved time-to-progression; however, the oxaliplatin based regimen was associated with meaningful reductions in Grade 3–4 AEs, including anemia, nausea, vomiting and renal toxicity, but with more neuropathy (Al-Batran 2008). Subsequent studies have supported the safety and efficacy of mFOLFOX6 as the first line of treatment for advanced GC (Keam 2008).

Accordingly, mFOLFOX6 is used as standard therapy in advanced/metastatic GC patients in the US, Europe, and Asia.

1.5 Rationale for Combination Therapy: FPA144 and mFOLFOX6

Since advanced GC is not cured with the currently available chemotherapy regimens, there is a continued need to provide improvement to available treatments. The FGFR pathway has been shown to play an important role in the transformation and proliferation of tumor cells, and inhibiting FGF ligand-stimulated FGFR2b phosphorylation and cell proliferation has been shown to reduce tumor growth in both FGFR2b overexpressing gastric and breast cell lines and xenograft models.

FPA144 as monotherapy has demonstrated objective tumor responses in preclinical studies, blocking ligand binding and downstream signaling, decreasing expression of the FGFR2b driver protein and enhancing ADCC. Preliminary data from the first-in-human study of FPA144 indicate that FPA144 monotherapy has activity in patients with heavily pretreated FGFR2b-selected GC. The safety profile has been tolerable, with no DLTs encountered to date.

The combination of FPA144 and paclitaxel demonstrated enhanced activity in both the OCUM-2M and HSC-39 xenograft models of GC compared to monotherapy of either agent at the doses tested (Gemo 2014). Using a more aggressive chemotherapy regimen in these same models, such as cisplatin and 5-FU or oxaliplatin and 5-FU chemotherapy, provided near complete growth suppression in the HSC-39 model and therefore no additional benefit was observed with the addition of FPA144. Alternatively, the OCUM-2M *FGFR2*-amplified model, demonstrated near complete tumor suppression with FPA144 at the doses tested, and therefore no additional benefit was observed in combination with cisplatin + 5-FU or oxaliplatin + 5-FU chemotherapy. Importantly, the addition of FPA144 to any of these chemotherapy regimens did not increase the toxicity associated with chemotherapy as measured by weight loss in mice.

Advanced stage GC has been demonstrated to be heterogeneous, and the development of additional heterogeneity is hypothesized to be induced by standard front line chemotherapy (Smyth 2016). Specifically, GC metastases are more likely to overexpress FGFR2b compared to the primary tumor, suggesting that emergence of an FGFR2b overexpressing tumor is a later stage event (Ahn 2016), and may even be induced by prior systemic chemotherapy. Sequential biopsies and circulating tumor DNA (ctDNA) testing have demonstrated that subclones of tumors with different phenotype emerge after targeted therapy treatment (Smyth 2016, Catenacci 2017). The hypothesis that chemotherapy and FPA144 target different subclones of GC is supported by the ability of FPA144 or mFOLFOX6 to drive complete growth suppression of GC tumors in distinct xenograft models (Gemo 2014).

Further, the hypothesis that adding a targeted biologic agent to standard chemotherapy in GC may be beneficial in selected patients is further supported by the demonstration of the clinical benefit (PFS and OS) of adding trastuzumab to chemotherapy in patients with GC whose tumors

overexpress HER2 (Bang 2010) and the addition of ramucirumab to paclitaxel in patients who progressed after front-line therapy (Wilke 2014).

1.6 FPA144 and mFOLFOX6 Starting Dose Justification

In study FPA144-001, no DLTs were reported at doses tested from 0.3 mg/kg to 15 mg/kg administered Q2W and no MTD of FPA144 was identified. Therefore, the RD for expansion was based on the observation of clinical efficacy and tolerability in the human FPA144-001 Phase 1 study, combined with preclinical data from the OCUM2 *FGFR2*-amplified GC xenograft mouse model, which identified 60 µg/mL as the target trough serum concentration to achieve maximum efficacy. Supporting the hypothesis that ≥ 60 µg/mL should be the target minimum trough serum concentration (C_{trough}), all patients who demonstrated a partial response in the ongoing FPA144-001 study achieved the target $C_{trough\ ss}$ of ≥ 60 µg/mL. Patients receiving a lower dose of 10 mg/kg Q2W also achieved a target trough of ≥60 µg/mL, but not until steady state approximately 3 months after the initiation of FPA144. At the earlier time point of 28 days, only 3 of 6 patients dosed at the 10 mg/kg dose achieved the target C_{trough} of ≥ 60 µg/mL compared to 21 of 29 patients dosed at 15 mg/kg Q2W based on data as of 20 March 2017.

To safely minimize the time needed to reach the target FPA144 target trough concentration while increasing the potential for earlier efficacy in this rapidly progressing cancer, a dose of 7.5 mg/kg FPA144 will be administered on Day 8 of Cycle 1 for patients enrolled in Cohort 2. PK modeling suggests that the schedule of 15 mg/kg Q2W with 1 dose of 7.5 mg/kg on Day 8 (Cycle 1 only) will allow at least 90% of patients to achieve the biologically active target trough concentration by Day 15 instead of by Day 28. Achieving the target trough concentration earlier is clinically important in this patient population with rapidly progressive disease.

No drug-drug interactions are expected between FPA144 and mFOLFOX6 based on known mechanisms of CL. However, based on FGFR2b expression in tissues of epithelial origin (eg, stomach and skin), and the AEs reported in the ongoing FPA144-001 study, FGFR2 inhibition could increase the rate of mucositis, nausea, vomiting and diarrhea observed with mFOLFOX6 alone.

The Phase 1 portion of this study will initiate FPA144 combined with mFOLFOX6 a dose of 6 mg/kg administered Q2W. Assuming the dose of 6 mg/kg is demonstrated to be safe, tolerable, and without clinical or pharmacologic evidence of a drug interaction, the second dose to be tested will be 15 mg/kg Q2W with 1 dose of 7.5 mg/kg on Day 8 (Cycle 1 only). If Cohort 1 (6 mg/kg Q2W) clears the 28 day DLT period, but ≥ 2 DLTs are observed in Cohort 2 (15 mg/kg Q2W with 1 dose of 7.5 mg/kg on Day 8 of Cycle 1 only), based on observed safety, tolerability and PK, a dose level between Cohorts 1 and 2 (this new cohort will be Cohort 1a, proposed to be 15 mg/kg Q2W) may be evaluated in a rolling 6 design. If ≥ 2 DLTs are observed in Cohort 1a, then the Cohort Review Committee (CRC) may decide to evaluate a dose between the dose levels tested in Cohort 1a and Cohort 1 (this new cohort will be Cohort 1b) to

achieve tolerability with optimal target exposure. At least 6 patients will be evaluated for safety, tolerability and PK at the final RD prior to initiating the Phase 2 portion of the study.

1.7 Risk-Benefit Assessment of FPA144 and mFOLFOX6

This overview is not intended to replace the complete information presented in the FPA144 IB. Please consult the IB for more detailed information.

GC is a highly lethal disease, the treatment of which depends significantly on the stage of the disease. Intensive multimodal therapy for locoregional disease fails to cure most patients and standard chemotherapy for metastatic disease provides only short-term benefits. First-line chemotherapy used in metastatic or recurrent disease generally consists of a fluoropyrimidine (5-FU, S1 or capecitabine) with a platinum agent (usually oxaliplatin or cisplatin) and the mOS is 9 to 11 months with a median PFS of 5 to 7.4 months (Kang 2009). Patients with GC and *FGFR2* gene amplification (Seo 2016) or FGFR2b overexpression (Ahn 2016) have a worse prognosis (Hattori 1996, Gemo 2014) thus warranting evaluation of a new targeted agent against FGFR2+ GC .

mFOLFOX6 chemotherapy is associated with myelosuppression, most frequently Grade 3-4 neutropenia reported in about 40–50% of patients, peripheral neuropathy (> Grade 2) reported in about 70% of patients, diarrhea (> Grade 2) reported in about 25% of patients, and nausea/vomiting reported in about 3% of patients each (Tournigand 2004, van Hazel 2016). Vomiting and mucositis were not observed in FPA144 toxicology studies, however, 20.4% of patients in the ongoing FPA144-001 study with monotherapy FPA144 reported nausea and/or vomiting, with 3.1% reporting Grade 3 (no Grade 4 or higher was reported). Although no mucositis or diarrhea has been reported (n=64), based on mechanism of action, inhibition of FGFR2 may increase this risk. In patients with underlying metastatic GC receiving mFOLFOX6 chemotherapy, an increase in the incidence of any of these GI symptoms could be clinically meaningful.

The protocol includes standard anti-emetic therapy, close clinical monitoring and drug modifications and discontinuation. Additionally, an independent data monitoring committee (DMC) will monitor safety and toxicity on the study (refer to Section 8.10.2).

The individual agents used in the FOLFOX regimen (5-FU, oxaliplatin and leucovorin) are also associated with risks. Refer to local prescribing information for complete details.

The risks associated with fluorouracil include: myelosuppression, diarrhea, nausea and vomiting, mucositis, anorexia, palmar-plantar erythrodysthesia, alopecia, cardiac toxicity, neurotoxicity and hyperammonemic encephalopathy. Due to a potential drug-drug interaction between 5-FU and warfarin, there is a risk of an elevated international normalized ratio (INR) for patients on warfarin who also receive 5-FU (Teva Pharmaceuticals USA Inc 2016).

The risks associated with oxaliplatin include allergic reactions, neuropathy, pulmonary toxicity, hepatotoxicity, cardiovascular toxicity, rhabdomyolysis, nausea/vomiting, diarrhea, mucositis, myelosuppression, fatigue.

As of November 2017, no drug has been approved in the US, EU, or Asia specifically for the subset of patients with FGFR2-selected GC. Based on the emerging data from the Phase 1 FPA144-001 trial, FPA144 may provide a meaningful clinical benefit with an acceptable tolerability profile in heavily pretreated patients with GC whose tumors overexpressed FGFR2. FGF signaling pathways appear to be a valid target for clinical investigation in human cancer based on preclinical models as well as ongoing clinical trials with other molecules that broadly target FGF signaling (Taiho Oncology Inc 2015, Hall 2016, GlaxoSmithKline 2017).

As detailed in Section 1.5, the addition of FPA144 to current standard of care first-line treatment for advanced GC with mFOLFOX6 is anticipated to improve PFS compared to chemotherapy alone. Preliminary data from the first-in-human study of FPA144 indicate that FPA144 monotherapy has activity in patients with FGFR2b-selected gastric and bladder cancer. The safety profile has been tolerable, with no DLTs reported.

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

- Based on non-clinical toxicology, FPA144 has an expected on-target effect leading to corneal thinning which may increase the risk of developing a corneal ulcer or a secondary corneal infection. Based on the aggregate clinical data, keratitis has been identified as an adverse drug reaction to bemarituzumab treatment. Accordingly, patients who at baseline have a history of corneal disease such as keratitis or corneal transplant will be excluded. Patients found to have ocular abnormalities involving the cornea during screening will also be excluded, including corneal defects, corneal ulcerations, keratoconus, or other abnormalities that can pose an increased risk of developing a corneal ulcer. Ophthalmology examinations will be performed at baseline and at regular protocol required intervals during the study to monitor potential ocular effects (described in Section 6.6.2).
- Based on non-clinical data, FPA144 may have on-target effects on the epithelium of the oropharynx, although redundancy in the FGF pathway in these organs may limit and the toxicity beyond what is anticipated from mFOLFX6 alone. To date, 1 event of Grade 1 dry mouth has been reported in a patient during Cycle 6 of FPA144 given at 3 mg/kg. Fluoropyrimidines have a known toxicity of mucositis (Teva Parenteral Medicines Inc 2016). Patients will undergo physical examination approximately every 2 weeks, including examination of the oropharynx.

- Patients will be closely monitored for infusion-related reactions which are known potential toxicities of both oxaliplatin and FPA144. The FPA144 infusion rate may be reduced 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.
    - Routine premedication is not generally administered for the initial FPA144 dose; patients who develop infusion-related AEs may be premedicated prior to subsequent infusions of FPA144 at the discretion of the investigator. Pre-medication for mFOLFOX6 should be at the discretion of the investigator, administered according to the institution's standard practice, and captured on the patient's electronic case report form (eCRF).
    - Epinephrine for subcutaneous injection, diphenhydramine (or equivalent) 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.

1.8 Rationale for Phase 2 Pre-Screening

FPA144 is an antibody designed to recognize the FGFR2 receptor when expressed on gastric tumors. The current hypothesis is that the presence of FGFR2 will be an important predictor of how patients with FGFR2-selected GC will respond to treatment with FPA144. This is based on the preclinical observation that only tumors that overexpressed FGFR2b responded to FPA144 treatment in xenograft studies, as well as early results from the ongoing first-in-human study demonstrating objective responses in patients with FGFR2b overexpression.

Eligibility for enrollment in the Phase 2 portion is based on FGFR2b overexpression **and/or** *FGFR2* gene amplification as determined by a centrally performed, validated IHC or ctDNA blood assay. Patients are required to provide both a tissue sample and a blood sample to test for FGFR2 and patients unable to provide both samples will not be eligible for this trial. Patients who are positive for FGFR2b overexpression and/or *FGFR2* gene amplification are referred to in this protocol as FGFR2-selected. Positivity based on only 1 assay is adequate to meet eligibility requirements (eg, positive by ctDNA blood assay, but negative by IHC) (refer to Section 4.2).

Pre-screening allows for collection of blood and tissue to determine FGFR2 positivity using ctDNA and IHC assays. Once a patient is confirmed to have a positive result based on central testing, the screening period initiates, allowing for evaluation of all other eligibility criteria (refer to Section 4.2).

Eligible patients for the Phase 2 portion must be naïve to prior chemotherapy for metastatic or unresectable disease, with the exception that patients may have received prior adjuvant or neo-adjuvant therapy (chemotherapy and/or chemoradiation) greater than 6 months prior to enrollment.

Since the IHC and ctDNA blood results may require approximately 2 weeks to complete, patients eligible for entering Phase 2 of this study are permitted to receive 1 dose of mFOLFOX6 during this interim time period (pre-screening period) at the discretion of the investigator. This 1 dose of chemotherapy is not a requirement of the study and is not considered part of this clinical study.

1.9 Rationale for Tumor Tissue and Blood Assessments

Patients who do not demonstrate either FGFR2b overexpression using IHC or *FGFR2* gene amplification using a ctDNA blood assay will not be eligible for enrollment. Positivity based on either 1 or both assays is adequate to meet the eligibility requirements (eg, positive by ctDNA blood assay, but negative by IHC). The blood test will reveal DNA amplification of *FGFR2*, while the IHC test will show the extent of protein expression. Five Prime has developed an anti-FGFR2 antibody for nonclinical use, whose sensitivity and specificity to detect FGFR2 by IHC has been optimized (Deshpande 2014).

In studies evaluating GC samples, *FGFR2* gene amplification has been uniformly associated with significant FGFR2b surface expression, as detected by IHC (Gemo 2014). The antitumor effect of FPA144 that was observed in preclinical testing was predicated upon the overexpression of FGFR2b in the tumor cell lines. Patients without overexpression of FGFR2 are unlikely to see a significant benefit from treatment with FPA144 in combination with mFOLFOX6.

The selection of patients with FGFR2-positive tumors for treatment with FPA144 is supported by data from the ongoing Phase 1, first-in-human study of FPA144-001. Confirmed responses have only been reported in patients having tumors with FGFR2b overexpression, validating the strategy of selecting these patients for treatment with FPA144 based on FGFR2 status. Additionally, since GC is heterogeneous, the use of ctDNA has been incorporated to identify tumors that shed FGFR2 into the blood stream, but whose tumors do not overexpress FGFR2b (due to tissue sampling error). Allowing patients to enroll who either test positive for FGFR2b by tissue or positive for FGFR2 by blood will maximize the inclusion of patients with FGFR2 amplified tumors in the trial.

2.0 STUDY OBJECTIVES AND ENDPOINTS

2.1 Phase 1 Objectives

2.1.1 Primary

To determine the RD of FPA144 combined with a fixed dose of mFOLFOX6 (hereinafter referred to as FPA144 + mFOLFOX6) in patients with advanced GI tumors

2.1.2 Secondary

- To evaluate the safety and tolerability of FPA144 + mFOLFOX6 in patients with GI tumors
- To characterize the PK profile of FPA144 + mFOLFOX6 in patients with GI tumors
- To characterize the immunogenicity of FPA144

2.1.3 Exploratory

To characterize the pharmacodynamic profile of FPA144 + mFOLFOX6 in patients with GI tumors

2.2 Phase 2 Objectives

2.2.1 Primary

To compare investigator-assessed PFS in patients with FGFR2-selected GC treated with FPA144 + mFOLFOX6 to those treated with placebo combined with mFOLFOX6 (hereafter referred to as placebo + mFOLFOX6)

2.2.2 Secondary

To compare the following in patients with FGFR2-selected GC treated with FPA144 + mFOLFOX6 to those treated with placebo + mFOLFOX6:

- Overall survival (OS)
- Investigator-assessed ORR
- Safety and tolerability

2.2.3 Exploratory

To compare the following in patients with FGFR2-selected GC treated with FPA144 + mFOLFOX6 to those treated with placebo + mFOLFOX6:

- DOR
- Patient-reported outcomes (PROs) and quality of life (QOL) outcomes until investigator-assessed disease progression

- To explore the association between FGFR2 status (in tumor tissue and/or blood) with clinical outcome
- To explore the concordance between FGFR2b overexpression in tumor tissue and *FGFR2* gene amplification in blood

To characterize the following:

- PK profile of FPA144 + mFOLFOX6 in patients with FGFR2-selected GC
- Immunogenicty of FPA144

2.3 Phase 1 Endpoints

2.3.1 Primary

- The incidence of Grade 2 or higher AEs assessed as related to FPA144 by the investigator and the incidence of clinical laboratory abnormalities defined as DLTs

2.3.2 Secondary

- The incidence of AEs, clinical laboratory abnormalities, corneal and retinal findings, and electrocardiogram (ECG) abnormalities
- PK parameters of FPA144, such AUC, C_{max}, C_{trough}, CL, $t_{1/2}$, volume of distribution, the time to achieve steady state, dose-linearity, and accumulation ratio
- Incidence of treatment-emergent anti-FPA144 antibody response

2.3.3 Exploratory

[redacted]

2.4 Phase 2 Endpoints

2.4.1 Primary

PFS, defined as time from randomization until the date of disease progression based on investigator assessment per RECIST v1.1 or death from any cause, whichever comes first

2.4.2 Secondary

- OS, defined as time from randomization until death from any cause
- ORR, defined as the proportion of patients with partial or complete response in all enrolled patients based on investigator assessment of tumor lesions per RECIST v1.1
- Incidence of AEs, clinical laboratory abnormalities, corneal and retinal findings, and ECG abnormalities

2.4.3 Exploratory

- DOR limited to patients who are responders to treatment, as determined by the investigator per RECIST v1.1, and defined as the time of first response to progression or death from any cause, whichever comes first
- Change from baseline in functional outcomes as measured by EuroQOL-5D-5L (EQ-5D-5L) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Version 3.0 (EORTC QLQ-C30)
- The correlation between identified FGFR2 status in tumor tissue and/or ctDNA blood assay, as determined by IHC and blood-based molecular diagnostic assay, with OS, PFS, and objective response per RECIST v1.1
- The correlation between identified FGFR2b overexpression in tumor tissue by IHC and *FGFR2* gene amplification as determined by ctDNA blood assay
- PK parameters, C_{max} and C_{trough} of FPA144 in combination with mFOLFOX6
- Incidence of treatment-emergent anti-FPA144 antibody response

3.0 STUDY DESIGN

3.1 Study Overview

The Phase 2 portion of this study was initially designed as a Phase 3 with overall survival as the primary endpoint. The study design has been changed considering the findings of a higher proportion of FGFR2 positive tumors in patients in the front-line gastric cancer setting than expected (~ 30% vs the expected rate of 10%) and that the vast majority of tumors are positive via IHC analysis for FGFR2b overexpression rather than by ctDNA analysis of FGFR2 amplification. The randomized, double-blind study design will be maintained through the primary analysis of the Phase 2 study.

This is a double-blind, randomized, controlled, multicenter Phase 1/2 study to evaluate the safety, tolerability, efficacy, and PK of FPA144 + mFOLFOX6 versus placebo + mFOLFOX6. Patients may enroll into either Phase 1 or Phase 2 but may not enroll in both phases of the study.

This study includes a Phase 1 safety run-in portion and a Phase 2 portion. The Phase 1 safety run-in is an open-label dose-escalation of FPA144 + mFOLFOX6 in patients with GI tumors (not FGFR2 selected). Provision of tissue for retrospective FGFR2b overexpression testing by IHC, and blood for FGFR2 gene amplification by ctDNA, are not required for enrollment in Phase 1, but will be tested retrospectively if available (refer to Section 6.1).

The Phase 2 portion of the study (to follow the Phase 1 safety run-in) is a global, randomized, double-blind, controlled, study to evaluate the efficacy of FPA144 + mFOLFOX6 versus placebo + mFOLFOX6 in patients with FGFR2-selected GC. FGFR2b overexpression will be determined by prospective IHC analysis and/or a ctDNA blood assay demonstrating FGFR2 gene amplification. The duration of the study is expected to be approximately 43 months to complete; this includes Phase 1 (6 months for completion) and Phase 2 (13 months for accrual and 24 months of long term follow up (LTFU) from the last patient enrolled).

In Phase 1, the starting dose level of FPA144 is 6 mg/kg per dose. Subsequent dose escalations between cohorts in Phase 1 are described in Section 3.2.1. The dose of FPA144 for Phase 2 will be determined by evaluation of the data from Phase 1 of the study, as described in Sections 3.2.3 and 3.2.4.

Additional study design details are provided below for each study phase. The study schemas are provided in Section 3.4.

3.2 Phase 1

3.2.1 Dose Escalation

In Phase 1, dose cohorts are planned at proposed doses beginning at an FPA144 dose level of 6 mg/kg per dose Q2W, and enrollment will depend on safety and tolerability. Phase 1 includes a 3+3 and rolling 6 design until the RD of FPA144 to be administered in combination with mFOLFOX6 in Phase 2 is determined. A minimum of 2 dosing cohorts of FPA144 + mFOLFOX6 will be included in Phase 1 to determine the RD of FPA144 in combination with mFOLFOX6.

Patients enrolled in Phase 1 will be treated with escalating doses of FPA144 in combination with a fixed-dose chemotherapy regimen of mFOLFOX6 in 2-week cycles, as outlined in Table 1. Intra-patient dose escalation will not be permitted.

Additional details regarding dose escalation and the DLT period are provided in Section 3.2.3. Proposed dose levels are outlined in Table 1 and also in Section 5.1.2 and Section 5.2 of the protocol; guidance for dose modification is provided in Section 5.1.3.4.

Decisions on how to next proceed will be based on safety, tolerability, and PK data, and will be determined by the CRC.

Administration of FPA144 will be over approximately 30 minutes (± 10 minutes) Q2W ± 3 days on Day 1 of each 2-week cycle. FPA144 will be administered prior to mFOLFOX6 chemotherapy. Patients treated in Cohort 2 (only) will receive 1 additional dose of FPA144 on Day 8 of Cycle 1 (mFOLFOX6 will not be administered on this day).

Table 1: Phase 1 Proposed Dose Levels by Cohort

Cohort	FPA144	mFOLFOX6 (mFOLFOX6 will be administered at a fixed dose to all FPA144 dose cohorts)
Cohort 1	6 mg/kg Q2W beginning on C1D1	Q2W beginning on C1D1, at least 30 minutes after the end of infusion of FPA144: • Oxaliplatin 85 mg/m^2 IV infusion over 120 minutes • Leucovorin 400 mg/m^2 IV infusion over 120 minutes, can be administered concurrently with oxaliplatin if using a Y connector, (if not using a Y connector, administer drugs sequentially) – If leucovorin is unavailable, 200 mg/m^2 levo-leucovorin may be used. Study treatment may be administered without either agent in the event that both are unavailable. Leucovorin (or levo-leucovorin) may be given at either the protocol-recommended doses or as deemed appropriate by the investigator in accordance with institutional standard of care • Immediately after oxaliplatin and leucovorin, 5 FU 400 mg/m^2 bolus over approximately 5 minutes • Immediately after the 5-FU bolus, 5-FU 2400 mg/m^2 as a continuous IV infusion over approximately 48 hours For further details, refer to the manufacturer's prescribing information for the respective chemotherapies and the study Pharmacy Manual.
Cohort 2	15 mg/kg Q2W beginning on C1D1, plus 1 dose of 7.5 mg/kg on Day 8 (Cycle 1 only)	
Cohort 1a	(if needed, eg, if the Cohort 2 dose level or schedule is not tolerated) 15 mg/kg Q2W beginning on C1D1	
Cohort 1b	(if needed, eg, if the Cohort 2 and 1a dose levels or schedules are not tolerated) Dose level lower than Cohort 1a, but higher than Cohort 1 to achieve tolerability with optimal target exposure	

Abbreviations: C1D1 = Cycle 1 Day 1; IV = intravenous; Q2W = every 2 weeks.

Note: If leucovorin is unavailable, 200 mg/m2 levofolinic acid may be used. Study treatment may be administered without either agent in the event that both are unavailable. Folinic acid (or levofolinic acid) may be given at either the protocol-recommended doses or as deemed appropriate by the investigator in accordance with institutional standard of care.

3.2.2 Definition of Dose-Limiting Toxicity

DLTs are defined as any of the following events that occur during the first 28 days of treatment and are assessed by the CRC as related to FPA144. As applicable, events will be classified according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) (Version 4.03).

- Absolute neutrophil count (ANC) $< 0.5 \times 10^9$/L $>$ 5 days' duration or febrile neutropenia (ie, ANC $< 1.0 \times 10^9$/L with a single temperature of $>$ 38.3°C, or fever $\geq$ 38 °C for more than 1 hour). Use of granulocyte-colony stimulating factor (G-CSF) is permitted in accordance with institutional standards
- Platelets $< 25 \times 10^9$/L
- Platelets $< 50 \times 10^9$/L with bleeding requiring medical intervention
- Platelets $< 50 \times 10^9$/L ($>$ 3 days)

- Grade 4 anemia (ie, life-threatening consequences, urgent intervention indicated)
- Any Grade 2–3 ophthalmologic AE that does not resolve within 7 days
- Any Grade 4 ophthalmologic AE
- Any Grade 4 laboratory value
- Any Grade 3 laboratory values that are not of clinical significance according to investigator and Sponsor agreement that do not resolve within 72 hours
- AST/ alanine aminotransferase (ALT) ≥ 3 × upper limit of normal (ULN) and concurrent total bilirubin ≥ 2 × ULN not related to liver involvement with cancer
- Any non-hematological AE Grade 3 or greater (except nausea, vomiting, and diarrhea)
- Grade 3 nausea, vomiting, or diarrhea that does not resolve with supportive care in 72 hours
- Grade 4 nausea, vomiting, or diarrhea

3.2.3 Observation of Dose-Limiting Toxicity (the DLT Period)

Beginning on the first day (Cycle 1 Day 1 [C1D1]) of treatment with FPA144 and mFOLFOX6, each patient will be observed for 28 days (the DLT period) for safety, PK, and occurrence of DLTs. DLTs are defined in Section 3.2.2.

FPA144 dose escalation will occur as follows (refer to Table 2 for the dose escalation algorithm):

- Cohort 1 begins with a FPA144 dose of 6 mg/kg per dose in a 3+3 design.
- If Cohort 1 at 6 mg/kg (3+3 design) clears the 28-day DLT period, then Cohort 2 at 15 mg/kg Q2W with 1 dose of 7.5 mg/kg on Day 8 (Cycle 1 only) will be tested in a rolling 6 design and enroll 6 patients.
- Upon initiation of enrollment in Cohort 2, 6 patients will be enrolled to explore the safety, tolerability and PK at this dose level.
- If ≥ 2 DLTs are observed in Cohort 2, then a dose level between Cohorts 1 and 2 may be evaluated in a rolling 6 design (this cohort will be Cohort 1a 15 mg/kg Q2W).
- If ≥ 2 DLTs are observed in Cohort 1a, then a dose level lower than Cohort 1a, but higher than Cohort 1 may be evaluated in a rolling 6 design (this cohort will be Cohort 1b at a dose to be determined).

Dose escalation decisions will be agreed upon by the CRC, consisting of the Sponsor and investigators. Dose escalation decisions will be based on an assessment of DLTs, overall safety, and tolerability, and will be made after the last patient enrolled in each cohort has completed the 28-day DLT period (completion of 2 treatment cycles of FPA144 and mFOLFOX6). Review of

safety and PK parameters may inform decisions to add cohorts with alternative dose levels to reach an optimal target exposure.

No additional doses of FPA144 or more than 2 doses of mFOLFOX6 should be administered during the 28-day DLT period. The doses of FPA144 and mFOLFOX6 on Day 1 of Cycle 2 do not need to be synchronized. For example, if mFOLFOX6 is delayed due to an AE that is deemed related only to mFOLFOX6 and not to FPA144, FPA144 should be administered as described in Section 5.1 for Cycles 1 and 2 regardless of delays in the mFOLFOX6 dosing schedule.

DLTs are defined in detail in Section 3.2.2. The algorithm shown in Table 2 will be used for Phase 1 dose escalation decisions.

Table 2: Phase 1 Dose Escalation Algorithm

Number of Patients with DLTs	Action
0/3	Open next cohort
1/3	Enroll 3 more patients in same cohort
≥ 2/3	Stop enrollment. If Cohort 1, then the study will end.
1/6	Open next cohort
≥ 2/6	Stop enrollment at that level. If at Cohort 1, the study will end. If at Cohort 2 or Cohort 1a, then Cohort 1a or Cohort 1b will open respectively and 6 patients will be enrolled.

Abbreviations: DLT = dose-limiting toxicity.

Upon completion of the DLT period (starting with Cycle 3), patients may continue to receive FPA144 + mFOLFOX6. Additional doses may be administered Q2W (1 cycle) until disease progression, unacceptable toxicity, or until the patient meets any of the other protocol-specified withdrawal criteria (refer to Section 4.0). There is no maximum number of doses of FPA144. Ongoing administration of the mFOLFOX6 regimen beyond the DLT period will be according to local standard of care.

3.2.4 Determination of Maximum Tolerated Dose and Recommended Dose

The RD of FPA144 for Phase 2 will be identified by the CRC based on an evaluation of the overall safety, tolerability, and PK and will not exceed 15 mg/kg administered IV Q2W with 1 dose of 7.5 mg/kg on Day 8 of Cycle 1 only. In determining the RD, the CRC will consider toxicities observed during the DLT evaluation period, any toxicities observed beyond the DLT evaluation period, as well as dose reductions and discontinuations of mFOLFOX6 or FPA144 due to toxicities that do not meet the DLT criteria. Based on the totality of the data, the chosen RD of FPA144 will be a dose that is not anticipated to lead to a decrease in the dose intensity of mFOLFOX6 to be administered. The RD, therefore, may or may not be the same as the identified MTD. For example, if the MTD is not reached, or if data from subsequent cycles of

treatment from Phase 1 provide additional insight on the safety profile, then the RD may be a different, though not higher, dose than the MTD.

The MTD is defined as the maximum dose at which < 33% of patients experience a DLT during the DLT period. If a DLT is observed in 1 of 3 patients in Cohort 1, then 3 additional patients will be enrolled at that same dose level. Dose escalation may continue until 2 of 3 to 6 patients treated at a dose level experience a DLT (dose level not to exceed the highest dose level tolerated in Phase 1). The next lower dose will then be considered the MTD.

3.2.5 Phase 2 Dose of FPA144

There were no DLTs observed during the Phase 1 safety run-in and an MTD was not reached. Based on an assessment of overall safety, tolerability, and PK of FPA144 in combination with mFOLFOX6 by the CRC, the dose of 15 mg/kg Q2W with an additional dose of 7.5 mg/kg on Cycle 1 Day 8 will be used for the Phase 2 portion of the trial.

3.2.6 Patient Replacement

Any patient who does not receive the total number of doses of FPA144 defined by the cohort or 2 complete doses of mFOLFOX6 during the DLT period due to a reason that is not a DLT or an AE related to FPA144, will be considered unevaluable and the patient will be replaced. The replaced patient may continue on study at the investigator's discretion and after discussion with the Sponsor.

3.2.7 Number of Doses

There is no protocol-mandated maximum number of doses for FPA144 or mFOLFOX6. Ongoing administration of the mFOLFOX6 regimen beyond the DLT period will be according to Section 3.2 or 5.2 with dose adjustments as detailed in Section 5.2.3.1. Initiation of a new cycle of mFOLFOX6 following a dosing delay may be synchronized with administration of an FPA144 infusion but is not a study requirement. In the Phase 1 portion of the study, if FPA144 is permanently discontinued for any reason the patient will undergo an EOT visit approximately 28 days after the last dose of FPA144 or mFOLFOX6. For these patients, the end of FPA144 treatment is the end of study (EOS) and no further follow-up will be conducted.

If mFOLFOX6 is discontinued for any reason other than investigator-assessed disease progression, or any of the other protocol-specified withdrawal criteria, FPA144 may be continued as a single agent therapy at the investigator's discretion, and administered Q2W until investigator-assessed disease progression, unacceptable toxicity, or until the patient meets any of the other protocol-specified withdrawal criteria.

In the event a cycle of mFOLFOX6 is delayed beyond the next scheduled administration due to chemotherapy-related toxicity during the first 3 cycles of treatment, FPA144 should be administered on schedule (± 3 days). After the first 3 cycles, FPA144 may be delayed up to 7 days to be synchronized with administered mFOLFOX6.

3.3 Phase 2

Enrollment in Phase 2 will begin when an RD for FPA144 has been identified by the CRC which does not exceed the highest dose level evaluated and tolerated in Phase 1. Opening Phase2 for enrollment will be at the discretion of the Sponsor.

Provision of archival (or fresh biopsy if archival tissue is not available) for pre-screening FGFR2b overexpression testing by IHC is required (refer to Section 6.1); a blood sample is also required for pre-screening by ctDNA for FGFR2 amplification. FGFR2 positive status by 1 of these testing methods is required for enrollment in Phase 2. The results of the centralized FGFR2 testing may take approximately 2 weeks; patients are permitted to receive up to 1 dose of mFOLFOX6 during this interim time period (pre-screening) at the discretion of the investigator. This 1 dose of chemotherapy is not a requirement of the study and is not considered part of this clinical study.

In the Phase 2, a patient is considered enrolled when he/she is randomized. The enrollment date is the same as randomization date. Phase 2 patients must initiate the first administration of study treatment within 3 days of enrollment.

FPA144 will be prepared and administered as in Phase 1 (Section 5.1), and the dosing and schedule of FPA144 will be at the RD as determined in Phase 1.

3.3.1 Treatment Arms

Phase 2 will be randomized 1:1 to 1 of 2 treatment arms, as outlined in Table 3.

Table 3: Phase 2 Treatment Arms

Arm 1 **FPA144 + mFOLFOX6**	**FPA144** 15 mg/kg Q2W with an additional dose of 7.5 mg/kg on Cycle 1 Day 8	**mFOLFOX6 will be administered at a fixed dose to both Phase 2 treatment arms:** Q2W beginning on C1D1, at least 30 minutes after the end of infusion of FPA144: • Oxaliplatin 85 mg/m^2 IV infusion over 120 minutes • Leucovorin 400 mg/m^2 IV infusion over 120 minutes, can be administered concurrently with oxaliplatin if using a Y connector, (if not using a Y connector, administer drugs sequentially) If leucovorin is unavailable, 200 mg/m^2 levo-leucovorin may be used. Study treatment may be administered without either agent in the event that both are unavailable. Leucovorin (or levo-leucovorin) may be given at either the protocol-recommended doses or as deemed appropriate by the investigator in accordance with institutional standard of care • Immediately after oxaliplatin and leucovorin, 5 FU 400 mg/m^2 bolus over approximately 5 minutes • Immediately after the 5-FU bolus, 5-FU 2400 mg/m^2 as a continuous IV infusion over approximately 48 hours For further details, refer to the manufacturer's prescribing information for the respective chemotherapies and the study Pharmacy Manual.
Arm 2 **Placebo + mFOLFOX6**	Placebo	

Abbreviations: C1D1 = Cycle 1 Day 1; IV = intravenous; Q2W = every 2 weeks; RD = recommended dose.

Note: If leucovorin is unavailable, 200 mg/m2 levofolinic acid may be used. Study treatment may be administered without either agent in the event that both are unavailable. Folinic acid (or levofolinic acid) may be given at either the protocol-recommended doses or as deemed appropriate by the investigator in accordance with institutional standard of care.

Enrolled patients may continue treatment in 2-week cycles of mFOLFOX6 with or without FPA144 until investigator-assessed disease progression, unacceptable toxicity, or the patient meets any of the other protocol-specified withdrawal criteria. There is no protocol-mandated maximum number of doses for FPA144 or mFOLFOX6.

Discontinuation of any component of the study (mFOLFOX6, a component of mFOLFOX6, or FPA144) for any reason other than disease progression, does not necessarily mandate discontinuation of the other components. An exception is the permanent discontinuation of 5-FU for any reason, which requires concurrent discontinuation of oxaliplatin and leucovorin.

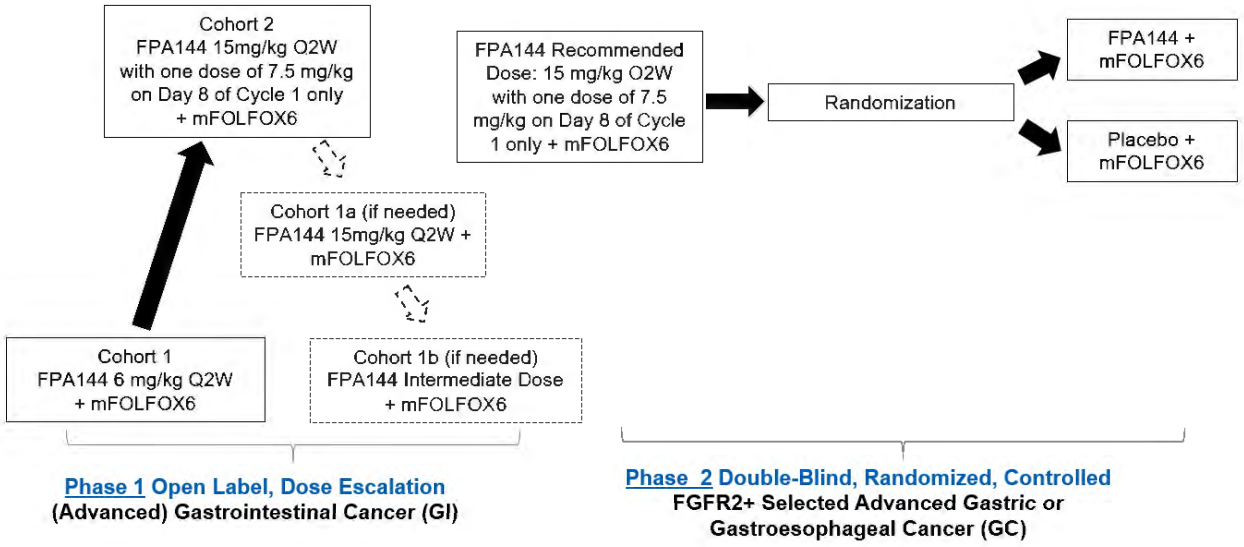
The first 3 cycles of FPA144 should be administered as scheduled (± 3 days) regardless of delays in mFOLFOX6 treatment. After the first 3 cycles, FPA144 may be delayed up to 7 days to be synchronized with administered mFOLFOX6. However, synchronization of FPA144 and mFOLFOX6 is not a protocol requirement. If after 7 days, the patient is still unable to receive mFOLFOX6, FPA144 should continue as monotherapy Q2W.

Patients who discontinue study treatment (FPA144 and/or mFOLFOX6) for reasons other than disease progression or withdrawal of consent will continue to undergo tumor assessments according to the protocol schedule until disease progression or the initiation of additional anticancer therapy, at which point they would undergo LTFU for survival.

3.4 Study Schemas

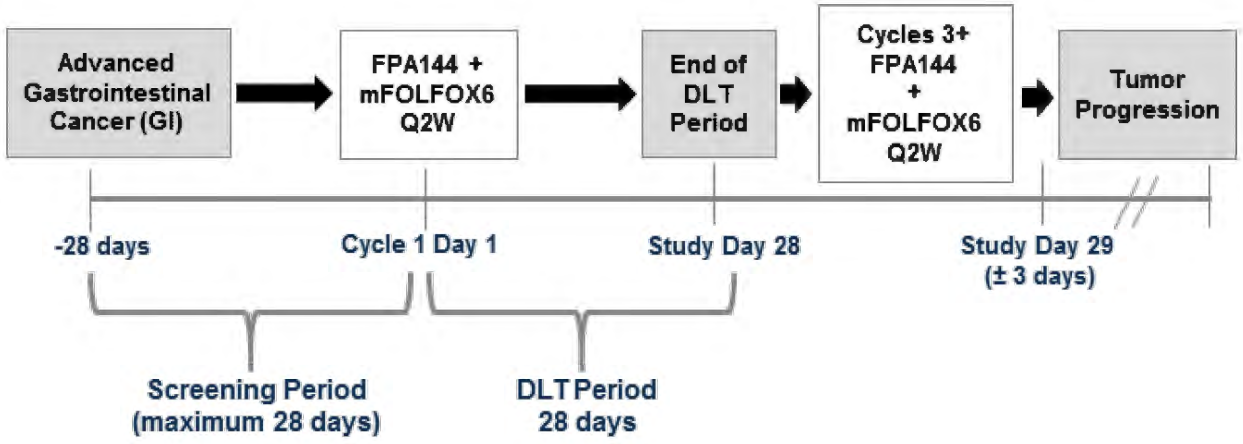
The study schema (Phase 1/2) is shown in Figure 4. Patient timelines are shown in both Figure 5 (Phase 1) and Figure 6 (Phase 2).

Figure 4: Phase 1/2 Study Schema



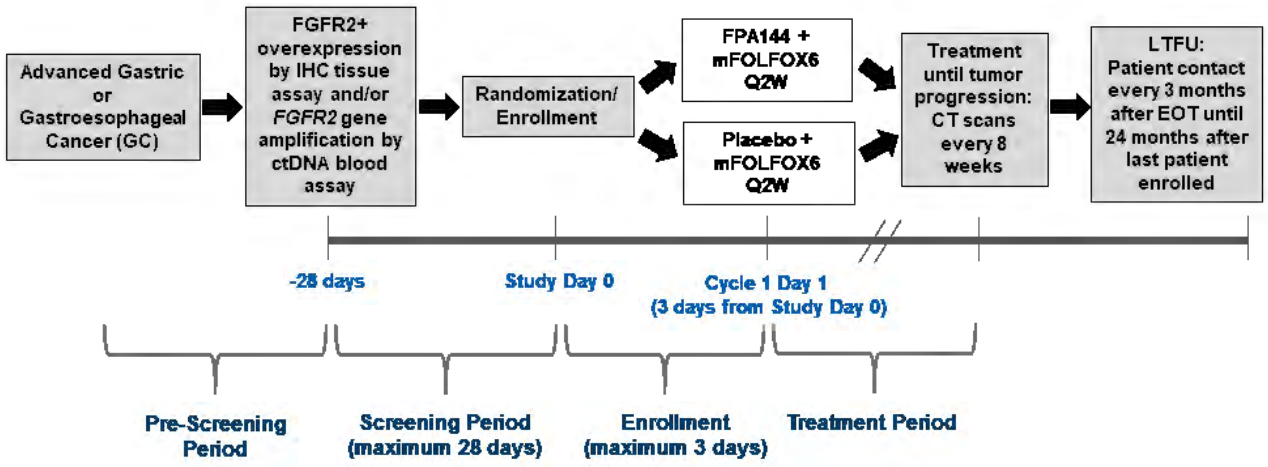
Abbreviations: Q2W = every 2 weeks.

Figure 5: Phase 1 Patient Timeline



Abbreviations: DLT = dose-limiting toxicity; Q2W = every 2 weeks.

Figure 6: Phase 2 Patient Timeline



Abbreviations: CT = computed tomography; ctDNA = circulating tumor DNA; EOT = end of treatment; FGFR2 = fibroblast growth factor receptor 2; LTFU = long term follow up; Q2W = every 2 weeks.

3.5 Rationale for the Study Design

The aim of this study is to compare efficacy and safety of FPA144 versus placebo in combination with an accepted standard therapy, mFOLFOX6, in previously untreated patients with metastatic GC that is classified as both HER2 negative and FGFR2 positive. A placebo control will be administered with the chemotherapy to avoid any observational or other potential bias in the assessment of both efficacy and safety of the study treatment. This control group will be instrumental in assessing the relative benefit or risk of adding FPA144 to chemotherapy.

3.5.1 Rationale for Selection of Patients for FGFR2

Selecting patients for *FGFR2* gene amplification and overexpression targets patients that are most likely to obtain a clinical benefit from FPA144. It is hypothesized that the presence of FGFR2 will be an important predictor of how patients with FGFR2-selected gastric or gastroesophageal cancer will respond. This is based on the preclinical observation that only tumors that overexpressed FGFR2b responded to FPA144 treatment in xenograft studies, as well as early results from the ongoing first-in-human study (FPA144-001) demonstrating objective responses in patients with FGFR2b overexpression. To be eligible, patients must demonstrate either FGFR2b overexpression using IHC or *FGFR2* gene amplification using a ctDNA blood assay. Positivity based on either 1 or both assays is adequate to meet the eligibility requirements. The blood test will reveal DNA amplification of *FGFR2*, while the IHC test will show the extent of protein expression. In studies evaluating GC samples, *FGFR2* gene amplification has been uniformly associated with significant FGFR2b surface overexpression, as detected by IHC (Gemo 2014). Patients without overexpression of FGFR2 are unlikely to see a significant benefit from treatment with FPA144 and mFOLFOX6.

3.6 Rationale for Stratification

To balance the disease-related risk factors across the treatment arms, patients will be stratified at study entry. A permuted-block randomization scheme will be used to ensure an approximately equal sample size and a similar distribution of stratification factors for the two treatment arms. Patients will be stratified as outlined in Sections 3.6.1, 3.6.2, and 3.6.3.

3.6.1 Geographic Region

Although GC is a global disease, there is significant heterogeneity with respect to survival outcomes between Eastern and Western populations, with better OS reported in Asian populations and in particular Japanese patients (Ohtsu 2011, Davidson 2016). The cause of the different outcomes is unknown, but has been hypothesized to be driven by variation in initial staging, biology or subsequent treatment (Ohtsu 2006). Historically, large global trials have not included a significant proportion of patients from China, so it is unknown if the outcome is more similar to US and EU or the rest of Asia (Davidson 2016). As it is anticipated that approximately half the enrollment in this clinical trial will be from China, China will be a separate geographic region from the rest of Asia and accordingly, stratification will be by 4 geographic areas:

- Region 1: including US, Europe, and Australia
- Region 2: China
- Region 3: Rest of Asia including Japan, South Korea, Taiwan, and Thailand
- Region 4: Rest of World

3.6.2 Prior Therapy

Patients will be stratified based on history of prior chemotherapy administered for neo-adjuvant or adjuvant therapy. This stratification is included because this has been shown to be a prognostic factor associated with longer OS in some studies (Bang 2010, Ohtsu 2011, Sawaki 2011).

3.6.3 Administration of mFOLFOX6 Prior to Enrollment

Patients will be stratified based on whether they have received a single dose of mFOLFOX6 chemotherapy for advanced stage disease prior to enrollment. Although it is anticipated that a low proportion of patients will receive this single dose of mFOLFOX6 prior to enrollment, patients who receive a prior dose of chemotherapy are likely have characteristics that would be associated with a different prognosis than patients who do not receive this single dose of mFOLFOX6. Specifically, their extent of disease is likely to be greater or the rate of progression of the disease in these patients is likely to be greater than patients who can wait until results for FGFR2 testing is available.

4.0 STUDY ELIGIBILITY AND WITHDRAWAL CRITERIA

4.1 Planned Number of Patients and Study Centers

In the dose escalation Phase 1, at least 2 dose cohorts of FPA144 are anticipated using a 3+3 design for patients enrolled in Cohort 1 and a minimum of 2 patients enrolled in subsequent cohorts, which will enroll using a rolling 6 design. The total enrollment for Phase 1 will therefore be approximately 9 to 21 patients.

In Phase 2, approximately 155 FGFR2-selected GC patients will be randomized 1:1 to be treated with FPA144 + mFOLFOX6 or placebo + mFOLFOX6 in 2-week cycles at an RD selected after assessment of data obtained in Phase 1. Opening of Phase 2 for enrollment will be at the discretion of the Sponsor.

The total enrollment planned for this study is approximately 167 patients.

The Phase 1 study will be conducted only in the US, while the Phase 2 study will be conducted at up to approximately 190 global study centers.

4.2 Inclusion Criteria for Phase 1 and Phase 2

Patients enrolling in either Phase 1 or Phase 2 of the study must meet ***all*** of the following inclusion criteria:

1) Disease that is unresectable, locally advanced, or metastatic (not amenable to curative therapy)
2) Understand and sign an Institutional Review Board (IRB)/Independent Ethics Committee (IEC)-approved ICF prior to any study-specific evaluation
3) Life expectancy of at least 3 months in the opinion of the investigator
4) Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1
5) Age ≥ 18 years at the time the ICF is signed
6) In sexually active patients (women of child bearing potential [WOCBP] and males), willingness to use 2 effective methods of contraception, of which 1 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 include:
    - Permanent sterilization (hysterectomy and/or bilateral oophorectomy, or bilateral tubal ligation with surgery, or vasectomy) at least 6 months prior to screening
    - WOCBP who are 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

7) Adequate hematological and biological function, confirmed by the following laboratory values within 96 hours prior to enrollment:

Bone Marrow Function

- ANC ≥ 1.5 × 10^9/L
- Platelets ≥ 100 × 10^9/L
- Hemoglobin ≥ 9 g/dL

Hepatic Function

- AST and ALT < 3 × ULN; if liver metastases, then < 5 × ULN
- Bilirubin < 1.5 × ULN except in patients with Gilbert's disease

Renal Function

- Calculated CrCl using Cockcroft Gault formula ≥ 50 mL/min *or* estimated glomerular filtrate rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula ≥ 50 mL/min (refer to Appendix 1)

8) INR or prothrombin time (PT) < 1.5 × the ULN except for patients receiving anticoagulation, who must be on a stable dose of warfarin for 6 weeks prior to enrollment

9) Measurable or non-measurable, but evaluable disease using RECIST v1.1

Additional Inclusion Criteria for Phase 1 Only

Patients enrolling in **Phase 1** of the study must also meet the following inclusion criteria:

10) Histologically or cytologically confirmed GI malignancy for which mFOLFOX6 is considered an appropriate treatment (eg, GC, colorectal carcinoma, pancreatic adenocarcinoma)

11) Patient must be a candidate to receive at least 2 doses of mFOLFOX6 chemotherapy (according to Section 3.2 of the protocol)

Additional Inclusion Criteria for Phase 2 Only

Patients enrolling in **Phase 2** of the study must also meet the following inclusion criteria:

14) Histologically documented gastric or gastroesophageal junction (GEJ) adenocarcinoma (not amenable to curative therapy)

15) Radiographic imaging of the chest, abdomen and pelvis (computed tomography [CT] preferred, magnetic resonance imaging [MRI] acceptable) performed within 28 days (+3 days) of treatment (C1D1)

16) FGFR2b overexpression as determined by a centrally performed IHC tissue test and/or *FGFR2* gene amplification as determined by a centrally performed ctDNA blood based assay

17) Patient must be a candidate for mFOLFOX6 chemotherapy

18) No prior chemotherapy for metastatic or unresectable disease (except a maximum of 1 dose of mFOLFOX6 administered while waiting for results of FGFR2 testing during the pre-screening period)

19) If prior adjuvant or neo-adjuvant therapy (chemotherapy and/or chemoradiation) has been received, more than 6 months must have elapsed between the end of adjuvant therapy and the confirmation of radiographic disease progression

4.3 Exclusion Criteria for Phase 1 and Phase 2

Patients enrolling in either Phase 1 or Phase 2 will be excluded if *any* of the following criteria apply:

1) Untreated or symptomatic central nervous system (CNS) metastases (CNS imaging not required). 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 any of the following (Criteria a through g):
   a) Unstable angina pectoris ≤ 6 months prior to enrollment
   b) Acute myocardial infarction ≤ 6 months prior to enrollment
   c) New York Heart Association Class II-IV congestive heart failure
   d) Uncontrolled hypertension (as defined as ≥ 160/90 despite optimal medical management)
   e) Uncontrolled cardiac arrhythmias requiring anti-arrhythmic therapy other than beta blockers or digoxin
   f) Active coronary artery disease
   g) Fridericia's correction formula (QTcF) ≥ 480
3) Peripheral sensory neuropathy ≥ CTCAE Grade 2
4) Active infection requiring systemic treatment or any uncontrolled infection ≤ 14 days prior to enrollment
5) Known human immunodeficiency virus (HIV) or acquired immunodeficiency syndrome (AIDS)-related illness, or known active or chronic hepatitis B or C infection
6) History of interstitial lung disease (eg, pneumonitis or pulmonary fibrosis)
7) Evidence or history of bleeding diathesis or coagulopathy

8) Radiotherapy ≤ 28 days of enrollment. Patients must be recovered from all acute radiotherapy-related toxicities. No radiopharmaceuticals (strontium, samarium) within 8 weeks of enrollment
9) Prior treatment with any selective inhibitor (eg, AZD4547, BGJ398, JNJ-42756493, BAY1179470) of the FGF-FGFR pathway
10) Ongoing adverse effects from prior systemic treatment > NCI CTCAE Grade 1 (with the exception of Grade 2 alopecia and anemia)
11) Participation in another therapeutic clinical study or receiving any investigational agent within 28 days of enrollment or during this clinical study
12) Corneal defects, corneal ulcerations, keratitis, keratoconus, history of corneal transplant, or other known abnormalities of the cornea that may pose an increased risk of developing a corneal ulcer
13) Known positivity for HER2 (as defined by a positive IHC test of 3+ or IHC of 2+ with fluorescent in situ hybridization [FISH])
14) Major surgical procedures not permitted ≤ 28 days prior to enrollment. Surgery requiring local/epidural anesthesia must be completed at least 72 hours before enrollment. In all cases, the patient must be sufficiently recovered and stable before treatment administration
15) Women who are pregnant or breastfeeding (unless the patient is willing to interrupt breastfeeding during study treatment administration and then resume 6 months after study discontinuation); WOCBP must not consider getting pregnant during the study
16) Presence of any serious or unstable concomitant systemic disorder incompatible with the clinical study (eg, substance abuse, psychiatric disturbance, uncontrolled intercurrent illness including arterial thrombosis, or symptomatic pulmonary embolism)
17) 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 in the study
18) Known allergy, hypersensitivity or contraindication to components of the FPA144 formulation including polysorbate or to platinum-containing medications, 5-FU, or leucovorin
19) History of prior malignancy, except (Criteria a through f):
    a) Curatively treated non-melanoma skin malignancy
    b) Cervical cancer in situ
    c) Curatively treated Stage I uterine cancer
    d) Curatively treated ductal or lobular breast carcinoma in situ and not currently receiving any systemic therapy

e) Localized prostate cancer that has been treated surgically with curative intent and presumed cured

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

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

4.4 Patient Identification and Enrollment

Patients must be able to provide written informed consent and meet all eligibility criteria prior to enrollment. Patients who qualify for Phase 1 of the study will be enrolled in the first available cohort. A patient may be enrolled in either Phase 1 or Phase 2 of the study, but not both.

In Phase 2, patients first undergo pre-screening in which both a tissue test and a ctDNA blood assay are required. Tissue may be archival or fresh and if archival must be fresh section (cannot be previously cut slides). Patients who are determined to be FGFR2 positive by either test may immediately enter the screening period and be evaluated for eligibility for the Phase 2 study (refer to Section 3.3).

Table 4: Eligibility Based on FGFR2 Status

***FGFR2* Gene Amplification[1] (using a ctDNA blood assay)[2]**	**FGFR2b Overexpression[1] (using a tissue-based IHC assay)[3]**	**Eligibility**
Blood (+)	IHC (+)	Eligible
Blood (-)	IHC (+)	Eligible
Blood (+)	IHC (-)	Eligible
Blood (-)	IHC (-)	Ineligible

Abbreviations: ctDNA = circulating tumor DNA; FGFR2 = fibroblast growth factor receptor 2; IHC = immunohistochemistry.
Note: Patients must be FGFR2-positive by 1 of the 2 methods to be enrolled in the trial.
[1] Both tests will be carried out at central laboratories
[2] Requires 2 × 10 mL
[3] Minimum of 5 slides required

In both Phase 1 and 3, the investigator may repeat qualifying laboratory tests and vital signs/ECGs during the screening period one time 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 Patient Withdrawal and Replacement

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 as assessed by the investigator per RECIST v1.1

- 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
- Pregnancy at any time during the study
- At the specific request of the Sponsor or its authorized representative (eg, if the study is terminated for reasons of patient safety)

Patient replacement will be as follows:

- Patients in the Phase 1 safety run-in will be replaced if they are unevaluable for DLT (according to Section 3.2.6)
- Patients in the Phase 2 study will not be replaced

5.0 STUDY TREATMENT

5.1 FPA144

5.1.1 Identity, Packaging, Storage

FPA144 drug product is supplied for IV administration as a sterile, aqueous, colorless to slightly yellowish, pyrogen-free 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, and 0.01% (w/v) polysorbate 20 at pH 6.0. The final drug product will be provided as 2° to 8°C refrigerated liquid protected from light which is diluted for administration according to instructions provided in a separate Pharmacy Manual.

FPA144 will be supplied in a sterile vial for dilution in an IV bag for administration by the study center.

5.1.2 Administration (Phase 1 and Phase 2)

The FPA144 proposed doses were outlined above in Table 1. In Phase 1 the starting dose level of FPA144 is 6 mg/kg per dose in combination with a fixed dose chemotherapy regimen of mFOLFOX6 (Section 5.2). In Phase 2, the dose of FPA144 in combination with a fixed dose chemotherapy regimen of mFOLFOX6 will be determined by evaluation of the data from Phase 1 of the study.

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 C1D1 and should be recalculated only if the weight changes > 10% from the C1D1 weight. If the dose is recalculated due to a >10% weight change from C1D1, the weight used for the recalculated dose should function as the new baseline for subsequent evaluation of dose recalculations. Doses should be rounded to the nearest 10 mg.

A pharmacist (or other responsible person) will prepare FPA144 for administration. After calculating the number of vials based on the patient's weight, FPA144 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 (± 10 minutes) 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 according to Sections 3.2.2 and 5.1.3.4. If a patient experiences an infusion reaction, the patient's vital signs (temperature, blood pressure [BP], heart rate [HR], and respiration rate [RR]) 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.

Patients may continue receiving FPA144 administered in 2-week cycles until investigator-assessed disease progression (Phase 2 only), unacceptable toxicity, or until the patient meets any of the other protocol-specified withdrawal criteria. There is no maximum number of doses of FPA144.

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

5.1.3 FPA144 Dose Modifications

Dose modifications discussed in this section include intrapatient dose modifications. Dose escalations/modifications between cohorts in Phase 1 are described in Section 3.2.1. The dose of FPA144 for Phase 2 was determined by evaluation of the data from Phase 1 of the study, as described in Sections 3.2.3 and 3.2.4.

5.1.3.1 Dose Escalation

In Phase 1, intrapatient dose escalation will not be permitted. In Phase 2, patients will be treated at the MTD and/or RD as determined from Phase 1.

5.1.3.2 Weight

A complete physical examination including height and weight will be performed at Screening. The dose of FPA144 will be based on body weight at C1D1 and should be recalculated only if the weight changes > 10% from the C1D1 weight. If the dose is recalculated due to a >10% weight change from C1D1, the weight used for the recalculated dose should function as the new baseline for subsequent evaluation of dose recalculations.

5.1.3.3 Infusion or Hypersensitivity Reactions

If a patient experiences a Grade 3 or higher infusion or hypersensitivity reaction prior to completion of FPA144 infusion, the infusion must be stopped, and the patient promptly managed and monitored according to signs, symptoms, and local standard protocol until complete resolution of the event. Signs and symptoms of infusion or hypersensitivity reactions may include, but are not limited to fever, chills, rigors, urticaria, hypotension or hypertension, headache, wheezing, shortness of breath, hypoxia, and pulmonary infiltrates. Appropriate interventions include, but are not limited to antihistamines, corticosteroids, bronchodilators, and/or IV fluids.

If a patient experiences an infusion reaction, the patient's vital signs (temperature, BP, HR, and RR) should be monitored every 30 minutes after the infusion has been discontinued for a minimum of 2 hours or resolution of the infusion reaction, whichever takes longer.

At the investigator's discretion, the infusion of FPA144 may also be stopped if a less severe AE (Grade 1 or 2) occurs during the infusion.

If the infusion reaction resolves, at investigator discretion the infusion may be restarted at half the previous infusion rate. If, despite appropriate premedication, signs or symptoms of a hypersensitivity/infusion reaction recur, the infusion should be discontinued, and no further dosing of FPA144 will occur without consultation with the Sponsor or Sponsor's designee.

After experiencing a Grade 3 or higher infusion or hypersensitivity reaction, all subsequent infusions of FPA144 for the patient should be administered at the reduced rate (over 60 minutes) with premedication. Pre-medication may include medications such as corticosteroids, antihistamine and/or acetaminophen in accordance with local standard of care.

5.1.3.4 Toxicity: FPA144 Dose Modification Guidelines

Dose reductions for FPA144 may be permitted for patients on treatment beyond the DLT period in Phase 1 or any patient in Phase 2 and are based on local laboratories and clinical assessment. If a patient in Phase 1 requires a dose reduction or is unable to receive FPA144 during the DLT period, their reported toxicity is considered a DLT and be permanently discontinued from FPA144. Doses may be held or reduced for FPA144-related AEs following the guidelines outlined in Table 5 (Phase 2 FPA144 dose levels for dose reductions), Table 6 (non-corneal toxicities), and Table 7 (corneal toxicities).

Any patient with a corneal event which occurs within 100 days of last receiving a dose of FPA144, regardless if deemed related or not related to FPA144 should be evaluated by an ophthalmologist. Any patient with FPA144-related retinal toxicity should permanently discontinue FPA144. 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 or designee. Patients may resume the FPA144 if the event returns to baseline or ≤ Grade 1 in accordance with the guidelines outlined in Table 6, and Table 7.

Patients who require FPA144 dose reductions will receive the reduced dose for the remainder of the study. Cycles may be delayed to manage toxicity. Cycle delays of longer than 28 days should be discussed with the medical monitor prior to reinitiation.

Table 5: Phase 2 FPA144 Dose Levels for Dose Reductions

Dose Level	FPA144 Dose
0	15 mg/kg Q2W + 7.5mg/kg D8[1]
-1	6 mg/kg Q2W

[1] For patients who require dose reduction prior to C1D8, the C1D8 dose should be skipped, continuing with 15mg/kg Q2W

Table 6: Dose Modification Guidelines for FPA144 Related Adverse Events (Any Noncorneal, Noninfusion Toxicity[1])

FPA144-Related Toxicity Grade	Dose Schedule	New FPA144 Dose
Grade 1 or 2	No delay or missed dose required	100% of dose
Grade 3 (first occurrence)	Delay or miss dose until recovery to baseline or Grade 1	If recovery to baseline or Grade 1 within 28 days, may resume at 100% of starting dose or 1 dose lower[2]
Grade 3 (second occurrence)	Delay or miss dose until recovery to baseline or Grade 1	If recovery to baseline or Grade 1 within 28 days, may resume at 1 dose level lower[2] than previous dose or discontinue
Grade 3 (third occurrence) Grade 3 which does not recover to baseline or Grade 1 within 28-day of onset event Any Grade 4	Permanently Discontinue	N/A

Abbreviations: N/A = not applicable.

[1] mFOLFOX6 dosing in case of FPA144 toxicity may continue regardless of FPA144 dose modifications.

[2] See Table 5 for dose levels for dose reductions in Phase 2.

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

Table 7: Dose Modification Guidelines for FPA144 (Any Related Corneal Toxicity[1])

FPA144/IMP-related Toxicity Grade	Dose Schedule	New FPA144 Dose
Grade 1	No Delay	100%
Grade 2 and Grade 3	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 or Grade 3 which does not return to baseline within 28 days since last dose Any Grade 4	Permanently discontinue dosing of FPA144	N/A

Abbreviations: N/A = not applicable.

[1] mFOLFOX6 dosing may continue regardless of FPA144 dose modifications.

There is a ± 3-day window for the first 3 cycles (42 days) of FPA144 dosing regardless of delays in mFOLFOX6 in Phase 2 only. After the first 3 cycles, FPA144 can be delayed up to a maximum of 7 days to synchronize with mFOLFOX6 chemotherapy infusion. However, synchronization of administration of FPA144/placebo and mFOLFOX6 is not a protocol requirement. Vital signs and clinical laboratory tests must be performed within 72 hours prior to either FPA144 or mFOLFOX6 administration. Patients should only have 2 consecutive doses of FPA144 within 7 days during Cycle 1 of treatment if enrolled in Cohort 2 (Phase 1) or if the RD

of FPA144 is the dose used in Cohort 2 (Phase 2). In subsequent cycles, FPA144 is administered Q2W. The first dose of each cycle is considered Day 1 of each cycle. Cycles will repeat every 2 weeks unless there is a treatment delay. Intrapatient dose escalation above the starting dose for each patient will not be permitted. Any patient whose dose of FPA144 is decreased cannot be subsequently increased.

5.2 mFOLFOX6

Leucovorin (or levo-leucovorin), 5-FU, and oxaliplatin will be obtained from commercial sources at each participating site. Management (ie, handling, storage, administration, and disposal) of these products will be in accordance with the relevant local guidelines. For countries where the Sponsor is required to provide all study drugs, including standard-of-care drugs, the Sponsor designee will provide leucovorin, 5-FU, and oxaliplatin from a commercial supply that is clinically labelled in accordance with relevant local guidelines. For further details, refer to the manufacturer's prescribing information for the respective chemotherapies and the study Pharmacy Manual.

5.2.1 Identity, Packaging, Storage

Refer to the most current package insert for packaging, labeling, and storage information of mFOLFOX6.

FPA144 will be packaged and labeled as a 20 mL fill in ISO 20R vials by the Sponsor (or designee).

All FPA144 vials must be stored refrigerated at 2° to 8°C in accordance with the manufacturer's instructions as provided in the Pharmacy Manual. Until dispensed to patients, FPA144 will be stored in a securely locked area, accessible to authorized personnel only.

5.2.2 Administration (Phase 1 and Phase 2)

mFOLFOX6 will be administered Q2W beginning on C1D1, and will be administered at least 30 minutes after the end of the infusion of FPA144.

For further prescribing information, refer to the manufacturer's prescribing information for the respective chemotherapies and the study Pharmacy Manual. Oxaliplatin, 5-FU, and leucovorin will be administered by each site as detailed below (and as was outlined above in Table 1). The mFOLFOX6 regimen will be administered Q2W (± 3 days) until investigator-assessed disease progression (Phase 2 only), clinical disease progression, unacceptable toxicity, or the patient meets any of the other protocol-specified withdrawal criteria.

Instructions for mFOLFOX6 administration include the following:

On Day 1 of each cycle (at least 30 minutes after FPA144/placebo):

- Oxaliplatin 85 mg/m^2 IV infusion over 120 minutes
- Leucovorin 400 mg/m^2 IV infusion over 120 minutes, can be administered concurrently with oxaliplatin if using a Y connector, (if not using a Y connector, administer drugs sequentially)
  - If leucovorin is unavailable, 200 mg/m^2 levo-leucovorin may be used. Study treatment may be administered without either agent in the event that both are unavailable. Leucovorin (or levo-leucovorin) may be given at either the protocol-recommended doses or as deemed appropriate by the investigator in accordance with institutional standard of care
- Immediately after oxaliplatin and leucovorin, 5 FU 400 mg/m^2 bolus over approximately 5 minutes
- Immediately after the 5-FU bolus, 5-FU 2400 mg/m^2 as a continuous IV infusion over approximately 48 hours

Premedication may be used at the discretion of the investigator based on the local standard of care.

5.2.3 mFOLFOX6 Dose Modifications

Guidelines for dose interruptions, delays, and modifications due to toxicity are outlined in Section 5.2.3.1. If mFOLFOX6 is delayed due to toxicity, vital signs and clinical laboratory tests need to be performed within 72 hours of its administration.

In the event that oxaliplatin administration is discontinued for any reason prior to disease progression, 5-FU/leucovorin therapy may continue on a Q2W schedule until disease progression, unacceptable toxicity, or other cause for study withdrawal. In the case 5-FU/leucovorin therapy is permanently discontinued then oxaliplatin must be discontinued.

5.2.3.1 Toxicity: mFOLFOX6 Dose Modifications Guidelines

Patients should be closely monitored for mFOLFOX6 toxicity. In Phase 1, any patient who does not receive 2 complete doses of mFOLFOX6 during the DLT period due to a reason that is not a DLT or an AE related to FPA144, will be considered unevaluable and the patient will be replaced. Beyond the DLT period in Phase 1, or at any time in Phase 2, dose adjustments for any component of mFOLFOX6 are permitted according to the guidelines outlined below.

The dose of mFOLFOX6 is based on body weight at C1D1 and should be recalculated only if the weight changes > 10% from the C1D1 weight. If the dose is recalculated due to a >10% weight change from C1D1, the weight used for the recalculated dose should function as the new baseline for subsequent evaluation of dose recalculations.

Patients should be counseled to avoid exposure to cold weather during and for approximately 72 hours after each infusion.

Correct hypokalemia and hypomagnesemia prior to initiating oxaliplatin.

Evaluation for dihydropyrimidine dehydrogenase deficiency should be considered if the following events occur after 5-FU: severe diarrhea, mucositis, and myelosuppression.

The leucovorin dose is given for d, l-racemic mixture. Use half the dose for levo-leucovorin (l-leucovorin). Leucovorin will stay at a fixed dose of (400 mg/m2 and or as deemed appropriate by the investigator) will be given prior to each 5-FU dose. If 5-FU is delayed, leucovorin will be delayed. If leucovorin is not available, levo-leucovorin (200 mg/m2 or as deemed appropriate by the investigator) may be administered. Leucovorin or levo-leucovorin may be omitted from study treatment in the event that they are both unavailable.

Patients who require chemotherapy dose reductions will receive the reduced dose for the remainder of the study. The only exception to this practice will be in the case of nausea/ vomiting. If nausea and/or vomiting occur despite antiemetic therapy, the chemotherapy dose should be reduced by 25% for the next dose. If tolerated, an increase back to a 100% dose may be allowed at the investigator's discretion. Any patient who required 2 dose reductions and experienced persistent toxicity with a third dose reduction will be discontinued from all chemotherapy. Chemotherapy cycles may be delayed to manage toxicity. Cycle delays of longer than 28 days should be discussed with the medical monitor prior to reinitiation of treatment.

Dose adjustments at the start of each 14-day cycle will be based on nadir hematologic counts or maximum non-hematologic toxicity from the preceding cycle of therapy.

Dose adjustments of each agent may be made independently based on the specific types of toxicities observed.

Recommended dose adjustments for mFOLFOX6 toxicity are shown in Table 8.

Table 8: Dose Reductions and Delays for mFOLFOX6 Chemotherapy

Toxicity	Grade	Oxaliplatin	5-FU
Neurotoxicity	Persistent (≥14 days) Grade 2 neurotoxicity	Decrease from 85 mg/m^2 to 65 mg/m^2 [a]	No change
	Transient (> 7 days and ≤ 14 days) Grade 3 neurotoxicity	Decrease from 85 mg/m^2 to 65 mg/m^2 [a]	No change
	Persistent (> 14 days) ≥ Grade 3 neurotoxicity or any Grade 4 neurotoxicity	Permanent Discontinuation	No change
Gastrointestinal	≥ Grade 3 (after prophylaxis)	Hold until toxicity is ≤ Grade 1, decrease from 85 mg/m^2 to 65 mg/m^2 [a]	Hold until toxicity is ≤ Grade 1, decrease by 20% [a]
Hematologic	≥ Grade 3 platelets	Hold until platelets are ≥ 75,000 then decrease from 85 mg/m^2 to 65 mg/m^2 [a]	Reduce by 20% [a]
	≥ Grade 3 neutropenia	Hold until ANC is ≥ 1500, then decrease from 85 mg/m^2 to 65 mg/m^2 [a]	Reduce by 20% [a]
Skin	≥ Grade 3 hand/foot syndrome	Hold until 5-FU resumes, then no change	Hold until ≤ Grade 1, then decrease by 20% [a]
Other	≥ Grade 3	Hold until ≤ Grade 1, then decrease from 85 mg/m^2 to 65 mg/m^2 [a]	Hold until ≤ Grade 1, then reduce by 20% [a]
Pharyngolaryngeal dysesthesia	Any	Stop infusion, then consider increase duration of infusion up to 6 hours	No change
Pneumonitis	Any	Hold, investigate; discontinue permanently if confirmed	
Hepatic Impairment	Bilirubin 1–2× ULN	No change	No change, consider decrease by 20%[a]
	Bilirubin > 2–4× ULN and/or AST/ALT is 2–4× ULN	No change	No change, consider decrease by 20%
	Bilirubin > 4× ULN and/or AST/ALT is > 4× ULN	Discontinue	Discontinue
Renal Impairment (Creatinine Clearance)	> 50 mL/min	No change	No change
	30 to < 50 mL/min	No change, consider decrease to 65 mg/m^2[a]	No change
	< 30 mL/min	Discontinue	Decrease dose by 20%[a]

[a] If toxicity recurs at the same grade level after dose reduction; consider permanent discontinuation. Note that if 5-FU is permanently discontinued, oxaliplatin and leucovorin should be permanently discontinued.

Adapted from (Cheeseman 2002, Hochster 2008, Teva Pharmaceuticals USA 2012, Teva Parenteral Medicines Inc 2014, Teva Parenteral Medicines Inc 2016)

If a patient experiences Grade 1 or 2 allergic reaction to oxaliplatin, premedication should be given according to institutional practice prior to subsequent further study drug administration. If Grade 1–2 allergic reaction persists into the next cycle, escalating the appropriate premedication should be given according to institutional practice prior to administration of oxaliplatin.

For patients experiencing Grade 3-4 allergic reactions, treatment with oxaliplatin should be discontinued.

5.3 Placebo

Placebo product (only used in Phase 2) will match the FPA144 drug product. It will be supplied for IV administration as a sterile, aqueous, colorless to slightly yellowish, pyrogen-free solution supplied in single-use vials. The composition of matching placebo contains 20 mM L-histidine, 270 mM sucrose, and 0.01% (w/v) polysorbate 20 at pH 6.0. Placebo will be administered in a method that matches the administration of FPA144 to maintain blinding.

5.4 Unblinding Treatment Assignment

The Phase 2 portion of this study is double-blind. Placebo will be matched to FPA144. Treatment codes should not be broken except in emergency situations. With the exception of unblinding for the analysis (to be defined in the Statistical Analysis Plan [SAP]), all individuals involved in the conduct of the study (eg, all site staff and participants, monitoring personnel, Sponsor personnel) will be blinded to randomized treatment assignment. The decision and ability to unblind the treatment code in emergency situations resides with the investigator.

The investigator should document and provide an explanation for any premature unblinding (eg, accidental unblinding or unblinding because of a serious adverse event).

5.5 Drug Accountability

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

The investigator is responsible for destroying or returning all unused study treatment 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 unused, used or partially used study treatment vials according to the site policy once Sponsor (or designee) 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.

5.6 Investigational Product Compliance

Only qualified trained study center personnel may administer FPA144. Pharmacy personnel trained in the study requirements will monitor compliance with the treatment assignments. Records of study medication administered (date, time, and dose administered relative to time of preparation) will be recorded on the patient's eCRF.

5.7 Concomitant Medication and Treatment

Supportive care (eg, antiemetics, analgesics for pain control) may be used at the investigator's discretion and in accordance with institutional procedures. Patients should receive antiemetic and other prophylactic treatments according to the local standard of care and manufacturer's instruction. Patients should receive full supportive care, transfusions of blood and blood products, antibiotics, antiemetics, etc., when appropriate. Hematopoietic stimulating agents may be used if indicated. Concomitant anticancer therapies of any kind are not permitted.

Patients receiving oxaliplatin should not receive oral cryotherapy as this may exacerbate laryngopharyngeal dysesthesia caused by oxaliplatin. For patients on anticoagulant therapy, close monitoring of coagulation parameters is recommended.

5.8 Prohibited Therapy

Vaccination with a live vaccine should be avoided in patients receiving 5-FU because of the potential for serious or fatal infections.

6.0 STUDY ASSESSMENTS AND PROCEDURES

Unless otherwise specified, all assessments and procedures must be conducted in accordance with the Schedule of Assessments (Appendix 2 and Appendix 3).

Descriptions of assessments are provided in Sections 6.1 through 6.19 below.

Additional guidance for study assessments and procedures is provided in the following appendices:

- Schedule of Assessments for Phase 1: Appendix 2
- Schedule of Assessments for Phase 2: Appendix 3
- List of safety laboratory assessments for Phase 1 and Phase 2: Appendix 4
- Clinical Fixed Time Point Assessments: Appendix 5
- Instructions for the collection time points of PK, immunogenicity, and [redacted] for Phase 1 are provided in Appendix 6
- Instructions for the collection time points of PK and immunogenicity samples for Phase 2 are provided in Appendix 7

6.1 Tumor Tissue Collection: Analysis for FGFR2b Overexpression for Patient Selection

6.1.1 Phase 1

Provision of tissue for retrospective FGFR2b overexpression testing by IHC, and blood for FGFR2 amplification by ctDNA, are not required for enrollment in Phase 1, but will be tested retrospectively if available.

Patients eligible for Phase 1 have unselected GI cancer (with or without FGFR2 positive status) with unresectable, locally advanced, or metastatic disease, and are candidates to receive both FPA144 and mFOLFOX6 chemotherapy. FGFR2b overexpression will be determined retrospectively using central assessment by IHC and *FGFR2* gene amplification will be determined retrospectively by using central assessment by a ctDNA blood assay.

6.1.2 Phase 2

Provision of archival (or fresh biopsy if archival tissue is not available) for Pre-Screening FGFR2b overexpression testing by IHC is required; a blood sample is also required for Pre-Screening by ctDNA for FGFR2 gene amplification. FGFR2 positive status by one of these testing methods is required for enrollment in Phase 2. Results of the centralized FGFR2 testing may take approximately 2 weeks; patients are permitted to receive up to 1 dose of mFOLFOX6 during this interim time period (pre-screening) at the discretion of the investigator. This 1 dose

of chemotherapy is not a requirement of the study and is not considered part of this clinical study.

Patients in Phase 2 of this study must consent to tumor tissue analysis and blood sample analysis. Patients will be selected for enrollment based on FGFR2b overexpression and/or *FGFR2* gene amplification, as determined by a validated IHC or ctDNA blood assay, respectively, using the central laboratory. Patients who do not demonstrate either FGFR2b overexpression using IHC or *FGFR2* gene amplification using a ctDNA blood assay will not be eligible for enrollment. However, positivity based on 1 or both of the assays is adequate to meet eligibility requirements (eg, positive by ctDNA blood assay, but negative by IHC, and vice versa) (refer to Table 4). It is the responsibility of each investigator to obtain an adequate tumor specimen for analysis of FGFR2 positivity for enrollment. A minimum of 5 slides are required. Tumor slide or tumor block specimen processing, labeling, and shipping instructions are detailed in the Laboratory Manual that will be distributed with the specimen collection kit.

Central laboratories will perform the FGFR2b overexpression and *FGFR2* gene amplification analysis using a validated IHC test and ctDNA blood assay.

For Phase 2, once tumor and blood specimens are received, analysis will be performed as efficiently as possible, and results will be communicated back to the investigator or designee.

6.2 Informed Consent Requirements

Written, signed informed consent must be collected prior to any study-specific procedures (including pre-screening). Patients who have fully consented to participation in the main study will undergo screening assessments within 28 days prior to administration of the first infusion of study treatment.

6.3 Screening

Unless otherwise specified, all Screening assessments must be completed prior to enrollment in accordance with the Schedule of Assessments (Appendix 2). During the screening period, the patient will undergo protocol-specified screening procedures to ensure all eligibility criteria are met.

6.3.1 Phase 1

For Phase 1, all patients will undergo screening assessments within 28 days (as outlined in Appendix 2). After a maximum 28-day screening period, eligible patients will initiate study treatment as described in Section 5.0. Patients who screen fail may undergo repeat screening procedures one time, but all procedures must be done within the 28-day screening window, inclusive of informed consent.

Patients may have initiated or received mFOLFOX6 chemotherapy prior to enrollment in Phase 1, but eligibility requires that the patient be a candidate to receive at least 2 additional doses of mFOLFOX6 chemotherapy (there is no upper limit on the number of previous mFOLFOX6 doses that patients may have received, nor is there a requirement for prior treatment with mFOLFOX6 in Phase 1).

Patients should have tumor tissue collected from archival material (if available) for analysis of FGFR2b overexpression by IHC retrospectively.

6.3.2 Phase 2

For Phase 2, all patients will undergo screening assessments within 28 days. After a maximum 28-day screening period, eligible patients will initiate randomized study treatment as described below. Patients who screen fail for Phase 2 may repeat screening procedures one time (not applicable to pre-screening when tissue or blood sample is determined to be evaluable and FGFR2 negative), but all procedures must be done within the 28-day screening window, inclusive of informed consent.

The description of testing for FGFR2 positivity is described in Section 3.3. Eligibility for Phase 2 will be evaluated in 2 steps:

- Step 1: Patients will provide informed consent to allow testing for FGFR2b overexpression by archival or fresh tissue with IHC and a blood sample for FGFR2 amplification by ctDNA. The time between providing informed consent and site notification of the result of the test is considered the pre-screening period (refer to Section 3.3).
- Step 2: Pre-screening allows for collection of blood and tissue to determine FGFR2 positivity using ctDNA and IHC assays. Once a patient is confirmed to have a positive result based on central testing, the screening period initiates, allowing for evaluation of all other eligibility criteria (refer to Section 4.2). Patients who test negative for FGFR2b overexpression or FGFR2 amplification will be considered pre-screen failed. Patients who test positive and enter the screening period, but do not enroll, will be considered screen failed.

6.4 Study Enrollment

6.4.1 Phase 1

Phase 1 is an open-label dose-escalation safety run-in. There is no randomization in this phase. Patients who are determined to be eligible will be enrolled sequentially. For patients participating in Phase 1, the date of enrollment is the date of first administration of study treatment.

FGFR2 status is not a requirement for enrollment in Phase 1. FGFR2b overexpression will be tested retrospectively by IHC (if tissue is available) and FGFR2 gene amplification will be tested retrospectively by ctDNA blood assay.

6.4.2 Phase 2

In Phase 2, patients who meet eligibility will be randomized 1:1 to FPA144 + mFOLFOX6 or placebo + mFOLFOX6. The date of enrollment is the date of randomization. Patients must initiate the first administration of study treatment within 3 days of enrollment. The date of first administration of study treatment is C1D1 or Study Day 1.

Enrollment in Phase 2 will begin when an RD for FPA144 has been identified by the CRC, which will not exceed the highest dose level evaluated and tolerated in Phase 1; based on the Phase 1 results, the Phase 2 dose of FPA144 is 15 mg/kg Q2W with an additional dose of 7.5 mg/kg on Cycle 1 Day 8. Patients may enroll in either Phase 1 or Phase 2, but may not enroll in both phases of the study. Opening the Phase 2 portion of the study for enrollment will be at the discretion of the Sponsor. A patient is considered enrolled when he/she is randomized.

In Phase2, FGFR2b overexpression will be determined by prospective IHC analysis and/or a ctDNA blood assay demonstrating FGFR2 gene amplification.

Eligible patients whose tumors have FGFR2b overexpression by IHC and/or *FGFR2* gene amplification by blood may consent to study participation and subsequently undergo Screening procedures, including a comprehensive ophthalmologic examination, to ensure the eligibility criteria are met.

Baseline radiographic imaging is also a study requirement. Imaging performed as standard of care that includes imaging of chest, abdomen and pelvis may be used if it has been performed within 28 days (+3 days) of treatment (C1D1).

6.4.3 Blinding

The Phase 1 part of this study will be open label.

For Phase 2, all individuals involved in the conduct of the study (ie, site staff and patients, CRO personnel, Sponsor personnel) will be blinded to randomized treatment assignment.

To facilitate the Phase 2 analysis, certain Sponsor representatives and Sponsor designees will be unblinded to treatment assignments prior to and during the analysis (including the biostatistician and external groups for bioanalytical PK/pharmacodynamic, and PRO analyses). Additional details of the analyses and unblinding will be provided in the SAP.

6.5 Medical/Oncology History and Demographics

In both Phase 1 and Phase 2, patient medical and surgical history recorded during the Screening visit includes a thorough review of significant past medical and surgical history, current conditions, concomitant therapies, alcohol and smoking history, and smoking status. At C1D1,

the medical, disease, and medication history should be updated to capture any changes from Screening.

Demographics including age, gender, race, and ethnicity will be recorded.

6.6 Safety Assessments

Safety measures will include AEs, hematology, clinical chemistry, urinalysis, vital signs, body weight, concomitant medications/procedures, ECOG performance status, targeted physical examinations, ECGs, and ophthalmology examinations. Safety measures are to be collected in both Phase 1 and Phase 2 in accordance with the Schedules of Assessments (Appendix 2, Appendix 3, and Appendix 4).

Safety measures will also include evaluation for DLTs in Phase 1 only (refer to Section 3.2.3).

An independent DMC will evaluate safety study data (AEs and SAEs) on a regular basis throughout the entire treatment phase (as prescribed in the DMC Charter) in Phase 2 (refer to Section 8.10.2).

6.6.1 Vital Signs

Vital signs (BP, HR, RR, and temperature) are to be measured in both Phase 1 and Phase 2 in accordance with the Schedules of Assessments (Appendix 2, Appendix 3, Appendix 5).

6.6.2 Physical Examinations, Height, and Weight

A complete physical examination including height and weight will be performed at Screening. Limited physical examinations (eg, symptom-directed examination of specific organ systems/body area) should be conducted in both Phase 1 and Phase 2 in accordance with the Schedules of Assessments (Appendix 2, Appendix 3) and include weight and examination of the oropharynx.

The dose of FPA144 and mFOLFOX6 is based on body weight at C1D1 and should be recalculated only if the weight changes > 10% from the C1D1 weight. If the dose is recalculated due to a > 10% weight change from C1D1, the weight used for the recalculated dose should function as the new baseline for subsequent evaluation of dose recalculations.

6.6.3 Ophthalmologic Examinations

Ophthalmologic examinations, including comprehensive ophthalmologic examinations and slit lamp examinations with fluorescein score, will be performed in both Phase 1 and Phase 2 according to Appendix 2, Appendix 3, Appendix 5. Any abnormal OCT examinations reports should be provided to the Sponsor. In addition, if a patient has any persistent ophthalmologic findings, the ophthalmologic assessments should continue every 8 weeks until resolution of findings, withdrawal of consent, death, or loss to follow up.

Comprehensive ophthalmologic examinations include fundoscopic and slit lamp examination, OCT, visual acuity, completion of fluorescein staining score form (Appendix 9), determination of intraocular pressure (IOP), and review of ocular/visual symptoms. When performing the ocular examination by the ophthalmologist, the following should be noted:

- IOP can be measured by tonometer or applanation, but should be done before dilation
- Confrontation visual fields is adequate
- OCT should include the macula: Any abnormal OCT examinations identified during the study should be provided to the Sponsor.
- Corneal staining and scoring should be done before dilation and before the IOP check as both may disrupt corneal integrity

During Phase 1, comprehensive ophthalmologic examinations will be performed during Screening, at approximately 4 weeks from C1D1, at approximately 8 weeks from C1D1, at the EOT visit (± 7 days), and at any time there are ophthalmologic symptoms up to 100 days after the last dose of FPA144. In addition to the comprehensive ophthalmologic exams, slit lamp examinations with completion of fluorescein staining score will be performed starting at Week 16 (± 7 days) from C1D1 and continue every 8 weeks until study completion.

During Phase 2, comprehensive ophthalmologic examinations will be conducted at Screening, at 8 weeks from C1D1 (± 7 days), at the EOT visit (± 7 days), and at any time there are ophthalmologic symptoms up to 100 days after the last dose of FPA144. In addition to the comprehensive ophthalmologic examinations, slit lamp examinations with completion of fluorescein staining score form will be performed starting at 16 weeks (± 7 days) from C1D1 and then every 8 weeks (± 7 days) until study completion.

In both Phase 1 and Phase 2, after the EOT visit, if the patient has any persistent corneal findings, the assessments should continue every 8 weeks until resolution of findings, withdrawal of consent, death, or loss to follow up.

6.6.4 Electrocardiograms

Twelve-lead ECGs will be performed in both Phase 1 and Phase 2 in accordance with the Schedules of Assessments (Appendix 2, Appendix 3), and Table of Clinical Fixed Time Point Assessments (Appendix 5). 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.

6.6.5 Eastern Cooperative Oncology Group Performance Status

ECOG performance status will be assessed in all patients in both Phase 1 and Phase 2 at the time points outlined in Appendix 2 and Appendix 3. The ECOG performance status is a scale used to assess how a patient's disease is progressing, assess how the disease affects the daily living

abilities of the patient, and determine appropriate treatment and prognosis. The ECOG scale is shown in Appendix 8.

6.7 Clinical Laboratory Parameters

Laboratory assessments (listed in Appendix 4) will be performed locally in both Phase 1 and Phase 2 at each study center'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. Local hematology and blood chemistry test results must be obtained within 96 hours prior to enrollment. On subsequent dosing days for both FPA144 and mFOLFOX6 (Phase 1) or FPA144/placebo and mFOLFOX6 (Phase 2), hematology and blood chemistry results must be obtained within 72 hours prior to dosing. Coagulation results need to be obtained at baseline, at Day 1 of Cycles 1 through 4 within 72 hours prior to dosing with FPA144, and whenever clinically indicated. Ongoing evaluation of INR or PT should be continued for patients who are receiving therapeutic anticoagulation according to the local standard of care.

Blood samples should be taken using standard venipuncture techniques. Laboratory assessments will be performed in both Phase 1 and Phase 2 in accordance with the Schedule of Assessments (Appendix 2, Appendix 3). Abnormal laboratory results that lead to a change in patient treatment management (eg, 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. Refer to Section 6.17.2 for details around the reporting of abnormal laboratory findings as AEs.

6.8 Urinalysis

Urinalysis will be performed in both Phase 1 and Phase 2 in accordance with the Schedule of Assessments (Appendix 2, Appendix 3). Urinalysis includes protein, glucose, blood, pH, and ketones on Day 1 for both FPA144 and mFOLFOX6 of odd cycles (every other cycle). If findings clinically significant, a microscopic evaluation will be performed per institutional standard.

6.9 Pregnancy

Pregnancy is an exclusion criterion and WOCBP must not be considering getting pregnant during the study. Serum beta-human chorionic gonadotropin (ß-hCG) (evaluated by local laboratories) and urine pregnancy tests will be performed only on WOCBP. A serum pregnancy test in WOCBP obtained within 96 hours prior to enrollment is mandatory in both Phase 1 and Phase 2. Subsequent pregnancy tests should be performed in accordance with the Schedule of Assessments (Appendix 2, Appendix 3).

In the event of suspected pregnancy, a serum pregnancy test should be repeated. Patients who become pregnant during the study must discontinue study treatment immediately.

The Sponsor must be notified of any patient who becomes pregnant while participating in this study. Although pregnancy is not an AE, all pregnancies must be followed to conclusion to determine their outcome. Male patients should immediately inform the investigator if their partner becomes pregnant during the study or within 6 months after the last dose of study medication. 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 upon learning of a pregnancy.

Notification of the pregnancy including the anticipated date of birth should be provided on a Pregnancy Reporting Form within 24 hours of awareness and reported using the same procedure as described for reporting SAEs (Section 6.17.4). If the pregnancy is to be terminated, the anticipated date of termination should be provided. A pregnancy report form should also be completed by the investigator within 24 hours after learning of the pregnancy in the partner of a male patient during the study or within 6 months after the last dose of study medication using the procedure for SAE reporting (Section 6.17.4). An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

The patient will be asked to provide information on the outcome of the pregnancy, including premature termination should the case arise. Spontaneous miscarriages, premature termination of the pregnancy, congenital abnormalities and any other abnormalities in the mother or fetus/newborn will be reported as SAEs. Information on the status of the mother and child will be forwarded to the Sponsor. Attempts should also be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to drug. The pregnant partner will need to sign and Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up of the pregnancy. Once the authorization has been signed the investigator will update the Pregnancy Report reform with additional information on the course and outcome of the pregnancy. Generally, follow-up will be in accordance with regulatory guidance and at least 6 to 8 weeks after the estimated delivery date.

Pregnancies that occur during the first 6 months of the Follow-up Period should be reported to the Sponsor and followed as described above.

6.10 Tumor Assessments

Tumor assessments will be performed in Phase 2 only. Tumor assessments should consist of clinical examination and appropriate imaging techniques (preferably CT scans with appropriate slice thickness per RECIST v1.1; MRIs are acceptable). The same methods used to detect lesions at baseline are to be used to follow the same lesions throughout the clinical study.

Tumor response assessment will be performed by the investigator per RECIST v1.1 guidelines.

Tumor scans will be performed at Screening (within 28 days +3 days) of treatment [C1D1] and then every 8 weeks (± 7 days) from C1D1 until 12 months and then every 12 weeks (± 14 days) thereafter. Scans should be obtained per schedule regardless of drug interruption or discontinuation.

Patients who discontinue study treatment (the last administered dose of FPA144/placebo and mFOLFOX6) for reasons other than disease progression or withdrawal of consent, radiographic tumor assessments will continue according to the protocol (approximately every 8 weeks ± 7 days) until 12 months and then every 12 weeks ± 14 days thereafter) until either the patient initiates additional anticancer therapy or experiences disease progression.

6.11 Pharmacokinetic Assessment

Blood samples to determine serum FPA144 concentration will be acquired from each patient as outlined in the Study Flowchart for PK, Immunogenicity, and [redacted] for Phase 1 (Appendix 6) and in the Study Flowchart for PK and Immunogenicity Blood Samples Collections for Phase 2 (Appendix 7). These samples will be collected and processed according to the instructions provided in a separate Laboratory Manual.

PK parameters will be estimated using noncompartmental analysis, though compartment analysis may be employed if appropriate. Serum concentration-time data from FPA144-004 will be pooled with data from other studies for integrated population PK analysis and exposure-response relationship assessment.

6.12 Pharmacodynamic Biomarker Analysis Using Blood

Pharmacodynamic assessments will only be conducted in Phase 1.

Pharmacodynamic samples will be collected at the time points specified in Appendix 6. Tumor tissue provided for evaluation of FGFR2 status, if available, will be retrospectively analysed for FGFR2b overexpression using IHC.

Blood samples provided for evaluation of FGFR2 status will be collected prior to the first dose of study treatment and analysed retrospectively for *FGFR2* gene amplification using a ctDNA blood assay.

[redacted]

6.13 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 ADA concentration. Additional characterization of a confirmed anti-FPA144 antibody response may be conducted.

Samples for immunogenicity, anti-drug antibody (ADA) assessment will be drawn in both Phase 1 and Phase 2 from each patient at the time points outlined in Appendix 6 and Appendix 7. Samples for immunogenicity testing will be collected and processed at central laboratory according to the instruction provided in the Laboratory Manual.

6.14 Immunohistochemistry

In Phase 1 collection of samples is optional for FGFR2b overexpression using IHC (archival sample with fresh cuts).

Phase 2 requires collection of samples for FGFR2b overexpression using IHC (archival sample with fresh cuts or a fresh biopsy). Patients whose samples show FGFR2b overexpression will be considered positive. For patients in Phase 1, results of the IHC do not need to be available prior to enrollment and dosing. For patients participating in the Phase 2 portion of the trial, a blood sample for ctDNA testing is required prior to consent and enrollment. Patients may be enrolled on Phase 2 based on positive IHC or ctDNA (refer to Section 6.15).

6.15 Circulating Tumor DNA Blood Assay

In both phases of the study, samples for ctDNA blood assay will be collected prior to the first dose of study treatment (C1D1) and analyzed for *FGFR2* gene amplification in the central laboratory. For patients in Phase 1, results of the ctDNA do not need to be available prior to enrollment and dosing. For patients participating in the Phase 2 portion of the trial, a blood sample for ctDNA testing is required prior to consent and enrollment. Patients may be enrolled based on a positive ctDNA or IHC test.

6.16 Patient Reported Outcomes / Quality of Life Scales

In Phase 2, the EQ-5D-5L QOL questionnaire and the EORTC QLQ-C30 will be administered in accordance with Appendix 3.

The EQ-5D-5L questionnaire was developed by the EuroQol Group, which is a standardized measure to provide utilities for clinical and economic appraisal. It uses a descriptive system and a visual analogue scale (VAS). The descriptive system has 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, and each dimension has 5 levels consisting of no problems, slight problems, moderate problems, severe problems, and extreme problems.

The EORTC QLQ is an integrated system for assessing the health-related quality of life of cancer patients participating in international clinical trials. The EORTC uses a modular approach to QOL assessment, consisting of a core questionnaire (EORTC QLQ-C30) to be administered, if necessary with a module specific to tumor site, treatment modality or a QOL dimension (eg, GC-specific module is QLQ-STO22).

6.17 Adverse Events

Assessment of AEs will follow the guidelines provided in the NCI CTCAE version 4.03 in Phase 1 and version 5.0 in Phase 2. AEs will be assessed as outlined in Section 6.17.3. Abnormal laboratory results that lead to a change in patient treatment management (eg, 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. Events meeting SAE criteria must be reported as SAEs (Section 6.17.3.1).

6.17.1 Collection of Adverse Events

In Phase 1, any new symptoms, injury, or worsening of symptoms that occur during the screening period (ie, following signing of the ICF, but prior to first infusion [C1D1]), will be considered pretreatment events and reported on the Medical History page of the eCRF, unless they directly correlate to a study-related procedure in which case they will be reported on the AE eCRF page. Otherwise, AE reporting will begin at the time of infusion of C1D1 (day of first infusion) and continue until completion of the EOT visit or 4 weeks (28 days) after the last dose of FPA144.

In Phase 2, AEs should not be reported during the pre-screening period unless they are related to a pre-screening procedure, as patients are not yet enrolled on the study at that time. The worst grade of AEs occurring during the screening period should be reported as described above for the Phase 1 screening period. AE reporting will continue until the EOT visit. SAE reporting will initiate at study enrollment unless the event is related to a study procedure. Symptomatic corneal and all retinal events are considered of special interest and should be reported up to 100 days from the last dose of FPA144.

Since the IHC and ctDNA blood results may require up to 2 weeks to complete, patients eligible for entering Phase 2 of this study may not be able to delay start of standard chemotherapy while waiting to receive the IHC or ctDNA blood result. Therefore, patients are permitted to receive 1 dose of mFOLFOX6 prior to enrolling in this clinical trial, while waiting for FGFR2 status to be confirmed. AEs due to this single dose of therapy that are ongoing on Study Day 1 will be captured on the medical history eCRF.

SAEs occurring after the EOT visit should be reported to the Sponsor by the investigator only if the investigator considers them related to FPA144 or mFOLFOX6. SAEs should always be recorded on the AE eCRF and reported to the Sponsor using the SAE report form.

6.17.2 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. 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 eCRF. Relationship (reasonable causal relationship) to drug therapy and counter measures undertaken will be noted on the eCRF.

All AEs including intercurrent illnesses that occur during the study, from the time of administration of study treatment, will be documented on the AE 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 in Phase 1 and version 5.0 in Phase 2. 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 treatment (FPA144 and/or mFOLFOX6) 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 the procedure precedes the initiation of study-prescribed treatment). Signs and symptoms associated with disease progression itself should not be reported as an AE or SAE if the diagnosis is available. Disease progression itself is an endpoint and not an AE or SAE.

6.17.3 Assessment of Adverse Events

Each AE will be assessed by the investigator with regard to seriousness, intensity (severity), causality, and the outcome and action taken. All AEs, regardless of the relationship to study treatment, will be recorded on the AE eCRF. This includes potential end-organ toxicity, eg, renal (proteinuria), hepatic, and cardiovascular (increased BP) effects, and effects on wound healing. All AE reports should contain a brief description of the event, date of onset, ongoing or date of resolution, intensity, treatment required, relationship to study treatment, action taken with the study treatment, outcome, and whether the event is classified as serious as described below.

6.17.3.1 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 study treatment 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

Medically significant 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 considered medically significant or 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.

6.17.3.1.1 Adverse Events of Special Interest (AESI)

An AESI (serious or non-serious) is an event of medical concern considered potentially associated to the investigational product or disease under study, for which ongoing monitoring and rapid communication by the investigator to the Sponsor is necessary. Ocular events associated with symptomatic corneal involvement and symptomatic and asymptomatic retinal involvement are considered events of special interest in this study. Such events might warrant further investigation in order to characterize the safety profile of the product. Depending on the nature of these events, rapid communication by FivePrime to other parties (eg, regulators) might also be warranted.

6.17.3.1.2 Intensity (Severity)

Investigators need to assess the severity of AEs according to the guidelines provided in NCI-CTCAE, version 4.03 in Phase 1 and version 5.0 in Phase 2.

CTCAE v 4.03 and v 5.0 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.

6.17.3.2 Causality

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

The most likely cause of an SAE (eg, 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 treatment will be assessed by means of a question: 'Is there a reasonable possibility that the AE may have been caused by the study treatment?' Answer Yes or No.

The description below provides guiding principles for the investigator to make casualty assessments.

- Yes, there is a reasonable possibility that the AE may have been caused by the study treatment:
  - Follows a reasonable temporal sequence from administration of the study treatment
  - 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 treatment
  - Follows a known pattern of response to the study treatment
  - Reappears or worsens on re-challenge
- No, there is no reasonable possibility that the AE may have been caused by the study treatment:
  - Does not follow a reasonable temporal sequence from administration of the study treatment
  - 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 treatment
  - Does not reappear or worsen on re-challenge

The relatedness for SAEs will also be assessed and documented on the AE eCRF.

If the causality of the AE requiring discontinuation is confirmed to be due to one of the study treatments in the combination therapy, the other drug may be continued according to the protocol schedule under the following scenarios:

- Timely resolution of the AE based on the treatment modification table
- Clinical benefit is shown by the patient based on investigator assessment

6.17.3.3 Outcome and Action Taken

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

- Action Taken
  - Dose Not Changed
  - Drug Interrupted
  - Drug Withdrawn

  - Drug Delayed
  - Dose Increased
  - Dose Reduced
  - Not Applicable
  - Unknown
- Outcome
  - Fatal
  - Not Recovered/Not Resolved
  - Recovered/Resolved
  - Recovered/Resolved with Sequelae
  - Recovering/Resolving

6.17.4 Reporting Serious Adverse Events

Any SAEs, whether or not considered related to treatment with FPA144 or mFOLFOX6, 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 must be recorded on both the SAE form and AE eCRF. Additional SAE information including medications or other therapeutic measures used to treat the event, action taken with the study treatment due to the event, and outcome/resolution of the event will be recorded on the SAE form. Forms for reporting SAEs will also be provided to the study centers.

A copy of the SAE forms must be faxed or electronically communicated **within 24 hours** to the attention of the ICON Pharmacovigilance Safety Specialist:

ICON Medical and Safety Services
Fax number: +1-866-955-7492
SAE Hotline: +1-888-723-9952
Email: icon-mads@iconplc.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 study number
- Investigator name and study center number
- Event term
- Event onset date

- Serious criteria
- Relationship to study treatment(s)

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

Serious AEs occurring after the EOT visit should be reported to the Sponsor by the investigator if the investigator considers the event related to the study treatment. Events of special interest (symptomatic corneal and all retinal events) should be reported to the Sponsor up to 100 days from last dose of FPA144.

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 most conservative assessment will be used. In addition, the Sponsor will evaluate the expectedness according to the FPA144 IB. 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 the Food and Drug Administration (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 IRB or IEC.

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

6.17.5 Follow-up of Adverse Events

All treatment-related SAEs experienced by a study patient, 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 Sponsor, there is a satisfactory explanation for the changes observed, or the patient is lost to follow-up.

All unresolved related AEs should be followed by the investigator until the events are resolved, the patient is lost to follow-up, or the AE is otherwise explained. The investigator should notify the study Sponsor of any death or AE occurring at any time after a patient has discontinued or terminated study participation that may reasonably be related to this study. Follow-up of events of special interest (symptomatic corneal and all retinal events) will be determined on a case by case basis depending on the prognostic resolution of the event. The Sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a patient that has participated in this study.

6.18 End of Treatment

EOT assessments are outlined in Appendix 2 and in Appendix 3 for Phase 1 and Phase 2, respectively. All patients should return to the clinic approximately 28 days after their last dose of study treatment (ie, the last administered dose of FPA144 or any component of mFOLFOX6), or in the event that a patient discontinues prematurely from the study, for EOT follow-up assessments.

In Phase 2, after discontinuation of study treatment for reasons other than disease progression or withdrawal of consent, tumor assessments will continue until the patient initiates additional anticancer therapy or progresses.

Symptomatic corneal and all retinal events are considered of special interest and should be reported up to 100 days from the last dose of FPA144.

6.19 Long Term Follow Up (Phase 2)

LTFU assessments are outlined in Appendix 3 for Phase 2 only. In Phase 2, LTFU assessments for survival consist of clinic visits, telephone calls, or patient registries (in line with national legislation and prevailing data protection laws) approximately every 3 months (± 1 month) after the EOT visit until up to 24 months after the last patient is enrolled in the study, or until death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor (whichever occurs first), which will be considered the EOS. During the Follow-up Period, if the patient undergoes anticancer therapy, this should be documented.

During the first 6 months of the LTFU Period (for patients in Phase 2), and for the first 6 months after the EOT visit (for patients in Phase 1), any known pregnancy that occurs should be reported to the Sponsor and followed as described in Section 6.9.

Serious AEs occurring after the EOT visit should be reported to the Sponsor by the investigator if the investigator considers there is a causal relationship with the study treatment (refer to Section 6.17.3.2).

6.19.1 Additional Follow-up for Patients without Progression at the End of Treatment Visit (Phase 2) (Scan Follow-up)

Scan Follow-Up assessments are outlined in Appendix 3 for Phase 2 only. If a patient discontinues study treatment (FPA144 and/or mFOLFOX6) for reasons other than disease progression or withdrawal of consent, they will have follow-up visits and continue to undergo tumor assessments until disease progression or the initiation of additional anticancer therapy.

7.0 STATISTICAL METHODS

Before database lock, a SAP will be finalized, providing detailed methods for the analyses including the summary of conduct of study and comparability of treatment group in Phase 2. Any deviations from the planned analyses will be described and justified in the final clinical study report.

7.1 Analysis Populations

The following analysis populations are defined for the study:

- Safety Population: all enrolled patients who have received any portion of at least 1 dose of study treatment (FPA144 + mFOLFOX6 or placebo + mFOLFOX6).
- DLT-evaluable Population: all patients enrolled in Phase 1 of the study who received at least 2 doses of FPA144 (except for Cohort 2 [must have received 3 doses of FPA144]) and mFOLFOX6 and completed Cycles 1 and 2 of treatment, or who experienced a DLT in Cycle 1 or Cycle 2.
- PK-evaluable Population: all patients who have received at least 1 dose of FPA144 and have had adequate PK assessments drawn for determination of the FPA144 concentration. Adequacy will be determined on a case-by-case basis and will be assessed prior to analysis of the blood samples.
- Intent-to-treat (ITT) Population: all randomized patients (Phase 2).
- Efficacy-evaluable Population: all patients who met eligibility criteria, received at least 1 dose of study treatment (FPA144 + mFOLFOX6 or placebo + mFOLFOX6), and have at least 1 postbaseline disease assessment and no major protocol deviation that could introduce bias in any efficacy assessment.

7.2 General Considerations

The total enrollment planned for this study is approximately 167 patients. 12 patients evaluable for DLT were enrolled into Phase 1.

For Phase 2, efficacy and tolerability will be examined by enrollment of approximately 155 patients with FGFR2-selected GC, randomized 1:1 to receive FPA144 + mFOLFOX6 or placebo + mFOLFOX6. Eligible patients will be stratified according to geographic region, prior treatment status (*de novo* versus adjuvant/neo-adjuvant), and administration of a single dose of mFOLFOX6 prior to enrollment (yes or no).

7.3 Power and Sample Size in Phase 2

This Phase 2 study is designed to assess the hazard ratio (HR) of PFS for FPA144 + mFOLFOX6 compared with placebo + mFOLFOX6. It is planned to observe 84 PFS events in order to achieve 71% power to detect an HR of 0.67 for PFS, at the 1-sided alpha of 0.1. Assuming an

exponential distribution, this corresponds approximately to an 50% increase in median PFS (e.g. from 5 months to 7.5 months). Statistical significance (at 1-sided alpha of 0.1) for PFS will occur with an observed HR=0.756, corresponding approximately to a 32.3% increase in observed median PFS (e.g. from 5 months to 6.6 months).

One hundred fifty-five patients have been randomized (1:1) during 13 months of accrual. It is projected to observe 84 PFS events with approximately 11 additional months of follow-up.

There is no planned interim analysis for this study.

Statistical significance for PFS will occur with an estimated HR= 0.756 at the final analysis, corresponding approximately to an increase of 32.3% in median progression-free survival of from 5 months to 6.61 months.

Approximately 155 patients will be randomized (1:1) during 13 months of accrual, with approximately 12 additional months of follow-up in order to achieve the targeted number of primary events with 15% dropout.

Power and sample size estimates were estimated using EAST®(V6.4).

7.4 Efficacy Analyses

7.4.1 Analysis of Primary Efficacy Endpoint

In Phase 2, the primary efficacy analysis is the comparison of PFS in patients treated with FPA144 + mFOLFOX6 versus placebo + mFOLFOX6.

The primary endpoint, PFS, is defined as time from randomization until the date of radiological disease progression based on investigator assessment (using RECIST v1.1) or death from any cause, whichever comes first. A clinical deterioration determined by an investigator will not be considered as a progression event. Data will be censored at the date of last adequate tumor assessment for subjects:

- who do not have documented progression or die, or
- who start new anticancer therapy before documented progression or death without documented progression, or
- who have ≥ 2 consecutive missing tumor assessments before documented progression or death without documented progression

If a subject does not have a baseline tumor assessment, then PFS will be censored at the date of randomization, regardless of whether or not radiographic progression or death has been observed.

The analyses of PFS will be performed using the ITT population, and will be conducted using a stratified log-rank test. The stratification factors will be the same used to stratify the randomization schedule as documented in the interactive voice and web response system (IXRS).

The median PFS and the associated 95% CI for each treatment arm will be estimated using the Kaplan-Meier method. The hazard ratio (HR= $\lambda_{FPA144+ mFOLFOX6}$/ $\lambda_{placebo+mFOLFOX6}$) will be estimated using a Cox regression model with treatment group as the only main effect and stratifying by the same stratification factors as were used for the stratified log-rank test. An unstratified HR will also be presented.

The detailed sensitivity analyses of PFS based upon different definitions of progression events and censoring rules will be provided in a SAP to address the following:

- To correct for potential ascertainment bias in follow-up schedules between the 2 treatment groups;
- To evaluate PFS based upon investigator claims: progression events will include investigator assessment of disease progression and initiation of subsequent anticancer therapy

7.4.2 Analysis of Secondary Efficacy Endpoints

Analyses of secondary endpoints OS and ORR will be conducted hierarchically. The formal hypotheses regarding effects on OS and ORR will be tested hierarchically at a one-sided level of 0.1. The OS will be tested first and if it is significant, the ORR will be tested next. The family-wise type I error rate of testing primary and secondary endpoints will be in a control by employing this gate-keeping testing procedure at a one-sided level of 0.1.

Overall survival is defined as time from randomization until death from any cause. Subjects who are lost to follow-up or do not have a date of death at the time of data cutoff will be censored at the last date that they were known to be alive. Overall survival will be analyzed in the similar manner as for PFS.

The analysis of ORR will be performed based on the ITT population. In the analysis of ORR, patients who don't have any postbaseline adequate tumor assessments will be counted as non-responders. Formal hypothesis testing of ORR will be performed using the stratified Cochran-Mantel-Haenszel test at a one-sided level of 0.1. The stratification factors will be the same used to stratify the randomization schedule as documented in the IXRS. In addition, the analysis of ORR will be performed based on Efficacy-evaluable Population as sensitivity analysis.

7.4.3 Analysis of Exploratory Endpoints

7.4.3.1 Efficacy

Duration of response (DOR) is defined, for patients with an objective response, as the time from onset of radiographic documentation of objective response to disease progression evaluated by investigator using RECIST v1.1 or death due to any cause. Patients who have not experienced disease progression or death at the time of analysis will be censored at the time of the last adequate tumor assessment. Median duration of response and its associated 95% CI will be estimated, by treatment group, using Kaplan-Meier methods.

The detailed analyses of exploring correlation between identified FGFR2 status in tumor tissue and/or ctDNA blood assay, as determined by IHC and blood-based molecular diagnostic assay, with PFS, OS, and objective response per RECIST v1.1 will be provided in the SAP.

7.4.3.2 Quality of Life

The analysis of PROs (assessed using the EORTC QLQ-C30 questionnaires) will be performed according to the EORTC Scoring and Reference Values Manual. The details of the analyses will be specified in the Statistical Analysis Plan. The respective subscales from the EORTC QLQ-C30 will be used to evaluate and compare the time to deterioration in abdominal pain, reflux, eating restrictions (premature safety), weight loss, appetite loss, and fatigue between treatment arms. All scores and subscales will be assessed through descriptive summary statistics.

7.5 Safety Analyses

All AEs will be coded using the Medical Dictionary for Regulatory Activities Version 20.1 (MedDRA v 20.1). The investigator will classify the severity of AEs using the CTCAE v 4.03 in Phase 1 and version 5.0 in Phase 2. A treatment-emergent adverse event (TEAE) is defined as any event with an onset date on or after date of first dose of study treatment, or any event present before treatment that worsens after treatment. Only TEAEs with an onset date prior to 28 days after the date of last dose will be tabulated in summary tables. The exceptions are symptomatic corneal events or any retinal events which will be captured within 100 days of the last dose of FPA144.

Clinical laboratory data will be summarized by the type of laboratory test. The number and percentage of patients who experience abnormal (ie, outside of reference ranges) and/or clinically significant abnormal laboratories after study treatment administration will be presented for each clinical laboratory measurement. For each clinical laboratory measurement, descriptive statistics will be provided for baseline and all subsequent posttreatment scheduled visits. Changes from baseline to the posttreatment visits will also be provided. Descriptive statistics of vital signs will also be provided in a similar manner. In addition, shift from baseline in CTCAE

grade (where applicable) and by high/low flags (where CTCAE grades are not defined) will be presented in a similar manner.

7.5.1 Safety Analyses in Phase 1

Safety analyses will be performed for patients included in the safety population. The incidence of DLTs, incidence of TEAEs, clinical laboratory abnormality (eg, shift table), vital signs, corneal and retinal findings, and ECGs will be tabulated and summarized by dose level. Additionally, incidence of TEAEs leading to dosing reduction or dose discontinuation will be tabulated and summarized

7.5.2 Safety Analyses in Phase 2

The analyses of safety will include all patients who receive any study treatment (FPA144 + mFOLFOX6, or placebo + mFOLFOX6) throughout the study and provide any posttreatment safety information. The incidence of TEAEs, clinical laboratory abnormality (eg, shift table), vital signs, corneal and retinal findings, and ECGs will be tabulated and summarized by treatment group.

No formal comparisons of safety endpoints are planned.

7.6 Pharmacokinetic Analyses

PK blood samples will be collected to measure the concentration of FPA144 in serum. Immunogenicity blood samples will be collected to measure the level of anti-FPA144 antibodies in serum. Samples for PK and immunogenicity assessment will be drawn from each patient at the time points outlined in Appendix 6 (for Phase 1) and Appendix 7 (for Phase 2). These samples will be collected and processed according to the instructions provided in a separate Laboratory Manual.

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 FPA144 concentration-time data from Phase 1 using a non-compartmental analysis method with IV infusion input. Alternative methods may be considered. The C_{max} and C_{trough} of FPA144 will be estimated from the serum concentration-time data for Phase 2. The time to achieve steady state, dose linearity, and accumulation ratio will be evaluated as data allow. 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.

The impact of immunogenicity on FPA144 exposure will be assessed, tabulated, and summarized by dose level as appropriate and applicable.

Serum concentration-time data from FPA144-004 will be pooled with data from other studies for integrated population PK analysis and exposure-response relationship assessment, which will be presented in a separate report.

7.7 Changes in the Planned Analyses

If discrepancies exist between the text of the statistical analysis as planned in the protocol and the final SAP, a protocol amendment will not be issued, and the SAP will prevail.

8.0 ETHICAL, LEGAL, AND ADMINISTRATIVE ASPECTS

8.1 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 (ie, medical records).

8.2 Data Protection

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 in the case histories or eCRFs for this study must be consistent with the patients' source documentation (ie, medical records).

Investigator and study center must maintain the anonymity of participating patients. Each patient will be assigned a unique patient identifier by the Sponsor that may consist of one or more of the following: the patient's patient number, initials, and/or birth date. Investigator and study center will include only such patient identifier on any eCRFs or other patient records, datasets or other documents that are transferred or submitted to the Sponsor or Sponsor's designee during the course of the study and will redact patient's name and all other personally-identifiable patient information from such documents. In addition, investigator must maintain in confidence any documents that include personally-identifiable patient information (e.g., the signed ICF) and take all reasonable precautions to prevent the disclosure of any personally identifiable patient information by any employee or agent of the study center to any third party or otherwise into the public domain.

The investigator or study center must inform study patients that their personal study-related data will be used by the Sponsor in accordance with local data protection law and must explain the level of disclosure to patients. In addition, each patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by IRB/IEC members of the study center, and by inspectors from regulatory authorities.

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 investigator's responsibilities for ensuring study compliance and procedures for preparing and maintaining adequate and correct eCRFs.

8.3 Electronic Case Report Forms and Source Documentation

All data obtained during this study should be entered in 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 examination reports, nursing notes, ECG recordings, hospital records, CT scans, and/or 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.

8.4 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 Good Clinical Practices (GCP) guidelines, the investigator must ensure provision of sufficient time, reasonable space, and adequate qualified personnel for the monitoring visits. The purpose of the visits is 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 must assure 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 (e.g., 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.

8.5 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.

8.6 Archiving Study Records

Each study site will maintain a study file, which should contain, at minimum, the IB, 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 the Sponsor 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 the Sponsor. Should the investigator wish to assign the study records to another party or move them to another location, the Sponsor must be notified in writing of the new responsible person and/or the new location, as applicable.

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

8.7 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.

8.8 Informed Consent

All information about the clinical study, including the patient information and the ICFs, 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 any patient is enrolled on the study. Written informed consent will be obtained from each patient according to applicable regulatory and legal requirements. Copies of the signed ICFs will be retained by the patient and the original will be filed in the investigator's study center file, unless otherwise agreed by the Sponsor the the study center. 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 ICFs may need to be revised to reflect the changes to the protocol. If the ICF is revised, it must be reviewed and approved by the appropriate IRB/IEC and the revised version signed by all patients subsequently enrolled in the study as well as those currently enrolled in the study.

8.9 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 IND application under which the study is being conducted.

8.10 Study Committee and Central Review

8.10.1 Cohort Review Committee

The Phase 1 safety run-in for this study will have a CRC consisting of representatives from the Sponsor, the Medical Monitors and 1 or more investigators from actively participating sites. The CRC will assess the safety of the dose escalation (Phase 1) on a regular basis. 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 2 treatment cycles. In addition, when selecting the dose(s) to be developed further, consideration will be made of toxicities observed both during and beyond the DLT evaluation period and assessment

of the proportion of patients who receive planned doses at various dose levels and the percentage of patients that required dose reductions and dose discontinuations for toxicity.

8.10.2 Data Monitoring Committee

The study will have a DMC that will operate independently from the Sponsor and the clinical investigators. The primary responsibilities of the DMC are to review the accumulating safety data from the Phase 2 study on a regular and ad hoc basis. In addition, the DMC will review the unblinded results of the OS interim analysis along with safety data to balance risk and benefit, and make recommendations to the Sponsor based on the data totality. Safety data from the Phase 2 study will be provided at regular intervals to the DMC in the form of unblinded summary reports and/or data listings from an independent statistical center designated by the Sponsor.

The first meeting of the DMC is planned to occur after a minimum number of patients (ie, 50 patients) have had the opportunity to complete a cycle of study treatment. Subsequent meetings are planned to occur periodically (eg, quarterly) and ad hoc at the request of the DMC members or the Sponsor. Details regarding DMC membership, schedule and format of meetings, format for presentation of data, access to interim data, method and timing of providing interim reports to the DMC, and other issues relevant to committee operations will be described in the DMC charter.

8.11 Premature Termination of the Study

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

8.12 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 numbers. Documents that include the name of the patient (e.g., the signed informed consent) must be maintained in confidence by the investigator. The investigator will 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.

8.13 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.

9.0 REFERENCES

Ahn, S., J. Lee, M. Hong, *et al.* (2016). "FGFR2 in Gastric Cancer: Protein Overexpression Predicts Gene Amplification and High H-Index Predicts Poor Survival." Modern Pathology: 1-9.

Al-Batran, S.-E., J. T. Hartmann, R. Hofheinz, *et al.* (2008). "Biweekly Fluorouracil, Leucovorin, Oxaliplation. and Docetaxel (FLOT) for Patients with Metastatic Adenocarcinoma of the Stomach or Esophagogastric Junction: A Phase II Trial of the Arbeitsgemeinschaft Internistische Onkologie " Annals of Oncology **19**: 1882-1887.

Andre, F., M. Ranson, E. Dean, *et al.* (2013). Abstract LB-145: Results of a Phase I Study of AZD4547, an Inhibitor of Fibroblast Growth Factor Receptor (FGFR), in Patients with Advanced Solid Tumors. AACR 104th Annual Meeting 2013, Washington, DC, American Association of Cancer Research.

Bang, Y., E. Cutsem, A. Feyereislova, *et al.* (2010). "Trastuzumab in Combination with Chemotherapy Versus Chemotherapy Alone for Treatment of HER2-Positive Advanced Gastric or Gastro-Oesophageal Junction Cancer (ToGA): A Phase 3, Open-Label, Randomised Controlled Trial." The Lancet **376**: 687-697.

Bron, A., V. Evans and J. Smith (2003). "Grading of Corneal and Conjuctival Staining in the Context of Other Dry Eye Tests." Cornea **22**(7): 640-650.

Brown, A. P., C. L. Courtney, L. M. King, *et al.* (2005). "Cartilage Dysplasia and Tissue Mineralization in the Rat Following Administration of a FGF Receptor Tyrosine Kinase Inhibitor." Toxicologic Pathology **33**: 449-455.

Catenacci, D., S. Rha, Y.-J. Bang, *et al.* (2017). "Updated AntiTumor Activity and Safety of FPA144, and ADCC-Enhanced Isoform-Specific Monoclonal Antibody, in Patients with FGFR2b+ Gastric Cancer." Journal of Clinical Oncology **35**(15): 4067.

Cheeseman, S., S. Joel, J. Chester, *et al.* (2002). "A 'Modified de Gramont' Regimen of Fluorouracil, Alone and With Oxaliplatin, for Advanced Colorectal Cancer." British Journal of Cancer **87**: 393-399.

Chen, J., D. Hunter, M. Stampfer, *et al.* (2003). "Polymorphism in the Thymidylate Synthase Promoter Enhancer Region Modifies the Risk and Survival of Colorectal Cancer." Cancer Epidemiology, Biomarkers & Prevention **12**: 958-962.

Davidson, M. and I. Chau (2016). "Variations in Outcome for Advanced Gastric Cancer Between Japanese and Western Patients: A Subgroup Analysis of the RAINBOW Trial." Transl Gastroenterol Hepatol **1**(46): 1-4.

Deshpande, A. M., S. Palencia, D. I. Bellovin, *et al.* (2014). Expression of FGFR2b in Gastric Cancer as Measured by Immunohistochemistry With a Highly Specific Monoclonal Antibody. American Association for Cancer Research, San Diego, CA, Five Prime Therapeutics, Inc.

Dienstmann, R., R. Bahleda, A. Barbara, *et al.* (2014). First in human study of JNJ-42756493, a potent pan fibroblast growth factor receptor (FGFR) inhibitor in patients with advanced solid tumors. AACR 105th Annual Meeting, San Diego, CA.

Ford, H., A. Marshall, J. Bridgewater, *et al.* (2014). "Docetaxel Versus Active Symptom Control for Refractory Oesophagogastric Adenocarcinoma (COUGAR-02): An Open-Label, Phase 3 Randomised Controlled Trial." Lancet Oncology **15**: 78-86.

Fuchs, C., T. Doi, R. Jang, *et al.* (2017). "KEYNOTE-059 Cohort 1: Efficacy and Safety of Pembrolizumab (Pembro) Monotherapy in Patients with Previously Treated Advanced Gastric Cancer." Journal of Clinical Oncology **35**(15): 4003.

Fuchs, C., J. Tomasek, C. Yong, *et al.* (2014). "Ramucirumab Monotherapy for Previously Treated Advanced Gastric or Gastro-Oesophageal Junction Adenocarcinoma (REGARD): an International, Randomised, Multicentre, Placebo-Controlled, Phase 3 Trial." Lancet Oncology **383**: 31-39.

Gemo, A., A. Deshpande, S. Palencia, *et al.* (2014). FPA144: A Therapeutic Antibody for Treating Ptients with Gastric Cancers Bearing FGFR2 Gene Amplification. AACR 105th Annual Meeting 2014, San Diego California.

GlaxoSmithKline (2017). "Study to Evaluate GSK3052230 in Combination with Paclitaxel and Carboplatin, or Docetaxel or as Single Agent in Subjects with Solid Malignancies and Deregulated Fibroblast Growth Factor (FGF) Pathway Signaling ". from https://clinicaltrials.gov/ct2/show/NCT01868022?term=NCT01868022&rank=1.

Gravalos, C. and A. Jimeno (2008). "HER2 in Gastric Cancer: A New Prognostic Factor and a Novel Therapeutic Target." Annals of Oncology **19**: 1523-1529.

Hall, T., Y. Yu, S. Eathiraj, *et al.* (2016). "Preclinical Activity of ARQ 087, a Novel Inhibitor Targeting FGFR Dysregulation." PLoS ONE **11**(9): 1-19.

Hattori, Y., H. Itoh, S. Uchino, *et al.* (1996). "Immunohistochemical Detection of K-sam Protein in Stomach Cancer." Clinical Cancer Research **2**: 1373-1381.

Hattori, Y., H. Odagiri, H. Nakatani, *et al.* (1990). "K-sam, an Amplified Gene in Stomach Cancer, is a Member of the Heparin-Binding Growth Factor Receptor Genes." Proceedings of the National Academy of Sciences (PNAS) **87**: 5983-5987.

Hochster, H., L. Hart, R. K. Ramanathan, *et al.* (2008). "Safety and Efficacy of Oxaliplatin and Fluoropyrimidine Regimens with or without Bevacizumab As First-Line Treatment of Metastatic Colorectal Cancer: Results of the TREE Study." Journal of Clinical Oncology **26**(21).

Hofmann, M., O. Stoss, D. Shi, *et al.* (2008). "Assessment of a HER2 Scoring System for Gastric Cancer: Results from a Validation Study." Histopathology **52**: 797-805.

Jung, E., E. Jung , S. Min, *et al.* (2012). "Fibroblast Growth Factor Receptor 2 Gene Amplification Status and its Clinicopathologic Significance in Gastric Carcinoma." Human Pathology **43**(10): 1559-1566.

Kamangar, F., G. Dores and W. Anderson (2006). "Patterns of Cancer Incidence, Mortality, and Prevalence Across Five Continents: Defining Priorities to Reduce Cancer Disparities in Different Geographic Regions of the World." Journal of Clinical Oncology **24**(14): 2137-2150.

Kang, Y.-K., W.-K. Kang, D.-B. Shin, *et al.* (2009). "Capecitabine/Cisplatin Versus 5-Fluorouracil/Cisplatin as First-Line Therapy in Patients with Advanced Gastric Cancer: A Randomised Phase III Noninferiority Trial." Annals of Oncology **20**: 666-673.

Kang, Y., N. Boku, T. Satoh, *et al.* (2017). "Nivolumab in Patients with Advanced Gastric or Gastro-Oesophageal Junction Cancer Refractory to or Intolerant of, at Least Two Previous Chemotherapy Regimens (ONO-4538-12, ATTRACTION-2): A Randomised, Double-Blind, Placebo-Controlled, Phase 3 Trial." The Lancet **390**: 2461-2471.

Keam, B., S.-A. Im, S.-W. Han, *et al.* (2008). "Modified FOLFOX-6 Chemotherapy in Advanced Gastric Cancer: Results of Phase II Study and Comprehensive Analysis of Polymorphisms as A Predictive and Prognostic Cancer." BMC Cancer **8**(148): 1-10.

Kim, D., J. Kim, S.-H. Lee, *et al.* (2003). "Phase II Study of Oxaliplatin, 5- Fluorouracil and Leucovorin in Previously Platinum-Treated Patients with Advanced Gastric Cancer." Annals of Oncology **14**: 383-387.

Li, B., L. Zhao, H. Guo, *et al.* (2009). "Characterization of a Rituximab Variant with Potent Antitumor Activity Against Rituximab-Resistant B-Cell Lymphoma." Blood **114**(24): 5007-5015.

Matsumoto, K., T. Arao, T. Hamaguchi, *et al.* (2012). "FGFR2 Gene Amplification and Clinicopathological Features in Gastric Cancer " British Journal of Cancer **106**(4): 727-732.

Miki, T., D. P. Bottaro, T. P. Fleming, *et al.* (1992). "Determination of Ligand-Binding Specificity by Alternative Splicing: Two Distinct Growth Factor Receptors Encoded by a Single Gene." Proceedings of the National Academy of Sciences **69**: 246-250.

National Cancer Institute (2015). "SEER Stat Fact Sheets: Stomach Cancer." Retrieved February 25, 2016, from http://seer.cancer.gov/statfacts/html/stomach.html.

Ohtsu, A., M. Shah, E. Van Cutsem, *et al.* (2011). "Bevacizumab in Combination with Chemotherapy As First-Line Therapy in Advanced Gastric Cancer: A Randomized, Double-Blind, Placebo-Controlled Phase III Study." Journal of Clinical Oncology **29**(30): 3968-3976.

Ohtsu, A., S. Yoshida and N. Saijo (2006). "Disparities in Gastric Cancer Chemotherapy Between the East and West " Journal of Clinical Oncology **24**(14): 2188-2196.

Okines, A., A. Norman, P. McCloud, *et al.* (2009). "Meta-Analysis of the REAL-2 and ML17032 Trials: Evaluating Capecitabine-Based Combination Chemotherapy and Infused 5-Fluorouracil-Based Combination Chemotherapy for the Treatment of Advanced Oesphago- Gastric Cancer." Annals of Oncology **20**(9): 1529-1534.

Powers, J., S. Palencia, S. Foy, *et al.* (2016). "FPA144, A Therapeutic Monoclonal Antibody Targeting the FGFR2b Receptor, Promotes Antibody Dependent Cell-Mediated Cytotoxicity and Stimulates Sensitivity to PD-1 Blockade in the 4T1 Syngeneic Tumor Model in Mice." 1.

Pullarkat, S., J. Stoehlmacher, V. Ghaderi, *et al.* (2001). "Thymidylate Synthase Gene Polymorphism Determines Response and Toxicity of 5-FU Chemotherapy." The Pharmacogenics Journal **1**: 65-70.

Sawaki, A., Y. Ohashi, Y. Omuro, *et al.* (2011). "Efficacy of Trastuzumab in Japanese Patients with HER2-Positive Advanced Gastric or Gastroesophageal Junction Cancer: A Subgroup Analysis of the Trastuzumab for Gastric Cancer (ToGA) Study." Gastric Cancer **15**: 313-322.

Seo, S., S. Park, M. Ryu, *et al.* (2016). "Prognostic Impact of Fibroblast Growth Factor Receptor 2 Gene Amplification in Patients Receiving Fluoropyrimidine and Platinum Chemotherapy for Metastatic and Locally Advanced Unresectable Gastric Cancers." Oncotarget: 1-11.

Sequist, L. V., P. Cassier, A. Varga, *et al.* (2014). Phase I Study of BGJ398, a Selective Pan-FGFR Inhibitor in Genetically Preselected Advanced Solid Tumors. AACR 2014 Annual Meeting, San Diego, CA.

Shinkawa, T., K. Nakamura, N. Yamane, *et al.* (2003). "The Absence of Fucose but Not the Presence of Galactose or Bisecting N-Acetylglucosamine of Human IgG1 Complex-type Oligosaccharides Shows the Critical Role of Enhancing Antibody-dependent Cellular Cytotoxicity." THe Journal of Biological CHemisty **278**(5): 3466-3473.

Smyth, E., M. Verheij, W. Allum, *et al.* (2016). "Gastric Cancer: ESMO Clinical Practice Guidelines for Diagnosis, Treatment, and Follow-up " Annals of Oncology **27**(5): v38-v49.

Su, X., P. Zhan, P. Gavine, *et al.* (2014). "FGFR2 Amplification has Prognostic Significance in Gastric Cancer: Results From a Large International MultiCentre Study " British Journal of Cancer **110**: 967-975.

Taiho Oncology Inc (2015). "A Dose Finding Study Followed by a Safety and Efficacy Study in Patients with Advanced Solid Tumors or Multiple Myeloma with FGF/FGFR-Related Abnormalities." from https://clinicaltrials.gov/ct2/show/NCT02052778?term=NCT02052778&rank=1.

Teva Parenteral Medicines Inc (2014). "Leucovorin Calcium for Injection Package Insert." 1-13.

Teva Parenteral Medicines Inc (2016). "ADRUCIL- Highlights of Prescribing Information." 1-12.

Teva Pharmaceuticals USA (2012). "Oxaliplatin: Highlights of Prescribing Information." 1-43.

Teva Pharmaceuticals USA Inc (2016). "Warfarin Sodium Highlights of Prescribing Information." 1-51.

The GASTRIC Group (2010). "Benefit of Adjuvant Chemotherapy for Resectable Gastric Cancer." JAMA **303**(1729-1737): 1729.

Thuss-Patience, P., A. Kretzschmar, D. Bichev, *et al.* (2011). "Survival Advantage for Irinotecan Versus Best Supportive Care as Second-Line Chemotherapy in Gastric Cancer- A Randosmied Phase III Study of the Arbeitsgemeinschaft Internistische Onkologie (AIO)." European Journal of Cancer **47**: 2306-2314.

Tournigand, C., T. Andre, E. Achille, *et al.* (2004). "FOLFIRI Followed by FOLFOX6 or the Reverse Sequence in Advanced Colorectal Cancer: A Randomized GERCOR Study." Journal of Clinical Oncology **22**(2): 229-237.

Turner, N. and R. Grose (2010). "Fibroblast Growth Factor Signalling: From Development to Cancer." Nature **10**: 116-129.

Ulrich, C., J. Bigler, C. Velicer, *et al.* (2000). "Searching Expressed Sequence Tag Databases: Discovery and Confirmation of a Common Polymorphism in the Thymidylate Synthase Gene." Cancer Epidemiology, Biomarkers & Prevention **9**: 1381-1385.

van Hazel, G., V. Heinemann, N. Sharma, *et al.* (2016). "SIRFLOX: Randomized Phase III Trial Comparing First-Line mFOLFOX6 (Plus or Minus Bevacizumab) Versus mFOLFOX6 (Plus or Minus Bevacizumab) Plus Selective Internal Radiation Therapy in Patients with Metastatic Colorectal Cancer." Journal of Clinical Oncology **34**(15): 1723-1731.

Waddell, T., M. Verheij, W. Allum, *et al.* (2014). "Gastric Cancer: ESMO-ESSO-ESTRO Clinical Practice Guidelines for Diagnosis, Treatment, and Follow-up " Radiotherapy and Oncology **110**: 189-194.

Wagner, A., W. Grothe, J. Haerting, *et al.* (2006). "Chemotherapy in Advanced Gastric Cancer: A Systematic Review and Meta-Analysis Based on Aggregrate Date." Journal of Clinical Oncology **24**(18): 2903-2909.

Wilke, H., K. Muro, E. Custem, *et al.* (2014). "Ramucirumab Plus Paclitaxel Versus Placebo Plus Paclitaxel in Patients with Previously Treated Advanced Gastric or Gastro-Oesophageal Junction Adenocarcinoma (RAINBOW): A Double-Blind, Randomised Phase 3 Trial." Lancet Oncology **15**: 1224-1235.

Wu, Y.-M., F. Su, S. Kalyana-Sundaram, *et al.* (2013). "Identifi cation of Targetable FGFR Gene Fusions in Diverse Cancers." Cancer Discovery **3**(6): 636-647.

Zhao, X., S. Singh, C. Pardoux, *et al.* (2010). "Targeting C-type Lectin-Like Molecule-1 for Antibody-Mediated Immunotherapy in Acute Myeloid Leukemia." Haematologica **95**(1): 71-78.

10.0 APPENDICES

APPENDIX 1: FORMULAS TO CALCULATE RENAL FUNCTION

Renal function should be determined using either the Cockcroft Gault formula *or* the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.

Cockcroft Gault formula:

$$CrCl = \frac{(140-age)*weight}{72*SCr} (* 0.85\ if\ female)$$

Abbreviations/Units: age in years; weight in kg; SCr = serum creatinine in mg/dL.

CKD-EPI formula:

eGFR = 141 x min(SCr/κ, 1)α x max(SCr /κ, 1)-1.209 x 0.993Age x 1.018 [if female] x 1.159 [if Black]

Abbreviations/Units: eGFR (estimated glomerular filtration rate) = mL/min/1.73 m^2; SCr = standardized serum creatinine in mg/dL; κ = 0.7 (females) or 0.9 (males); α = -0.329 (females) or -0.411 (males); min = indicates the minimum of SCr.

APPENDIX 2: SCHEDULE OF ASSESSMENTS: DOSE-ESCALATION SAFETY RUN-IN (PHASE 1)

	Screening	Study Treatment Period: Cycles 1 and 2					Study Treatment Period: Cycle 3, Cycle 4 and Subsequent Cycles					
	Day --28 to Day 0	Cycle 1 Day 1	Cycle 1 Day 3	Cycle 1 Day 8	Cycle 2 Day 1	Cycle 2 Day 3	Cycle 3[b] Day 1	Cycle 4[c] Day 1	Clinical Fixed Time Point Assessments[d]	As Clinically Indicated	Other Time Points	EOT[e,f]
Procedure[a]	Week 0	Week 1	Week 1	Week 2	Week 3	Week 3	≥Week 4					
Archival Tissue Provided for IHC (if available)[g]	X											
Sample for ctDNA Blood Assay[h]		X										
Informed Consent[i]	X											
Review/Confirm Eligibility Criteria	X											
Medical/Oncology and Medication History	X	X										
Demography/Baseline Characteristics	X											
Physical Examination[j,k]	X[j]	X		X	X		X	X				X
ECOG Performance Status[l]	X						X[l]				X[l]	X
Vital Signs[m]	X	X	X	X	X	X	X	X		X		X
12-lead ECG[n]	X									X		X
Comprehensive Ophthalmologic Examination (including Slit Lamp)[o]	X								X[d,o]	X	X[o]	X
Slit Lamp Examination[p]									X[d,p]		X[p]	
Clinical Safety Laboratory Sampling[q]	X[q]	X[q]		X	X[q]		X[q]	X[q]		X		X
Pregnancy Test[r]	X[r]	X[r]					X[r]			X	X[r]	X
Urinalysis[s]	X	X					X[s]			X	X[s]	X
PK Samples[t]		X	X	X	X	X	X	X			X	X
Immunogenicity Sampling[u]		X			X		X				X	X

APPENDIX 2: SCHEDULE OF ASSESSMENTS: DOSE-ESCALATION SAFETY RUN-IN (PHASE 1) (CONTD)

	Screening	Study Treatment Period: Cycles 1 and 2					Study Treatment Period: Cycle 3, Cycle 4 and Subsequent Cycles					
	Day --28 to Day 0	Cycle 1 Day 1	Cycle 1 Day 3	Cycle 1 Day 8	Cycle 2 Day 1	Cycle 2 Day 3	Cycle 3[b] Day 1	Cycle 4[c] Day 1	Clinical Fixed Time Point Assessments[d]	As Clinically Indicated	Other Time Points	EOT[e,f]
Procedure[a]	**Week 0**	**Week 1**	**Week 1**	**Week 2**	**Week 3**	**Week 3**	**≥Week 4**					
FPA144 Administration[j,w,x]		X		X[x]	X		X	X				
mFOLFOX6 Administration[y]		X			X		X	X				
Adverse Events[z]	X[z]	X ——— X										
Concomitant Medications	X	X ——— X										

Note: A cycle of treatment is 2 weeks.

[a] Unless specified, procedure is to be completed within ± 72 hours of scheduled time point and to be synchronized with the study treatment administration day.

[b] And subsequent odd cycles beyond Cycle 3 (except for PK, immunogenicity, and pharmacodynamic blood sample collections, which are described in Appendix 6).

[c] And subsequent even cycles beyond Cycle 4 (except for PK, immunogenicity, and pharmacodynamic blood sample collections, which are described in Appendix 6).

[d] Clinical Fixed Time Point Assessments should be completed as originally scheduled from C1D1 regardless of dosing days or dose delays. Refer to Appendix 5 for collection days.

[e] EOT assessments should be performed approximately 28 (+3) days following the last study treatment administration

[f] For the first 6 months after the EOT visit, any pregnancy that occurs should be reported to the Sponsor.

[g] Tumor tissue collection from archival material (if available) for retrospective IHC analysis of FGFR2b overexpression by IHC upon eligibility confirmation.

[h] Sample for ctDNA blood assay will be collected prior to the first dose of study treatment (Cycle 1 Day 1; C1D1) and analyzed retrospectively for *FGFR2* gene amplification.

[i] Written, signed informed consent must be collected prior to any study-specific procedures. The most recent IRB/EC approved ICF must be signed.

[j] Complete physical examination including height and weight will be measured at Screening only. Limited physical examinations should be conducted, including weight and examination of the oropharynx, thereafter.

[k] After Cycle 1, the FPA144 should be recalculated only if the weight changes > 10% from the C1D1 weight. If the dose is recalculated due to a >10% weight change from C1D1, the weight used for the recalculated dose should function as the new baseline for subsequent evaluation of dose recalculations. Doses should be rounded to the nearest 10 mg.

[l] ECOG Performance Status will be assessed at Cycle3 Day 1 and Day 1 of every other subsequent cycle (odd cycles) until the EOT visit.

[m] Vital signs (blood pressure, heart rate, respiration, and temperature [°C]) are to be measured after 5 minutes of rest, at one time at the Screening visit and Cycle 1 Day 3, Cycle 2 Day 3, EOT and as clinically indicated. On C1D1 (all cohorts), and Cycle 1 Day 8 (Cohort 2 only) vital sign measurements should be at the following time points: Predose, and 0.5, 1, 2, and 4 hours from the start of the FPA144 infusion. On subsequent dosing days, vital sign measurements should be predose and at 0.5, 1, and 2 hours from the start of FPA144 infusion.

[n] 12-lead ECG after patient rests for 5 minutes prior to recording.

[o] Comprehensive ophthalmologic examinations (conducted at Screening, at 4 weeks from C1D1, at 8 weeks from C1D1, and at the EOT visit only, ±7 days) include fundoscopic and slit lamp examination (with fluorescein staining score form), ocular coherence tomography (OCT), visual acuity, completion of fluorescein staining score form, determination of intraocular pressure, and review of ocular/visual symptoms. The comprehensive ophthalmologic examination will be repeated at any time if clinically indicated when changes in visual acuity or visual symptoms are reported by patients up to 100 days after the last dose of FPA144. After the EOT visit if the patient has any persistent ophthalmologic findings, the assessments should continue every 8 weeks until resolution of findings, withdrawal of consent, death, or loss to follow up. All abnormal OCT examinations should be submitted to the Sponsor.

[p] Slit lamp examinations alone, (with completion of fluorescein staining score form), should be conducted for all patients starting at approximately week 16 and then every 8 weeks through EOT visit and at any time if clinically indicated including after the EOT visit. After the EOT visit if the patient has any persistent corneal findings, the assessments should continue every 8 weeks until resolution of findings, withdrawal of consent, death, or loss to follow up.

[q] Blood tests (evaluated by local laboratories) are listed in Appendix 4. Baseline hematology and blood chemistry test results must be obtained within 96 hours prior to enrollment. On subsequent dosing days, for both FPA144 or mFOLFOX6, hematology and blood chemistry results must be obtained within 72 hours prior to the start of dosing. Coagulation results need to be obtained at baseline, at Day 1 of Cycles 1 through 4 within 72 hours prior to dosing with FPA144, and at any time clinically indicated (eg, patients on anticoagulant therapy requiring close monitoring). Hematology, blood chemistry and coagulation samples are collected at the EOT visit.

[r] Serum ß-hCG (evaluated by local laboratories) will be performed on all women of childbearing potential at Screening within 96 hours prior to enrollment and when clinically indicated. If serum B-hCG test is performed at Screening and is not within 96 hours prior to enrollment, the test must be repeated to confirm the patient is not pregnant. Urine pregnancy tests and results are required on Day 1 for subsequent odd cycles (every other cycle) for both FPA144 and mFOLFOX6 prior to dosing. Urine pregnancy tests are also required at EOT.

[s] Includes protein, glucose, blood, pH, and ketones on Day 1 for both FPA144 and mFOLFOX6 of odd cycles (every other cycle). If findings are clinically significant, a microscopic evaluation will be performed per institutional standard.

[t] Blood samples for PK analysis. Refer to Appendix 6 for collection times.

[u] Blood samples for anti-FPA144 antibodies. Refer to Appendix 6 for collection times.

[v] [redacted]

[w] FPA144 is administered Q2W as a 30-minute infusion starting C1D1. The first 3 doses (cycles) of FPA144 should be administered Q2W (±3 days) regardless of delays in mFOLFOX6 treatment. After the first 3 doses, FPA144 may be delayed up to 7 days to be synchronized with administered mFOLFOX6.

[x] FPA144 is administered only for Cohort 2 at Cycle 1 Day 8; subsequent cycles for Cohort 2 do not receive Day 8 study treatment. No other dose levels receive a Cycle 1 Day 8 FPA144 administration.

[y] mFOLFOX6 is administered Q2W at least 30 minutes after FPA144 as a continuous IV infusion over approximately 48 hours, starting on Day 1 and completing on Day 3.

[z] AE collection begins after signing of the ICF for Screening. Events reported prior to the first on-study 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 28 days after the last dose of study treatment. SAE reporting will initiate at study enrollment unless the event is related to a study procedure. All treatment-related SAEs 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 Sponsor, there is a satisfactory explanation for the changes observed, or the patient is lost to follow-up. Serious AEs occurring after the EOT visit and ophthalmological events of any grade occurring up to 100 days after EOT visit should be reported to the Sponsor if the investigator considers there is a causal relationship with the study treatment.

APPENDIX 3: SCHEDULE OF ASSESSMENTS: RANDOMIZED, PLACEBO-CONTROLLED PORTION (PHASE 2)

Procedure[a]	Pre-Screening	Screening	Study Treatment: Cycles 1 and 2			Study Treatment: Cycle 3, Cycle 4 and Subsequent Cycles					EOT[e]	Follow-up Scans Follow-up[ff]	Long Term Follow Up[g]
		Day -28 to Day 0	Cycle 1 Day 1	Cycle 1 Day 8	Cycle 2 Day 1	Cycle 3[b] Day 1	Cycle 4[c] Day 1	Clinical Fixed Time Points Assessments[d]	As Clinically Indicated	Other Time Points			
		Week 0	Week 1	Week 2	Week 3	≥Week 4							
Pre-Screening Informed Consent[h]	X												
IHC Analysis of FGFR2b Overexpression[i]	X												
Sample for Blood-Based (ctDNA) Assay[j]	X												
Informed Consent[k]		X											
Review/Confirm Eligibility Criteria		X											
Medical/Oncology and Medication History		X	X										
Demography/Baseline Characteristics		X											
Physical Examination[l]		X[l]	X	X	X	X	X				X	X	
ECOG Performance Status[n]		X				X[n]				X[n]	X		
Patient-Reported Outcomes (EQ-5D-5L and the EORTC QLQ-C30)[o]		X					X[o]			X[o]	X		
Vital Signs[p]		X	X	X	X	X	X		X		X	X	
12-lead ECG[q]		X							X		X		
Comprehensive Ophthalmologic Examination (including Slit Lamp) [r]		X						X[d,r]	X	X[r]	X		

APPENDIX 3: SCHEDULE OF ASSESSMENTS: RANDOMIZED, PLACEBO-CONTROLLED PORTION (PHASE 2) (CONTD)

Procedure[a]	Pre-Screening	Screening	Study Treatment: Cycles 1 and 2			Study Treatment: Cycle 3, Cycle 4 and Subsequent Cycles					EOT[e]	Follow-up Scans Follow-up[ff]	Long Term Follow Up[g]
		Day -28 to Day 0	Cycle 1 Day 1	Cycle 1 Day 8	Cycle 2 Day 1	Cycle 3[b] Day 1	Cycle 4[c] Day 1	Clinical Fixed Time Points Assessments[d]	As Clinically Indicated	Other Time Points			
		Week 0	Week 1	Week 2	Week 3	≥Week 4							
Slit Lamp Examination[t]								X[d,t]		X[t]			
Clinical Safety Laboratory Sampling[u]		X	X[u]	X	X[u]	X[u]	X[u]		X		X		
Pregnancy Test[v]		X[v]	X[v]			X[v]			X	X[v]	X		
Urinalysis[w]		X	X			X[w]			X	X[w]	X		
Radiological/Tumor Assessment[x]		X						X[ff]		X[x]	X[s]	X	
Randomization[y]		X											
Survival Assessment													X
Immunogenicity Sampling[z]			X			X				X[z]	X		
PK Samples[aa]			X			X				X[aa]	X		
mFOLFOX6 Administration[bb]			X		X	X	X						
FPA144 Administration[m,y,cc]			X	X[f]	X	X	X						
Adverse Events[dd]		X[dd]	X[dd]	X ———	-----	———	———	———	———	——— X		X[dd]	X[dd]
Concomitant Medications[ee]		X	X	X ———	———	———	———	———	———	——— X		X	X[ee]

A cycle of treatment is 2 weeks

[a] Unless specified, procedure is to be completed within ± 72 hours of scheduled time point and to be synchronized with the study treatment administration day.

[b] And subsequent odd cycles from Cycle 3 (except for PK, immunogenicity, and pharmacodynamic blood sample collections, which are described in Appendix 7).

[c] And subsequent even cycles from Cycle 4 (except for PK, immunogenicity, and pharmacodynamic blood sample collections, which are described in Appendix 7).

[d] Clinical Fixed Time Point Assessments should be completed as originally scheduled from C1D1 regardless of dosing days or dose delays. Refer to Appendix 5 for collection days.

[e] EOT assessments should be performed 28 (+14) days following the last study treatment administration. In Phase 2, after discontinuation of study treatment for reasons other than disease progression or withdrawal of consent, tumor assessments will continue until the patient initiates additional anticancer therapy or progresses.

[f] One dose of FPA144 is administered at 7.5 mg/kg on Cycle 1 Day 8 only; subsequent cycles do not receive Day 8 study treatment. For all other dose levels, no FPA144 administration on Cycle 1 Day 8.

[g] Patients will complete LTFU for survival approximately every 3 months ± 1 month after the EOT visit until up to 24 months after the last patient is enrolled in the study, or until death, loss to follow-up, withdrawal of consent or study termination by the Sponsor (whichever occurs first) (refer to Section 6.19).

[h] Informed consent must be obtained prior to obtaining blood for ctDNA and provision of tumor sample (refer to Section 1.8)

[i] Provision of archival tissue (or fresh biopsy if archival tissue is not available) for pre-screening FGFR2b overexpression testing by IHC is required. FGFR2 positive status by IHC or ctDNA testing methods is required for enrollment in Phase 2.

[j] Sample for blood-based biopsy (ctDNA) assay at Pre-Screening for prospective analysis of *FGFR2* gene amplification (refer to Appendix 7). FGFR2 positive status by IHC or ctDNA testing methods is required for enrollment in Phase 2.

[k] Written, signed informed consent must be collected prior to study related screening procedures. The most recent IRB/EC approved ICF must be signed. Patients who have fully consented to participation in the study will undergo screening assessments within 28 days prior to enrollment.

[l] Complete physical examination including height and weight will be measured at screening only. Limited physical examinations should be conducted, including weight and examination of the oropharynx, thereafter.

[m] After Cycle 1, the FPA144 dose should be recalculated only if the weight changes > 10% from the C1D1 weight. If the dose is recalculated due to a >10% weight change from C1D1, the weight used for the recalculated dose should function as the new baseline for subsequent evaluation of dose recalculations. Doses should be rounded to the nearest 10 mg.

[n] ECOG Performance Status will be assessed at Screening, Cycle 3 Day 1 and Day 1 of every other subsequent cycle (odd cycles), and at the EOT visit.

[o] The EQ-5D-5L and the EORTC QLQ-C30 will be collected at Screening (within 28 days of C1D1), prior to dosing on Cycle 4 Day 1, every 8 weeks until EOT, and at the EOT visit.

[p] Vital signs (blood pressure, heart rate, respiratory rate, and temperature) are to be measured, after 5 minutes of rest, at one time at the Screening visit, EOT and as clinically indicated. On C1D1, vital sign measurements should be at the following time points: Pre-dose, and 0.5, 1, 2, and 4 hours from the start of FPA144 infusion. On subsequent dosing days, vital sign measurements should be measured at the following time points: Predose and at 0.5, 1, and 2 hours from the start of FPA144 infusion.

[q] 12-lead ECG after patient rests for 5 minutes prior to recording.

[r] Comprehensive ophthalmologic examinations (conducted at Screening, at 8 weeks from C1D1 (±7 days), and at the EOT visit only (±7 days), include fundoscopic and slit lamp examination (with fluorescein staining score form), ocular coherence tomography (OCT), visual acuity, completion of fluorescein staining score form, determination of intraocular pressure, and review of ocular/visual symptoms. The comprehensive ophthalmologic examination will be repeated at any point if clinically indicated when changes in visual acuity or visual symptoms are reported by patients up to 100 days after the last dose of

FPA144. After the EOT visit if the patient has any persistent ophthalmologic findings, the assessments should continue every 8 weeks until resolution of findings, withdrawal of consent, death, or loss to follow up. All abnormal OCT examinations should be submitted to the Sponsor.

[s] This scan can be omitted if the last scan was performed < 8 weeks prior to EOT visit or if tumor progression was previously determined.

[t] Slit lamp examinations (with completion of fluorescein staining score form), should be conducted for all patients starting at Week 16 from C1D1 then every 8 weeks through EOT visit and at any time if clinically indicated including after the EOT visit. After the EOT visit if the patient has any persistent corneal findings, the assessments should continue every 8 weeks until resolution of findings, withdrawal of consent, death, or loss to follow up.

[u] Blood tests (evaluated by local laboratories) are listed in Appendix 4. Screening hematology and blood chemistry test results must be obtained within 96 hours of enrollment. On dosing days for both FPA144/placebo and mFOLFOX6, hematology and blood chemistry results must be obtained within 72 hours prior to dosing. Coagulation results need to be obtained at Screening, at Day 1 of Cycles 1 through 4 within 72 hours prior to dosing with FPA144, and at any time clinically indicated (eg, patients on anticoagulant therapy requiring close monitoring). Hematology, blood chemistry and coagulation samples are collected at EOT.

[v] Serum ß-hCG (evaluated by local laboratories) will be performed on all women of childbearing potential at Screening within 96 hours prior to enrollment and when clinically indicated. If serum B-hCG test is performed at Screening and is not within 96 hours prior to enrollment, the test must be repeated to confirm the patient is not pregnant. Urine pregnancy tests and results are required on Day 1 for subsequent odd cycles (every other cycle) for both FPA144/placebo and mFOLFOX6 prior to dosing. Urine pregnancy tests are also required at EOT.

[w] Includes protein, glucose, blood, pH, and ketones on Screening, C1D1, dosing days of odd cycles (every other cycle), and EOT. If findings are clinically significant, a microscopic evaluation will be performed per institutional standard.

[x] Radiological/tumor assessments will be performed within 28 days (+3 days) prior to start of treatment (C1D1) and including clinical examination and appropriate imaging techniques (preferably CT scans with appropriate slice thickness per RECIST v1.1; MRIs are acceptable); imaging performed as standard of care that includes imaging of chest, abdomen and pelvis may be used if it has been performed within 28 days (+3 days) of treatment (C1D1). Tumor scans will be performed at Screening (within 28 days [+3 days] of Cycle 1 Day 1), then every 8 weeks from Cycle 1 Day 1 (± 7 days) until 12 months and then every 12 weeks (± 14 days) thereafter. In Phase 2, after discontinuation of study treatment for reasons other than disease progression or withdrawal of consent, tumor assessments will continue until radiographic progression or the initiation of additional anticancer therapy.

[y] Patients must initiate the first administration of study treatment within 3 days of enrollment.

[z] Blood samples for anti-FPA144 antibodies. Refer to Appendix 7 for collection times

[aa] Blood samples for PK analysis. Refer to Appendix 7 for specific collection times.

[bb] mFOLFOX6 is administered Q2W as a continuous IV infusion over approximately 48 hours, starting on Day 1 and completing on Day 3 (if mFOLFOX6 is delayed secondary to toxicity, vital signs and clinical laboratory tests need to be performed within 72 hours of its administration).

[cc] C1D1 of FPA144 administered by IV infusion over 30 minutes (± 10 minutes) must occur within 3 days of being enrolled. FPA144 is administered Q2W starting C1D1. The first 3 doses (cycles) of FPA144 should be administered every 14 days (±3 days) regardless of delays in mFOLFOX6 treatment. After the first 3 doses, FPA144 may be delayed up to 7 days to be synchronized with administered mFOLFOX6.

[dd] AEs should not be reported during the pre-screening period unless they are related to a study procedure, as patients are not yet enrolled on the study at that time. AE collection begins following signing of the ICF for Screening. Events reported prior to the first on-study 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 28 days after the last dose of study treatment. SAE reporting will initiate at study enrollment unless the event is related to a study procedure. All treatment-related SAEs experienced by a study patient 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 Sponsor, there is a satisfactory explanation for the changes observed, or the patient is lost to follow-up. SAEs occurring after the EOT visit and ophthalmological events of any grade occurring up to 100 days after EOT visit should be reported to the Sponsor by the investigator if the investigator considers there is a causal relationship with the study treatment.

[ee] For long term follow up, the only concomitant medication that needs to be collected is anticancer medication.

[ff] If a patient discontinues study treatment (FPA144 and/or mFOLFOX6) for reasons other than disease progression or withdrawal of consent, they will have follow-up visits and continue to undergo tumor assessments according to the protocol schedule until radiographic progression or the initiation of additional anticancer therapy (at which point the patient would begin the long term follow up for survival).

APPENDIX 4: LABORATORY EVALUATIONS

The following laboratory parameters will be determined in accordance with the Schedule of Assessments and can be performed locally:

Hematology:

Complete blood cell (CBC) with differential:

white blood cells (WBC)	platelets
absolute neutrophil count (ANC)	hemoglobin
neutrophils (%)	hematocrit
eosinophils (%)	red blood cells (RBC)
basophils (%)	
lymphocytes (%)	
monocytes (%)	

Urinalysis:

Appearance, color, pH, specific gravity, ketones, protein, glucose, bilirubin, nitrite, urobilinogen, and occult blood

If findings are clinically significant, a microscopic evaluation will be performed per institutional standard.

Clinical chemistry:

albumin	lactate dehydrogenase (LDH)
alkaline phosphatase	magnesium
ALT (SGPT)	phosphate
AST (SGOT)	potassium
blood urea nitrogen (BUN) or urea	sodium
calcium	total bilirubin
chloride	total cholesterol
creatinine	total protein
direct bilirubin	glucose
uric acid	

Coagulation:

international normalized ratio (INR)	activated partial thromboplastin time (APTT)

Serum and urine pregnancy testing:

In women of childbearing potential only.

APPENDIX 5: CLINICAL FIXED TIME POINT ASSESSMENTS

Clinical Fixed Time Point Assessments should be completed as originally scheduled from Cycle 1 Day 1 (C1D1), regardless of dosing days or dose delays. Cycles are 2 weeks in length. Collection days are as follows:

Procedure:	**Study Treatment Period: Cycle 3, Cycle 4 and Subsequent Cycles**
Comprehensive Ophthalmologic Examination (including Slit Lamp)	Should be conducted at: Phase 1: • At Screening (within 28 days of C1D1) • At 4 weeks from C1D1 • At 8 weeks from C1D1 ±7 days thereafter • At the EOT visit ±7 days Phase 2: • At Screening (within 28 days of C1D1) • At 8 weeks from C1D1 ±7 days • At the EOT visit ±7 days For both Phase 1 and Phase 2, should include fundoscopic and slit lamp examination (with fluorescein staining score form), ocular coherence tomography (OCT), visual acuity, completion of fluorescein staining score form, determination of intraocular pressure, and review of ocular/visual symptoms. The comprehensive ophthalmologic examination should be repeated at any time if clinically indicated when changes in visual acuity or visual symptoms are reported by patients up to 100 days after the last dose of FPA144. After the EOT visit if the patient has any persistent ophthalmologic findings, the assessments should continue every 8 weeks until resolution of findings, withdrawal of consent, death, or loss to follow up. All abnormal OCT examinations should be submitted to the Sponsor.
Slit Lamp Examination	Phase 1 and Phase 2: Should be conducted at: • Week 16 and then every 8 weeks through EOT visit • at any time if clinically indicated, including after the EOT visit

APPENDIX 5: CLINICAL FIXED TIME POINT ASSESSMENTS (CONTD)

Procedure:	Study Treatment Period: Cycle 3, Cycle 4 and Subsequent Cycles
Radiological/Tumor Assessment	Phase 2 only: Should be conducted at: • At Screening (within 28 days +3 days of treatment C1D1) • Every 8 weeks from C1D1 ±7 days until 12 months and then every 12 weeks ±14 days thereafter. Scans should be obtained per schedule regardless of drug interruption or discontinuation. • At the EOT visit ±7 days (this scan can be omitted if the last scan was performed < 8 weeks prior to EOT visit or if tumor progression was previously determined) • *Scan follow-up visits, if applicable Tumor assessments will be performed within 28 days (+3 days) prior to start of treatment (C1D1) and including clinical examination and appropriate imaging techniques (preferably CT scans with appropriate slice thickness per RECIST v1.1; MRIs are acceptable); imaging performed as standard of care that includes imaging of chest, abdomen and pelvis may be used if it has been performed within 28 days +3 days of treatment (C1D1). • *After discontinuation of study treatment for reasons other than disease progression or withdrawal of consent, tumor assessments will continue until radiographic progression or the initiation of additional anticancer therapy.

APPENDIX 6: STUDY FLOWCHART FOR PHARMACOKINETIC, IMMUNOGENICITY, AND [redacted] OR PHASE 1

Study Cycle	Study Day	Time Point	Type of Sample
Cycle 1	Day 1	≤ 4 hours prior to infusion (predose)	ctDNA blood assay sample
			FPA144 PK (serum)
			ADA (serum)
			[redacted]
		15 (±10) minutes after end of infusion	FPA144 PK (serum)
		4 hours (±60 minutes) after end of infusion	FPA144 PK (serum)
	Day 3	48 hours (±6 hours) after end of infusion	FPA144 PK (serum)
			[redacted]
	Day 8	168 hours (±1 day) after end of infusion	FPA144 PK (serum)
	Day 8* (Cohort 2 patients only)	≤ 4 hours prior to infusion (predose)	FPA144 PK (serum)
		15 (±10) minutes after end of infusion	FPA144 PK (serum)
		4 hours (±60 minutes) after end of infusion	FPA144 PK (serum)
Cycle 2	Day 1	≤ 4 hours prior to infusion (predose)	FPA144 PK (serum)
			ADA (serum)
		15 (±10) minutes after end of infusion	FPA144 PK (serum)
	Day 3	48 hours (±6 hours) after end of infusion	FPA144 PK (serum)
Cycle 3	Day 1	≤ 4 hours prior to infusion (predose)	FPA144 PK (serum)
			ADA (serum)
			[redacted]y
		15 (±10) minutes after end of infusion	FPA144 PK (serum)

APPENDIX 6: STUDY FLOWCHART FOR PHARMACOKINETIC, IMMUNOGENICITY, AND [redacted] OR PHASE 1 (CONTD)

Study Cycle	Study Day	Time Point	Type of Sample
Cycle 4	Day 1	≤ 4 hours prior to infusion (predose)	FPA144 PK (serum)
		15 (±10) minutes after end of infusion	[redacted]
			FPA144 PK (serum)
Cycle 5, 7, 9, 11	Day 1	≤ 4 hours prior to infusion (predose)	FPA144 PK (serum)
			ADA (serum) (Cycle 7)
			[redacted]
		15 (±10) minutes after end of infusion	FPA144 PK (serum)
Cycle 10	Day 1	15 (±10) minutes after end of infusion	FPA144 PK (serum)
	Day 3	48 hours (± 6 hours)	FPA144 PK (serum)
			[redacted]
	Day 1	≤ 4 hours prior to infusion (predose)	FPA144 PK (serum)
			ADA (serum)
Every 8 Cycles Starting from Cycle 15			[redacted]
End of Treatment Follow-up	Visit date	Single time point	FPA144 PK (serum)
			ADA (serum)
			[redacted]

* For Cohort 2 patients only

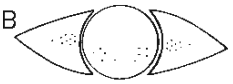
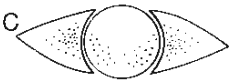
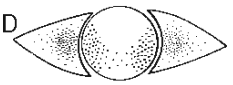
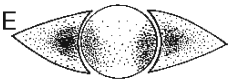
APPENDIX 7: STUDY FLOWCHART FOR FPA144 PHARMACOKINETIC AND IMMUNOGENICITY BLOOD SAMPLE COLLECTIONS FOR PHASE 2

Study Cycle	Study Day	Time Point	Type of Sample
Cycle 1	Day 1	≤ 4 hours prior to infusion (predose)	FPA144 PK (serum)
			ADA (serum)
		15 (±10) minutes after end of infusion	FPA144 PK (serum)
Cycle 3	Day 1	≤ 4 hours prior to infusion (predose)	FPA144 PK (serum)
			ADA (serum)
		15 (±10) minutes after end of infusion	FPA144 PK (serum)
Cycles 5, 9, and 17	Day 1	≤ 4 hours prior to infusion (predose)	FPA144 PK (serum)
			ADA (serum)
End of Treatment Follow-up	Visit date	Single time point	FPA144 PK (serum)
			ADA (serum)

APPENDIX 8: ECOG PERFORMANCE STATUS

Grade	Performance Status Criteria
0	Fully active, able to carry on all predisease 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 9: 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 9: FLUORESCEIN STAIN GRADING SYSTEMS (CONTD)

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 9: FLUORESCEIN STAIN GRADING SYSTEMS (CONTD)

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 9: FLUORESCEIN STAIN GRADING SYSTEMS (CONTD)

<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.
| | Cornea | Conjunctiva |
| Observer 1 | 0.86 | 0.69 |
| Observer 2 | 0.65 | 0.83 |

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>
</table>

APPENDIX 9: FLUORESCEIN STAIN GRADING SYSTEMS (CONTD)

<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.

(Bron 2003)

Summary of Changes Protocol FPA144-004

FIGHT: A Phase 2 Randomized, Double-Blind, Controlled Study Evaluating FPA144 and Modified FOLFOX6 in Patients with Previously Untreated Advanced Gastric and Gastroesophageal Cancer: Phase 2 Preceded by Dose-Finding in Phase 1

Protocol Version: **Amendment 4**

Date of Protocol Amendment: **10 Mar 2021**

Supersedes: *Amendment 3 –dated 05June 2020*

Protocol Section	Change	Rationale
Protocol Synopsis, Protocol Sections 3.1, 3.4 (Figure 6), 6.19, Appendix 3	Extended duration of LTFU visits from 12 to 24 months.	In the analysis performed on results as of 23 Sep 2020, fewer than 50% of subjects in the treatment arm had an event evaluable for overall survival. The study long-term follow-up duration is being extended by 12 months to more fully evaluate the secondary endpoint of overall survival (OS).
Global	Minor administrative changes updating version number and accompanying date have been made throughout the document.	

Summary of Changes Protocol FPA144-004

FIGHT: A Phase 2 Randomized, Double-Blind, Controlled Study Evaluating FPA144 and Modified FOLFOX6 in Patients with Previously Untreated Advanced Gastric and Gastroesophageal Cancer: Phase 2 Preceded by Dose-Finding in Phase 1

Protocol Version: **Amendment 3**

Date of Protocol Amendment: **05 June 2020**

Supersedes: *Amendment 2 –dated 19 November 2018*

Protocol Section	Change	Rationale
Global	Changed study design from Phase 3 to Phase 2. Study remains double-blind, placebo-controlled. No further enrollment is planned.	• The Phase 3 study in the front-line setting with SOC chemotherapy initiated from promising monotherapy activity of bemarituzumab (FPA144) in a Phase 1 study in late-line gastric cancer. • The Phase 3 statistical design assumed incidence of FGFR2b positivity in front-line gastric cancer to be ~10%. Over the conduct of the study, the true incidence has been 30%. • Two methods of testing for FGFR2b status were utilized to capture eligible patients: IHC and ctDNA. Although the expectation was that majority of positive tumors would be identified by both tests, the vast majority of tumors have been identified by IHC alone, resulting in a question of adequate study power.
Protocol Synopsis, Protocol Sections 2.2.1, 2.2.2, 2.4.1, 2.4.2, 3.1, 3.4, 4.1, 6.19, 7.3, 7.4.1, 7.4.2, Appendix 3	Primary endpoint of study changed to investigator-assessed progression-free survival. No interim analysis is planned. Overall survival is changed to a secondary endpoint. Sample size changed to 155 patients. Study duration is now 31 months to reflect current completion of enrollment and minimum of 12 months follow-up after last patient enrolled.	Modifications accommodate the change to a Phase 2 design with PFS rather than OS as the primary endpoint.

Protocol Section	Change	Rationale
Protocol Synopsis	Characterization of PK profile of FPA144 +mFOLFOX6 in patients with FGFR2-selected GC and immunogenicity of FPA144 changed to exploratory endpoint	To align with change in study design
Protocol Synopsis, Protocol Sections 3.2.7, Appendix 2, Appendix 3	After the first 3 cycles, FPA144/placebo may be delayed up to ±7 days to be synchronized with administered mFOLFOX6.	Clarified language regarding synchronization of FPA144/placebo with mFOLFOX6 administration
Protocol Sections 1.3.5, 1.7	Updated safety information from current IB and to include identification of keratitis as an adverse drug reaction of IP.	To provide updated safety information in the protocol consistent with revised safety language in the bemarituzumab Investigator's Brochure (version 7)
Protocol Section 6.15, Appendix 3	[redacted]	
Global	Minor administrative changes and clarifications involving grammar, diction, punctuation, and other editorial changes that do not affect study design have been made throughout the document.	

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SUMMARY OF CHANGES PROTOCOL FPA144-004

FIGHT: A Phase 3 Randomized, Double-Blind, Controlled Study Evaluating FPA144 and Modified FOLFOX6 in Patients with Previously Untreated Advanced Gastric and Gastroesophageal Cancer: Phase 3 Preceded by Dose-Finding in Phase 1

Protocol Version: **Amendment 2**
Date of Protocol Amendment: **19 November 2018**
Supersedes: *Amendment 1 –dated 04 January 2018*

Protocol Section	Change	Rationale
Protocol Synopsis, Protocol Section 6.2	Removed language regarding informed consent requirements in Protocol Synopsis and removed Sections 6.2.1. and 6.2.2, instead addressing this in Section 6.2.	Language has been clarified to avoid inconsistency as applies to informed consent process introduced by regional and/or site requirements. Informed consent framework for pre-screening and screening is unchanged.
Protocol Synopsis	Screening Period ~~The time between signing the study ICF (for enrollment/participation) and enrollment in the study is considered the Screening Period. During the Screening Period, the patient will undergo protocol-specified Screening procedures to ensure all eligibility criteria are met.~~ ~~Additional details are provided below for each study portion under Phase 1 Safety Run-in and Phase 3.~~ Pre-screening allows for collection of blood and tissue to determine FGFR2 positivity using ctDNA and IHC assays. Once a patient is confirmed to have a positive result based on central testing, the screening period initiates, allowing for evaluation of all other eligibility criteria.	Simplification of language explaining distinction between pre-screening and screening periods.

Protocol Section	Change	Rationale
Protocol Synopsis, Protocol Sections 3.2.5, 3.3.1, 3.4, and 6.4.2	Added the Phase 3 Recommended Dose	To include the Phase 3 dose that was identified in Phase 1 in the protocol text.
Protocol Synopsis, Protocol Section 4.2	Added the CKD-EPI formula as an additional method for measurement of CrCl to inclusion criterion #7.	The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation may provide a more accurate representation of kidney function for patients anticipating platinum-containing chemotherapy globally. To ensure that the most appropriate gastric cancer population is eligible for and treated in the FPA144-004 study the Sponsor is allowing for inclusion of patients with adequate renal function per either the Cockcroft-Gault or CKD-EPI calculations.
Protocol Synopsis, Protocol Section 4.2	Added an exception for anemia to exclusion criterion #10.	Addresses inconsistency with inclusion criterion for hemoglobin for assessment of patient eligibility.
Protocol Synopsis, Protocol Sections 4.2, 6.4.2, 6.10, Appendix 3, and Appendix 5	Revised window for baseline radiographic imaging to be within 28 days (+3 days) in inclusion criterion #13 and other corresponding sections.	Clarified that intent of prior language was to allow for baseline radiographic assessment within the screening window (ie, within 28+3 days of enrollment), not within 3 days of Day -28.
Protocol Synopsis	~~If the testing for OS is significant, then~~ **The** analysis of PFS will be performed using a stratified log-rank test at a one-sided level of 0.025. ~~This analysis will be based on 350 PFS events. Statistical significance for PFS at one-sided p=0.025 will occur with an estimated HR=0.81, corresponding approximately to an improvement of 23.4% in median PFS from 6 months to 7.41 months. The final analysis of PFS will be conducted using a stratified log-rank test. The stratification factors will be the same used to stratify the randomization schedule as documented in the IXRS.~~	Clarified language with regards to secondary endpoint of PFS to be consistent with prior regulatory feedback.

Protocol Section	Change	Rationale
Protocol Synopsis	A TEAE is defined as any event with an onset date on or after date of first dose of study treatment, or any event present before treatment that worsens after treatment. ~~Only TEAEs with an onset date prior to 28 days after the date of the last dose will be tabulated in summary tables. The exceptions are symptomatic corneal events or any retinal events which should be captured within 100 days of the last dose of FPA144.~~	Simplified language in synopsis to be more concise. Details removed here are already stated in Section 7.5.
Protocol Sections 1.8 and 6.3.2	~~Patients must sign the Pre- Screening informed consent form (ICF)~~ **Pre-screening allows** for collection of blood and tissue to determine FGFR2 positivity using ctDNA and IHC assays. ~~Only patients determined to be FGFR2 selected are eligible to sign the Screening ICF and enter~~ **Once a patient is confirmed to have a positive result based on central testing,** the screening period **initiates, allowing for evaluation of**~~. Enrollment in the study requires achieving~~ all other eligibility criteria (refer to Section 4.2).	Simplified language to make distinction and transition between pre-screening and screening periods clear. Informed consent is already addressed in Section 6.2.
Protocol Section 3.2.7	In the Phase 1 portion of the study, if FPA144 is permanently discontinued for any reason the patient will undergo an EOT follow-up visit approximately 28 days after the last dose of FPA144 **or mFOLFOX6.**	Clarified that the EOT follow-up visit is done approximately 28 days after the last dose of all study treatment.

Protocol Section	Change	Rationale
Protocol Sections 5.1.2, 5.1.3.2, Appendix 2, and Appendix 3	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 C1D1 and adjusted if the patient's weight changes > 10% from either C1D1 or from the time of the most recent dose of FPA144, whichever change in dose is greater.~~ **The dose of FPA144 is based on body weight at C1D1 and should be recalculated only if the weight changes > 10% from the C1D1 weight. If the dose is recalculated due to a >10% weight change from C1D1, the weight used for the recalculated dose should function as the new baseline for subsequent evaluation of dose recalculations.**	Clarified when and how dose recalculations for FPA144 should be performed to be consistent with general consensus in the weight-based administration of cancer therapy.
Protocol Section 5.1.3.4	Patients who require ~~chemotherapy~~ **FPA144** dose reductions will receive the reduced dose for the remainder of the study. ~~The only exception to this practice will be in the case of nausea/ vomiting. If nausea and/or vomiting occur despite antiemetic therapy, the chemotherapy dose should be reduced by 25% for the next dose. If tolerated, an increase back to a 100% dose may be allowed at the investigator's discretion. Any patient who required 2 dose reductions and experienced persistent toxicity with a third dose reduction will be discontinued from all chemotherapy. Chemotherapy~~ **C**ycles may be delayed to manage toxicity. Cycle delays of ~~up to~~ **longer than** 28 days ~~are permitted~~ **should be discussed with the medical monitor prior to reinitiation**. ~~Any delay longer than 28 days will require permanent discontinuation of all chemotherapy.~~	Simplified language to avoid duplication as this information is already contained within Protocol Section 5.2.3.1. Additionally, modified language around study drug discontinuation to incorporate flexibility to be consistent with global variation in standard-of-care management in front-line therapy for gastric cancer.

Protocol Section	Change	Rationale
Protocol Section 5.1.3.4	Added Table 5 to address dose levels for dose reductions in Phase 3.	Inclusion of explicit statement of dose levels for dose reductions in Phase 3 following determination of Phase 3 dose.
Protocol Section 5.2.3	Removed rounding convention for oxaliplatin and 5-FU.	Rounding will be addressed in the study pharmacy manual and be consistent with general consensus in the weight-based administration of cancer therapy.
Protocol Section 5.2.3.1	Patients should be closely monitored for mFOLFOX6 toxicity. **In Phase 1, any patient who does not receive 2 complete doses of mFOLFOX6 during the DLT Period due to a reason that is not a DLT or an AE related to FPA144, will be considered unevaluable and the patient will be replaced.** ~~In Phase 1, dose adjustments for mFOLFOX6 are permitted, but patients who require dose adjustments or delay of any component of mFOLFOX6 during the DLT period will not be considered evaluable unless the dose adjustment or delay is due to an AE deemed related to FPA144, in which case the AE will be considered a DLT (refer to Section 3.2.2 for DLT definitions).~~	To address an inconsistency with the dose limiting toxicity (DLT) language in Section 3.2.5. This change was previously communicated in a Protocol Clarification Memo dated 30 April 2018.
Protocol Section 5.2.3.1	~~If there is a change in body weight of >10% compared to baseline or to the weight at the time of the most recent dose, doses should be recalculated.~~ **The dose of mFOLFOX6 is based on body weight at C1D1 and should be recalculated only if the weight changes > 10% from the C1D1 weight. If the dose is recalculated due to a >10% weight change from C1D1, the weight used for the recalculated dose should function as the new baseline for subsequent evaluation of dose recalculations**	Clarified when and how dose recalculations for mFOLFOX6 should be performed to be consistent with general consensus in the weight-based administration of cancer therapy.

Protocol Section	Change	Rationale
Protocol Section 5.2.3.1	~~In the event that oxaliplatin administration is discontinued for any reason prior to disease progression, 5-FU/leucovorin therapy may continue on an every 2-week schedule until disease progression, unacceptable toxicity, or other cause for study withdrawal. In the case 5-FU/leucovorin therapy is permanently discontinued then oxaliplatin must be discontinued.~~ Patients who require chemotherapy dose reductions will receive the reduced dose for the remainder of the study. The only exception to this practice will be in the case of nausea/ vomiting. If nausea and/or vomiting occur despite antiemetic therapy, the chemotherapy dose should be reduced by 25% for the next dose. If tolerated, an increase back to a 100% dose may be allowed at the investigator's discretion. Any patient who required 2 dose reductions and experienced persistent toxicity with a third dose reduction will be discontinued from all chemotherapy. Chemotherapy cycles may be delayed to manage toxicity. Cycle delays of ~~up to~~ **longer than** 28 days ~~are permitted~~ **should be discussed with the medical monitor prior to reinitiation of treatment**. ~~Any delay longer than 28 days will require permanent discontinuation of all chemotherapy.~~	Removed redundant language on oxaliplatin discontinuation as it is included in Section 5.2.3. Additionally, modified language around study drug discontinuation to incorporate flexibility to be consistent with global variation in standard-of-care management in front-line therapy for gastric cancer
Protocol Section 5.4	~~If the investigator needs to know the study drug assignment for any reason, he or she should contact the Sponsor's Medical Monitor.~~ **The decision and ability to unblind the treatment code in emergency situations resides with the investigator.**	To specify that the investigator has the prerogative and ability to break the treatment code in the case of a medical emergency without a requirement to contact the sponsor prior to unblinding.

Protocol Section	Change	Rationale
Protocol Section 6.3.2	Step 1: Patients will ~~sign a Pre-Screening ICF~~ **provide informed consent** to allow testing for FGFR2b overexpression by archival or fresh tissue with IHC and a blood sample for FGFR2 amplification by ctDNA. The time between signing ~~the Pre-Screening ICF (for enrollment/participation)~~ **informed consent** and site notification of the result of the test is considered the pre-screening period (refer to Section 3.3).	Language has been clarified to avoid inconsistency as applies to informed consent process introduced by regional and/or site requirements. Informed consent framework for pre-screening and screening is unchanged.
Protocol Section 6.6.2	~~After Cycle 1, the FPA144 dose will be recalculated at each infusion visit only if the patient's weight has changed > 10% from either C1D1 or from the time of the most recent dose of FPA144, whichever change in dose is greater.~~ **The dose of FPA144 and mFOLFOX6 is based on body weight at C1D1 and should be recalculated only if the weight changes > 10% from the C1D1 weight. If the dose is recalculated due to a > 10% weight change from C1D1, the weight used for the recalculated dose should function as the new baseline for subsequent evaluation of dose recalculations.**	Clarified when and how dose recalculations for FPA144 and mFOLFOX6 should be performed to be consistent with general consensus in the weight-based administration of cancer therapy.
Protocol Section 6.6.3	During Phase 3, comprehensive ophthalmologic examinations will be conducted at Screening, at 8 weeks from C1D1 (**± 7** ~~14~~ days), at the EOT visit (± 7 days), and at any time there are ophthalmologic symptoms up to 100 days after the last dose of FPA144.	Revised the allowable window for comprehensive ophthalmologic exams at 8 weeks from C1D1 to ± 7 days.

Protocol Section	Change	Rationale
Protocol Section 6.8, Appendix 2, Appendix 3, and Appendix 4	Urinalysis includes ~~dipstick for~~ protein, glucose, blood, pH, and ketones on Day 1 for both FPA144 and mFOLFOX6 of odd cycles (every other cycle). If ~~dipstick~~ findings are **clinically significant,** ~~2+ or greater, then~~ a microscopic evaluation will be performed ~~to assess the abnormal findings~~ **per institutional standard**.	Removed requirement of dipstick use as long as analyte testing is performed per institutional standard.
Protocol Section 6.18	Added language for reporting of corneal and all retinal events to this section of the protocol referring to end of treatment procedures.	To align with language already included in Section 6.17.1.
Protocol Section 7.1	Intent-to-treat (ITT) Population: all randomized patients (Phase 3). ~~The final analysis of efficacy outcomes will be conducted in the ITT population.~~	Simplified language on the definition of ITT population. Second sentence is redundant to information already contained in statistical analysis section.
Protocol Section 7.4.2	~~The hypothesis of OS will be tested first.~~ As described above in Section 7.4.1, there will be 1 planned interim analysis and a final analysis for OS; both analyses (the interim and the final) will be event-based analyses. The O'Brien-Fleming monitoring boundary will be used to preserve the 2.5% false-positive error rate (1-sided), with a Lan-DeMets implementation to allow flexibility in the number and timing of the interim analysis. ~~The hypothesis of OS will be tested at $\alpha 1=0.01$ (1-sided) at the interim, and $\alpha 2=0.022$ (1-sided) at final.~~	This information will be contained more appropriately in the Statistical Analysis Plan (SAP).

Protocol Section	Change	Rationale
Protocol Section 7.4.3	~~If the testing for OS is significant, PFS will be tested further. This analysis will be based on 350 PFS events. Statistical significance for PFS at 1-sided p=0.025 will occur with an estimated HR=0.81, corresponding approximately to an improvement of 23.4% in median PFS from 6 months to 7.41 months.~~ The ~~final~~ analysis of PFS will be conducted using a stratified log-rank test. The stratification factors will be the same used to stratify the randomization schedule as documented in the IXRS. The PFS analysis will ~~be event-driven analysis and conducted based on the ITT principle, in which the final analysis of PFS will~~ include ~~only radiographic~~ progression events as determined by the investigator's assessment per RECIST v1.1 and deaths. ~~A clinical deterioration determined by an investigator will not be considered as a progression event in the final analysis~~.	Clarified language with regards to secondary endpoint of PFS such that language is consistent with prior regulatory feedback.
Protocol Section 7.4.3	Included additional details for ORR analysis. **In addition, the analysis of ORR will be performed based on Efficacy-evaluable Population as sensitivity analysis.**	Specified that a sensitivity analysis will be performed for the secondary endpoint of ORR by restricting subjects to those in the efficacy-evaluable population.
Protocol Section 7.5	Included language around capturing treatment emergent adverse events beyond an onset date of +28 days after the date of the last dose.	This language was previously in the Protocol Synopsis and has been moved to this section for clarity and ease of reference.
Protocol Section 8.2	Added Section 8.2 on Data Protection.	Added language to address privacy and data protection.

Protocol Section	Change	Rationale
Appendix 1	Addition of the CKD-EPI CrCl formula and clarification of the CG formula: **Cockcroft Gault formula:** $\boldsymbol{CrCl = \frac{(140-age)*weight}{72*SCr}(*\ 0.85\ if\ female)}$ **Abbreviations/Units: age in years; weight in kg; SCr = serum creatinine in mg/dL.** **CKD-EPI formula:** **eGFR = 141 x min(SCr/κ, 1)α x max(SCr /κ, 1)-1.209 x 0.993Age x 1.018 [if female] x 1.159 [if Black]** **Abbreviations/Units: eGFR (estimated glomerular filtration rate) = mL/min/1.73 m^2; SCr = standardized serum creatinine in mg/dL; κ = 0.7 (females) or 0.9 (males); α = -0.329 (females) or -0.411 (males); min = indicates the minimum of SCr.**	To clarify calculation of CrCl per the CG formula (added units that the variables should be in) and provide a reference for calculation of eGFR per the CKD-EPI formula.

Protocol Section	Change	Rationale
Appendix 4	Chemistry panel updated to allow for collection of either blood urea nitrogen or urea.	This change was previously communicated in a Protocol Clarification Memo dated 30 April 2018.
Appendix 5	Clarified collection requirements for the comprehensive ophthalmologic examinations in both Phase 1 and Phase 3.	This change was previously communicated in a Protocol Clarification Memo dated 09 February 2018.
Global	Simplified language specifying assessment of disease progression per RECIST v1.1.	Clarified language to be consistent with the fact that radiographic progression is one component of assessment of progression per RECIST v1.1.
Global	Clarified language that time-dependent outcome variables are calculated starting from the time of randomization. No change in Protocol Section 3.3 which explains that a patient is considered enrolled at the time of randomization.	
Global	Updated the Medical Dictionary for Regulatory Activities (MedDRA) version and Common Terminology Criteria for Adverse Events (CTCAE) version to be used. MedDRA version 20.1 will be used, and CTCAE version 4.03 will be used in Phase 1 and version 5.0 in Phase 3.	
Global	Minor administrative changes and clarifications involving grammar, diction, punctuation, and other editorial changes that do not affect study design have been made throughout the document.	

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