FPA144-004 Statistical Analysis Plan   Version 1.0, 20 October 2020

STATISTICAL ANALYSIS PLAN

Study 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

Name of Test Drug: FPA144

Protocol Number: FPA144-004

Protocol Version (Date):   Amendment 3 (5 June 2020)

Analysis Type: Final Analysis

Analysis Plan Version: 1.0

Analysis Plan Date: 20 October 2020

Analysis Plan Author: ███████ , PhD

NCT Number: NCT03694522
This NCT number has been applied to the document
for the purposes of posting on clinicaltrials.gov

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Protocol #: FPA144-004		
Version #: 1.0	Version Date:	20 October 2020
☒ New Statistical Analysis Plan	☐ Revised Statistical Analysis Plan	
Summary of changes provided for revised version? ☐ Yes ☐ No		

This Statistical Analysis Plan has been approved by Five Prime Therapeutics, Inc. The following signature documents this approval.

	Signature:	Date:
Lead Statistician Name: ▮▮▮▮▮	▮▮▮▮▮	▮▮▮▮▮
Clinical Pharmacology Lead Name: ▮▮▮▮		
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Head of Biometrics Name ▮▮▮	▮▮▮▮▮▮▮	▮▮▮▮▮
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FivePrime™ Protein Medicines for Life	**Statistical Analysis Plan Approval Form**	Document No.: FP-DOC-00650 Version No.: 1 Page 1 of 1

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LIST OF Abbreviations

ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ATC	Anatomical Therapeutic Chemical classification
AUC	area under the observed concentration-time curve
BMI	body mass index
BOR	best overall response
C_{max}	maximum observed concentration determined from the observed concentration values post first dose
C_{trough}	minimum observed concentration determined from the observed concentration values
CI	confidence interval
CL	total body clearance
CMH method	Cochran-Mantel-Haenszel method
CR	complete response
CSR	Clinical Study Report
CVT	computed tomography
DLT	dose-limited toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Version 3.0
EOT	end of treatment
EQ-5D-5L	EuroQOL-5D-5L
GC	gastroesophageal cancer
GI	gastrointestinal tumors
GLP	Good Laboratory Practices
HR	hazard ratio
ITT	intent-to-treat
IXRS	interactive voice or web response system
LTFU	long-term follow-up
MedDRA	Medical Dictionary for Regulatory Activities
NCA	non-compartmental analysis method
NCI-CTCAE	National Cancer Institute Common Toxicity Criteria for Adverse Events
NE	not evaluable
OECD	Organization for Economic Cooperation and Development
ORR	objective response rate
OS	overall survival
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response

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PROs	patient-reported outcomes
PT	preferred term
Q1, Q3	first quantile, third quantile
Q2W	every 2 weeks
QOL	quality of life
RECIST v1.1	New Response Evaluation Criteria in Solid Tumors (version 1.1)
SAE	serious adverse event
SAP	Statistical Analysis Plan
SE	standard error
SMQ	standardised MedDRA queries
SOC	system organ class
StD	standard deviation
$t_{1/2}$	terminal half-life
TEAE	treatment-emergent adverse event
TFLs	Tables, Figures, and Listings
TTR	time to response
WHODD	World Health Organization Drug Dictionary

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1   BACKGROUND AND RATIONALE

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures and listings (TFLs) of the final analysis in the clinical study report (CSR) for study FPA144-004. This SAP is based on the study protocol Amendment 3 dated 05 June 2020. The SAP will be finalized prior to data finalization for the final analysis (Section 1.5.1).

1.1   Study Design

This is a double-blind, randomized, controlled, multicenter Phase 1/2 study to evaluate the safety, tolerability, efficacy, pharmacokinetic (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 gastrointestinal (GI) tumors (not FGFR2 selected). 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 gastroesophageal cancer (GC), as determined by prospective IHC demonstrating FGFR2b overexpression and/or a ctDNA blood assay demonstrating FGFR2 gene amplification.

The study schema (Phase 1/2) is shown in Figure 1. Patient timelines are shown in Figure 2 (Phase 2).

Figure 1:   **Phase 1/2 Study Schema**
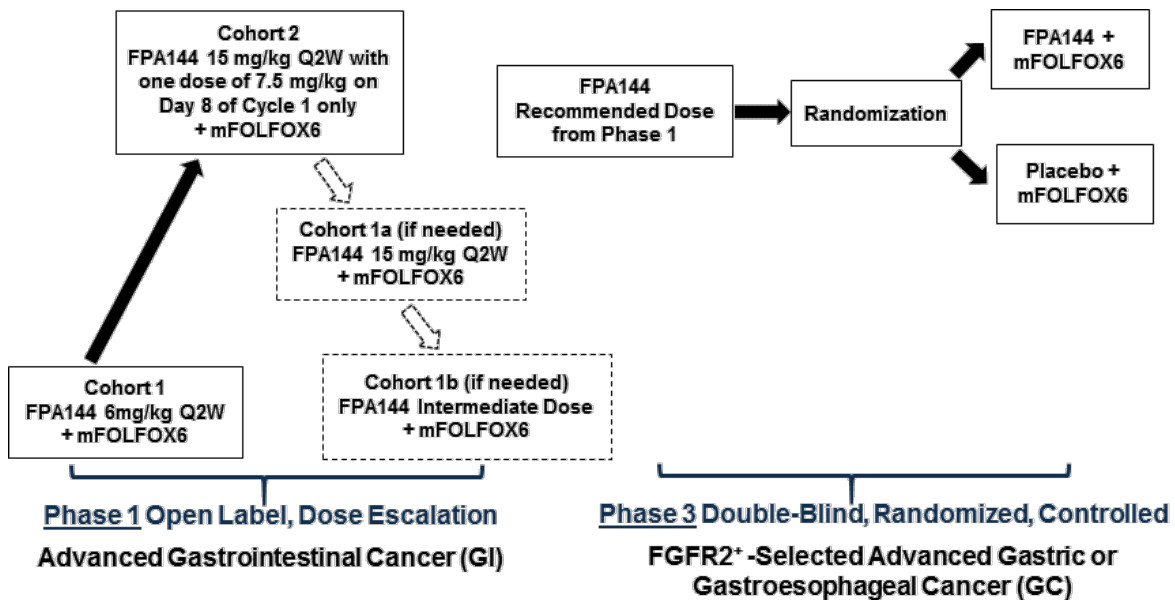
Abbreviations: Q2W = every 2 weeks.

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Figure 2:   **Phase 2 Patient Timeline**
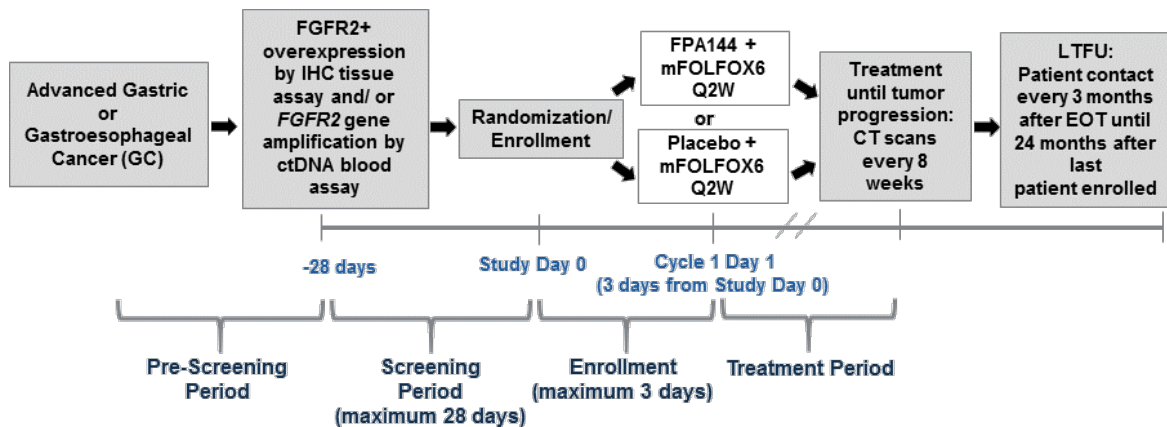
Abbreviations: CVT = computed tomography; EOT = end of treatment; LTFU = long term follow up; Q2W = every 2 weeks.

1.1.1   Treatment Assignment

Based on an assessment of Phase 1 overall safety, tolerability, and PK data 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.

In Phase 2, approximately 155 FGFR2-selected GC patients will be randomized 1:1 to be treated with either FPA144 + mFOLFOX6 or placebo + mFOLFOX6 in 2-week cycles.

1.1.2   Blinding and Unblinding

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, all individuals involved in the conduct of the study (eg, all site staff and participants, monitoring personnel, Sponsor personnel) will remain blinded to randomized treatment assignment.

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

1.2   Study Objectives

1.2.1   Phase 1 Objectives

The primary objective of the Phase 1 portion is 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.

The secondary objectives are:

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

The exploratory objective is to characterize the ████████████████████████████ ████████████████████████████

1.2.2 Phase 2 Objectives

The primary objective of the Phase 2 portion is to compare investigator-assessed progression-free survival (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).

The secondary objective is 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

The exploratory objective is 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 in the presence of mFOLFOX6 in patients with FGFR2-selected GC
- Immunogenicty of FPA144

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1.3 Study Endpoints

1.3.1 Phase 1 Endpoints

The primary endpoint of Phase 1 portion is 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-Limited Toxicity (DLT).

The secondary endpoints are:

- The incidence of AEs, clinical laboratory abnormalities, corneal and retinal findings, and electrocardiogram (ECG) abnormalities
- PK parameters of FPA144, such as 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

The exploratory endpoint is the ███████████████████████████████████ ███████████████████████████████████████

1.3.2 Phase 2 Endpoints

The primary endpoint of the Phase 2 portion is 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.

The secondary endpoints are:

- 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

The exploratory endpoints are:

- 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)

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- 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, such as C_{max} and C_{trough} of FPA144 in combination with mFOLFOX6

- Incidence of treatment-emergent anti-FPA144 antibody response

1.4 Sample Size and Power

The Phase 1 portion planned to 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.

The Phase 2 portion is designed to assess the hazard ratio (HR) for PFS for the FPA144 + mFOLFOX6 compared with placebo + mFOLFOX6. It is planned to observe at least 84 PFS events in order to achieve 71% power to detect an HR of 0.67 for PFS at a 1-sided significance level 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).

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2   TYPE OF PLANNED ANALYSES

2.1   Interim Analyses

No formal interim efficacy analysis, which may lead to early termination for efficacy or futility, is planned in the study.

2.2   Final Analysis

The final efficacy analysis will be conducted after at least 84 PFS events are observed. It is expected that this number of PFS events will occur approximately 11 months after the last patient is enrolled. Once outstanding data queries have been resolved, the database will be cleaned and finalized, and the final analysis of the data will be performed.

2.3   Follow-up Analysis

After the final analysis, additional supplemental analyses of efficacy and safety may be performed for long-term efficacy (eg, overall survival) and follow-up safety assessments.

3   GENERAL CONSIDERATIONS

All statistical tabulations and analyses will be done using SAS®, Version 9.3 or higher.

Unless otherwise noted, continuous variables will be summarized using the number of subjects (n), mean, standard error (SE) or standard deviation (StD), median, minimum, and maximum; categorical variables will be summarized using the number and percentage of subjects in each category.

By-subject listings will be presented for all subjects in the Safety Analysis Set (for Phase 1) or Intent-to-Treat (ITT) Analysis Set (for Phase 2) and sorted by subject ID number, visit date, and time (if applicable). Data collected on log forms, such as AEs, will be presented in chronological order within the subject. The treatment group to which subjects were enrolled/randomized will be used in the listings. Age, sex at birth, race, and ethnicity will be included in the listings, as space permits.

The summaries of the efficacy data will be presented by treatment group. Unless otherwise specified, non-efficacy analyses will be descriptive and will be presented by treatment group and overall.

Unless stated otherwise, Phase 1 and Phase 2 portions of the study will be summarized and listed separately.

3.1   Analysis Sets

3.1.1   Intent-to-treat (ITT) Analysis Set

The ITT Analysis Set is defined for Phase 2 portion of the study. It includes all subjects who were randomized in the study.

The ITT Analysis Set will be used in the summary of subject disposition, demographics and baseline characteristics and the primary analyses for efficacy endpoints.

3.1.2   Efficacy-Evaluable Analysis Set

The Efficacy-Evaluable Analysis Set is defined for Phase 2 portion of the study. It includes all randomized subjects who met key eligibility criteria and received at least 1 dose of study drug (FPA144 + mFOLFOX6 or placebo + mFOLFOX6), had at least 1 postbaseline evaluable tumor assessment, had ≥75% exposure intensity of FPA144/placebo, with no major protocol deviations that could introduce bias in efficacy analysis. Major protocol deviations that could bias efficacy analysis will be assessed and determined on a case-by-case basis prior to unblinding.

The Efficacy-Evaluable Analysis Set is the secondary analysis set for efficacy analyses.

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3.1.3 Safety Analysis Set

Phase 1

The Safety Analysis Set includes all enrolled subjects who have received any portion of at least 1 dose of study treatment (FPA144 + mFOLFOX6).

Phase 2

The Safety Analysis Set included all subjects in the ITT Analysis Set who have received any portion of at least 1 dose of study treatment (FPA144 + mFOLFOX6 or placebo + mFOLFOX6).

The Safety Analysis Set will be used in the summary for safety data as well as study treatment administration.

3.1.4 DLT-Evaluable Analysis Set

The DLT-Evaluable Analysis Set is defined for Phase 1 portion of the study. It includes all enrolled subjects who received at least 2 doses of FPA144 and mFOLFOX6 and completed Cycles 1 and 2 of treatment, or who experienced a DLT in Cycle 1 or Cycle 2.

3.1.5 PK-Evaluable Analysis Set

The PK-Full Analysis Set and the PK-Evaluable Analysis Set are defined for Phase 1 and Phase 2 portion separately. The PK-Full Analysis Set includes all enrolled subjects (for Phase 1) or all randomized subjects (for Phase 2) who received at least 1 dose of FPA144 and have at least 1 serum FPA144 concentration datapoint.

Pharmacokinetic-Evaluable Analysis Set includes all subjects in the PK Full Analysis Set who had sufficient PK data for the reliable calculation of at least one PK parameter.

The PK-Evaluable Analysis Set is the primary analysis set for all PK analyses.

3.1.6 ADA-Evaluable Analysis Set

The Anti-Drug Antibody (ADA)-Evaluable Analysis Set is defined for Phase 1 and Phase 2 portion separately. It includes all enrolled subjects (for Phase 1) or all randomized subjects (for Phase 2) who received at least 1 dose of FPA144 and have at least 1 ADA sample drawn at any timepoint with available ADA data.

The ADA-Evaluable Analysis Set is the primary analysis set for ADA analyses.

3.2 Subject Grouping

For analyses based on the ITT Analysis Set or Efficacy-Evaluable Analysis Set, subjects will be grouped according to the treatment to which they were randomized.

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For analyses based on the Safety Analysis Set, DLT-Evaluable Analysis Set, PK-Evaluable Analysis Set, or ADA-Evaluable Analysis Set, subjects will be grouped according to the actual treatment received. In the Phase 2 portion, the actual treatment received will differ from the randomized treatment only when their actual treatment differs from randomized treatment for the entire treatment duration.

3.3   Stratification Factors

In the Phase 2 portion of the study, subjects will be randomized 1:1 to receive FPA144 + mFOLFOX6 or placebo + mFOLFOX6, stratified based on the following factors:

- Geographic region: Region 1 (including US, Europe and Australia) vs. Region 2 (China) vs. Region 3 (Rest of Asia including Japan, South Korea, Taiwan and Thailand) vs. Region 4 (Rest of World)

- Prior treatment status: *de novo* vs. adjuvant/neo-adjuvant

- Administration of a single dose of mFOLFOX6 prior to enrollment: Yes vs. No

If there are discrepancies in stratification factor values between the interactive voice or web response system (IXRS) and the clinical database, the values recorded in the clinical database will be used for analyses.

Given the small number of subjects in the adjuvant/neo-adjuvant stratums, the stratification factor of prior treatment status will not be considered for the stratified efficacy analysis in the final analysis.

Analyses for efficacy endpoints will be adjusted for the stratification factors. In the situation where there is insufficient information in a stratum (ie, if there are < 20 subjects or there are no informative events in a stratum), pooling of the stratum with the smallest adjacent stratum for stratified analyses will be considered; the smallest stratum is defined as the stratum having the fewest number of subjects or the fewest number of events in case the former is a tie and the adjacent stratum is defined as a stratum having 1 factor of the 2 at the same level and the other factor at an adjacent level.

3.4   Examination of Subject Subgroups

In the analysis of the primary and secondary efficacy endpoints, subgrouping of subjects based on randomization stratification factors will be explored for subgroup analyses. In addition, subgroups defined by presumed prognostic baseline characteristics may also be explored. The presumed prognostic baseline characteristics include but not limited to the following:

- Age (<65 years and ≥65 years)

- Sex (male and female)

- FGFR2b expression

    o Overexpression by IHC irrespective of ctDNA

    o Amplification by ctDNA irrespective of IHC

    o Both overexpressed by IHC and amplified by ctDNA

    o Tumor IHC staining score of 2+ or 3+ in greater than 10% of cells

    o Tumor IHC staining score of 2+ or 3+ in greater than 5% of cells

To graphically display treatment effect changes across subsets, forest plots of PFS and OS hazard ratios, and difference in ORR will be provided.

3.5   Multiple Comparisons

In the Phase 2 portion of the study, the primary endpoint, PFS, will be tested first at a one-sided level of 0.1. If the null hypothesis is rejected, then the secondary endpoints OS and ORR will be tested hierarchically at the same one-sided level of 0.1. OS will be tested first and if it is significant, the ORR will be tested. The family-wise Type I error rate of testing the primary and the secondary endpoints will be controlled by employing this gate-keeping testing procedure at one-sided level of 0.1.

3.6   Missing Data and Outliers

3.6.1   Missing Data

In general, missing data will not be imputed unless methods for handling missing data are specified.

The handling of missing or incomplete dates for disease diagnosis and prior anticancer therapy is described in Section 5.3; for prior and concomitant medications in described in Section 5.4; for the single dose of mFOLFOX6 allowed prior to enrollment is described in Section 5.5; for new anticancer therapy is described in Section 6.1.1, for death date is described in Section 6.3.1, for AE onset is described in Section 7.1.5.

3.6.2   Outliers

Outliers will be identified during the data management and data analysis process, but no sensitivity analyses will be conducted. All data will be included in the data analysis.

3.7   Data Handling Conventions and Transformations

In PK analysis, individual serum FPA144 concentrations, if deemed to be anomalous, may be excluded from the analysis at the discretion of the pharmacokineticist following a review of

available documentation (eg, bioanalytical report). Any such exclusion will be communicated and clearly listed in the study report along with a justification for the exclusion.

Individual serum concentrations will be excluded from descriptive statistics for serum concentration data, including mean concentration versus time plots, if the sample was planned to be collected predose but was actually collected postdose.

Entire serum concentration-time profiles for a patient may be excluded following review of available documentation (eg, bioanalytical report) and communication. Any such exclusion will be communicated and clearly listed in the study report along with justification for exclusion. Results of the analysis with and without the excluded profiles will be presented in the study report when it is necessary.

All serum concentrations reported as No Result (NR or Not Collected/Not Done, ND) values will be treated as missing and will appear in the data set as ".". For the purpose of calculating or plotting mean concentration-time data, or calculating PK parameters, concentration values determined to be below the limit of quantitation (BLQ) will be treated as zero if they occur prior to the first measurable concentration; all other BLQ values will be treated as missing and set to ".". Quantifiable concentrations after two consecutive BLQ values following the same dose will also be set to "." for the purposes of calculating PK parameters.

3.8 Analysis Visit Windows

3.8.1 Definition of Study Day

For subjects in the Phase 1 portion, study day will be calculated from the first dosing date of any portion of the study drug:

- Postdose Study Days = Assessment Date – First Dosing Date + 1

- Study Day prior to First Dose = Assessment Date – First Dosing Date

For subjects in the Phase 2 portion, study day will be calculated from the randomization date:

- Postdose Study Days = Assessment Date – Randomization Date + 1

- Study Day prior to Randomization = Assessment Date – Randomization Date

3.8.2 Analysis Visit Windows

No analysis visit window will be assigned in the analysis. No summary by visit is planned except for PK analysis. In the by-visit summary provided for PK data, nominal visit will be used.

In general, the baseline value will be the last nonmissing value on or prior to the first dosing date of study drug (for Phase 1 subjects) or randomization date (for Phase 2 subjects) unless specified differently.

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For continuous measurements, if multiple measurements occur on the same day, the last nonmissing value will be considered as the baseline value. If these multiple measurements occur at the same time or the time is not available, the average of these measurements will be considered the baseline value. For categorical measurements, if multiple measurements occur on the same day, the last nonmissing value will be considered as the baseline value. If these multiple measurements occur at the same time or the time is not available, the value with the lowest severity will be considered the baseline value.

Values collected after the first dosing date of study drug (for Phase 1 subjects) or randomization date (for Phase 2 subjects) will be considered as postbaseline values. For PK data, the measurement collected at protocol specified nominal timepoint will be selected for analysis.

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4   SUBJECT DISPOSITION

4.1   Subject Enrollment and Disposition

A summary of subject disposition will be provided by treatment group. Percentages will be based on the Safety Analysis Set for Phase 1 portion, and ITT Analysis Set for Phase 2 portion. The number of subjects in the following categories will be provided:

- Pre-screened (Phase 2 only)

- Signed the inform consent

- Randomized (Phase 2 only)

- Randomized but not treated (Phase 2 only)

- Received any study treatment

- Continuing study treatment

- Discontinued from study treatment with reasons for treatment discontinuation

- Continuing study

- Discontinued from study with reasons for study discontinuation

4.2   Extent of Exposure and Adherence

Descriptive statistics of extent of exposure will be presented by treatment group for each component of treatment (FPA144/placebo, Oxaliplatin, Leucovorin, 5FU) separately:

- Duration of exposure (weeks)

- Cumulative exposure by week

- Number of infusions

- Dose intensity (Phase 2 only)

Total duration of exposure to study drug (in weeks) will be defined as (last available dosing date – first dosing date + 14)/7, regardless of any temporary interruptions in study drug administration.

Dose intensity is defined as 100* (Total study drug administered in mg/ Total study drug expected to be administered in mg during exposure to study drug). Percentage of subjects in the intensity categories (<75% and ≥75%) will be provided.

The number and percentage of subjects who have dose reduction, dose delay or interruption, and infusion interruption will be summarized with reasons.

Summaries of exposure will be performed with the Safety Analysis Set. A by-subject listing of study drug administration will be provided.

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5   DEMOGRAPHICS AND BASELINE CHARACTERISTICS

5.1   Demographics

Demographic data will be summarized using descriptive summary statistics for the Safety Analysis Set (Phase 1 portion) or the ITT Analysis Set (Phase 2 portion). The demographic characteristics include age, sex, race, ethnicity, body height (in cm), body weight (in kg) and body mass index (BMI; in kg/m^2).

A by-subject listing will be provided for demographic data.

5.2   Other Baseline Disease Characteristics

Baseline characteristics including baseline Eastern Cooperative Oncology Group Performance Status (ECOG PS), geographic region (US and EU vs China versus Rest of Asia [including Japan, South Korea, Taiwan and Thailand]), prior treatment status (de novo vs adjuvant/neo-adjuvant), and administration of a single dose of mFOLFOX6 prior to enrollment (yes vs no) will be summarized by treatment group for the Safety Analysis Set (Phase 1 portion) or the ITT Analysis Set (Phase 2 portion) as part of the disease-specific baseline characteristics.

5.3   Medical History

Medical history will be collected at screening for disease-specific and general conditions (ie, conditions not specific to the disease being studied).

A summary of disease-specific medical history will be provided for the Safety Analysis Set (Phase 1 portion) or the ITT Analysis Set (Phase 2 portion) as part of the disease-specific baseline characteristics. Time since initial diagnosis of cancer (months) and time since diagnosis of unresectable disease (months) will be calculated by (date of randomization – date of diagnosis) / 30.4375. They will be summarized using summary statistics for a continuous variable. Disease stage at diagnosis and at screening will be summarized using summary statistics for a categorical variable.

In deriving the time since diagnosis, all partial dates of diagnosis and last regimen will be identified, and the partial dates will be imputed as follows:

- If day and month are missing but year is available, then the imputed day and month will be 01 Jan.

- If day is missing but the month and year are available, then the imputed day will be the first day of the month.

- Partial date will not be imputed if the year is missing.

General medical history data will be coded according to Medical Dictionary for Regulatory

Activities (MedDRA) Version 20.1. It will be listed only. A by-subject listing will be provided for disease-specific medical history.

5.4   Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODD) and classified according to Anatomical Therapeutic Chemical classification (ATC) codes levels 2 (therapeutic sublevel) and 4 (chemical sublevel).

All medications with an end date prior to the first dose of any study drug will be considered as prior medication regardless of the stop date. If a partial start date is entered the medication will be considered prior unless the month and year (if day is missing) or year (if day and month are missing) of the start date are after the first dosing date. Medications with a completely missing start date will be considered as prior medication, unless otherwise specified

Concomitant medications are defined as medications taken while a subject took study drug. If a partial stop date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) prior to the date of first study drug administration will not be considered as concomitant medication. If a partial start date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) after the study drug stop date will not be considered as concomitant medication. Medications with completely missing start and stop dates will be considered as concomitant medication, unless otherwise specified.

All prior and concomitant medications (other than per-protocol study drugs) will be provided in a by-subject listing.

5.5   Prior Anticancer Therapy

Number of prior regimens, time since the completion of last regimen will be summarized by treatment group using descriptive statistics. The best response to the last regimen will be summarized using summary statistics for a categorical variable. The summaries will be based on the Safety Analysis Set (Phase 1 portion) or the ITT Analysis Set (Phase 2 portion) as part of the disease-specific baseline characteristics. A partial completion date will be imputed using the algorithm defined in Section 4.3. The prior anticancer therapy will be listed by subject.

For the single dose of mFOLFOX6 allowed prior to enrollment, a partial dose date will be imputed as follows:

- If the day is missing but the month and year are available, then impute the day as first day of the month, or the informed consent date for pre-screening if they have the same month and year, whichever is later.

- If the day and month are missing but year is available, then impute the day and the month as 01Jan, or the informed consent date for prescreening if they have the same year, whichever is later.

- Partial date will not be imputed if the year is missing.

6   EFFICACY ANALYSES

The efficacy analysis for Phase 1 and Phase 2 portions will be performed and reported separately. Efficacy summaries will be presented by treatment group based on the Safety Analysis Set (Phase 1 portion) or the ITT Analysis Set (Phase 2 portion).

6.1   Efficacy Endpoints in Phase 1

Best overall response (BOR) is reported directly by the investigators in the Phase 1 portion of the study. A summary of the number of subjects in response categories and the overall response rate, defined as the proportion of subjects who achieve BOR of either complete response (CR) or partial response (PR), will be provided. A by-subject listing of BOR will also be provided.

6.2   Primary Efficacy Endpoint in Phase 2

6.2.1   Definition of the Primary Efficacy Endpoint

The primary efficacy endpoint in the Phase 2 portion of the study is PFS, defined as time from randomization until the date of radiographic disease progression based on investigator assessment (using RECIST v1.1) or death from any cause, whichever comes first.

The PFS analysis 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. Data will be censored on 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.

When the date of initiation of new anticancer therapy other than the study treatment is incomplete or missing, the following algorithm will be followed:

- If the day is missing but the month and year are available, then the imputed day will be the last day of the month.

- If day and month are missing but year is available, then the imputed day and month will be the last day of the month for the last adequate disease assessment if they have the

same year.

6.2.2   Statistical Hypothesis for the Primary Efficacy Endpoint

The primary efficacy hypothesis to be tested is that there is no difference in PFS between FPA144 + mFOLFOX6 and placebo + mFOLFOX6. Using $S_T(t)$ and $S_C(t)$ to denote the PFS distribution functions of FPA144 + mFOLFOX6 and placebo + mFOLFOX6, respectively, the statistical hypotheses to be tested in this study will be:

H_0: $S_T(t) = S_C(t)$

H_1: $S_T(t) > S_C(t)$ (FPA144 + mFOLFOX6 is superior to placebo + mFOLFOX6 in terms of PFS)

6.2.3   Analysis of the Primary Efficacy Endpoint

The primary analysis of PFS will be performed using the Kaplan-Meier method for the ITT Analysis Set. The PFS distribution of 2 treatment groups will be compared using the stratified log-rank test, stratified by the stratification factors at randomization. Medians, Q1, Q3, the proportion of subjects who progression-free at 6, 9, and 12 months from randomization will be provided along with corresponding 95% confidence intervals (CI). The unstratified log-rank test will also be performed. Kaplan-Meier curves will be provided by treatment group.

In addition, the HR between the 2 treatment groups and its 95% CI will be estimated using the Cox proportional hazards regression model with treatment group as the only main effect and stratified by the stratification factors at randomization.

A listing will be provided for the information of subject PFS, including randomization date, date of PFS event or censor date.

6.2.4   Sensitivity Analysis of the Primary Efficacy Endpoint

To assess the robustness of the primary PFS results, the following sensitivity analyses will be performed:

- PFS will be analyzed by considering initiation of new anticancer therapy as a PFS event. Furthermore, PFS will not be censored by having ≥2 consecutive missing tumor assessments before documented progression or death or initiation of new anticancer therapy.

- PFS will be analyzed by considering clinical progression as a PFS event. The date of documented radiographic progression, clinical progression, or death, whichever is earlier, will be considered as PFS event date.

- PFS will be analyzed based on the Efficacy-Evaluable Analysis Set with the same analysis methods specified for the primary analysis.

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Other methods, e.g., restricted mean survival time, may be considered for PFS as exploratory analysis if the proportional hazard assumption is not hold.

6.2.5   Exploratory Analysis of the Primary Efficacy Endpoint

Exploratory analysis will be performed to investigate the potential prognostic factors influencing PFS using the Cox regression model. The variables with prognostic potential will be included in the model to identify plausible significant factors on PFS. The potential variables include but not limit to the following:

- Age (<60 years and ≥60 years)

- Sex (male and female)

- 3 stratification factors at randomization: geographic region, prior treatment status, and administration of a single dose of mFOLFOX6 prior to enrollment

- Extent of disease (locally advanced and metastatic)

- Primary tumor site (gastric adenocarcinoma and gastroesophageal junction adenocarcinoma)

- Measurability of disease (measurable disease and non-measurable disease at baseline)

- Number of lesions at baseline (1-4 lesions and >4 lesions)

- Visceral metastasis (yes and no)

- Prior gastrectomy (yes and no)

- H score of IHC test (as continuous variable)

Each candidate variable will be preliminarily evaluated in the Cox regression model with treatment. Only the variables significant at the 0.4 level will be considered to build the multivariate model. A stepwise selection process with significance level of 0.3 for entering variables will then be applied to those candidate variables to identify the final subset of relevant covariates in the Cox regression model with treatment. The hazard ratio of the variables in the final set will be provided. Same analysis may be done on geographic subgroups.

PFS will also be analyzed based on the subgroups defined in Section 3.4. Same analysis as specified for the primary analysis will be performed, except that only the unstratified log-rank test will be provided and the hazard ratio estimated by the Cox proportional hazard model will not be adjusted by randomization stratification factors.

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6.3   Secondary Efficacy Endpoints in Phase 2

6.3.1   Definition of the Secondary efficacy Endpoints

The secondary efficacy endpoints of this study are OS and ORR.

OS 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 will be censored at the last date that they were known to be alive. Subjects with confirmed death or alive status after the data cutoff date will be censored at the data cutoff date.

Every attempt will be made to ensure that complete death dates are recorded. In those rare instances where complete death dates are not recorded, the following algorithm will be used:

- If day is missing but the month and year are available, then the imputed day will be the midpoint of the month or the last assessment date + 1, whichever is later.

- If day and month are missing but year is available, then the imputed day and month will be 01Jan or the last day of the latest month that the subject was known to be alive if they have the same year, whichever is later.

ORR is defined as the proportion of subjects who achieve BOR of either CR or PR based on investigator assessment tumor lesions per RECIST v1.1. The BOR is the best response documented from randomization until the end of study or data cut-off date, first disease progression, death, start of new anti-cancer therapy, or last documented assessment before ≥2 consecutive missing tumor assessments, whichever is earlier. Subjects, who do not have sufficient baseline or on-study tumor status information to be adequately assessed for response status (ie, those with BOR of not evaluable [NE]), received anticancer therapy other than the study treatment, or missing ≥2 consecutive missing tumor assessments prior to achieving CR or PR, will be considered as non-responders and will be included in the denominators in calculations of response rates.

To preserve the overall type I error rate across the primary and secondary endpoints of the study at a 1-sided significance level of 0.1, the primary efficacy hypothesis must be rejected at the 1-sided 0.1 significance level before the efficacy hypotheses for the secondary efficacy endpoints can be tested. The 2 secondary endpoints will be tested sequentially at the 1-sided 0.1 significance level in the order of OS then ORR. If a null hypothesis is not rejected, formal sequential testing will be stopped and only the nominal significance level will be presented for the remaining endpoints.

6.3.2   Analysis of the Secondary Efficacy Endpoints

OS

The primary analysis of OS will be performed using the Kaplan-Meier method for the ITT

Analysis Set. The OS distribution of 2 treatment groups will be compared using the stratified log-rank test, stratified by the stratification factors at randomization. Medians, Q1, Q3, the proportion of subjects who are alive at 6, 12, and 15 months from randomization will be provided along with corresponding 95% CIs. The unstratified log-rank test will also be performed. Kaplan-Meier curves will be provided by treatment group.

In addition, the HR between the 2 treatment groups and its 95% CI will be estimated using the Cox proportional hazards regression model with treatment group as the only main effect and stratified by the stratification factors at randomization.

A listing will be provided for the information of subject OS, including randomization date, date of OS event or censor date.

To assess the robustness of the primary OS results, the analysis will be performed based on the Efficacy-Evaluable Analysis Set with the same analysis methods specified for the primary analysis as the sensitivity analysis.

Exploratory analysis for OS will be performed with the same methods for PFS as descried in Section 6.2.5. Multivariate model with potential prognostic factors influencing OS will be built using Cox regression model. Subgroup analysis will also be performed.

ORR

The analysis of ORR will be performed based on the ITT Analysis Set. ORR with corresponding 2-sided 95% CI based on Clopper-Pearson method along with each category of BOR will be summarized by treatment group. Patients who don't have any postbaseline adequate tumor assessments will be counted as non-responders. A conventional 2-sided 95% CI of the difference in ORR of the two treatment groups and the corresponding p-value will be calculated based on stratum-adjusted Cochran-Mantel-Haenszel (CMH) proportions (Koch, Carr, Amara, Stokes, & Uryniak, 1989):

$$\hat{p}_t - \hat{p}_c \pm Z_{1-\alpha/2} \cdot SE(\hat{p}_t - \hat{p}_c),$$

where

- p_t and p_c denote the response rate in FPA144 + mFOLFOX6 and placebo + mFOLFOX6 treatment group, respectively.

- $\hat{p}_t - \hat{p}_c = \frac{\sum W_h d_h}{\sum W_h}$, where $d_h = \hat{p}_{th} - \hat{p}_{ch}$ is the stratum-adjusted CMH proportion difference in stratum h ($h = 1, 2, ..., K$).

- $W_h = \frac{n_{th} n_{ch}}{n_{th} + n_{ch}}$, is the weight based on the harmonic mean of sample size per treatment group for each stratum where n_{th} and n_{ch} are the sample sizes of each treatment group in stratum h.

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- $SE(\hat{p}_t - \hat{p}_c) = \dfrac{\sqrt{\sum W_h^2 \left(\frac{\hat{p}_{th}^*(1-\hat{p}_{th}^*)}{n_{th}-1} + \frac{\hat{p}_{ch}^*(1-\hat{p}_{ch}^*)}{n_{ch}-1} \right)}}{\sum W_h}$, where $\hat{p}_{th}^* = \dfrac{m_{th}+0.5}{n_{th}+1}$, $\hat{p}_{ch}^* = \dfrac{m_{ch}+0.5}{n_{ch}+1}$, m_{th} and m_{ch} are the number of responders in stratum h of each treatment group.

- $Z_{(1-\alpha/2)}$ is the $100(1-\alpha/2)$th percentile of normal distribution, where $\alpha = 0.05$.

To assess the robustness of the primary ORR results, the analysis will be performed based on the Efficacy-Evaluable Analysis Set with the same analysis methods specified for the primary analysis as the sensitivity analysis.

Exploratory analysis will be performed to investigate the potential prognostic factors influencing ORR using the logistic regression model. The potential variables include but not limit to the ones that have been identified in Section 6.2.5.

Each candidate variable will be preliminarily evaluated in the logistic regression model with treatment. Only the variables significant at the 0.4 level will be considered to build the multivariate model. A stepwise selection process with significance level of 0.3 for entering variables will be applied to those candidate variables to identify the final subset of relevant covariates in the logistic regression model with treatment. The odds ratio of the variables in the final set will be provided.

ORR will also be analyzed based on the subgroups defined in Section 3.4. Same analysis as specified for the primary analysis will be performed, except for p-value of the difference in ORR will not be provided and the 95% CI of the difference in ORR will be calculated without adjusting by the randomization stratification factors.

6.4   Exploratory Efficacy Endpoints in Phase 2

6.4.1   Duration of Response

Duration of response is defined as the time from the first documented CR or PR to the earlier of the first documented PD or death from any cause. DOR will be evaluated using the investigator assessments based on subset of subjects in ITT Analysis Set who achieve a response. DOR will be summarized using Kaplan-Meier methods (median, Q1, Q3, and corresponding 95% CI).

In the analysis of DOR, data will be censored on the date of the last 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

6.4.2   Time to Response

Time to response (TTR) is defined as the interval from randomization to the first documented CR or PR. TTR will be evaluated in the subset of subjects in ITT Analysis Set who achieve a response. Descriptive statistics of TTR will be provided.

6.4.3   Change in Tumor Size

Tumor size based on the sum of the diameters of target lesions is collected in the eCRF through an MRI/CT scan at each tumor assessment visit. Change from baseline and the percent change from baseline will be determined for each post baseline assessment. The best change from baseline and the best percent change from baseline are defined as change or the percentage change from baseline to postbaseline minimum in tumor size while the assessment was taken prior to the time of initiation of anticancer treatment other than the study treatment or have ≥2 consecutive missing tumor assessments before documented progression or death without documented progression.

Change in tumor size will be analyzed for subjects in the ITT Analysis Set who have assessments at baseline and at least 1 post-baseline time point. Baseline, postbaseline maximum, postbaseline minimum, and their percent (%) change from baseline will be calculated and summarized. Waterfall plot will be provided for the best percent (%) change from baseline. A listing of target lesion will be provided.

6.4.4   Patient-Reported Outcome Assessments

Patient-Reported Outcome includes EORTC QLQ-C30 and EQ-5D-5L. The EORTC QLQ-C30 is a self-reported cancer health-related questionnaire. It includes five function domains (physical, role, emotional, cognitive, social), eight symptoms (fatigue, pain, nausea/vomiting, constipation, diarrhea, insomnia, dyspnea, and appetite loss), as well as global health/quality-of-life and financial difficulties. The EQ-5D-5L is a self-report questionnaire used to assess a subject's general health quality of life consisting of five dimensions (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression) as well as a VAS for overall health.

Data from EORTC QLQ-C30 and EQ-5D-5L will be scored, processed, and standardized according to their user manuals. Data will be analyzed using appropriate methods specified in the user manuals to account for incomplete questionnaires. The maximum improvement postbaseline and change from baseline in subscales and global scores of EORTC QLQ-C30 and EQ-5D VAS, and the minimum and maximum postbaseline in dimensions of EQ-5D-5L will be summarized descriptively by treatment groups for subjects in the ITT Analysis Set. By subject listings will be provided for EORTC QLQ-C30 and EQ-5D-5L.

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6.4.5   ECOG PS

The ECOG PS score has a range from 0 (Fully active; able to carry on all pre-disease performance without restriction) to 5 (Dead). The best postbaseline performance status will be the lowest score and the worst postbaseline performance status will be the highest score after randomization. A listing of ECOG PS will be provided.

6.5   Changes from Protocol-Specified Efficacy Analysis

Analysis and summary are provided for time to response and change in tumor size.

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7   SAFETY ANALYSES

Unless otherwise specified, all analyses will be performed using the Safety Analysis Set. The safety analysis for Phase 1 and Phase 2 portions will be performed and reported separately.

No formal comparisons of safety endpoints are planned.

7.1   Adverse Events and Deaths

7.1.1   Adverse Event Dictionary

All AEs will be coded to system organ class (SOC) and preferred term (PT) using MedDRA Version 20.1.

7.1.2   Adverse Event Severity

Adverse events are graded for severity by the investigators using the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) Version 5. The severity grade of events for which the investigator did not record severity will be categorized as "missing" for tabular summaries and data listings.

7.1.3   Relationship of Adverse Event to Study Drug

A treatment related AE is an AE noted as related to FPA144/placebo, Oxaliplatin, Leucovorin, or 5FU by the investigator. Events for which the investigator did not record relationship to study drug will be considered related to study drug for summary purposes. However, by-subject data listings will show the relationship as missing.

7.1.4   Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if the AEs met the definitions of SAEs that were specified in the study protocol.

7.1.5   Treatment-Emergent Adverse Events

A treatment-emergent AE (TEAE) is defined as an AE that was not present prior to the start date of study drug or was worsened during treatment and 28 days after permanent discontinuation of study drug. An AE that was present at treatment initiation but resolved and then reappeared and the event severity increase while the subject was on treatment is also a TEAE.

If the onset date of the AE is incomplete and the AE stop date is not prior to the first dosing date of study drug, then the month and year (or year alone if month is not recorded) of onset determine whether an AE is treatment emergent. The event is considered treatment emergent if both of the following 2 criteria are met:

- The AE onset is the same as or after the month and year (or year) of the first dosing date

of study drug, and

- The AE onset date is the same as or before the month and year (or year) of the date corresponding to 28 days after the date of the last dose of study drug

An AE with completely missing onset and stop dates, or with the onset date missing and a stop date later than the first dosing date of study drug, will be considered treatment emergent. In addition, an AE with the onset date missing and incomplete stop date with the same or later month and year (or year alone if month is not recorded) as the first dosing date of study drug will be considered treatment emergent.

7.1.6 Summary of Adverse Events and Deaths

The number and percentage of subjects who experienced at least 1 TEAE will be provided and summarized by SOC, PT, and treatment group. For other AEs described below, summaries will be provided by SOC, PT, maximum severity, and treatment group

- TEAE (both Phase 1 and Phase 2)

- TE SAE (both Phase 1 and Phase 2)

- Summary of TEAE of Grade 3-5 (both Phase 1 and Phase 2)

- TEAE related to FPA144/Placebo

- TEAE related to mFOLFOX6

- TE SAE related to FPA144/Placebo

- TE SAE related to mFOLFOX6

- TEAE leading to FPA144/Placebo treatment discontinuation

- TEAE leading to mFOLFOX6 treatment discontinuation

- TEAE leading to death (both Phase 1 and Phase 2)

- TEAE leading to dose reduction in FPA144/Placebo

- TEAE leading to dose reduction in mFOLFOX6

- TEAE leading to dose delayed in FPA144/Placebo

- TEAE leading to dose delayed in mFOLFOX6

- TEAE leading to infusion interruption in FPA144/placebo

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- TEAE leading to infusion interruption in mFOLFOX6

- TEAE of dose limiting toxicity (Phase 1 only)

These summaries will be provided for the Phase 2 portion if not otherwise specified.

A brief, high-level summary of AEs described above will be provided for Phase 1 and Phase 2 portions by treatment group and by the number and percentage of subjects who experienced the above AEs.

Multiple events will be counted only once per subject in each summary. AEs will be summarized in alphabetic order of SOC and then by PT in descending order of total frequency within each SOC. For summaries by severity, the most severe severity will be used for those AEs that occurred more than once in a subject.

In addition to the above summary tables, TEAEs, TEAEs of Grade 3 or higher, TE treatment-related AEs, and TE SAEs will be summarized by PT only in descending order of total frequency.

All AE and recorded deaths for the safety population will be listed.

7.1.7   Adverse Events of Special Interest

An AE of special interest (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. The following events are considered events of special interest in this study:

- Ocular events associated with symptomatic corneal involvement and symptomatic and asymptomatic retinal involvement: these events are defined as those AEs in the Standardised MedDRA Queries (SMQs) (Broad) of Corneal Disorders and Retina Disorders

- Events of hypersensitivity: these events are defined as those AE in the SMQ (Broad) of Hypersensitivity

Treatment-emergent AESIs of ocular events are defined as those AEs present not prior to the start date of study drug or was worsened during treatment and 100 days after permanent discontinuation of study drug, as collected from CRF. The treatment-emergent definition for general AEs is still applied for AESIs of hypersensitivity events.

Treatment-emergent AESIs will be summarized by PT and maximum CTCAE Grade for the Phase 2 portion.

In addition, time to first onset of ocular events of any grade, Grade 2 and above, and Grade 3 and

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above will be summarized, respectively. Kaplan Meier estimates of the median, Q1, Q3, and the number of subjects with event and censored subjects will be provided. Time to first onset of ocular events is defined as the time from start of study treatment to the date of first incident of ocular events. In the absence of an ocular event, the censoring date will be the earliest from the following dates:

- Last dose date of FPA144/placebo + 100 days

- Death date

- Analysis cut-off date

In case when the AE onset date is incomplete and needs to be imputed, the following algorithm will be followed:

- If the day is missing but the month and year are available, then the imputed day will be the first day of the month or the first dosing date if they have the same month and year, whichever is later.

- If the day and month are missing but year is available, then the imputed day and month will be 01Jan or the first dosing date if they have the same year, whichever is later.

By subject listings of AESI will be provided.

7.1.8 Dose-Limiting Toxicity

The summary and listing of DLTs will be performed on the DLT-Evaluable Analysis Set for the Phase 1 portion. A summary of DLT will be provided by SOC, PT, and severity. All DLTs will be listed.

7.2 Clinical Laboratory Evaluations

Summaries of laboratory data will be provided in the Safety Analysis Set and will include data collected up to the last dose of study drug plus 28 days for subjects who have discontinued study drug, or all available data at the time of the final analysis data-cut for subjects who are ongoing at the time of the final analysis.

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline time point. If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment emergent.

The following summaries will be provided by lab test and treatment group. Subjects will be categorized according to the most severe postbaseline abnormality grade for a given laboratory test:

- Laboratory abnormalities (both Phase 1 and Phase 2)

- Grade 3 or 4 laboratory abnormalities (Phase 2 only)

Shift tables displaying subject counts and percentages classified by baseline grade and maximum grade on treatment will be provided for chemistry, hematology, and coagulation tests with CTCAE v5 grading for Phase 2 portion of the study.

By-subject listings of laboratory test results collected throughout the study will be provided for chemistry, hematology, and coagulation tests for both Phase 1 and Phase 2 portions of the study.

7.3 Body Weight and Vital Signs

Descriptive statistics will be provided for both Phase 1 and Phase 2 portions of the study by treatment group for body weight and vital signs as follows:

- Baseline

- Postbaseline maximum

- Postbaseline minimum

- Change and percentage change from baseline to postbaseline maximum

- Change and percentage change from baseline to postbaseline minimum

A baseline value is defined as the last available value collected on or prior to the first dose of study drug.

A by-subject listing of body weight and vital signs will be provided by subject ID and time point in chronological order.

7.4 Electrocardiograms

Subjects with abnormal ECG findings will be listed for both Phase 1 and Phase 2 portions of the study.

7.5 Other Safety Measures

Ocular examinations including fluorescein staining score, ocular symptoms, fundoscopy, ocular coherence tomography, visual acuity, intraocular pressure, slit lamp biomicroscopy, and confrontation visual field exams were performed at baseline and postbaseline in the study. The number of subjects shifted from Not Clinically Significant at baseline to Clinically Significant at any postbaseline assessment will be summarized by examination and treatment group. The summary will be provided for the Phase 2 portion of the study.

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In addition, shift in fluorescein staining score from baseline to most extreme postbaseline grade will be presented for the Phase 2 portion of the study.

A by-subject listing of the ocular examinations will be provided for both Phase 1 and Phase 2 portions of the study.

By-subject listings for pregnancy report and substance use of tobacco and alcohol will be provided for both Phase 1 and Phase 2 portions of the study.

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8   PHARMACOKINETIC AND IMMUNOGENICITY ANALYSES

8.1   Bioanalytical Methods

The PK and ADA samples will be analyzed by validated ligand binding assays. The bioanalysis will be performed at ICON Bioanalytical Laboratories and will be conducted in a manner consistent with the FDA and Organization for Economic Cooperation and Development (OECD) Good Laboratory Practices (GLP) principles as they apply to bioanalytical chemistry.

8.2   PK Analysis

8.2.1   PK Sample Collection

In the Phase 1 portion of the study, blood samples to determine serum FPA144 concentration will be acquired from each subject on C1D1 (predose, 15 minutes, 4 hours, 48 hours, and 168 hours postdose), C1D8 (Cohort 2 subjects only, predose, 15 minutes, and 4 hours postdose), C2D1 (predose, 15 minutes, and 48 hours postdose), C3D1 (predose and 15 minutes postdose), C4D1 (same as C3D1), C5D1 (same as C3D1), C7D1 (same as C3D1), C9D1 (same as C3D1), C10D1 (same as C2D1) C11D1 (same as C3D1), every 8 Cycles starting from Cycle 15 (same as C3D1), and EOT.

In the Phase 2 portion of the study, blood samples to determine serum FPA144 concentration will be acquired from each subject on C1D1 (predose and 15 minutes postdose), C3D1 (predose and 15 minutes postdose), C5D1 (predose), C9D1 (predose), C17D1 (predose), and EOT.

8.2.2   Estimation of Pharmacokinetic Parameters

FPA144 pharmacokinetic parameters will be derived from the serum concentration versus time profiles for C1D1 from Phase 1. Individual PK parameter values will be derived using a non-compartmental analysis (NCA) method for IV Infusion in Phoenix WinNonlin (Plasma 200 – 202). Actual elapsed sampling times relative to start of FPA144 infusion will be used for all parameter estimations. Individual C_{max} and C_{trough} as well as their accumulation ratios (RA1 and RA2, respectively) for Phase 1 and Phase 2 will be reported for the cycles with data. The PK parameters are defined below:

Variable	Units	Definition
AUC_{inf}	d*μg/mL (d=day)	Area under the observed concentration-time curve from the time of dose administration extrapolated to infinity post first dose, based on the last observed quantifiable concentration: $AUC_{inf} = AUC_{last} + C_{last}/\lambda_z$ where Clast is the last observed quantifiable serum concentration.
AUC_{inf}/Dose	[d*μg/mL]/[mg/kg]	AUC_{inf} normalized by dose administered.
AUC_{0-7}	d*μg/mL	Area under the observed concentration-time curve from the time of dosing to Day 7 (0-168h) post first

		dose calculated by log-linear trapezoidal approximation.
DN-AUC$_{0-7}$	[d*µg/mL]/[mg/kg]	AUC$_{0-7}$ normalized by dose administered.
AUC$_{0-14}$	d*µg/mL	Area under the observed concentration-time curve from the time of dosing to Day 14 (0-336h) calculated by log-linear trapezoidal approximation.
DN-AUC$_{0-14}$	[d*µg/mL]/(mg/kg)	AUC$_{0-14}$ normalized by dose administered.
Clast	µg/mL	Last observed temporal quantifiable serum concentration for both Cohorts of Phase 1 post first dose (Day 14 for Cohort 2 of Phase 1 post second dose).
CL	mL/d/kg	Total body clearance calculated post first dose. CL = Dose/AUC$_{inf}$.
C$_{max}$	µg/mL	Maximum observed concentration determined from the observed concentration values post first dose.
C$_{max}$ /Dose	[µg/mL]/[mg/kg]	C$_{max}$ normalized by dose administered.
C$_{max\,n}$ (dose 2 to last dose)	µg/mL	Observed concentration associated with the sample at the end of the infusion for each dose excluding the one on Study Day 8 for Cohort 2 of Phase 1. n = the dose number.
C$_{max\,n}$/Dose	[µg/mL]/[mg/kg]	C$_{max\,n}$ normalized by dose administered. n = the dose number.
C$_{trough\,n}$ (dose 1 to last dose)	µg/mL	Concentration associated with the sample at the end of each dose interval excluding the one on Study Day 8 for Cohort 2 of Phase 1. n = the dose number.
C$_{trough\,n}$/Dose (dose 1 to last dose)	[µg/mL]/[mg/kg]	C$_{trough\,n}$ normalized by dose administered. n = the dose number.
C$_{term}$	µg/mL	Observed concentration associated with the sample obtained at the end of the study.
λ_z	d$_{-1}$	Terminal phase rate constant of concentration-time profile.
λ_z lower	d	Time associated with the last observed concentration used to calculate λ_z.
λ_z upper	d	Time associated with the first observed concentration used to calculate λ_z.
MRT	d	Mean residence time. MRT = (AUMC/AUC$_{inf}$) – T/2 where AUMC=Area Under Moments Curve and T= infusion duration.
# Points Lambdaz		Number of points used in computing λ_z.
RA1		Accumulation ratio based on measurement at the end of infusion of C$_{max\,1}$ compared to C$_{max\,n}$ calculated as C$_{max\,n}$/C$_{max\,1}$.
RA2		Accumulation ratio based on measurement of C$_{trough\,1}$ compared to C$_{trough\,n}$ calculated as C$_{trough\,n}$/C$_{trough\,1}$.
Adjusted r2		Goodness of fit statistic for calculating λ_z.

$t_{1/2}$	d	Terminal half-life calculated post first dose. $t_{1/2}=$ $\ln(2)/\lambda_z$.
t_{last}	d	Time of the last quantifiable concentration for both Cohorts of Phase 1 post first dose (for Cohort 2 of Phase 1 post second dose).
t_{max}	d	Time to reach observed concentration corresponding to T_{last} for both Cohorts of Phase 1 post first dose (for Cohort 2 of Phase 1 post second dose).
V_{ss}	mL/kg	Steady-state distribution volume projected post first dose. $V_{ss}=$ CL*MRT.
V_z	mL/kg	Volume of distribution based on the terminal phase post first dose. $V_z = Dose/(AUC_{inf}*\lambda_z)$

In Phase 1, blood samples to determine serum FPA144 concentration before the second dose of 7.5 mg/kg on C1D8 were collected twice at the same time for some patients in Cohort 2 of Phase 1. One of the samples was named as Cycle 1 Day 8 pre-dose. Another one was named as unscheduled 1008.00002. Both samples were included in individual serum FPA144 concentration listing, but only the samples named as Cycle 1 Day 8 pre-dose were used to estimate any PK parameters as it is the protocol specified nominal timepoint.

Only data points that described the terminal elimination log-linear decline of the serum FPA144 concentrations are to be used in the regression equation for calculation of terminal elimination phase rate constant; C_{max} and any data point(s) in the distribution phase are not to be included in the calculation. A minimum of 3 points are to be used for determination of the terminal elimination phase rate constant. A general rule of adjusted $r^2 > 0.80$ will be considered as acceptable for calculation of the terminal elimination phase rate constant. If adjusted r^2 falls below 0.80, then the terminal elimination phase rate constant will be reported as not determined (ND) and that subject's AUC_{inf} and CL will be listed but excluded from descriptive summaries and statistical analysis. If the extrapolated AUC_{inf} is more than 20%, then both AUC_{inf} and CL will be listed but excluded from descriptive summaries and statistical analysis.

8.2.3 Assessment of Dose-Proportionality for Phase 1

Dose-proportionality will be assessed for C_{max}, AUC_{0-7}, and C_{trough} of C1D1 from Phase 1 at 6 mg/kg and 15 mg/kg using either a power model or a direct comparison of dose-normalized values. In power model, log(parameter) = a + b * log(dose), where a is the intercept, b is the slope and dose is actual dose in mg. Each log-transformed PK parameter will be fit with a power model with a fixed effect term for log-transformed dose. For each PK parameter, the slope and associated 90% CI will be presented. A minimum of 3 values per dose cohort must be available for a given parameter to estimate dose-proportionality with the power model. Dose-proportionality will be inferred if the 90% CI for the estimate of the slope contains 1.

8.2.4 Assessment of Steady-State Attainment for both Phase 1 and Phase 2

To assess steady-state attainment, graphical comparison will be performed using C_{max} and C_{trough}

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of FPA144 for each Q2W cycle.

8.2.5 Assessment of Immunogenicity Impact on Serum FPA144 Concentration and Pharmacokinetic Parameters

No FPA144 treatment induced ADA positive patients were identified in Phase 1. The impact of ADA on FPA144 exposure from Phase 2 will be assessed if there are any confirmed treatment induced ADA positive patient using descriptive statistics to compare C_{max} and C_{trough} values between ADA positive and ADA negative patients at each dose level by cycle and by dose.

8.2.6 Summary of Serum Concentration data and Pharmacokinetic Parameters

Pharmacokinetic parameters will be generated for all subjects in the PK-Evaluable Analysis Set. Individual subject concentration data and individual subject PK parameters for FPA144 will be listed and summarized using descriptive statistics by Cohort and by Phase. Summary statistics (n, mean, StD, geometric mean, coefficient of variation of geometric mean [GeoCV], median, min, max, 95% CI) will be presented for both individual subject concentration data by time point and individual subject PK parameters by Cohort and by Phase. Non-continuous variables such as t_{max} will be summarized using n, median, minimum, and maximum. For summary statistics, BLQ values will be treated as specified in Section 3.6.1. Subjects in Phase 1 and Phase 2 portion of the study will be analyzed and summarized separately.

The following tables will be provided:

- Summary of FPA144 serum concentration (Phase 1 and Phase 2)

- Summary of FPA144 serum concentration with response and ADA status (Phase 2)

- Summary of pharmacokinetic parameters (Phase 1 and Phase 2)

- Summary of pharmacokinetic parameters with response and ADA status (Phase 2)

The following figures will be provided:

- Group mean (+/-StD) FPA144 serum concentration vs time profiles post first and second doses (Phase 1)

- Summary plot of C_{max} and C_{trough} versus time (Phase 1 and Phase 2)

- Individual scatter plot of FPA144 C_{max} and C_{trough} versus time (Phase 1 and Phase 2)

- Boxplot of FPA144 C_{max} and C_{trough} versus time with total patients, and with response and ADA status (Phase 2)

The following listings will be provided:

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- Individual serum FPA144 concentration (Phase 1 and Phase 2)

- Individual Pharmacokinetic parameters (Phase 1)

- Individual Pharmacokinetic parameters with response and ADA status (Phase 2)

8.2.7 Quality Control Methods for PK data Analysis

The PK analysis will be subject to Quality Control (QC) review and reviewed by an independent pharmacokinetist at ICON.

8.3 Immunogenicity Analysis

8.3.1 Immunogenicity Samples Collection

In the phase 1 portion of the study, blood samples were collected before the infusion on Cycles 1, 2, 3, 7 and 10, and EOT to measure ADA for FPA144. In the phase 2 portion of the study, blood samples were collected before the infusion on Cycles 1, 2, 3, 5, 9, and 17, and EOT to measure ADA for FPA144.

8.3.2 Summary of Immunogenicity Results

The number (%) of subjects with the following anti-drug responses will be reported for immunogenicity subjects. The on-treatment period starts at first dose and beyond.

- Baseline FPA144 ADA-positive

- Baseline FPA144 ADA-negative

- FPA144 ADA-positive

- FPA144 ADA-negative

Postbaseline treatment induced ADA positive is derived as subjects with

- ADA negative at baseline and ADA positive at any postbaseline timepoint, or

- ADA positive at baseline and ADA positive with titer of at least 4-fold of the baseline titer at one or more postbaseline timepoint

The following table will be provided:

- Summary Statistics of Immunogenicity (Phase 2)

The following listings will be provided:

- Individual Immunogenicity Data (Phase 1 and Phase 2)

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9   REFERENCES

Koch, G., Carr, G., Amara, I., Stokes, M., & Uryniak, T. (1989). *Categorical Data Analysis.* Chapter 13 in Berry, D.A. (ed.). Statistical Methodology in the Pharmaceutical Sciences. New York: Karcel Dekker, Inc.

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10 SOFTWARE

SAS® Software Version 9.4. SAS Institute Inc., Cary, NC, USA