STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 1 Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of GS-5745 as Monotherapy and in Combination with Chemotherapy in Subjects with Advanced Solid Tumors
Name of Test Drug:	Andecaliximab (GS-5745)
Study Number:	GS-US-296-0101
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CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

ADA	anti-drug antibody
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	area under the drug concentration over time curve
BEV	bevacizumab
BLQ	below the limit of quantitation
CI	confidence interval
CSR	clinical study report
CR	complete response
CRC	colorectal cancer
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	dose limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form(s)
EOI	end of infusion
EOS	end of study
HLGT	high-level group term
HLT	high-level term
INR	international normalized ratio
LLT	lower-level term
MedDRA	Medical Dictionary for Regulatory Activities
MMP	matrix metalloproteinase
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NSCLC	non-small cell lung cancer
ORR	objective response rate
PE	physical exam
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response
PT	preferred term
Q1	first quartile

Q2W	once every two weeks
Q3	third quartile
Q3W	once every three weeks
QRS	electrocardiographic deflection between the beginning of the Q wave and termination of the S wave representing time for ventricular depolarization
QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave representing the time for both ventricular depolarization and repolarization to occur
QTc	corrected QT interval
QTcF	corrected QT interval based on Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SE	standard error
SOC	system organ class
StD	standard deviation
TEAE	treatment-emergent adverse event
ULN	upper limit of the normal range
VR	ventricular rate
WHO	World Health Organization

PHARMACOKINETIC ABBREVIATIONS

AUC_{last}	area under the concentration versus time curve from time zero to the last quantifiable concentration
AUC_{inf}	area under the concentration versus time curve extrapolated to infinite time, calculated as $AUC_{last} + (C_{last}/\lambda_z)$
C_{eoi}	observed concentration of drug at the end of infusion
C_{last}	last observed quantifiable concentration of the drug
C_{max}	maximum observed concentration of drug
CL	Systemic clearance of the drug after intravenous administration
$t_{1/2}$	estimate of the terminal elimination half-life of the drug, calculated by dividing the natural log of 2 by the terminal elimination rate constant (λ_z)
T_{last}	time (observed time point) of C_{last}
T_{max}	time (observed time point) of C_{max}
λz	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the concentration of drug versus time curve
V	volume of distribution of the drug after intravenous administration

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentations to be used in tables, figures, and listings (TFLs) in the synoptic clinical study report (CSR) for Study GS-US-296-0101. This SAP is based on the study protocol amendment 6 dated 01 August 2016 and the electronic case report form (eCRF). The SAP will be finalized before database finalization. Any changes made after the finalization of the SAP will be documented in the CSR.

1.1. Study Objectives

The primary objectives of this study are as follows:

- To determine the maximum tolerated dose (MTD) of GS-5745 monotherapy in subjects with advanced solid tumors
- To characterize the safety and tolerability of GS-5745 as monotherapy and in combination with various chemotherapy regimens in subjects with select tumor types.

The secondary objectives of this study are as follows:

- To characterize the pharmacokinetics (PK) of GS-5745
- To evaluate the formation of anti-GS-5745 antibodies

[redacted]

The exploratory objective of the study is as follows:

[redacted]

1.2. Study Design

This is an open-label, multicenter, sequential dose-escalation, and expansion study to evaluate the safety, tolerability, PK, and pharmacodynamics of GS-5745 alone and in combination with chemotherapy. The study will be conducted in 2 parts (Part A and Part B).

Dose Escalation – Part A:

Cohorts of subjects with advanced solid tumors who have failed or are intolerant to standard therapy or for whom no standard therapy exists will be sequentially enrolled at progressively higher dose levels to receive GS-5745 as monotherapy via intravenous (IV) infusion every 2 weeks (Q2W). Dose escalation [3+3] will be performed with cohort sizes of 3 to 6 subjects. The starting dose for Cohort 1 will be 200 mg. Subsequent doses of 600 and 1800 mg are planned. The decision to escalate to the next higher dose cohort will be made by a Dose Escalation Committee consisting of site investigators and Gilead study team members. Specifically, if 2 or more subjects experience dose limiting toxicities (DLTs) at 1800 mg, then 1200 mg will be explored. If 2 or more subjects experience DLTs at 600 mg, then 400 mg will be explored. The maximum tolerated dose (MTD) is the highest dose level with a subject incidence of DLT during the first 28 days of study drug dosing of 0 or 1 out of 6.

After determination of MTD, Part B will commence. During Part B of the study, up to 3 additional cohorts consisting of no more than 10 subjects each may be studied with GS-5745 at monotherapy doses up to MTD given every 2 weeks to obtain additional information on PK and pharmacodynamics.

Dose Expansion – Part B:

The dose expansion will begin once all subjects in the dose escalation portion of Part A have completed the 28-day DLT period. Subjects with advanced pancreatic adenocarcinoma (Cohort 4), lung adenocarcinoma (Cohort 5), lung squamous cell carcinoma (Cohort 6), esophagogastric adenocarcinoma (Cohort 7), colorectal cancer (CRC) in the first-line setting (Cohort 8), CRC in the second-line setting (Cohort 9), or breast cancer (Cohort 10) will be enrolled to receive GS-5745 via IV (Q2W for Cohorts 4, 7, 8, 9 and 10; Q3W for Cohorts 5 and 6) in combination with chemotherapy.

The cohort dose levels for GS-5745 in Part B are presented below and will be based on the MTD determined in Part A.

MTD from Part A (mg)	**Doses to be used in Part B (mg)**	
Q2W	**Q2W**	**Q3W**
200	133	200
400	267	400
600	400	600
1200	800	1200
1800	800	1200

The chemotherapies for each cohort in Part B are outlined in Table 1.

Table 1. Chemotherapy Treatments for Cohorts 4 through 10

Cohort	Chemotherapy Treatment(s)
Cohort 4 (pancreatic cancer)	gemcitabine nab-paclitaxel
Cohort 5 (lung adenocarcinoma)	carboplatin pemetrexed
Cohort 6 (lung squamous cell carcinoma)	carboplatin paclitaxel
Cohort 7 (esophagogastric adenocarcinoma)	mFOLFOX6[a]
Cohort 8 (colorectal cancer in first-line setting)	mFOLFOX6 bevacizumab
Cohort 9 (colorectal cancer in second-line setting)	FOLFIRI[b] bevacizumab
Cohort 10 (breast cancer)	paclitaxel

a mFOLFOX6 regimen includes 5-FU, leucovorin, and oxaliplatin
b FOLFIRI regimen includes 5-FU, leucovorin, and irinotecan

Subjects in both Part A and B will be treated until disease progression, unacceptable toxicity, withdrawal of consent, or other reasons specified in the study protocol Section 6.4.

For Part A tumor evaluation by computerized tomography (CT) or magnetic resonance imaging (MRI) will be performed during screening (within 4 weeks of Day 1) and every 8 weeks thereafter. CT or MRI should be conducted at the end of study (EOS) visit if not conducted within the previous 4 weeks.

For Part B tumor evaluation by CT or MRI scan will be performed during screening and during the last week of even-numbered cycles (ie, Cycles 2, 4, 6, etc.) for all cohorts except for Cohort 5 and 6, in which a CT or MRI scan will be performed during the last week of every third cycle (ie, Cycles 3, 6, 9, etc.). CT or MRI should be conducted at the EOS visit if not conducted within the previous 4 weeks.

The schedule of assessments is located in Appendix 1 to Appendix 7 of the SAP.

1.3. Sample Size and Power

The sample size of the study will be determined based on the number of dose levels evaluated and the emerging GS-5745-related toxicities. Part A will consist of 12 to 48 subjects, and Part B will consist of 115 to 295 subjects (35 subjects in Cohort 4, 10 subjects each in Cohort 5 and Cohort 6, and 15 subjects each in Cohort 7, Cohort 8, Cohort 9 and Cohort 10). Up to a maximum of 25 additional subjects may be enrolled in Cohorts 5-10 to obtain information on safety, PK, pharmacodynamics, and tumor response. This sample size also includes up to additional 15 replacement subjects for Cohort 8 and Cohort 9, respectively.

Table 2 below summarizes the number of subjects in each cohort for Part B.

Table 2. The number of subjects in each cohort for Part B

Part B: Dose Expansion		
Cohort	**Disease Subtype**	**No. Subjects**
4	Pancreatic adenocarcinoma	35
5	Lung adenocarcinoma	10-35
6	Lung squamous cell carcinoma	10-35
7	Esophagogastric adenocarcinoma	15-40
8	First-line colorectal cancer	15-55*
9	Second-line colorectal cancer	15-55**
10	Breast cancer	15-40

* For Cohort 8 (first-line CRC), the sample size of 40 subjects was initially planned. In protocol amendment 5, the dose of bevacizumab is corrected to be 5 mg/kg Q2W. Up to 15 subjects who previously started bevacizumab treatment at other dose levels will be replaced. Therefore, a total of up to 55 subjects may be enrolled in Cohort 8.

** For Cohort 9 (second-line CRC), the sample size of 40 subjects was initially planned. In protocol amendment 5, the dose of bevacizumab is corrected to be 5 mg/kg Q2W. Up to 15 subjects who previously started bevacizumab treatment at other dose levels will be replaced. Therefore, a total of up to 55 subjects may be enrolled in Cohort 9.

2. TYPE OF PLANNED ANALYSES

2.1. Interim Analyses

No formal interim efficacy analysis with the possibility of early termination for efficacy or futility is planned.

2.2. Final Analysis

After all subjects have discontinued the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized, the final analysis of the data will be performed.

2.3. Follow-up Analysis

No follow-up analysis is planned for this study.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSIS

Analysis results will be presented using descriptive statistics. For categorical variables, the number and percentage of subjects in each category will be presented; for continuous variables, the number of subjects (n), mean, standard deviation (StD) or standard error (SE), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be presented.

By-subject listings will be presented for all subjects in the All Enrolled Analysis Set and sorted by subject ID number, visit date, and time (if applicable). Data collected on log forms, such as adverse events (AEs), will be presented in chronological order within the subject. The treatment group to which subjects were initially assigned will be used in the listings. Age, sex at birth, race, and ethnicity will be included in the listings, as space permits.

3.1. Analysis Sets

Analysis sets define the subjects to be included in an analysis. Analysis sets and their definitions are provided in this section. The analysis set will be identified and included as a subtitle of each table, figure, and listing.

For each analysis set, the number and percentage of subjects included will be summarized.

3.1.1. All Enrolled Analysis Set

The All Enrolled Analysis Set includes all subjects who are assigned a study subject identification number in the study after screening.

The All Enrolled Analysis Set will be used for subject enrollment summary.

3.1.2. Safety Analysis Set

The Safety Analysis Set includes all subjects who received at least 1 infusion at any dose level of study drug GS-5745.

The Safety Analysis Set will be used for safety analyses.

3.1.3. Full Analysis Set

The Full Analysis Set includes all subjects in the Safety Analysis Set, except for those who were initially dosed with bevacizumab 10 mg/kg Q2W in Cohort 8 and Cohort 9. The Full Analysis Set will be used for efficacy analyses, unless otherwise specified.

The reason those subjects are excluded from efficacy analysis is that 10 mg/kg Q2W is not the intended bevacizumab dose (per protocol amendment 5) and it is not meaningful to summarize the efficacy under this treatment combination.

3.1.4. DLT Analysis Set

The DLT Analysis Set includes all subjects in the Safety Analysis Set who

- received 2 doses of GS-5745 prior to Day 29, or
- experienced a DLT prior to Day 29.

The DLT Analysis Set will be used for analyses related to DLT in Part A.

3.1.5. Pharmacokinetic (PK) Analysis Set

The Pharmacokinetic (PK) Analysis Set will include all subjects in the Safety Analysis Set who have at least 1 nonmissing post dose concentration value reported by the PK laboratory. It will be used for all PK analyses.

3.1.6. Immunogenicity Analysis Set

The Immunogenicity Analysis Set will include all subjects in the Safety Analysis Set who have at least 1 nonmissing postdose antidrug antibody (ADA) status reported. This is the primary analysis set for all immunogenicity analyses.

3.1.7. Biomarker Analysis Sets

The Biomarker Analysis Set will include subjects in the Safety Analysis Set who have at least 1 evaluable biomarker measurement available.

3.2. Subject Grouping

Unless otherwise specified, subjects will be analyzed by study part (A or B) and then by cohort.

In Part A, the cohorts are by dose levels:

- Cohort 1: 200 mg Q2W mono
- Cohort 2: 600 mg Q2W mono
- Cohort 3: 1800 mg Q2W mono

In Part B, the cohorts are disease types:

- Cohort 4: Pancreatic adenocarcinoma
- Cohort 5: Lung adenocarcinoma
- Cohort 6: Lung squamous cell carcinoma

- Cohort 7: Esophagogastric adenocarcinoma
- Cohort 8 BEV 5 mg/kg: Colorectal cancer (CRC) in first-line setting with bevacizumab initially dosed at 5 mg/kg
- Cohort 8 BEV 10 mg/kg: Colorectal cancer (CRC) in first-line setting with bevacizumab initially dosed at 10 mg/kg (not included in efficacy analysis)
- Cohort 9 BEV 5 mg/kg: Colorectal cancer (CRC) in second line setting with bevacizumab initially dosed at 5 mg/kg.
- Cohort 9 BEV 10 mg/kg: Colorectal cancer (CRC) in second line setting with bevacizumab initially dosed at 10 mg/kg. (not included in efficacy analysis)
- Cohort 10: Breast cancer

3.3. Strata and Covariates

This study does not use a stratified randomization schedule when enrolling subjects. No covariates will be included in efficacy and safety analyses.

3.4. Examination of Subject Subsets

Overall summary of treatment-emergent adverse events will be examined in the following subgroups for cohorts in Part B:

- Age group
  - < 65
  - ≥ 65
- Gender
  - Male
  - Female
- Race
  - White
  - Non-White

3.5. Multiple Comparisons

Adjustments for multiplicity will not be made, because no formal statistical testing will be performed in this study.

3.6. Missing Data and Outliers

3.6.1. Missing Data

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

For missing last dosing date of study drug, imputation rules are described in Section 4.2.1. The handling of missing or incomplete dates for the start date of new anti-cancer therapy is in Section 6.1.2, for date of death in Section 6.1.3, for AE onset in Section 7.1.5.2, and for prior and concomitant medications in Section 7.4.

3.6.2. Outliers

Unless otherwise specified, outliers will not be excluded from the analysis in general.

3.7. Data Handling Conventions and Transformations

In general, age (in years) on the date of the first dose of study drug will be used for analyses and presentation in listings. If an enrolled subject was not dosed with any study drug, the enrollment date will be used instead of the first dosing date of study drug. For screen failures, the date the informed consent was signed will be used for age calculation. If only the birth year is collected on the CRF, "01 July" will be used for the unknown birth day and month for the purpose of age calculation. If only birth year and month are collected, "01" will be used for the unknown birth day.

Non-PK data that are continuous in nature but are less than the lower limit of quantitation (LOQ) or above the upper LOQ will be imputed as follows:

- A value that is 1 unit less than the LOQ will be used for calculation of descriptive statistics if the datum is reported in the form of "< x" (x is considered the LOQ). For example, if the values are reported as < 50 and < 5.0, then values of 49 and 4.9 will be used for calculation of summary statistics, respectively. An exception to this rule is any value reported as < 1 or < 0.1, etc. For values reported as < 1 or < 0.1, a value of 0.9 or 0.09, respectively, will be used to calculate summary statistics.

- A value that is 1 unit above the LOQ will be used for calculation of descriptive statistics if the datum is reported in the form of "> x" (x is considered the LOQ). For example, if the values are reported as > 50 and > 5.0, then values of 51 and 5.1 will be used for calculation of summary statistics, respectively. Values with decimal points will follow the same logic as above.

- The LOQ will be used for calculation of descriptive statistics if the data is reported in the form of "≤ x" or "≥ x" (x is considered as the LOQ).

If analyses based on the assumption that the data are normally distributed are not adequate, analyses may be performed on log-transformed data or nonparametric analysis methods may be used, as appropriate.

Natural logarithmic transformation will be used for plasma/blood concentrations and analysis of PK parameters. Plasma concentration values that are below the limit of quantitation (BLQ) will be presented as "BLQ" in the concentration data listing. Values that are BLQ will be treated as 0 at predose time points, and one-half the value of the LOQ at postdose time points for determination of summary and order statistics.

The following conventions will be used for the presentation of summary and order statistics:

- If at least 1 subject has a concentration value of BLQ for the time point, the minimum value will be displayed as "BLQ."
- If more than 25% of the subjects have a concentration data value of BLQ for a given time point, the minimum and Q1 values will be displayed as "BLQ."
- If more than 50% of the subjects have a concentration data value of BLQ for a given time point, the minimum, Q1, and median values will be displayed as "BLQ."
- If more than 75% of the subjects have a concentration data value of BLQ for a given time point, the minimum, Q1, median, and Q3 values will be displayed as "BLQ."
- If all subjects have concentration data values of BLQ for a given time point, all order statistics (minimum, Q1, median, Q3, and maximum) and summary statistics will be displayed as "BLQ."

PK parameters that are BLQ will be imputed as one-half LOQ before log transformation or statistical model fitting.

3.8. Analysis Visit Windows

3.8.1. Definition of Study Day

Study day will be calculated from the date of first dose of study drug (GS-5745) administration and derived as follows:

- For post-dose study days: Assessment Date – First Dosing Date + 1
- For days prior to the first dose: Assessment Date – First Dosing Date

Therefore, study day 1 is the day of first dose of study drug administration.

3.8.2. Analysis Visit Windows

Subject visits might not occur on protocol-specified days. Therefore, for the purpose of analysis, observations will be assigned to analysis windows.

Baseline is defined as the last observation prior to the first dose, unless otherwise specified.

The visit windows are specified in Table 3, Table 4, Table 5, Table 6, Table 7, and Table 8. The visit windows for biomarkers, matrix metalloproteinase 9 (MMP9), are specified in Table 9, Table 10, and Table 11. The lowest and highest study days are inclusive.

Table 3. Post Baseline Visit Windows for Central Lab (Cohorts 1, 2 & 3)

Analysis Visit	Relative Day	Lowest Relative Day (inclusive)	Highest Relative Day (inclusive)
Week 1	8	Day 1 Post First GS-5745 Dose	11
Week 2	15	12	21
Week 4	29	22	35
Week 6	43	36	49
Week X=8, 10, …	7*x+1	7x-6	7*x + 7

Table 4. Post Baseline Visit Windows for Central Lab, Vital Signs, ECG, Performance Status (Cohorts 4 and 10)

Analysis Visit	Relative Day	Lowest Relative Day (inclusive)	Highest Relative Day (inclusive)
Week 1	8	Day 1 Post First GS-5745 Dose	11
Week 2	15	12	21
Week 4	29	22	32
Week X=4*k+1	28*k+8	28*k+5	28*k+11
Week X=4*k+2	28*k+15	28*k+12	28*k+21
Week X=4*k+4	28*k+29	28*k+22	28*k+32

Table 5. Post Baseline Visit Windows for Central Lab, Vital Signs, ECG, Performance Status (Cohorts 5 and 6)

Analysis Visit	Relative Day	Lowest Relative Day (inclusive)	Highest Relative Day (inclusive)
Week 3	22	Day 1 Post First GS-5745 Dose	33
Week 6	43	34	54
Week 9	64	55	75
Week X=12, 15, …	7*x+1	7*x-8	7*x+12

Table 6. Post Baseline Visit Windows for Central Lab, Vital Signs, ECG, Performance Status (Cohort 7, 8, 9)

Analysis Visit	Relative Day	Lowest Relative Day (inclusive)	Highest Relative Day (inclusive)
Week 2	15	Day 1 Post First GS-5745 Dose	21
Week 4	29	22	35
Week 6	43	36	49
Week X=8, 10, …	7*x+1	7*x-6	7*x+7

Table 7. Post Baseline Visit Windows for Tumor Assessment (Cohorts 4, 7, 8, 9, and 10)

Analysis Visit	Relative Day	Lowest Relative Day (inclusive)	Highest Relative Day (inclusive)
Week 8	57	Day 1 Post First GS-5745 Dose	85
Week 16	113	86	141
Week 24	169	142	197
Week X=32, 40, …	7*x+1	7*x-27	7*x+28

Table 8. Post Baseline Visit Windows for Tumor Assessment (Cohorts 5 and 6)

Analysis Visit	Relative Day	Lowest Relative Day (inclusive)	Highest Relative Day (inclusive)
Week 9	64	Day 1 Post First GS-5745 Dose	94
Week 18	127	95	157
Week 27	190	158	220
Week X=36, 45, …	7*x+1	7*x-31	7*x+31

Table 9. Post Baseline Visit Windows for Free and Total MMP9 (Cohorts 1, 2 and 3)

Analysis Visit	Relative Day	Lowest Relative Day (inclusive)	Highest Relative Day (inclusive)
Week 2	15	Day 1 Post First GS-5745 Dose	29
Week 6	43	30	50
Week 8	57	51	85
Week X=16, 24, 32, …	7*x+1	7*x-26	7*x+29

Table 10. Post Baseline Visit Windows for Free and Total MMP9 (Cohorts 4 and 7)

Analysis Visit	Relative Day	Lowest Relative Day (inclusive)	Highest Relative Day (inclusive)
Week 4	29	Day 1 Post First GS-5745 Dose	43
Week 8	57	44	71
Week X=12, 16, 20, …	7*x+1	7*x - 12	7*x +15

Table 11. Post Baseline Visit Windows for Free and Total MMP9 (Cohorts 5 and 6)

Analysis Visit	Relative Day	Lowest Relative Day (inclusive)	Highest Relative Day (inclusive)
Week 3	22	Day 1 Post First GS-5745 Dose	32
Week 6	43	33	53
Week X=9, 12, 15, …	7*x + 1	7*x - 9	7*x +11

For Cohorts 1, 2 and 3, the analysis window will not be applied to vital signs, electrocardiogram (ECG) and Eastern Cooperative Oncology Group (ECOG) performance status. Nominal visit name will be used. Any data relating to unscheduled visits will not be assigned to a particular visit or time point. However, the following exceptions will be made:

- An unscheduled visit prior to first dosing of study drug may be included in the calculation of the baseline value, if applicable.
- Unscheduled visits after the first dosing of study drug will be included in determining the maximum postbaseline toxicity grade.
- End of study visit data will be summarized as a separate visit, labeled as "End of Study".

3.8.3. Selection of Data in the Event of Multiple Records in an Analysis Window

Depending on the statistical analysis method, single values may be required for each analysis window. For example, change from baseline by visit usually requires a single value, whereas a time-to-event analysis would not require 1 value per analysis window.

If multiple, valid, non-missing values exist in an analysis window, records will be chosen based on the following rules if a single value is needed:

- For baseline, the last nonmissing value on or prior to the first dosing date of study drug will be selected, unless specified differently. If there are multiple records with the same time or no time recorded on the same day, the baseline value will be the average of the measurements for continuous data, or the measurement with the lowest severity (eg, normal will be selected over abnormal for safety ECG findings) for categorical data.
- For postbaseline values:
  - The record closest to the relative day for that visit will be selected.
  - If there are 2 records that are equidistant from the relative day, the later record will be selected.
  - If there is more than 1 record on the selected day, the last measurement will be used; if the measurement occur at the same time or time cannot be determined, the average will be taken for continuous data and the worse severity will be taken for categorical data, unless otherwise specified.

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

A summary of subject enrollment will be provided by study part and cohort for each investigator and overall. The summary will present the number and percentage of subjects enrolled. For each column, the denominator for the percentage calculation will be the total number of subjects analyzed for that column.

A summary of subject disposition will be provided by study part and cohort. This summary will present the number of subjects screened, the number of subjects enrolled, and the number of subjects in each of the categories listed below:

- Treated with study drug (GS-5745) (applicable to part A and B)
  - Treatment discontinued
    - Reasons for discontinuation
- Treated with chemotherapy (applicable to part B)
  - Treatment discontinued
    - Reasons for discontinuation
- Discontinued study
  - Reasons for study discontinuation

For the discontinuation reasons of chemotherapy with more than 1 drug component category, the reason of the earliest discontinued drug will be used for summary table. If multiple drug discontinued on the same day with different reasons category is selected, the reason with the highest rank (Adverse Event > Progressive Disease > Others) will be selected. Discontinuation reasons for each drug components will be provided in the listing.

For the status of study drug and study completion and reasons for premature discontinuation categories, the number and percentage of subjects in each category will be provided. The denominator for the percentage calculation will be the total number of subjects in the Safety Analysis Set corresponding to that column. In addition, a flowchart will be provided to depict the disposition.

A listing of subject enrollment will be provided to describe site, subject ID, informed consent date, and first screening date. Those enrolled but not treated will be flagged.

A separate listing of inclusion/exclusion findings for all screened subjects who did not meet all inclusion/exclusion criteria will also be provided.

A listing of subject disposition will be provided, including site ID, subject ID, cohort, date of first and last dose of study drug (GS-5745), duration of study drug exposure, date of last dose of chemotherapy (if applicable), reason for discontinuing treatments (GS-5745, chemotherapy respectively) (if applicable), and reason for study discontinuation.

4.2. Extent of Exposure

4.2.1. Exposure to Study Drug (GS-5745)

Exposure to GS-5745 will be summarized by study part and cohort for the Safety Analysis Set.

Duration of Exposure

Duration of exposure to study drug will be defined as (last dose date – first dose date + 1), regardless of temporary interruptions in study drug administration, and will be expressed in weeks using up to 1 decimal place (eg, 4.5 weeks). If the last study drug dosing end date is missing, the last study drug start date will be used to impute the end date of the last study drug.

Duration of exposure to study drug will be summarized using descriptive statistics (N, mean, standard deviation [StD], median, minimum and maximum). Summaries will be provided by study part and cohort for the Safety Analysis Set.

Number of Doses

The number and percentage of subjects receiving a given number of planned doses of GS-5745 will be presented. A subject is said to have received a dose of GS-5745 if he/she received any dose of GS-5745.

Actual Dose Amount

In addition, the total and average actual dose amount received for GS-5745 in mg will be summarized using descriptive statistics (N, mean, StD, median, Q1, Q3, minimum, and maximum).

The average actual dose amount of GS-5745 is defined as (total actual dose amount received in mg) / (number of doses given), regardless of whether the doses were interrupted/completed or full/reduced.

A by-subject listing of study drug (GS-5745) administration will be provided by subject ID number (in ascending order) and visit (in chronological order), including dosing date/time, planned dosage, actual dosage administered, infusion outcome and reason for dose reduction (if applicable).

4.2.2. Exposure to Chemotherapy

Exposure to chemotherapy will be listed and summarized for each drug component in a similar manner as for GS-5745. Chemotherapy received prior to study enrollment and after the start of other anti-cancer therapy will not be included in the summary.

4.3. Protocol Deviations

Subjects who did not meet the eligibility criteria for study entry, but enrolled in the study, will be summarized regardless of whether they were exempted by the sponsor or not. The summary will present the number and percentage of subjects who did not meet at least 1 eligibility criterion and the number of subjects who did not meet specific criteria by study part and cohort based on the All Enrolled Analysis Set. A by-subject listing will be provided for those subjects who did not meet at least 1 eligibility (inclusion or exclusion) criterion. The listing will present the eligibility criterion (or criteria if more than 1 deviation) that subjects did not meet and related comments, if collected.

Protocol deviations occurring after subjects entered the study are documented during routine monitoring. The number and percentage of subjects with important protocol deviations by deviation reason (eg, nonadherence to study drug, violation of select inclusion/exclusion criteria) will be summarized by study part and cohort for the All Enrolled Analysis Set. A by-subject listing will be provided for those subjects with important protocol deviation.

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

The following demographic and baseline characteristics will be listed and summarized for the Safety Analysis Set:

- Age
- Sex
- Race
- Ethnicity
- Weight (at baseline, overall and by sex)
- Height (at baseline, overall and by sex)
- Body Mass Index (at baseline, overall and by sex)
- ECOG Status at Baseline

Demographic and baseline characteristics summaries will be presented by study part and cohort using descriptive statistics (N, mean, StD, median, Q1, Q3, minimum, and maximum) for continuous data and displaying the number and percent of subjects for categorical data. Age at baseline is calculated in years at the first dosing date of study drug.

A by-subject demographic listing will be provided by subject ID number in ascending order.

5.2. Medical History

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

Disease-specific medical history will be summarized by cohort and overall by the number and percentage of subjects with each prepopulated condition. The summary will be provided for the Safety Analysis Set.

Variables to be summarized include:

- Stage at Screening
- Location of Tumor (applicable to esophagogastric cohort only)
- Histology of cancer (applicable to Gastric cancer only)

A by-subject listing of disease history will be provided by subject ID number in ascending order.

General medical history data will not be coded, but will be listed only. A by-subject listing of general medical history will be provided by subject ID number in ascending order.

5.3. Prior Chemotherapy and Radiotherapy

Number of prior chemotherapy and radiotherapy will be summarized using descriptive statistics and by number of subjects in each category for the Safety Analysis Set.

The details of prior chemotherapy will be listed including line of therapy, type of regimen, and regimen start/stop date.

The details of prior radiotherapy will also be listed, including site irradiated and radiotherapy start/stop date.

5.4. Concomitant Cancer Related Surgeries and Procedures

A listing of concomitant cancer related surgeries and procedures will be provided for the All Enrolled Analysis Set.

6. EFFICACY ANALYSES

Efficacy parameters will be listed for Parts A and B, and summarized for Part B only by cohort based on Full Analysis Set. The investigator assessments will be used for analyses of efficacy endpoints.

6.1. Definition and Analysis of Efficacy Endpoints

6.1.1. Objective Response Rate

Objective response rate (ORR) is defined as the proportion of subjects with best overall response during GS-5745 therapy of complete response (CR) or partial response (PR) based on RECIST 1.1. Response assessments occurring after new anticancer therapy, the assessments after missing 2 previous consecutive tumor scans, or the assessments after progressive disease (PD) will not be included for ORR analysis.

The following will be performed for the Full Analysis Set by cohort in Part B:

- Best overall response will be summarized using the number and the percentage of subjects in each category (eg, Complete Response [CR], Partial Response [PR], Stable Disease [SD], Non-CR/Non-PD [NN], Progressive Disease [PD] or Not Evaluable [NE]). Subject discontinued study before post-baseline scans are performed (NA) will also be summarized.

- Objective response rates will be presented with corresponding 2-sided 90% exact confidence intervals (CIs) based on Clopper-Pearson method. Subjects who do not have sufficient baseline or on-study tumor assessments to characterize response will be counted as non-responders and included in the denominator only.

The investigator assessment for tumor response will be listed in details including site of lesion, date and method of evaluation, longest diameters, sum of longest diameters of the measurable target lesions (SLD), and responses.

6.1.2. Progression-Free Survival

Progression-free survival (PFS) is defined as the time interval from the first dose of GS-5745 to the earlier of the first documentation of definitive disease progression or death from any cause. Definitive disease progression is determined based on RECIST 1.1. All scans, whether scheduled or unscheduled, will be considered.

The date of definitive progression will be the time point at which progression is first identified by relevant radiographic imaging data. Clinical progression is not considered as PFS event. Data will be censored on the date of last adequate tumor assessment (including assessments with a not evaluable [NE] outcome) prior to anti-cancer therapy or prior to ≥ 2 consecutive missing assessments, whichever is earlier for subjects:

- who do not have disease progression or die before study discontinuation, or
- who start new anticancer therapy prior to documented disease progression or death, or
- who have ≥ 2 consecutive missing or inadequate tumor assessments before disease progression or death

If subjects don't have an adequate baseline tumor assessment or any adequate post-baseline tumor assessments, they will be censored on the date of Study Day 1 unless they died before or on the 2nd scheduled post-baseline tumor assessment without receiving anti-cancer therapy.

PFS in months = (date of event/censoring – date of first GS-5745 infusion + 1) / 30.4375.

When imaging examinations for one visit are conducted on various dates, the following rules apply for the calculation of the assessment date:

- The response date will be the last date associated with that particular imaging time point.
- The progression date will be the first date associated with that particular imaging time point.

Follow up time for PFS will be summarized as continuous variable with descriptive statistics by cohorts.

- For subject who is censored from PFS and has discontinued from study, duration of PFS follow up = Date of censoring – date of first GS-5745 infusion +1
- For the remaining subjects (including subjects has PD based on RECIST 1.1), duration of PFS follow up = date of last tumor assessment in the database – date of first GS-5745 infusion +1

When the start date of new anti-cancer therapy is incomplete or missing, the following imputation rules will be applied.

- If 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 01 January or the last day of the month for the last adequate disease assessment if they have the same year, whichever is later.

PFS rates at 3, 6, 9, 12, and 18 months and median PFS times with 90% CIs using log-log transformation will be derived using Kaplan-Meier methods, by cohort for Part B. Kaplan-Meier curves will also be provided.

PFS derived from investigator assessment will be listed.

6.1.3. Overall Survival

Overall survival (OS) is defined as the time from the first dose of GS-5745 to death from any cause. Data from surviving subjects will be censored at the last time that subject was known to be alive.

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 known alive date + 1, whichever is later.
- If day and month are missing but year is available, then the imputed day and month will be 01 Jan of that year 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.

OS in months = (date of event/censoring – date of first GS-5745 infusion + 1) / 30.4375.

OS rates at 3, 6, 9, 12, 18, and 24 months and median OS times with 90% CIs using log-log transformation will be derived using Kaplan-Meier methods, by cohort for Part B. Kaplan-Meier curves will also be provided.

OS data will be analyzed for Cohort 8, 9, and 10. For the rest of cohorts, OS data will not be analyzed since the majority of discontinued subjects' OS status cannot be collected.

6.1.4. Duration of Response

Duration of response (DOR) is defined as the interval from the first time response (CR or PR) is achieved to the earlier of the first documentation of definitive disease progression or death from any cause. The analyses of DOR will be based on the subjects in the Full Analysis Set who achieve a CR or PR. The same censoring rules as for PFS will be applied to DOR.

DOR in months = (date of event/censoring – date of first response [CR or PR] + 1)/ 30.4375.

Median DOR and 90% CIs will be estimated using Kaplan-Meier methods, by cohort for Part B. Kaplan-Meier curves will also be provided.

DOR derived from investigator assessment will be listed.

6.1.5. Time to Response

Time to response (TTR) is defined as the time interval from the first dose of GS-5745 to time response (CR or PR) is first achieved. The analyses of TTR will be based on the subjects in the Full Analysis Set who achieve a CR or PR. TTR will be summarized using descriptive summary statistics by cohort in Part B.

TTR derived from investigator assessment will be listed.

6.1.6. Change in Tumor Size

The percent change from baseline in the sum of the diameters of target lesions as documented radiographically will be determined for each post-baseline assessment. The best percent change from baseline in the sum of the diameters is defined as the largest decrease (or smallest increase) in tumor size among all post baseline target lesion assessments with target lesions present at baseline measured. Tumor assessment after new anticancer therapy or after ≥ 2 consecutive missing or inadequate tumor assessments will not be included in the analysis for change in tumor size. The baseline sum of the diameters will be the value of last target lesion assessment prior to the start of GS-5745 therapy.

The best percent change in tumor size will be summarized by cohort for Part B for subjects in the Full Analysis Set with baseline and at least one post-baseline measurement available for tumor size.

Waterfall plots of the best percent change from baseline will be created.

Change in tumor size derived from investigator assessment by each visit will be listed.

6.1.7. ECOG Performance Status

The ECOG performance status score has a range from 0 (Fully active; able to carry on all pre-disease performance without restriction) to 5 (Dead). The baseline status will be the last score prior to the start of GS-5745 therapy. The worst post-baseline performance status will be the highest score following the start of GS-5745 therapy.

Shift table will be provided showing the change of ECOG performance status from baseline to the worst post-baseline performance status by cohort for Part B for subjects in the Full Analysis Set. Subjects without baseline or post-baseline ECOG performance status will be considered as missing in the shift table.

7. SAFETY ANALYSES

Safety will be evaluated for all subjects in the Safety Analysis Set through assessment of clinical laboratory tests, physical examination findings, 12-lead ECG abnormalities, vital signs measurements, and by the documentation of AEs. Concomitant medication intake will also be recorded, coded to the corresponding WHO drug term, and displayed in data listings.

All safety data collected at baseline and post-baseline through to the completion of the follow-up evaluation will be summarized. Data for the pre-treatment period will be included in data listings.

Safety analysis will be conducted by study part and cohort using Safety Analysis Set, unless otherwise specified. For Cohort 8 (first-line CRC) and Cohort 9 (second-line CRC), subjects initially dosed with bevacizumab 10 mg/kg Q2W will be summarized separately as grouped in Section 3.2.

7.1. Adverse Events

7.1.1. Adverse Event Dictionary

Clinical and laboratory adverse events (AEs) will be coded using the current version of MedDRA. System organ class (SOC), high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lower-level term (LLT) will be provided in the AE dataset.

7.1.2. Adverse Event Severity

Adverse events are graded by the investigator as Grade 1, 2, 3, 4, or 5 according to Common Toxicity Criteria for Adverse Events (CTCAE) Version 4.03. The severity grade of events for which the investigator did not record severity will be categorized as “missing” for tabular summaries and data listings. The missing category will be listed last in data presentation.

7.1.3. Relationship of Adverse Event to Study Treatment

Related AEs are those for which the investigator selected “Related” on the AE case report form (CRF) to the question of related to study treatment. Relatedness will always default to the investigator’s choice, not that of the medical monitor. Events for which the investigator did not record relationships to study treatment will be considered related to study treatment for summary purposes. However, by-subject data listings will show the relationship as missing from that captured on the CRF.

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if AEs met the definitions of SAE specified in the study protocol. Serious adverse events captured and stored in the clinical database will be reconciled with the SAE database from the Gilead Pharmacovigilance & Epidemiology before database finalization.

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent

Treatment-emergent AEs (TEAEs) are events in a given study period that meet 1 or both of the following criteria:

- Any AEs with onset date of on or after the study drug start date and no later than 30 days after permanent discontinuation of study drugs or
- AEs leading to premature discontinuation of study drug

7.1.5.2. Incomplete Dates

All AEs with partial onset dates will be identified and the partial dates will be imputed for TEAE determination. The imputation rules are as follows:

- If day and month are missing but year is available, then the imputed day and month will be 01 Jan or the first dosing date of the study drug if they have the same year, whichever is later.
- If 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.
- AE with completely missing onset dates 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 to be treatment emergent. In addition, an AE with the onset date missing and an 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. Summaries of Adverse Events

A brief summary of treatment-emergent AEs will show the number and percentage of subjects who had:

- any TEAE;
- any TEAE related to GS-5745;
- any TEAE related to any chemotherapy;
- any Grade 3 or higher TEAE;
- any Grade 3 or higher TEAE related to GS-5745;
- any Grade 3 or higher TEAE related to any chemotherapy;

- any TE SAE;
- any TE SAE related to GS-5745;
- any TE SAE related to any chemotherapy;
- any TEAE leading to GS-5745 dose modification or interruption;
- any TEAE leading to any chemotherapy dose modification or interruption;
- any TEAE leading to GS-5745 discontinuation;
- any TEAE leading to any chemotherapy discontinuation;
- any TEAE leading to death

For each SOC and PT, the number and percentage of subjects reporting an event will be calculated. In summary tables, SOC will be presented alphabetically and events within SOC will be presented by decreasing frequency count based on the total number of events.

Summary tables (number and percentage of subjects) of treatment-emergent AEs (by SOC and PT) will be provided by study part and cohort as follows:

- TEAEs
- Grade 3 or higher TEAEs
- TEAEs related to GS-5745
- TEAEs related to any chemotherapy
- Grade 3 or higher TEAEs related to GS-5745
- Grade 3 or higher TEAEs related to any chemotherapy
- TE SAEs
- TE SAEs related to GS-5745
- TE SAEs related to any chemotherapy
- TEAEs leading to GS-5745 interruption and/or dose modification
- TEAEs leading to any chemotherapy interruption and/or dose modification
- TEAEs leading to GS-5745 discontinuation

- TEAEs leading to any chemotherapy discontinuation
- TEAEs leading to deaths

All death will be summarized by whether it is considered as treatment emergent and the cause of the death (AE, PD, or other reasons).

Data listings will be provided as follows:

- AEs
- AEs with Grade 3 or higher
- SAEs
- AEs related to GS-5745
- AEs related to any chemotherapy
- Grade 3 or higher AEs related to GS-5745
- Grade 3 or higher AEs related to any chemotherapy
- AEs leading to GS-5745 dose modification, drug interruption or discontinuation
- AEs leading to any chemotherapy dose modification, drug interruption or discontinuation
- AEs occurred during the infusion or within 24 hours of infusion
- Deaths (if any)

7.1.7. Additional Analyses of Adverse Events

7.1.7.1. Dose Limiting Toxicity

A listing of the DLT AEs will be provided by cohort including cohort number with dose level, subject identification, actual dose amount prior to or on the start date of the AE, DLT term from investigator as well as CTCAE term and associated severity grade, if available.

A summary of DLT will be presented by SOC and decreasing frequency of preferred term within SOC using the DLT Analysis Set by cohort in Part A.

7.2. Laboratory Evaluations

Laboratory data collected during the study, scheduled and unscheduled, will be analyzed and summarized using both quantitative and qualitative methods. Summaries of selected laboratory parameters listed in Appendix 8 will be provided for the Safety Analysis Set. Data collected up

to the last dose of study drug plus 30 days for subjects who have permanently discontinued study drug, or all available data for subjects who were ongoing at the time of the database cut-off, will be included in the analysis. Local lab results will not be summarized, and will only be included in listings.

The analysis will be based on values reported in conventional units. When values are below the LOQ, they will be listed as such, and the closest imputed value will be used for the purpose of calculating summary statistics as specified in Section 3.7.

A by-subject listing for laboratory test results will be provided by subject ID number and time point in chronological order for hematology, serum chemistry, and coagulation separately. Values falling outside of the relevant reference range and/or having a severity grade of 1 or higher on the CTCAE severity grade will be flagged in the data listings, as appropriate.

No inferential statistics will be generated.

7.2.1. Graded Laboratory Values

CTCAE version 4.03 will be used for assigning toxicity grades (0 to 4) to laboratory results for analysis. Grade 0 includes all values that do not meet the criteria for an abnormality of at least Grade 1. Some laboratory tests have criteria for both increased and decreased levels; analyses for each direction (ie, increased, decreased) will be presented separately.

7.2.1.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any post-baseline time point, up to 30 days after the last dose of study drug for subjects who permanently discontinued study drug, or all available data in the database cut-off for subjects who were still on treatment at the time of analysis. If the relevant baseline laboratory value is missing, then any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment emergent.

7.2.1.2. Summaries of Laboratory Abnormalities

The summaries (number and percentage of subjects) for treatment-emergent laboratory abnormalities will be provided by lab test for each cohort in Part A and Part B separately; subjects will be summarized by the most severe post-baseline abnormality grade for given lab tests.

7.2.2. Shifts Relative to the Baseline Value

Shift tables will be presented by showing change in CTCAE grade from baseline to the worst post-baseline grade.

7.2.3. Summaries of Laboratory Results

If warranted, a summary of selected laboratory test results will be presented. Descriptive statistics (N, mean, StD, median, Q1, Q3, minimum, and maximum) will be provided by study part and cohort for numerical laboratory test as follows:

- Baseline values
- Values at each post-baseline time point
- Change from baseline at each post-baseline time point

Change from baseline to a post baseline visit will be defined as the visit value minus the baseline value. The mean, median, Q1, Q3, minimum, and maximum will be displayed to the reported number of digits; StD to the reported number of digits plus 1.

Categorical laboratory data will be summarized using the number and percentage of subjects with the given response at baseline and each post-baseline visit windows (as Section 3.8.2) by study part and cohort.

7.3. Vital Signs

Summaries of vital sign and change from baseline data will include values from all scheduled and unscheduled visits. A baseline value is defined as the last available value prior to the first dose of study drug. Each vital signs measurement (including temperature, pulse, systolic blood pressure, diastolic blood pressure, and respiratory rate) will be summarized by study part and cohort using descriptive statistics (N, mean, StD, median, Q1, Q3, minimum, and maximum).

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3.

A listing of all individual subject vital signs data will be provided.

7.4. Prior and Concomitant Medications

7.4.1. Prior Medications

Prior medications are defined as any medications begun before a subject took the first study drug.

For the purposes of analysis, any medication with a start date prior to the first dosing date of study drug will be considered as prior medication regardless of when the stop date is. 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.

A summary of prior medications will not be provided.

7.4.2. Concomitant Medications

Concomitant medications are defined as medications taken while a subject took study drug. Concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) drug class Level 2 and preferred name using the number and percentage of subjects for each treatment group. A subject reporting the same medication more than once will be counted only once when calculating the number and percentage of subjects who received that medication. The summary will be ordered alphabetically by ATC medical class and then by preferred term in descending overall frequency within each ATC medical class. For drugs with the same frequency, sorting will be done alphabetically.

Concomitant medication is defined as any medications

- started prior to or on the first dosing date of study drug and continued to take after the first dosing date, or
- started after the first dosing date but no later than last dosing date of study drug.

Medications started and stopped on the same day as the first dosing date or the last dosing date of study drug will also be considered concomitant. Medications with a stop date that is prior to the date of first dosing date of study drug or a start date that is after the last dosing date of study drug will be excluded from the concomitant medication summary.

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 be excluded from the concomitant medication summary. 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 be excluded from the concomitant medication summary. Medications with completely missing start and stop dates will be included in the concomitant medication summary.

Summaries of concomitant medications by study part and cohort will be provided for the Safety Analysis Set. A listing of prior and concomitant medications will also be provided.

7.5. Electrocardiogram (ECG) Results

Electrocardiogram (ECG) analysis results are intended to identify meaningful changes in the QT interval. If potential abnormalities of interest are identified, further analyses may be conducted. Summaries of investigator assessment of ECG readings will be provided for the Safety Analysis Set from all scheduled and unscheduled visits. In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3.

7.5.1. Investigator Electrocardiogram Assessment

The number and percentage of subjects in the Safety Analysis Set with an investigator's ECG assessment of normal, abnormal and clinically significant, or abnormal but not clinically significant will be summarized for baseline and for each visit.

A shift table of the investigators' assessment of ECG results at each visit compared with baseline values will be presented by study part and cohort using the following categories: normal; abnormal, not clinically significant; abnormal, clinically significant; or missing. The number and percentage of subjects in each cross-classification group of the shift table will be presented.

A by-subject listing for ECG assessment results will be provided by subject ID number and time point in chronological order.

7.5.2. Corrected QT Intervals

The QT interval (measured in millisecond [msec]) is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. The QT interval represents electrical depolarization and repolarization of the ventricles. The QT interval is affected by heart rate, and a number of methods have been proposed to correct QT for heart rate.

Corrected QT (QTc) intervals will be derived using Fridericia's correction (QTcF) as follows:

$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

where QT is measured in msec; RR = 60/Heart Rate (beats per min [bpm]) and RR is measured in seconds. Per Gilead data collection standard, ventricular rate (VR) is taken as heart rate and will be used to derive RR.

The maximum postdose QTcF interval values obtained during the study will be summarized within the following categories:

- > 450 msec
- > 480 msec
- > 500 msec

The maximum postdose change in QTcF interval values obtained during the study will also be summarized within the following categories:

- > 30 msec
- > 60 msec

QTcF and uncorrected QT values at each visit and change from baseline at each visit will be summarized for the Safety Analysis Set by study part and cohort using descriptive statistics.

7.5.3. PR and QRS Intervals

The PR interval (measured in msec) is a measure of the time between the start of the P wave (the onset of atrial depolarization) and the beginning of the QRS complex (the onset of ventricular depolarization). The QRS interval measures the duration of the QRS complex. The maximum ventricular rate (VR) and PR and QRS intervals observed during the study will be categorized. The number and percentage of subjects having values in the following ranges will be presented by treatment group:

- VR > 100 bpm
- PR interval > 200 msec
- QRS interval > 110 msec

In addition, VR, PR, RR, and QRS values at each visit and change from baseline at each visit will be summarized for the Safety Analysis Set by study part and cohort using descriptive statistics.

7.6. Other Safety Measures

A data listing will be provided for the results of all pregnancy tests conducted in the study. Post-treatment anti-cancer therapies will be listed for applicable subjects.

7.7. Changes From Protocol-Specified Safety Analyses

There are no deviations from the protocol-specified safety analyses.

8. PHARMACOKINETIC ANALYSES

8.1. PK Sample Collection

Plasma samples will be collected to measure concentrations of GS-5745 at protocol specified time points.

8.2. Statistical Analysis Methods

8.2.1. GS-5745 Plasma Concentration

GS-5745 plasma concentration data will be summarized using descriptive statistics for subjects in the PK Analysis Set in Part A by time point and visit. Subjects in different dose cohorts will be presented separately. The sample size for each time point will be based on the number of subjects with nonmissing concentration data at that time point. The number of subjects with concentration BLQ will be presented for each time point. For summary statistics, BLQ values will be treated as 0 at predose and one-half of the lower limit of quantitation (LLOQ) for postdose time points.

The following figures may be provided by dose level in Part A:

- Mean (± StD) concentration data versus time (on linear and semilogarithmic scales)
- Median (Q1, Q3) concentration data versus time (on linear and semilogarithmic scales)

The following table will be provided by dose level in Part A:

- Individual subject concentration data and summary statistics

GS-5745 plasma concentration data and PK sampling details will be listed for all subjects in the PK Analysis Set.

8.2.2. GS-5745 PK Parameters

For subjects in Part A, relevant PK parameters will be determined using Phoenix WinNonlin® software and utilizing standard noncompartmental methods. The linear/log trapezoidal rule will be applied in conjunction with the appropriate noncompartmental model, with input values for dose level, dosing time, plasma concentration, and corresponding real time values, based on drug dosing times whenever possible. Descriptive statistics will be presented for PK parameters of GS-5745 by dose cohort.

All predose sample times before time-zero will be converted to 0. For area under the curve (AUC), samples BLQ of the bioanalytical assays occurring prior to the achievement of the first quantifiable concentration will be assigned a concentration value of 0 to prevent overestimation of the initial AUC. Samples that are BLQ at all other time points will be treated as missing data in WinNonlin. The nominal time point for a key event or dosing interval (τ) may be used to permit direct calculation of AUC over specific time intervals. The appropriateness of this approach will be assessed by the PK scientist on a profile by profile basis.

Pharmacokinetic parameters such as λz and $t_{1/2}$ are dependent on an accurate estimation of the terminal elimination phase of drug. The appropriateness of calculating these parameters will be evaluated upon inspection of PK data on a profile-by-profile basis by the PK scientist.

The PK parameters for GS-5745 presented in Table 12 will be computed for all subjects in the PK Analysis Set in Part A, as applicable.

Table 12. PK parameters for GS-5745

Analyte	PK Parameters
GS-5745	C_{eoi}, C_{max}, T_{max}, AUC_{last}, $AUC_{0\text{-}336h}$, C_{336h}, C_{last}, T_{last}, λ_z, $T_{1/2}$

Individual PK parameter data listings and summaries will include all subjects for whom PK parameter(s) can be derived. The sample size for each PK parameter will be based on the number of subjects with nonmissing data for that PK parameter.

The following table will be provided by dose level:

- Individual subject plasma PK parameters and summary statistics will be presented for PK parameters of GS-5745 by dose cohort.

9. IMMUNOGENICITY ANALYSES

9.1. ADA Sample Collection

Serum samples will be collected to measure anti-GS-5745 antibody (ADA) at protocol specified time points.

9.2. Statistical Analyses Methods

Immunogenicity data will be listed and summarized for all subjects in the Immunogenicity Analysis Set. Subjects in different dose cohorts (Part A) and different disease cohorts (Part B) will be presented separately. Immunogenicity of andecaliximab will be evaluated based upon the positive ADA rate. The number and percentage of subjects exhibiting positive ADA status, defined as ADA presence in serum confirmed in validated assay and reported by bioanalytical laboratory, will be summarized at each specified time point. The number and percentage of subjects exhibiting positive ADA status at any post-andecaliximab time point will also be summarized.

A by-subject listing for ADA status at each time point and the titer for subjects with positive ADA status will be provided by subject ID number and time point in chronological order.

10. BIOMARKER ANALYSES

To evaluate GS-5745 coverage on MMP9 and to evaluate the pharmacodynamics effect of GS-5745, samples for assessment of drug activity are obtained at protocol-specified time points. A comprehensive analysis may be documented separately.

Biomarker Analysis Set will be used for biomarker analysis.

10.1. Statistical Analysis Methods

All summaries will be presented in tabular or graphical form. Descriptive statistics refers to number of subjects, mean, median, standard deviation (StD), 1st quartile (Q1), 3rd quartile (Q3), minimum, and maximum for continuous measurements and number and percentage of subjects in each level of a categorical measurement.

The following tables will be provided for each biomarker for Part A and Part B, separately:

- Descriptive Statistics for Peripheral Free MMP9 at Time Points by Cohort
- Descriptive Statistics for Peripheral Total MMP9 at Time Points by Cohort

The following figures will be provided for each biomarker for Part A and Part B, separately:

- Mean (± SE) Plot for Peripheral Free and Total MMP9 Over Time by Cohort
- Median (Q1, Q3) Plot for Peripheral Free and Total MMP9 Over Time by Cohort

Listings of free and total MMP9 will be provided for Part A and Part B, separately.

11. REFERENCES

Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03, U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute, 14 June 2010. http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

12. SOFTWARE

SAS® (SAS Institute Inc., Cary, NC) is to be used for all programming of tables, listings, and figures.

WinNonlin® (Pharsight Corporation, Mountain View, CA) is to be used for all PK analyses.

13. APPENDICES

Appendix 1. Study Procedures Table (Part A)

Weeks		**1**						**2**	**3**		**5**		**7**		**9**	**Q2W (l)**	**Q8W (m)**	**EOS (n)**
Days	**-28 to -1**	**1**			**2**	**3**	**5**	**8**	**15**		**29**		**43**		**57**			
Window									**± 1**		**± 1**		**± 2**		**± 2**	**± 2**	**± 5**	
Hours (relative to dosing)		**Pre-dose**	**EOI**	**6**	**24**	**48**	**96**	**168**	**Pre-dose**	**EOI**	**Pre-dose**	**EOI**	**Pre-dose**	**EOI**				
Study Assessments																		
Informed Consent	X																	
Medical History (a)	X																	
Physical Exam (b)	X	X						X	X		X		X		X			X
Vital signs (c)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
12-lead ECG	X	X	X	X					X		X		X	X	X			X
ECOG Performance Status	X	X			X	X	X	X	X		X		X		X	X		X
Prior/Concomitant Meds (d)	X	X			X	X	X	X	X		X		X		X	X	X	X
AEs (e)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CT or MRI (f)	X														X		X	X
Collect Archival Tumor Tissue (if available) (g)		X																
Register subject visit in IxRS	X	X							X		X		X		X	X		X
Sample Collection																		
Chemistry	X	X (j)						X	X		X		X		X	X	X (k)	X
Hematology	X	X (j)						X	X		X		X		X	X	X (k)	X
Coagulation	X	X (j)							X		X		X		X	X		X
Urinalysis	X	X (j)							X		X		X		X	X		X
Pregnancy test (h)	X	X (j)							X		X		X		X	X		X
GS-5745 Concentration (i)		X (j)	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X

Weeks		**1**						**2**	**3**		**5**		**7**		**9**	**Q2W (l)**	**Q8W (m)**	**EOS (n)**
Days	**-28 to -1**	**1**			**2**	**3**	**5**	**8**	**15**		**29**		**43**		**57**			
Window									**± 1**		**± 1**		**± 2**		**± 2**	**± 2**	**± 5**	
Hours (relative to dosing)		**Pre-dose**	**EOI**	**6**	**24**	**48**	**96**	**168**	**Pre-dose**	**EOI**	**Pre-dose**	**EOI**	**Pre-dose**	**EOI**				
Anti-GS-5745 Antibody		X (j)											X				X	X
Serum and plasma biomarkers	X	X (j)							X				X		X		X	X
Urine biomarkers	X	X (j)							X				X		X		X	X
Study Drug Dosing																		
GS-5745 IV Dosing			X							X		X		X	X	X		

a. Medical history includes significant past medical events (eg, prior hospitalizations or surgeries), a review of the disease under study, prior anti-cancer therapies, and any concurrent medical illnesses.
b. A complete PE will be performed at Screening. A modified PE capturing changes from prior exams will be performed at subsequent applicable visits. Weight (in kilograms and without shoes) should be measured at each PE. Height (in centimeters and without shoes) should be measured at Screening only.
c. Vital signs include blood pressure, respiratory rate, pulse, and temperature. Measurements of blood pressure should be taken after the subject has been sitting for at least 5 minutes.
d. Prior/concomitant medications include all medication taken up to 30 days prior to Screening, any and all medications taken during the course of the study, and supportive therapies given during the course of the study (eg, blood transfusion, growth factor).
e. AEs will be assessed before and after GS-5745 dosing during applicable visits.
f. Tumor evaluation by CT or MRI will be performed during screening (within 4 weeks of Day 1) and every 8 weeks thereafter. The same radiographic procedure used to define measurable lesions must be used throughout the study for each subject. CT or MRI should be conducted at the EOS visit if not conducted within the previous 4 weeks. If a subject discontinues study drug (for example, as a result of an AE), every attempt should be made to keep the subject in the study to collect tumor assessments (CT/MRI), chemistry, and hematology every 8 weeks until disease progression.
g. Unstained slides (10-12) from archival tumor tissues prepared within 2 weeks of shipment to Gilead or its designee will be requested after Day 1.
h. For females of childbearing potential, a serum pregnancy test will be performed at Screening and urine pregnancy tests will be performed prior to each dose of GS-5745 and at the End-of-Study visit.
i. Blood samples to measure GS-5745 concentration will be collected pre- and post-dose at each applicable visit.
j. Day 1 pre-dose samples for the specified assessments may be drawn up to 2 days prior to the Day 1 visit.
k. If a subject discontinues study drug (for example, as a result of an AE), every attempt should be made to keep the subject in the study to collect tumor assessments (CT/MRI), chemistry, and hematology every 8 weeks until disease progression.
l. A subject who does not show evidence of disease progression by clinical assessment or by CT or MRI may continue receiving GS-5745 every 2 weeks until disease progression (clinical or radiographic), unacceptable toxicity, withdrawal of consent, or other reasons specified in Study Protocol. Q2W visits will occur every 2 weeks (± 2 days) from the Day 57 visit.
m. Q8W visits will occur every 8 weeks (± 5 days) from the Day 57 visit.
n. Subjects will be contacted by phone 30 days (± 2 days) after the last dose of GS-5745 to assess AEs. For subjects who come off study for reasons other than PD, the site should also obtain information on post-study anti-cancer therapies, surgeries, and date of definitive PD.

Appendix 2. Study Procedures Table (Part B – Pancreatic Adenocarcinoma)

Study Phase	**Screening**	**Each Cycle (28 days)**			**Every 2 Cycles**	**EOS (l)**
Cycle Day	**Screening**	**1**	**8**	**15**		**N/A**
Window	**-28**	**0**	**±2**	**±2**		**N/A**
Treatment Day	**-28**	**1**	**8**	**15**		**N/A**
Study Assessments						
Informed Consent	X					
Medical History (a)	X					
Physical Exam (b)	X	X				X
Vital signs (c)	X	X	X	X		X
12-lead ECG	X	X				
ECOG Performance Status	X	X		X		X
Prior/Concomitant Meds (d)	X	X	X	X		X
AEs (e)	X	X	X	X		X
CT or MRI (f)	X				X (k)	X
Collect Archival Tumor Tissue (if available) (g)		X				
Register subject visit in IxRS	X	X		X		X
Sample Collection						
Chemistry	X	X (j)		X	X (k)	X
Hematology	X	X (j)	X	X	X (k)	X
Coagulation	X	X (j)				X
Urinalysis	X	X (j)				X
Pregnancy test (h)	X	X (j)		X		X
GS-5745 Concentration (i)		X		X		X

Study Phase	**Screening**	**Each Cycle (28 days)**			**Every 2 Cycles**	**EOS (l)**
Cycle Day	**Screening**	**1**	**8**	**15**		**N/A**
Window	**-28**	**0**	**±2**	**±2**		**N/A**
Treatment Day	**-28**	**1**	**8**	**15**		**N/A**
Anti-GS-5745 Antibody		X (j)				X
Serum and plasma biomarkers	X	X (j)				X
Urine biomarkers	X	X (j)				X
Study Drug Dosing/Chemotherapy						
GS-5745 IV Dosing		X		X		
Gemcitabine Dosing		X	X	X		
Nab-Paclitaxel Dosing		X	X	X		

a. Medical history includes significant past medical events (eg, prior hospitalizations or surgeries), a review of the disease under study, prior anti-cancer therapies, and any concurrent medical illnesses.
b. A complete PE will be performed at Screening. A modified PE capturing changes from prior exams will be performed at subsequent applicable visits. Weight (in kilograms and without shoes) should be measured at each PE. Height (in centimeters and without shoes) should be measured at Screening only.
c. Vital signs include blood pressure, respiratory rate, pulse, and temperature. Measurements of blood pressure should be taken after the subject has been sitting for at least 5 minutes.
d. Prior/concomitant medications include all medication taken up to 30 days prior to Screening, any and all medications taken during the course of the study, and supportive therapies given during the course of the study (eg, blood transfusion, growth factor).
e. AEs will be assessed before and after GS-5745 and gemcitabine dosing during applicable visits. The site will call subjects 30 days after the last dose of GS-5745 to assess AEs and SAEs.
f. Tumor evaluation by CT or MRI will be performed during screening (within 4 weeks of Day 1) and during the last week of even-numbered cycles (ie, Cycles 2, 4, 6, etc.). The same radiographic procedure used to define measurable lesions must be used throughout the study for each subject. CT or MRI should be conducted at the EOS visit if not conducted within the previous 4 weeks. If a subject discontinues study drug (for example, as a result of an AE), every attempt should be made to keep the subject in the study to collect tumor assessments (CT/MRI), chemistry, and hematology during the last week of even-numbered cycles (ie, Cycles 2, 4, 6, etc.) until disease progression.
g. Unstained slides (10-12) from archival tumor tissues prepared within 2 weeks of shipment to Gilead or its designee will be requested after Day 1 of Cycle 1 only.
h. For females of childbearing potential, a serum pregnancy test will be performed at Screening and urine pregnancy tests will be performed prior to each dose of GS-5745 and at the End-of-Study visit.
i. Blood samples to measure GS-5745 concentration will be collected pre-dose on Day 1 and Day 15 of each cycle.
j. Day 1 pre-dose samples for the specified assessments may be drawn up to 2 days prior to the Day 1 visit.
k. If a subject discontinues study drug (for example, as a result of an AE), every attempt should be made to keep the subject in the study to collect tumor assessments (CT/MRI), chemistry, and hematology during the last week of even-numbered cycles (ie, Cycles 2, 4, 6, etc.) until disease progression.
l. Subjects will be contacted by phone 30 days (± 2 days) after the last dose of GS-5745 to assess AEs. For subjects who come off study for reasons other than PD, the site should also obtain information on post-study anti-cancer therapies, surgeries, and date of definitive PD.

Appendix 3. Study Procedures Table (Part B – Esophagogastric Adenocarcinoma)

Study Phase	**Screening**	**Each Cycle (28 days)**		**Every 2 Cycles**	**EOS (l)**
Cycle Day	**Screening**	**1**	**15**		**N/A**
Window	**-28**	**0**	**±2**		**N/A**
Treatment Day	**-28**	**1**	**15**		**N/A**
Study Assessments					
Informed Consent	X				
Medical History (a)	X				
Physical Exam (b)	X	X			X
Vital signs (c)	X	X	X		X
12-lead ECG	X	X			
ECOG Performance Status	X	X	X		X
Prior/Concomitant Meds (d)	X	X	X		X
AEs (e)	X	X	X		X
CT or MRI (f)	X			X (k)	X
Collect Archival Tumor Tissue (if available) (g)		X			
Register subject visit in IxRS	X	X	X		X
Sample Collection					
Chemistry	X	X (j)	X	X (k)	X
Hematology	X	X (j)	X	X (k)	X
Coagulation	X	X (j)			X
Urinalysis	X	X (j)			X
Pregnancy test (h)	X	X (j)	X		X
GS-5745 Concentration (i)		X	X		X
Anti-GS-5745 Antibody		X (j)			X

Study Phase	**Screening**	**Each Cycle (28 days)**		**Every 2 Cycles**	**EOS (l)**
Cycle Day	**Screening**	**1**	**15**		**N/A**
Window	**-28**	**0**	**±2**		**N/A**
Treatment Day	**-28**	**1**	**15**		**N/A**
Serum and plasma biomarkers	X	X (j)			X
Urine biomarkers	X	X (j)			X
Study Drug Dosing/Chemotherapy					
GS-5745 IV Dosing		X	X		
mFOLFOX6 Dosing (m)		X	X		

a. Medical history includes significant past medical events (eg, prior hospitalizations or surgeries), a review of the disease under study, prior anti-cancer therapies, and any concurrent medical illnesses.
b. A complete PE will be performed at Screening. A modified PE capturing changes from prior exams will be performed at subsequent applicable visits. Weight (in kilograms and without shoes) should be measured at each PE. Height (in centimeters and without shoes) should be measured at Screening only.
c. Vital signs include blood pressure, respiratory rate, pulse, and temperature. Measurements of blood pressure should be taken after the subject has been sitting for at least 5 minutes.
d. Prior/concomitant medications include all medication taken up to 30 days prior to Screening, any and all medications taken during the course of the study, and supportive therapies given during the course of the study (eg, blood transfusion, growth factor).
e. AEs will be assessed before and after GS-5745 and mFOLFOX6 dosing during applicable visits. The site will call subjects 30 days after the last dose of GS-5745 to assess AEs and SAEs.
f. Tumor evaluation by CT or MRI will be performed during screening (within 4 weeks of Day 1) and during the last week of even-numbered cycles (ie, Cycles 2, 4, 6, etc.). The same radiographic procedure used to define measurable lesions must be used throughout the study for each subject. CT or MRI should be conducted at the EOS visit if not conducted within the previous 4 weeks. If a subject discontinues study drug (for example, as a result of an AE), every attempt should be made to keep the subject in the study to collect tumor assessments (CT/MRI), chemistry, and hematology during the last week of even-numbered cycles (ie, Cycles 2, 4, 6, etc.) until disease progression.
g. Unstained slides (10-12) from archival tumor tissues prepared within 2 weeks of shipment to Gilead or its designee will be requested after Day 1 of Cycle 1 only.
h. For females of childbearing potential, a serum pregnancy test will be performed at Screening and urine pregnancy tests will be performed prior to each dose of GS-5745 and at the End-of-Study visit.
i. Blood samples to measure GS-5745 concentration will be collected pre-dose on Day 1 and Day 15 of each cycle.
j. Day 1 pre-dose samples for the specified assessments may be drawn up to 2 days prior to the Day 1 visit.
k. If a subject discontinues study drug (for example, as a result of an AE), every attempt should be made to keep the subject in the study to collect tumor assessments (CT/MRI), chemistry, and hematology during the last week of even-numbered cycles (ie, Cycles 2, 4, 6, etc.) until disease progression.
l. Subjects will be contacted by phone 30 days (± 2 days) after the last dose of GS-5745 to assess AEs. For subjects who come off study for reasons other than PD, the site should also obtain information on post-study anti-cancer therapies, surgeries, and date of definitive PD.
m. mFOLFOX6 dosing regimen will consist of *l*-LV 200 mg/m^2 or *dl*-LV 400 mg/m^2 and oxaliplatin 85 mg/m^2 followed by bolus 5-FU 400 mg/m^2 and a 46-hour infusion 5-FU 2400 mg/m^2.

Appendix 4. Study Procedures Table (Part B – NSCLC)

Study Phase	**Screening**	**Each Cycle (21 days)**	**Every 3 Cycles**	**EOS (l)**
Cycle Day	**Screening**	**1**		**N/A**
Window	**-28**	**±2**		**N/A**
Treatment Day	**-28**	**1**		**N/A**
Study Assessments				
Informed Consent	X			
Medical History (a)	X			
Physical Exam (b)	X	X		X
Vital signs (c)	X	X		X
12-lead ECG	X	X		
ECOG Performance Status	X	X		X
Prior/Concomitant Meds	X	X		X
AEs (d)	X	X		X
CT or MRI (e)	X		X (k)	X
Collect Archival Tumor Tissue (if available) (f)		X		
Register subject visit in IxRS	X	X		X
Sample Collection				
Chemistry	X	X (j)	X (k)	X
Hematology	X	X (j)	X (k)	X
Coagulation	X	X (j)		X
Urinalysis	X	X (j)		X
Pregnancy test (g)	X	X (j)		X
GS-5745 Concentration (h)		X		X
Anti-GS-5745 Antibody		X (j)		X

Study Phase	Screening	Each Cycle (21 days)	Every 3 Cycles	EOS (l)
Cycle Day	**Screening**	**1**		**N/A**
Window	**-28**	**±2**		**N/A**
Treatment Day	**-28**	**1**		**N/A**
Serum and plasma biomarkers	X	X (j)		X
Urine biomarkers	X	X (j)		X
Study Drug Dosing/Chemotherapy				
GS-5745 IV Dosing		X		
Chemotherapy Dosing (i)		X		

a. Medical history includes significant past medical events (eg, prior hospitalizations or surgeries), a review of the disease under study, prior anti-cancer therapies, and any concurrent medical illnesses.
b. A complete PE will be performed at Screening. A modified PE capturing changes from prior exams will be performed at subsequent applicable visits. Weight (in kilograms and without shoes) should be measured at each PE. Height (in centimeters and without shoes) should be measured at Screening only.
c. Vital signs include blood pressure, respiratory rate, pulse, and temperature. Measurements of blood pressure should be taken after the subject has been sitting for at least 5 minutes.
d. AEs will be assessed before and after GS-5745 dosing during applicable visits. The site will call subjects 30 days after the last dose of GS-5745 to assess AEs and SAEs.
e. Tumor evaluation by CT or MRI will be performed during screening (within 4 weeks of Day 1) and during the last week of every third cycle (ie, Cycles 3, 6, 9, etc.). The same radiographic procedure used to define measurable lesions must be used throughout the study for each subject. CT or MRI should be conducted at the EOS visit if not conducted within the previous 4 weeks. If a subject discontinues study drug (for example, as a result of an AE), every attempt should be made to keep the subject in the study to collect tumor assessments (CT/MRI), chemistry, and hematology during the last week of every third cycle (ie, Cycles 3, 6, 9, etc.) until disease progression.
f. Unstained slides (10-12) from archival tumor tissues prepared within 2 weeks of shipment to Gilead or its designee will be requested after Day 1 of Cycle 1 only.
g. For females of childbearing potential, a serum pregnancy test will be performed at Screening and urine pregnancy tests will be performed prior to each dose of GS-5745 and at the End-of-Study visit.
h. Blood samples to measure GS-5745 concentration will be collected pre-dose on Day 1 of each cycle.
i. NSCLC chemotherapy regimen: carboplatin IV dosed to AUC 6 on Day 1 of each 21-day treatment cycle and pemetrexed 500 mg/m^2 IV on Day 1 of each 21-day treatment cycle in subjects with lung adenocarcinoma. Chemotherapy will consist of carboplatin IV dosed to AUC 6 on Day 1 of each 21-day treatment cycle and paclitaxel 200 mg/m^2 IV on Day 1 of each 21-day treatment cycle in subjects with lung squamous cell carcinoma. Subjects who have not had disease progression after 4 cycles of treatment may have some of their treatment reduced based upon the Investigator's assessment of what is in the subject's best interests. However, dosing with GS-5745 should be continued per protocol.
j. Day 1 pre-dose samples for the specified assessments may be drawn up to 2 days prior to the Day 1 visit.
k. If a subject discontinues study drug (for example, as a result of an AE), every attempt should be made to keep the subject in the study to collect tumor assessments (CT/MRI), chemistry, and hematology during the last week of every third cycle (ie, Cycles 3, 6, 9, etc.) until disease progression.
l. Subjects will be contacted by phone 30 days (± 2 days) after the last dose of GS-5745 to assess AEs. For subjects who come off study for reasons other than PD, the site should also obtain information on post-study anti-cancer therapies, surgeries, and date of definitive PD.

Appendix 5. Study Procedures Table (Part B – First Line CRC)

Study Phase	Screening	Each Cycle (28 Days)		Cycle 2	Cycle 3	Every 2 Cycles	EOS[m]	LTFU Every 3 Months
Cycle Day	**Screening**	**1**	**15**	**15**	**1**		**N/A**	**N/A**
Window	**−28**	**0[r]**	**± 2**	**+14 Days / −7 Days**			**N/A**	**N/A**
Treatment Day	**−28**	**1**	**15**				**N/A**	**N/A**
Study Assessments								
Informed Consent	X							
Medical History[a]	X							
Physical Exam[b]	X	X					X	
Vital Signs[c]	X	X	X				X	
12-Lead ECG	X	X						
ECOG Performance Status	X	X	X				X	
Prior/Concomitant Meds[d]	X	X	X				X	
AEs[e]	X	X	X				X	
CT or MRI[f]	X					X[l]	X	
Collect Archival Tumor Tissue (if Available)[g]		X[g]						
Register Subject Visit in IxRS	X	X	X				X	
Sample Collection								
Chemistry	X	X[k]	X			X[l]	X	
Hematology	X	X[k]	X			X[l]	X	
Coagulation	X	X[k]					X	

Study Phase	**Screening**	**Each Cycle (28 Days)**		**Cycle 2**	**Cycle 3**	**Every 2 Cycles**	**EOS[m]**	**LTFU Every 3 Months**
Cycle Day	**Screening**	**1**	**15**	**15**	**1**		**N/A**	**N/A**
Window	**−28**	**0[r]**	**± 2**	**+14 Days / −7 Days**			**N/A**	**N/A**
Treatment Day	**−28**	**1**	**15**				**N/A**	**N/A**
Urinalysis	X	X[k]					X	
Pregnancy Test[h]	X	X[k]	X				X	
GS-5745 Concentration[i]		X	X		X		X	
Anti-GS-5745 Antibody		X[k]					X	
Serum and Plasma Biomarkers		X[k,n]	X[n]				X[n]	
CCI								
Stool Sample	X[o]			X[o]				
CCI								
Overall Survival								X
Study Drug Dosing / Chemotherapy								
GS-5745 IV Dosing		X	X					
mFOLFOX6/Bev Dosing[j]		X	X					

EOS = End-of-Study (visit); PE = physical examination

a Medical history includes significant past medical events (eg, prior hospitalizations or surgeries), a review of the disease under study, prior anti-cancer therapies, and any concurrent medical illnesses.

b A complete PE will be performed at Screening. A modified PE capturing changes from prior exams will be performed at subsequent applicable visits. Weight (without shoes) should be measured at each PE and reported in kilograms. Height (without shoes) should be measured at Screening only and reported in centimeters.

c Vital signs include blood pressure, respiratory rate, pulse, and temperature. Measurements of blood pressure should be taken per institutional guidelines.

d Prior/concomitant medications include all medication taken up to 30 days prior to Screening, any and all medications taken during the course of the study, and supportive therapies given during the course of the study (eg, blood transfusion, growth factor).

e AEs will be assessed before and after GS-5745 and mFOLFOX6 dosing during applicable visits. The site will call subjects 30 days after the last dose of GS-5745 to assess AEs and SAEs.

f Tumor evaluation by CT or MRI will be performed during screening (within 4 weeks of Day 1) and during the last week of even-numbered cycles (ie, Cycles 2, 4, 6, etc.). The same radiographic procedure used to define measurable lesions must be used throughout the study for each subject. CT or MRI should be conducted at the EOS visit if not conducted within the previous 4 weeks. If a subject *discontinues study drug (for example, as a result of an AE), every attempt should be made to keep the subject in the study to collect tumor assessments (CT/MRI), chemistry, and hematology* during the last week of even-numbered cycles (ie, Cycles 2, 4, 6, etc.) until disease progression.

g Unstained slides (5×10 micron and 10×5 micron) from archival tumor tissues prepared within 2 weeks of shipment to Gilead or its designee will be requested after Day 1 of Cycle 1 only.

h For females of childbearing potential, a serum pregnancy test will be performed at Screening and urine pregnancy tests will be performed prior to each dose of GS-5745 and at the EOS visit.

i Blood samples to measure GS-5745 concentration will be collected pre-dose on Day 1 and Day 15 of each cycle, end of GS-5745 infusion on Day 1 of Cycle 1 and Cycle 3, and at the EOS visit.

j mFOLFOX6 and bevacizumab dosing regimen on Days 1 and 15 of each 28-day treatment cycle will consist of: bevacizumab at 5 mg/kg IV and mFOLFOX6 dosing regimen will consist of l-leucovorin (LV) 200 mg/m2 or dl-LV 400 mg/m2 and oxaliplatin 85 mg/m2 followed by bolus 5 FU 400 mg/m2 and a 46-hour infusion of 5-FU 2400 mg/m2

k Day 1 pre-dose samples for the specified assessments may be drawn up to 2 days prior to the Day 1 visit.

l *If a subject discontinues study drug (for example, as a result of an AE), every attempt should be made to keep the subject in the study to collect tumor assessments (CT/MRI), chemistry, and hematology* during the last week of even-numbered cycles (ie, Cycles 2, 4, 6, etc.) until disease progression.

m Subjects will be contacted by phone 30 days (± 2 days) after the last dose of GS-5745 to assess AEs. For subjects who come off study for reasons other than disease progression, the site should also obtain information on post-study anti-cancer therapies, surgeries, and date of definitive disease progression.

n Blood samples for biomarkers should be drawn pre-dose on all specified visits. Note that Day 15 is only required for Cycle 1 and that a blood sample at EOS is required if due to disease progression. The exact schedule of blood draws is outlined in the laboratory manual.

o A stool sample is required at study start and can be collected any time within the screening window prior to first dose. An additional stool sample at Cycle 2 Day 15 (+14 days/−7 days) is requested.

[redacted]

r A ± 2 day window applies to visits following Cycle 1 Day 1. There is no window for Cycle 1 Day 1.

Appendix 6. Study Procedures Table (Part B- Second Line CRC)

Study Phase	Screening	Each Cycle (28 Days)		Cycle 2	Cycle 3	Every 2 Cycles	EOS[m]	LTFU Every 3 Months
Cycle Day	**Screening**	**1**	**15**	**15**	**1**		**N/A**	**N/A**
Window	**-28**	**0[r]**	**±2**	**+14 Days / −7 Days**			**N/A**	**N/A**
Treatment Day	**-28**	**1**	**15**				**N/A**	**N/A**
Study Assessments								
Informed Consent	X							
Medical History[a]	X							
Physical Exam[b]	X	X					X	
Vital Signs[c]	X	X	X				X	
12-Lead ECG	X	X						
ECOG Performance Status	X	X	X				X	
Prior/Concomitant Meds[d]	X	X	X				X	
AEs[e]	X	X	X				X	
CT or MRI[f]	X					X[l]	X	
Collect Archival Tumor Tissue (if Available)[g]		X						
Register Subject Visit in IxRS	X	X	X				X	
Sample Collection								
Chemistry	X	X[k]	X			X[l]	X	
Hematology	X	X[k]	X			X[l]	X	
Coagulation	X	X[k]					X	

Study Phase	Screening	Each Cycle (28 Days)		Cycle 2	Cycle 3	Every 2 Cycles	EOS[m]	LTFU Every 3 Months
Cycle Day	**Screening**	**1**	**15**	**15**	**1**		**N/A**	**N/A**
Window	**-28**	**0[r]**	**±2**	**+14 Days / −7 Days**			**N/A**	**N/A**
Treatment Day	**-28**	**1**	**15**				**N/A**	**N/A**
Urinalysis	X	X[k]					X	
Pregnancy Test[h]	X	X[k]	X				X	
GS-5745 Concentration[i]		X	X		X		X	
Anti-GS-5745 Antibody		X[k]					X	
Serum and Plasma Biomarkers		X[k,n]	X[n]				X[n]	
CCI								
Stool Sample	X[o]			X[o]				
CCI								
Overall Survival								X
Study Drug Dosing / Chemotherapy								
GS-5745 IV Dosing		X	X					
FOLFIRI/Bev Dosing[j]		X	X					

EOS = End-of-Study (visit); PE = physical examination

a Medical history includes significant past medical events (eg, prior hospitalizations or surgeries), a review of the disease under study, prior anti-cancer therapies, and any concurrent medical illnesses.

b A complete PE will be performed at Screening. A modified PE capturing changes from prior exams will be performed at subsequent applicable visits. Weight (without shoes) should be measured at each PE and reported in kilograms. Height (without shoes) should be measured at Screening only and reported in centimeters.

c Vital signs include blood pressure, respiratory rate, pulse, and temperature. Measurements of blood pressure should be taken per institutional guidelines.

d Prior/concomitant medications include all medication taken up to 30 days prior to Screening, any and all medications taken during the course of the study, and supportive therapies given during the course of the study (eg, blood transfusion, growth factor).

e AEs will be assessed before and after GS-5745 and FOLFIRI dosing during applicable visits. The site will call subjects 30 days after the last dose of GS-5745 to assess AEs and SAEs.

f Tumor evaluation by CT or MRI will be performed during screening (within 4 weeks of Day 1) and during the last week of even-numbered cycles (ie, Cycles 2, 4, 6, etc.). The same radiographic procedure used to define measurable lesions must be used throughout the study for each subject. CT or MRI should be conducted at the EOS visit if not conducted within the previous 4 weeks. If a subject *discontinues study drug (for example, as a result of an AE), every attempt should be made to keep the subject in the study to collect tumor assessments (CT/MRI), chemistry, and hematology* during the last week of even-numbered cycles (ie, Cycles 2, 4, 6, etc.) until disease progression.

g Unstained slides (10 to 12) from archival tumor tissues prepared within 2 weeks of shipment to Gilead or its designee will be requested after Day 1 of Cycle 1 only.

h For females of childbearing potential, a serum pregnancy test will be performed at Screening and urine pregnancy tests will be performed prior to each dose of GS-5745 and at the EOS visit.

i Blood samples to measure GS-5745 concentration will be collected pre-dose on Day 1 and Day 15 of each cycle, end of GS-5745 infusion on Day 1 of Cycle 1 and Cycle 3, and at the EOS visit.

j FOLFIRI and bevacizumab dosing regimen on Days 1 and 15 of each 28-day treatment cycle will consist of: bevacizumab at 5 mg/kg IV, and FOLFIRI at l-leucovorin 200 mg/m^2 or dl-leucovorin 400 mg/m^2 as a 2-hour infusion, and irinotecan 180 mg/m^2 given as a 90-minute infusion in 500 mL dextrose 5% via a Y-connector, followed by bolus 5-FU 400 mg/m^2 and a 46-hour infusion 5-FU 2400 mg/m^2.

k Day 1 pre-dose samples for the specified assessments may be drawn up to 2 days prior to the Day 1 visit.

l *If a subject discontinues study drug (for example, as a result of an AE), every attempt should be made to keep the subject in the study to collect tumor assessments (CT/MRI), chemistry, and hematology* during the last week of even-numbered cycles (ie, Cycles 2, 4, 6, etc.) until disease progression

m Subjects will be contacted by phone 30 days (± 2 days) after the last dose of GS-5745 to assess AEs. For subjects who come off study for reasons other than disease progression, the site should also obtain information on post-study anti-cancer therapies, surgeries, and date of definitive disease progression.

n Blood samples for biomarkers should be drawn pre-dose on all specified visits. Note that Day 15 is only required for Cycle 1 and that a blood sample at EOS is required if due to disease progression. The exact schedule of blood draws is outlined in the laboratory manual.

o A stool sample is required at study start and can be collected any time within the screening window prior to first dose. An additional stool sample at Cycle 2 Day 15 (+14 days/−7 days) is requested.

[redacted]

r A ± 2 day window applies to visits following Cycle 1 Day 1. There is no window for Cycle 1 Day 1.

Appendix 7. Study Procedures Table (Part B – Breast Cancer)

Study Phase	Screening	Each Cycle (28 Days)			Cycle 2	Cycle 3	Every 2 Cycles	EOS[m]	LTFU
Cycle Day	**Screening**	**1**	**8**	**15**	**15**	**1**		**N/A**	**N/A**
Window	**−28**	**0[q]**	**± 2**	**± 2**	**+14 Days / −7 Days**			**N/A**	**N/A**
Treatment Day	**−28**	**1**	**8**	**15**				**N/A**	**N/A**
Study Assessments									
Informed Consent	X								
Medical History[a]	X								
Physical Exam[b]	X	X						X	
Vital Signs[c]	X	X	X	X				X	
12-Lead ECG	X	X							
ECOG Performance Status	X	X		X				X	
Prior/Concomitant Meds[d]	X	X	X	X				X	
AEs[e]	X	X	X	X				X	
CT or MRI[f]	X						X[l]	X	
Collect Archival Tumor Tissue (if Available)[g]		X							
Register Subject Visit in IxRS	X	X		X				X	
Sample Collection									
Chemistry	X	X[k]		X			X[l]	X	
Hematology	X	X[k]	X	X			X[l]	X	
Coagulation	X	X[k]						X	
Urinalysis	X	X[k]						X	

Study Phase	**Screening**	**Each Cycle (28 Days)**			**Cycle 2**	**Cycle 3**	**Every 2 Cycles**	**EOS[m]**	**LTFU**
Cycle Day	**Screening**	**1**	**8**	**15**	**15**	**1**		**N/A**	**N/A**
Window	**−28**	**0[q]**	**± 2**	**± 2**	**+14 Days / −7 Days**			**N/A**	**N/A**
Treatment Day	**−28**	**1**	**8**	**15**				**N/A**	**N/A**
Pregnancy Test[h]	X	X[k]		X				X	
GS-5745 Concentration[i]		X		X		X		X	
Anti-GS-5745 Antibody		X[k]						X	
Serum and Plasma Biomarkers		X[k,n]		X[n]				X[n]	
CCI									
Overall Survival									X
Study Drug Dosing / Chemotherapy									
GS-5745 IV Dosing		X		X					
Paclitaxel[j]		X	X	X					

EOS = End-of-Study (visit); PE = physical examination

a. Medical history includes significant past medical events (eg, prior hospitalizations or surgeries), a review of the disease under study, prior anti-cancer therapies, and any concurrent medical illnesses.
b. A complete PE will be performed at Screening. A modified PE capturing changes from prior exams will be performed at subsequent applicable visits. Weight (without shoes) should be measured at each PE and reported in kilograms. Height (without shoes) should be measured at Screening only and reported in centimeters.
c. Vital signs include blood pressure, respiratory rate, pulse, and temperature. Measurements of blood pressure should be taken per institutional guidelines.
d. Prior/concomitant medications include all medication taken up to 30 days prior to Screening, any and all medications taken during the course of the study, and supportive therapies given during the course of the study (eg, blood transfusion, growth factor).
e. AEs will be assessed before and after GS-5745 and Paclitaxel dosing during applicable visits. The site will call subjects 30 days after the last dose of GS-5745 to assess AEs and SAEs.
f. Tumor evaluation by CT or MRI will be performed during screening (within 4 weeks of Day 1) and during the last week of even-numbered cycles (ie, Cycles 2, 4, 6, etc.). The same radiographic procedure used to define measurable lesions must be used throughout the study for each subject. CT or MRI should be conducted at the EOS visit if not conducted within the previous 4 weeks. If a subject *discontinues study drug (for example, as a result of an AE), every attempt should be made to keep the subject in the study to collect tumor assessments (CT/MRI), chemistry, and hematology* during the last week of even-numbered cycles (ie, Cycles 2, 4, 6, etc.) until disease progression.

g. Unstained slides (10 to 12) from archival tumor tissues prepared within 2 weeks of shipment to Gilead or its designee will be requested after Day 1 of Cycle 1 only.
h. For females of childbearing potential, a serum pregnancy test will be performed at Screening and urine pregnancy tests will be performed prior to each dose of GS-5745 and at the EOS visit.
i. Blood samples to measure GS-5745 concentration will be collected pre-dose on Day 1 and Day 15 of each cycle, end of GS-5745 infusion on Day 1 of Cycle 1 and Cycle 3, and at the EOS visit.
j. Paclitaxel dosing regimen will consist of Paclitaxel 80 mg/m^2 IV.
k. Day 1 pre-dose samples for the specified assessments may be drawn up to 2 days prior to the Day 1 visit.
l. *If a subject discontinues study drug (for example, as a result of an AE), every attempt should be made to keep the subject in the study to collect tumor assessments (CT/MRI), chemistry, and hematology* during the last week of even-numbered cycles (ie, Cycles 2, 4, 6, etc.) until disease progression.
m. Subjects will be contacted by phone 30 days (± 2 days) after the last dose of GS-5745 to assess AEs. For subjects who come off study for reasons other than disease progression, the site should also obtain information on post-study anti-cancer therapies, surgeries, and date of definitive disease progression.
n. Blood samples for biomarkers should be drawn pre-dose on all specified visits. Note that Day 15 is only required for Cycle 1 and that a blood sample at EOS is required if due to disease progression. The exact schedule of blood draws is outlined in the laboratory manual.
[redacted]
q. A ± 2 day window applies to visits following Cycle 1 Day 1. There is no window for Cycle 1 Day 1.

Appendix 8. List of Laboratory Tests for Safety Summary

Serum Chemistry	Hematology	Coagulation
Sodium	White Blood Cell Count	PT/INR
Potassium	Hemoglobin	aPTT
Chloride	Hematocrit	
Glucose	Platelet Count	
BUN	ANC	
Creatinine	Neutrophils	
ALT	Lymphocytes	
AST	Monocytes	
Alkaline phosphatase		
Total bilirubin		
Total protein		
Albumin		
Calcium		
Magnesium		
Phosphate		