STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 1a/1b Study of GS-1423, an Anti-CD73-TGFβ-Trap Bifunctional Antibody, as Monotherapy or in Combination with a Chemotherapy Regimen in Subjects with Advanced Solid Tumors
Name of Test Drug:	GS-1423
Study Number:	GS-US-505-5452
Protocol Version (Date):	Amendment 2 (29 April 2020)
Analysis Type:	Final Analysis
Analysis Plan Version:	Version 1.0
Analysis Plan Date:	13 July 2021
Analysis Plan Author(s):	PPD PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BLQ	below the limit of quantitation
BMI	body mass index
CI	confidence interval
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FAS	Full Analysis Set
HLT	high-level term
LLT	lower-level term
LOQ	limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
PK	Pharmacokinetic
PT	preferred term
Q1, Q3	first quartile, third quartile
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	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
RR	electrocardiographic interval representing the time measurement between the R wave of one heartbeat and the R wave of the preceding heartbeat
SAP	statistical analysis plan
StD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
WHO	World Health Organization

PHARMACOKINETIC ABBREVIATIONS

AUC_{last}	area under the concentration versus time curve from time zero to the last quantifiable concentration
AUC_{tau}	area under the concentration versus time curve over the dosing interval
C_{last}	last observed quantifiable concentration of the drug
C_{max}	maximum observed concentration of drug
C_{tau}	observed drug concentration at the end of the dosing interval
C_{trough}	plasma [serum] concentration at the end of the dosing interval
CL_{ss}	steady-state clearance
T_{last}	time (observed time point) of C_{last}
T_{max}	time (observed time point) of C_{max}
V_{ss}	volume of distribution at steady state

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 (sCSR) for Study GS-US-505-5452. This SAP is based on the study protocol Amendment 2 dated 29 April 2020 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. The study was terminated early at the completion of Phase 1a Part A (dose escalation). Phase 1a Part B (flat dose regimens) and Phase 1b (expansion cohorts) will not be initiated. The following SAP includes study design components and statistical analysis plans associated with Phase 1a Part A only.

1.1. Study Objectives

Objectives for Phase 1a (Part A dose escalation only)

The primary objective(s) are:

- To assess safety and tolerability and to define the dose limiting toxicity (DLT) and maximum tolerated dose (MTD) or recommended Phase 2 dose (RP2D) of GS-1423 monotherapy in subjects with advanced solid tumors

The secondary objectives are:

- To characterize GS-1423 pharmacokinetics (PK)
- To evaluate GS-1423 immunogenicity

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1.2. Study Design

Study design for Phase 1a

Part A – Dose escalation

Part A is a Phase 1 open-label study to evaluate the safety, tolerability, and PK profile of GS-1423 and to define the DLT and MTD or RP2D of GS-1423 monotherapy in subjects with advanced solid tumors.

In Part A, an accelerated titration design schema will be used by enrolling 1 subject each at the first 2 dose levels of 0.3 mg/kg and 1 mg/kg, followed by a 3+3 dose escalation design (Table 1). At the first 2 dose levels of 0.3 mg/kg and 1 mg/kg, if 2 or more drug-related adverse events (AEs) of Grade 2 or higher or at least 1 DLT are observed during the 28-day DLT observation period, the 3+3 escalation scheme will be used at that dose and subsequent doses. Each subject will stay on the dose level and schedule assigned at study entry. GS-1423 will be administered on Day 1 of each 2-week cycle (Q2W) for up to 1 year or until any progressive disease (PD) or unacceptable toxicity. The starting dose was selected to be 0.3 mg/kg derived from minimally anticipated biologic effect level (MABEL). A Safety Review Team (SRT) will be established to assess safety and decide on dose escalation.

Table 1. Phase 1a Part A GS-1423 Dose Levels and Cohorts

Cohort	No. of Subjects	Escalation Type	Dose of GS-1423 (mg/kg)
1 (starting dose)	1 or 3-6	Accelerated titration	0.3
2	1 or 3-6	Accelerated titration	1
3	3-6	3+3	3
4	3-6	3+3	10
5	3-6	3+3	20
6	3-6	3+3	30
7	3-6	3+3	45

Note: An additional 6 subjects may be enrolled at a dose level at or below maximum tolerated dose to obtain additional safety, pharmacokinetics, and CCI information. Gilead may choose not to enroll any cohort if it is deemed unnecessary.

The initial block of each dose in 3+3 escalation scheme consists of 3 subjects. Dose escalation will occur if no subjects experience a DLT during the first 28 days of study drug dosing. If 2 or more subjects experience DLTs within the first 28 days, dose de-escalation to a lower dose will occur. If 1 of the first 3 evaluable subjects enrolled has a DLT within the first 28 days, then 3 additional subjects will be enrolled at the same dose level. If no DLTs are observed in the additional 3 subjects, dose escalation will occur. If a DLT occurs in ≥ 2 subjects in the total cohort of 6 subjects, the MTD will be deemed to be exceeded, and the prior dose level will be evaluated to determine the MTD by increasing enrollment to 6 subjects. If the prior dose level was already deemed to be safe (ie, 0 or 1 DLT) and enrolled 6 subjects, then it will be defined as the MTD. The MTD is the highest dose level with an incidence of DLTs of 0 or 1 out of 6 subjects during the first 28 days of study drug dosing. A minimum of 6 subjects need to be treated at a dose level before this dose level can be deemed as the MTD. A subject who fails to receive all GS-1423 treatments or fails to complete all safety assessments in the DLT period for reasons other than DLT will be replaced.

Figure 1. Accelerated Dose Escalation Scheme

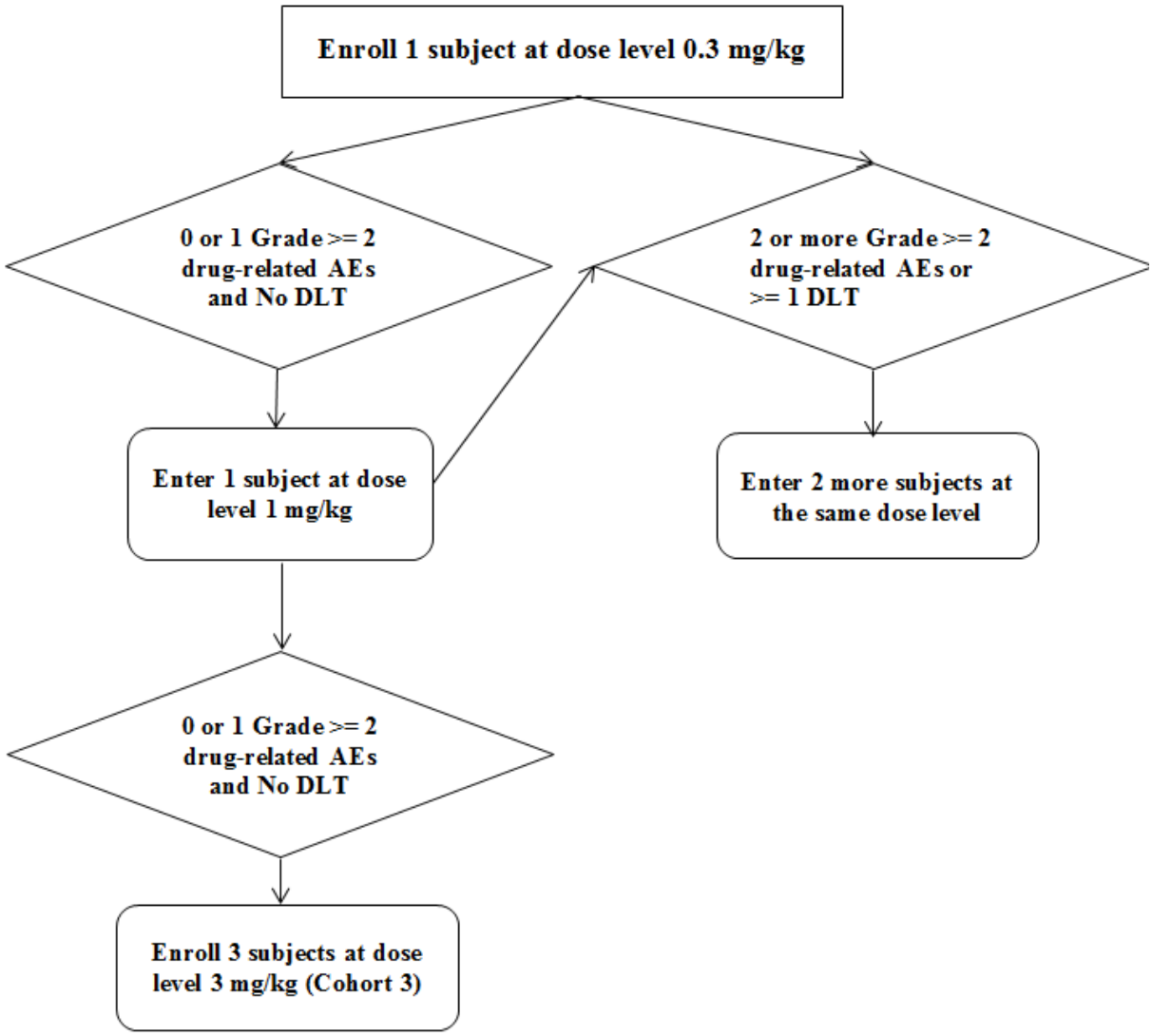
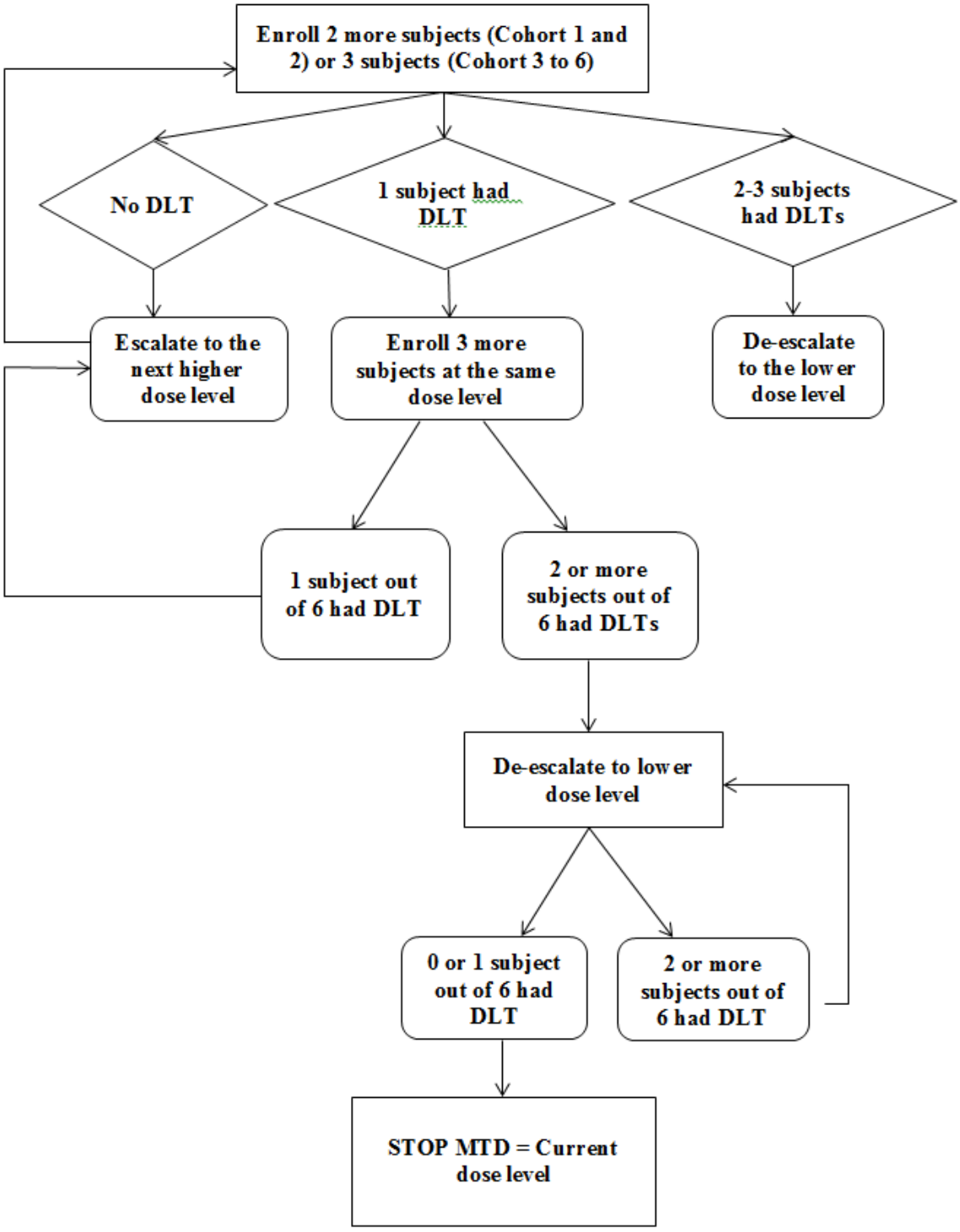


Figure 2. 3+3 Dose Escalation Scheme



Legend: DLT= dose limiting toxicity; MTD = maximum tolerated dose
Note: if MTD is attained at the 1st dose level, discussion with investigators and medical monitor to change dose or schedules in a protocol amendment

Starting at Cohort 4 (10 mg/kg), if no DLT is observed during the 28-day DLT observation period in the first 3 subjects, 3 additional subjects may be enrolled at the respective dose level to obtain more safety, PK, and CCI data. If ≥ 2 subjects have experienced DLTs in the last 3 (of 6) subjects, dose escalation will halt and up to 3 additional subjects will be enrolled at the preceding dose level (if there were only 3 subjects in that cohort) for DLT assessment. If 6 subjects were already evaluated, the preceding dose level will be considered as MTD.

Efficacy Assessment Schedule

For Phase 1a Part A, tumor response assessment will be performed per RECIST 1.1 at baseline (≤ 28 days prior to first dose), every 6 weeks(± 7 days) for the first 24 weeks from the first treatment dose and then every 12 weeks thereafter until PD is assessed by investigator, initiation of new line of therapy, or 1 year after first treatment dose, whichever occurs first. Any CR or PR should be confirmed by CT or MRI scan no less than 28 days after initial assessment. The investigator may perform scans in addition to a scheduled study scan for medical reasons or if PD is suspected.

The Schedule of Assessments is located in Appendix 1.

1.3. Sample Size and Power

Phase 1a Part A

Assuming that up to 7 planned dose levels for escalation will be tested with up to 6 subjects per dose level (42 subjects for escalation) and 10% of subjects are not evaluable, and 6 additional subjects may be enrolled at a dose level at or below MTD to obtain additional safety, PK, and CCI information, up to 53 subjects will be enrolled.

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analyses

2.1.1. Dose Escalation Analysis

For the purpose of making the decision to escalate to the next dose level/cohort, interim analyses of relevant safety and PK (if available) data will be conducted by Gilead after all subjects in each cohort have completed dosing and the 28-day DLT observation period. Safety assessments (ie, AEs, ECG, and laboratory results) will be displayed by dose level/cohort to facilitate the decision to dose escalate.

2.2. Final Analysis

The final analysis will be performed after all subjects have completed or discontinued from the study, outstanding data queries have been resolved or adjudicated as unresolvable, and the data have been cleaned and finalized. The final analysis of this study will include Phase 1a Part A only.

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

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 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 eligible for inclusion, will be summarized by dose cohort.

A listing of reasons for exclusion from analysis sets will be provided by subject.

3.1.1. All Enrolled Analysis Set

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

The All Enrolled Analysis Set will be used for subject enrollment summary and for data listings, unless otherwise specified.

3.1.2. Full Analysis Set

The Full Analysis Set (FAS) includes all enrolled subjects who were administered any amount of GS-1423. This is the primary analysis set for efficacy analyses.

3.1.3. Safety Analysis Set

The Safety Analysis Set includes all enrolled subjects who were administered any amount of GS-1423. This is the primary analysis set for safety analyses.

3.1.4. Dose-Limiting Toxicity (DLT) Analysis Set

The DLT Analysis Set includes all subjects in the Safety Analysis Set who complete all study treatment and have safety assessments through the protocol specified DLT assessment window, Day 28, inclusive, or have experienced a DLT prior to Day 28.

During the DLT observation window, if a subject was not administered both of first 2 GS-1423 doses for reasons other than DLT, another subject was to be enrolled at the same dose level for replacement. Subjects who are replaced but received at least 1 dose of study drug will be included in the Safety Analysis Set and not in the DLT Analysis Set.

The DLT Analysis Set will be used for analyses related to DLT in Part A of Phase 1a.

3.1.5. Pharmacokinetic Analysis Set

The Pharmacokinetic (PK) Analysis Set will include all subjects in the Safety Analysis Set who have at least 1 nonmissing postdose concentration value reported by the PK laboratory. This is the primary analysis set 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.

3.2. Subject Grouping

For analyses based on the Full Analysis Set (FAS), subjects will be grouped according to the treatment to which they were assigned. For analyses based on the Safety Analysis Set, subjects will be grouped according to the actual treatment received. The actual treatment received will differ from the assigned treatment only when their actual treatment differs from the assigned treatment for the entire treatment duration.

For the PK Analysis Set, subjects will be grouped according to the actual treatment they received.

In Phase 1a Part A, The subjects will be grouped by cohorts (dose levels):

Cohort 1: 0.3 mg/kg

Cohort 2: 1 mg/kg

Cohort 3: 3 mg/kg

Cohort 4: 10 mg/kg

Cohort 5: 20 mg/kg

Cohort 6: 30 mg/kg

Cohort 7: 45 mg/kg

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 Subgroups

There are no prespecified subject subgroupings for efficacy and safety analyses.

3.5. Multiple Comparisons

There are no adjustments for multiplicity in this study.

3.6. Missing Data and Outliers

3.6.1. Missing Data

In general, missing data will not be imputed unless methods for handling missing data are specified. Exceptions are presented in this document.

For missing last dosing date of study drug, imputation rules are described in Section 4.2.1.1. The handling of missing or incomplete dates for the completion of last prior anti-cancer therapy is in Section 5.3, for the start date of new anti-cancer therapy is in Section 6.1.3, for date of death in Section 6.1.4, for AE onset in Section 7.1.5.2, and for prior and concomitant medications in Section 7.4.

3.6.2. Outliers

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

3.7. Data Handling Conventions and Transformations

In general, the subject's age collected at Day 1 (in years) will be used for analyses and presented in listings. If age at Day 1 is not available for a subject, then age derived based on date of birth and the Day 1 visit date will be used instead. If an enrolled subject was not dosed with any study drug, the enrollment date will be used instead of the Day 1 visit date. For screen failures, the date the first informed consent was signed will be used for the age derivation. 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.

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 to calculate descriptive statistics if the datum is reported in the form of "< x" (where x is considered the LOQ). For example, if the values are reported as < 50 and < 5.0, values of 49 and 4.9, respectively, will be used to calculate summary statistics. 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 to calculate descriptive statistics if the datum is reported in the form of "> x" (where x is considered the LOQ). Values with decimal points will follow the same logic as above.

- The LOQ will be used to calculate descriptive statistics if the datum is reported in the form of "≤ x" or "≥ x" (where x is considered the LOQ).

If methods 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.

Sparse PK concentration values that are below the limit of quantitation (BLQ) will be presented as "BLQ" in the data listing.

Natural logarithm transformation will be used for analyzing concentrations and PK parameters in intensive PK samples. Concentration values that are 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 at postdose time points for summary purposes. The following conventions will be used for the presentation of summary and order statistics for intensive PK concentrations:

- 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) will be displayed as "BLQ."

PK parameters that are BLQ will be excluded from 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 first dosing date of study drug and derived as follows:

- For postdose 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.

3.8.2. Analysis Visit Windows

The nominal visit as recorded on the CRF will be used when data are summarized by visit. 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 the 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.

3.8.3. Selection of Data in the Event of Multiple Records in an Analysis Visit 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, nonmissing measurements 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 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 electrocardiogram [ECG] findings) for categorical data.

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

A summary of subject enrollment will be provided by treatment group 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 dose cohort. The summary will present the number of subjects in each of the following categories:

- Screened
- Enrolled
- DLT Analysis Set
- Safety Analysis Set
- Full Analysis Set
- GS-1423 completion status
  - Completed study drug dosing as specified per protocol
  - Discontinued study drug dosing with reasons
- Study completion status
  - Completed the protocol-planned duration of the study
  - Discontinued the study with reasons

For the status of study drug and study completion and reasons for discontinuation, 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.

The following by-subject listing will be provided by subject identification (ID) number in ascending order to support the above summary tables:

- Reasons for premature study drug or study discontinuation
- Reasons for screen failure (will be provided by screening ID number in ascending order)

4.2. Extent of Study Drug Exposure

Extent of exposure to study drug will be examined by assessing the total duration of exposure to study drug, total number of doses, and the actual dose amount.

4.2.1. Exposure to GS-1423

A listing of GS-1423 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 that entire dose was delayed or not administered. Exposure to GS-1423 will be summarized by cohort for the safety analysis set.

4.2.1.1. Duration of Exposure

Total duration of exposure to study drug will be defined as (last dosing date - first dosing date + 1)/7, regardless of any 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 date is missing, the latest date among the study drug end date, clinical visit date, laboratory sample collection date, and vital signs assessment date that occurred during the on-treatment period will be used.

The total duration of exposure to study drug will be summarized using descriptive statistics. Summaries will be provided by treatment group for the Safety Analysis Set. The number and percentage of subjects who have dose interruptions, and the reasons, will be summarized by treatment.

4.2.1.2. Number of Doses

The number of doses subjects were exposed to study drug will be summarized using descriptive statistics, as well as the number and percentage of subjects exposed to the following number of doses: ≥1, ≥2, ≥4 , ≥6, ≥8, ≥10 dose(s). A subject is said to have received a dose of GS-1423 if he/she received any amount of the planned dose of GS-1423.

4.2.1.3. Actual Dose Amount

In addition, the total and average actual dose amount received for GS-1423 in mg will be summarized using descriptive statistics (N, mean, StD, median, Q1, Q3, minimum, and maximum). The average actual dose amount of GS-1423 is defined as (total actual dose amount received in mg) / (number of doses given), regardless of whether the doses were interrupted/completed.

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 treatment group 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 cohorts for the All Enrolled Analysis Set. A by-subject listing will be provided for those subjects with important protocol deviation.

4.4. Assessment of COVID-19 Impact

This study was ongoing during the novel coronavirus (COVID-19) pandemic which has an impact on the study conduct. Some subjects were unable to attend onsite visits due to shelter in place guidelines, site closures, or other reasons. This section describes how special situations due to COVID-19 will be handled in the analysis.

4.4.1. Study Drug or Study Discontinuation Due to COVID-19

A by-subject listing of reasons for premature study drug or study discontinuation due to COVID-19 will be created.

4.4.2. Protocol Deviations Due to COVID-19

A by-subject listing will be provided for subjects with important protocol deviation related to COVID-19. A separate listing will be provided for subjects with non-important protocol deviation related to COVID-19.

4.4.3. Missed and Virtual Visits Due to COVID-19

A by-subject listing of subjects with missed or virtual visits due to COVID-19 will be provided by subject ID number in ascending order.

Information regarding virtual or missed visits due to COVID-19 was collected as free text in the CRF comment fields. The determination of missing or virtual visits due to COVID-19 was done using Natural Language Processing (NLP) to search the CRF comment fields. A detailed explanation of the algorithm is given in Appendix 3.

4.4.4. Adverse Events Due to COVID-19

AEs of COVID-19 will be included in analyses of AEs if applicable, which will be determined through COVID-19 SMQ broad search (Appendix 2). A by-subject listing of AEs of COVID-19 will be provided if applicable.

5. BASELINE CHARACTERISTICS

5.1. Demographics and Baseline Characteristics

Subject demographic variables (ie, age, sex, race, and ethnicity) and baseline characteristics (body weight [in kg], height [in cm], body mass index [BMI; in kg/m^2], Eastern Cooperative Oncology Group (ECOG) Performance Status at baseline) will be summarized by dosage cohort and overall using descriptive statistics for continuous variables and using number and percentage of subjects for categorical variables. The ECOG status at baseline is the ECOG status at screening. The summary of demographic data will be provided for the Safety Analysis Set.

A by-subject demographic listing, including the informed consent date, will be provided by subject ID number in ascending order. A by-subject baseline characteristics will also 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).

A by-subject listing of disease-specific medical history and general medical history will be provided by subject ID number in ascending order. General medical history will not be coded.

5.3. Prior Anti-cancer Therapy and Radiotherapy

Number of prior regimens, time since the completion of last regimen, and time since progression in the last regimen will be summarized by treatment group using descriptive statistics based on the Safety Analysis Set.

Time since the completion of last regimen (months) will be calculated by (first dosing date of study drug – date of completion of last regimen) /30.4375. Time since progression of last regimen (months) will be calculated by (first dosing date of study drug – date of progression in last regimen)/30.4375. In deriving the time since the completion of last regimen and time since progression in the last regimen, all partial dates of last regimen will be identified, and the partial dates will be imputed as follows:

- If day and month are missing but year is available, then the imputed day and month will be 01 January.
- If day is missing but the month and year are available, then the imputed day will be the first day of the month.
- Partial date will not be imputed if the year is missing.

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

The details of prior radiotherapy and surgery will also be listed.

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.

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CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

CCI [redacted]

[redacted]

7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

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 CTCAE Version 5.0. The severity grade of events for which the investigator did not record will be categorized as "missing" for tabular summaries and data listings. The missing category will be listed last in summary presentation.

7.1.3. Relationship of Adverse Events to Study Drug

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 relationship to study drug will be considered related to study drug for summary purposes. However, by-subject data listings will show the relationship as missing from that captured on the CRF.

7.1.4. Serious Adverse Events

Serious adverse events (SAEs) will be identified and captured as SAEs if the AEs met the definitions of SAEs that were specified in the study protocol. SAEs captured and stored in the clinical database will be reconciled with the SAE database from the Gilead Global Patient Safety Department before data finalization.

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as 1 or both of the following:

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

7.1.5.2. Incomplete Dates

All AEs with incomplete onset dates will be imputed for TEAE determination. The imputation rules are as follows:

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

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

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

7.1.6. Summaries of Adverse Events and Deaths

Treatment-emergent AEs will be summarized based on the Safety Analysis Set.

7.1.6.1. Summaries of AE Incidence by Severity

A brief, high-level summary of number and percentage of subjects who experienced the following TEAEs will be provided by treatment group:

- Any TEAE;

- Any grade 1 or 2 TEAE;

- Any grade 3 or 4 TEAE;

- Any TEAE related to GS-1423;

- Any grade 1 or 2 TEAE related to GS-1423;

- Any grade 3 or 4 TEAE related to GS-1423;

- Any TE SAE;

- Any grade 1 or 2 TE SAE;

- Any grade 3 or 4 TE SAE;

- Any TEAE leading to death;

- Any TE SAE related to GS-1423;
- Any TEAE leading to premature discontinuation of GS-1423;
- Any TEAE leading to temporary interruption of GS-1423;
- Any grade 1 or 2 TEAE leading to temporary interruption of GS-1423;
- Any grade 3 or 4 TEAE leading to temporary interruption of GS-1423;
- Any dose limiting toxicity

For the AE categorizes described below, the number and percentage of subjects who experienced at least 1 TEAE summaries will be provided by SOC, PT, maximum severity, and treatment group:

- TEAEs
- TE treatment related AEs

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

- TEAEs
- TEAEs with Grade 3 or higher
- TE treatment-related AEs
- TE Treatment-related AEs with Grade 3 or higher
- TE SAEs
- TE treatment-related SAEs
- TEAEs leading to premature discontinuation of GS-1423
- TEAEs leading to temporary interruption of GS-1423
- TEAEs leading to deaths

The above TEAEs excluding TEAEs leading to deaths will also be summarized by PT only in descending order of total frequency. Additionally, all TEAEs will be summarized by PT and severity.

Multiple events will be counted only once per subject in each summary. Adverse events will be summarized and listed first in alphabetic order of SOC and then by PT in descending order of

total frequency within each SOC. For summaries by severity, the most severe severity will be used for those AEs that occurred more than once in a given subject during the study.

In addition, data listings will be provided for the following:

- All AEs, indicating whether the event is treatment emergent and related to study drug
- All AEs with Grade 3 or higher
- All SAEs
- All AEs leading to death
- All AEs leading to premature discontinuation of study drug
- TEAEs leading to temporary interruption of study drug

7.1.6.2. Summary of Deaths

A summary (number and percentage of subjects) of deaths will be provided by treatment group and overall, with the cause of the death (AE, PD, or other reasons). The summary will include the following categories:

- All deaths
- Deaths within 30 days of the last dosing of study drug
- Deaths after 30 days of the last dosing of study drug

A list of all deaths with primary cause of death will be provided.

7.1.6.3. 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 the investigator as well as CTCAE term and associated severity grade, if available.

A summary of DLT will be presented by PT.

Late onset AEs meeting DLT definition occurring beyond the 28-day DLT observation period will be listed and summarized by PT as well.

7.2. Laboratory Evaluations

CCI [redacted]

CCI

[redacted]

CCI [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

CCI [redacted]

[redacted]

CCI [redacted]

7.2.2.1. Treatment-Emergent Laboratory Abnormalities

Treatment-emergent laboratory abnormalities are defined as values that increase at least 1 toxicity grade from baseline at any postbaseline time point, up to and including the date of last dose of study drug plus 30 days subjects who permanently discontinued study drug. If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment emergent.

7.2.2.2. Summaries of Laboratory Abnormalities

The summaries (number and percentage of subjects) for treatment-emergent laboratory abnormalities will be provided by lab test and dose cohort; subjects will be categorized according to the most severe postbaseline abnormality grade for a given lab test:

- Graded TE laboratory abnormalities
- TE Grade 3 or 4 laboratory abnormalities

For all summaries of laboratory abnormalities, the denominator is the number of subjects with nonmissing postbaseline values up to 30 days after the last dosing date.

A by-subject listing of treatment-emergent Grade 3 or 4 laboratory abnormalities will be provided by subject ID number and visit in chronological order. This listing will include all test results that were collected throughout the study for the lab test of interest, with all applicable severity grades displayed.

7.3. Body Weight, Body Mass Index and Vital Signs

Descriptive statistics will be provided by dose cohort for body weight, body mass index (BMI) and vital signs as follows:

- Baseline value
- Postbaseline maximum value
- Postbaseline minimum value
- Change and percentage change from baseline to postbaseline maximum value
- Change and percentage change from baseline to postbaseline minimum value

A baseline value will be defined as the last available value collected on or prior to the date/time of first dose of study drug. Weight, BMI and each vital signs measurement (including

temperature, pulse, respiratory rate, and blood pressure) will be summarized. Change from baseline to a postbaseline visit will be defined as the postbaseline value minus the baseline value.

In the case of multiple values in an analysis window, data will be selected for analysis as described in Section 3.8.3. No formal statistical testing is planned.

A by-subject listing of vital signs will be provided by subject ID number and visit in chronological order. Body weight and BMI will be included in the vital signs listing, if space permits. If not, they will be provided separately.

7.4. Prior and Concomitant Medications

Medications collected at screening and during the study will be coded using the current version of the World Health Organization (WHO) Drug dictionary.

7.4.1. Prior Medications

Prior medications are defined as any medications taken before a subject was administered the first dose of study drug.

Prior 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 dose cohort and overall. A subject reporting the same medication more than once will be counted only once within each ATC drug class when calculating the number and percentage of subjects who received that medication. [Medications may appear under multiple ATC drug classes.] The summary will be ordered alphabetically by ATC medical class and then by preferred term in order of descending overall frequency within each ATC medical class. For drugs with the same frequency, sorting will be done alphabetically.

For the purposes of analysis, any medication with a start date prior to the first dosing date of study drug will be included in the prior medication summary 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 included in the prior medication summary, unless otherwise specified.

Summaries will be based on the Safety Analysis Set. No formal statistical testing is planned.

7.4.2. Concomitant Medications

Concomitant medications are defined as medications taken while a subject took study drug. Use of concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) classification Level 2 (therapeutic subgroup) and preferred name using the number and percentage of subjects for each dose cohort and overall. A subject reporting the same medication more than once within each ATC drug class will be counted only once when calculating the number and percentage of subjects who received that medication. Medications may appear under multiple ATC drug classes. The summary will be ordered alphabetically by ATC classification

and by preferred term in descending overall frequency within each ATC classification. For drugs with the same frequency, sorting will be performed alphabetically.

For the purposes of analysis, any medications with a start date prior to or on the first dosing date of study drug and continued to be taken after the first dosing date, or started after the first dosing date but prior to or on the last dosing date of study drug will be considered concomitant medications. 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 prior to the date of first dosing date of study drug or a start date 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, unless otherwise specified. Summaries will be based on the Safety Analysis Set. No formal statistical testing is planned.

All prior and concomitant medications (other than per-protocol study drugs) will be provided in a by-subject listing sorted by subject ID number and administration date in chronological order.

7.5. Electrocardiogram 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. Investigator assessment of ECG readings and ECG data will be provided for the Safety Analysis Set for each scheduled time point. No formal statistical testing is planned.

7.5.1. Investigator Electrocardiogram Assessment

A shift table of the investigators' assessment of ECG results at worst outcome during study compared with baseline values will be presented by dose 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. Subjects with a missing value at baseline or postbaseline will not be included in the denominator for percentage calculation. No formal statistical testing is planned.

A by-subject listing for ECG assessment results will be provided by subject ID number and visit 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

QTcF will be listed by-subject.

7.6. Other Safety Measures

No additional safety measures are specified in the protocol.

7.6.1. Post Treatment Anti-cancer Therapies

All post treatment anti-cancer therapies will be provided in a by-subject listing sorted by subject ID number and administration date in chronological order.

7.7. Echocardiogram

A by-subject listing will be provided for echocardiogram and multigated acquisition (MUGA) scan results by subject ID number and visit/time point in chronological order.

7.8. Changes From Protocol-Specified Safety Analyses

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

8. PHARMACOKINETIC (PK) ANALYSES

8.1. PK Sample Collection

Blood samples will be collected to measure concentrations and to estimate PK parameters of GS-1423 at protocol specified time points.

8.2. Statistical Analysis Methods

8.2.1. GS-1423 Plasma Concentration

Plasma concentration for GS-1423 will be summarized using descriptive statistics (n, arithmetic mean, StD, coefficient of variation [%CV], median, min, max, Q1, Q3, geometric mean and 95% CI) for subjects in the PK Analysis Set by sampling 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.

The following table will be provided by dose level:

- Individual subject concentration data and summary statistics

The following figures may be provided by dose level:

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

GS-1423 plasma concentration data and PK sampling details will be listed for all subjects in the PK Analysis Set. Mean and median postdose concentration values that are ≤ LOQ, if any, will not be displayed in the figures and remaining points connected.

8.2.2. GS-1423 PK Parameters

For subjects in Phase 1a Part A, relevant PK parameters will be estimated using Phoenix WinNonlin® software and utilizing standard noncompartmental methods. The linear up log down 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-1423 by dose level/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-1423 presented in Table 2 will be computed for all subjects in the PK Analysis Set using profiles from Cycle 1 [predose through Cycle 2 predose (Cycle 1 Day 15)] and Cycle 4 [predose through Cycle 5 predose (Cycle 4 Day 15)], as applicable.

Table 2. PK Parameters for GS-1423

Analyte	Parameters
GS-1423	AUC_{tau}, C_{max}, C_{trough}, T_{max}, CLss, Vss, C_{last}, T_{last}, AUC_{last}, AUC_{tau}/Dose, C_{max}/Dose, and C_{trough}/Dose, if applicable

Individual subject PK parameter data will be listed and summarized using descriptive statistics (n, arithmetic mean, StD, coefficient of variation [%CV], median, min, max, Q1, Q3, geometric mean, 95% CI, mean and StD of the natural log-transformed values) for 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-1423 by dose cohort.

Individual data on determination of half life and corresponding intra-subject correlation coefficient will be listed.

9. IMMUNOGENICITY ANALYSES

9.1. ADA Sample Collection

Plasma samples will be collected to measure anti-drug antibody (ADA) against GS-1423 at protocol specified time points.

9.2. Statistical Analyses Methods

Immunogenicity data will be summarized for all subjects by different dose cohorts and across dose cohorts in the Immunogenicity Analysis Set. Immunogenicity of GS-1423 will be evaluated based upon the incident of ADA. The number and proportion of subjects exhibiting positive ADA status, defined as ADA presence in plasma confirmed in validated assay and reported by bioanalytical laboratory, will be summarized at each specified time point. The number and proportion of subjects exhibiting positive ADA status at any post-baseline time point will also be summarized.

A by-subject listing for ADA status at each time point, along with treatment, nomimal sampling day, actual date and time of sampling, and reason of sample not collected and titer for subjects with positive ADA status will be provided by subject ID number and time point in chronological order.

CCI [redacted]

[redacted]

11. REFERENCES

Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0, U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute, 27 November 2017.
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

12. SOFTWARE

SAS® Software Version 9.X. SAS Institute Inc., Cary, NC, USA.

13. APPENDICES

Appendix 1. Schedule of Assessments

Study Procedures Table for Q2W/Q3W Dosing Schedule

	Screening	Treatment Phase (For Q2W and Q3W Dosing Schedules)								End-of-Treatment		Posttreatment Follow-up[a]			Survival Follow-up
		Cycle 1			Cycle 2			Every Subsequent Odd Cycle	Every Subsequent Even Cycle	End-of-Treatment Visit	30-Day Follow-up	Visit 1	Visit 2	Visits 3 and 4	
Visits Schedule (days)		**1**	**2**	**8**	**1**	**2**	**8**	**1**	**1**	**At End-of-Treatment**	**30d from last dose**	**3m from last dose**	**6m from last dose**	**3m from last visit**	**3m from last visit**
Schedule Window (days)[b]		**+ 2**			**+ 2**			**+ 2[aa]**	**+ 2[aa]**	**≤ 7**	**± 7**	**± 7**	**± 7**	**± 7**	**± 7**
Administrative Procedures	**< -28 days**														
Informed consent	X														
Review of inclusion/exclusion criteria	X	X													
Issue Emergency Medical Support and Subject Card	X														
Review of medical history and demographics	X														
Review of baseline symptoms	X	X													
Review of prior and concomitant medications	X	X	X	X	X	X	X	X	X	X	X				
Cancer disease details and prior treatment	X														
Subsequent anticancer therapy status										X	X	X	X	X	
Clinical Procedures/Assessments	**< -7 days**														
Review AEs[c]	X	X	X	X	X	X	X	X	X	X	X				
Full Physical Examination	X									X					
Focused Physical Examination		X[d]			X			X	X		X	X	X	X	
Vital Signs, Weight and Height[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG[f]	X	X[f]	X[f]	X[f]				X		X	X				
Echocardiogram or MUGA[g]	X[g]							X							
ECOG Performance Status[d]	X	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	
Imaging Assessments[h]	**< -28 days**														
Tumor Imaging[h]	X	Every 6 weeks (± 7 days) the first 4 assessments then see footnote.													

	Screening	Treatment Phase (For Q2W and Q3W Dosing Schedules)								End-of-Treatment		Posttreatment Follow-up[a]			Survival Follow-up
		Cycle 1			Cycle 2			Every Subsequent Odd Cycle	Every Subsequent Even Cycle	End-of-Treatment Visit	30-Day Follow-up	Visit 1	Visit 2	Visits 3 and 4	
Visits Schedule (days)		1	2	8	1	2	8	1	1	At End-of-Treatment	30d from last dose	3m from last dose	6m from last dose	3m from last visit	3m from last visit
Schedule Window (days)[b]		+ 2			+ 2			+ 2[aa]	+ 2[aa]	≤ 7	± 7	± 7	± 7	± 7	± 7
Laboratory Procedures/Assessments[i]	< -28 days														
Blood for PK Assays[j]		X									X	X			
Blood for ADA Assays[k]		X									X	X			
CCI															
Blood for pharmacogenomics	X[p]														
CCI															
CCI															
Collection of required pretreatment biopsy (Phase 1b Cohort 2)[z]	X														
CCI															
Collection of required on-treatment biopsy (Phase 1b Cohort 2)[y]								X							
CCI															
Serum chemistry[t]	X	X[d]		X	X		X		X	X	X	X			
Hematology tests[t]	X	X[d]		X	X		X	X	X	X	X	X			
Coagulation tests[t]	X				X		X	X		X	X	X			
Endocrine function tests[t]	X				X		X	X		X	X	X			
Hepatitis Serology	X														
Urinalysis[t]	X			X	X		X	X		X	X	X			
Serum pregnancy test	X[u]														
Urine pregnancy test[v,bb]		X[u]						X		X	X	X	X[bb]		

	Screening	Treatment Phase (For Q2W and Q3W Dosing Schedules)								End-of-Treatment		Posttreatment Follow-up[a]			Survival Follow-up
		Cycle 1			Cycle 2			Every Subsequent Odd Cycle	Every Subsequent Even Cycle	End-of-Treatment Visit	30-Day Follow-up	Visit 1	Visit 2	Visits 3 and 4	
Visits Schedule (days)		1	2	8	1	2	8	1	1	At End-of-Treatment	30d from last dose	3m from last dose	6m from last dose	3m from last visit	3m from last visit
Schedule Window (days)[b]		+ 2			+ 2			+ 2[aa]	+ 2[aa]	≤ 7	± 7	± 7	± 7	± 7	± 7
HER2 Testing[cc]	X														
Study drug administration															
GS-1423 (All cohorts)[w]		X			X			X	X						
mFOLFOX6 (Phase 1b Cohort 1)[x]		X			X			X	X						
CCI															

5-FU = 5-fluorouracil; ADA = anti-drug antibody against GS-1423; AEs = adverse events; CRF = case report form; ECG = electrocardiogram; eCRF = electronic case report form; ECOG = Eastern Cooperative Oncology Group; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; ISH = in situ hybridization; MUGA = multigated acquisition; PBMC = peripheral blood mononuclear cell; PD = progressive disease; PK = pharmacokinetics; Q2W = every 2 weeks; Q3W = every 3 weeks; SAE = serious adverse event

Note: Where applicable, assessments are to be performed prior to treatment unless otherwise indicated.

a All subjects who discontinue treatment will have at least one 30-Day Follow-up Visit 30 days (± 7 days) from last treatment dose. Subjects who discontinue due to PD and/or start of a new line of therapy will then enter the Survival Follow-up Period for up to 12 months for survival status. Subjects who have discontinued treatment due to reasons other than PD and/or start of a new line of therapy will be in Posttreatment Follow-up for up to approximately 12 months from last treatment dose or until PD and/or start of a new line of therapy. Every effort should be made to collect subject information on the start of new anticancer therapy, PD, and death.

b Treatment administration and associated procedures for that visit may be delayed for treatment-related AEs beyond the window and subsequent schedule adjusted accordingly.

c After informed consent, but prior to initiation of study medication, the following types of events should be reported on the case report form (CRF/eCRF): all SAEs and AEs related to protocol-mandated procedures.

d 72-hour window for C1D1 physical examination, safety labs, and ECOG performance status collection.

e Vital signs will only be measured while subject is in seated or semi-recumbent position. Height only collected at screening. Phase 1a and Phase 1b (Cohort 2): Vital signs are to be measured prior to each infusion commencing, at the end of each infusion, and for the first 2 cycles, 1 hour (± 15 minutes) after the end of the GS-1423 infusion. Thereafter, the final vital signs can be taken 30 minutes (-10/+20 minutes) after the end of each GS-1423 infusion. Subjects will remain in the clinic under close supervision for the duration of this monitoring period. Phase 1b (Cohort 1): Additional vital signs for subjects being administered the mFOLFOX6 regimen will be measured as per standard institutional guidelines.

f 12-lead ECG on Cycle 1 Day 1, before and 2 hours (-10/+20 minutes) after GS-1423 administration; on subsequent cycles, 12-lead ECG will be collected every odd cycle, on Day 1, at end of GS-1423 infusion(-10/+20 minutes), or as indicated. For subjects in Cohorts 5 through 8 and Cohort 10, a triplicate ECG will be performed at Cycle 1, Day 1 predose, at end of infusion, at 24 hours postdose (Day 2), and 168 hours postdose (Day 8).

g Complete echocardiogram assessment will be conducted at screening to determine baseline (may be done within 14 days prior to the first dose of study treatment); and at every odd cycle, on Day 1, starting at Cycle 3 (±3 days). A MUGA scan is allowed.

h The initial tumor imaging will be performed within 28 days prior to first dose. Scans performed as part of routine clinical management are acceptable for use as screening scan if they are of diagnostic quality and < -28 days prior to first dose. On-study imaging will be performed at 6, 12, 18, and 24 weeks (± 7 days) from first treatment dose and then every 12 weeks thereafter. Imaging assessments will continue until PD as assessed by the investigator, unexpected toxicity occurs, or a new line of therapy is initiated for up to 1 year (Phase 1a and Phase 1b Cohort 2) or 2 years (Phase 1b Cohort 1. The timing of on-study treatment imaging should follow calendar days and should not be adjusted for delays in treatment administration or for visits. The same imaging technique should be used in a subject throughout the study. In general, lesions detected at baseline should be followed using the same imaging methodology and preferably the same imaging equipment at subsequent tumor evaluation visits.

i Unless otherwise specified, samples should be collected before treatment administration. Refer to the Laboratory Manual for instructions and additional information.

j PK Assays: Refer to Section 6; Table 6-3, Table 6-4, Table 6-5 and Table 6-6 in the body of the protocol.

k ADA Assays: Refer to Section 6; Table 6-9 and Table 6-10 in the body of the protocol.

l Not applicable (This footnote is obsolete with Amendment 1.)

m Not applicable (This footnote is obsolete with Amendment 1.)

n Not applicable (This footnote is obsolete with Amendment 1.)

[redacted]

p Blood pharmacogenomics sample collected from enrolled subject before or at C1D1, predose. If the sample is missed, it can be taken later on in the study.

[redacted]

t Laboratory tests for screening should be performed within 28 days prior to the first dose of study treatment. After Cycle 1, predose laboratory procedures can be conducted up to 72 hours prior to dosing.

u Serum β-human chorionic gonadotropin (β-HCG) pregnancy test for women of childbearing potential at screening within 72 hours of first treatment dose (if performed earlier in screening period, then a urine pregnancy test may be performed prior to first dose); urine pregnancy test at all other indicated visits; results must be available prior to dosing.

v Urine pregnancy results to be obtained on site.

w GS-1423 should be administered intravenously within 60 minutes (-10/+20 minutes). Subjects must be observed for 1 hour postinfusion for infusion-related reaction for the first 2 cycles and thereafter, 30 minutes after the end of the GS-1423 infusion. If administration of GS-1423 is delayed due to an AE, treatment visits may be delayed beyond the window of 3 days and schedules for subsequent visits should be adjusted accordingly.

x The mFOLFOX6 regimen consists of leucovorin 200 mg/m^2 and oxaliplatin 85 mg/m^2 followed by bolus 5-FU 400 mg/m^2 and a 46-hour infusion of 5-FU 2400 mg/m^2. Administration of mFOLFOX6 will immediately follow administration of GS-1423 on Day 1 of each cycle. The chemotherapy regimen mFOLFOX6 will be administered Q2W for up to 12 cycles (6 months). After 12 cycles, subjects may continue to receive 5-FU and leucovorin at the investigator's discretion until the subject meets study treatment discontinuation criteria.

y Required on-treatment biopsy should be collected at C3D1 or up to 1 week prior on Q2W treatment cycle.

z Required pretreatment biopsy must be obtained prior to C1D1 on a tumor from which 2 biopsies can be obtained (1 pretreatment and 1 on treatment).

aa Treatment Phase visit window starting at Cycle 4 until End of Treatment is ± 2 days.

bb This will only be performed for subjects receiving mFOLFOX6. Urine pregnancy tests will be performed at 4 months and 6 months after the last dose of mFOLFOX6.

cc For subjects in Phase 1b Cohort 1 (gastric cohort) tumor tissue will be tested for HER2 status, if unknown, with an approved IHC and ISH kit.

CCI [redacted]

Appendix 2. COVID-19 SMQ with Broad Scope

Note: The list presented below is based on MedDRA Version 23.1. The actual list will be up-versioned to the MedDRA version used at the time of database finalization.

MedDRA Preferred Term	PT Code
Asymptomatic COVID-19	10084459
Coronavirus infection	10051905
Coronavirus test positive	10070255
COVID-19	10084268
COVID-19 immunisation	10084457
COVID-19 pneumonia	10084380
COVID-19 prophylaxis	10084458
COVID-19 treatment	10084460
Exposure to SARS-CoV-2	10084456
Multisystem inflammatory syndrome in children	10084767
Occupational exposure to SARS-CoV-2	10084394
SARS-CoV-2 antibody test positive	10084491
SARS-CoV-2 carrier	10084461
SARS-CoV-2 sepsis	10084639
SARS-CoV-2 test false negative	10084480
SARS-CoV-2 test positive	10084271
SARS-CoV-2 viraemia	10084640
Suspected COVID-19	10084451
Antiviral prophylaxis	10049087
Antiviral treatment	10068724
Coronavirus test	10084353
Coronavirus test negative	10084269
Exposure to communicable disease	10049711
Pneumonia viral	10035737
SARS-CoV-2 antibody test	10084501
SARS-CoV-2 antibody test negative	10084509
SARS-CoV-2 test	10084354
SARS-CoV-2 test false positive	10084602
SARS-CoV-2 test negative	10084273

Appendix 3. Determining Missing and Virtual Visits Due to COVID-19

This appendix describes the clinical trial site collection of COVID-19 data pertaining to missed/virtual visits and the data processing algorithm used to determine which visits were missing and which visits were virtual.

Data collection

A COVID-19 supplement to the eCRF Completion Guidelines (CCG) was provided by data management to instruct clinical trial sites with respect to data entry expectations pertaining to scenarios related to the COVID-19 pandemic. If a visit was missed, sites should enter "Visit missed due to COVID-19." If an in-person visit was conducted virtually, sites should enter "Virtual visit due to COVID-19."

Determination of Missed and Virtual visits

NLP was used to search the CRF comment fields to identify instances of "COVID-19" (or synonyms, see the table below) and "Virtual" (or synonyms, see the table below). The search terms are maintained in a global lookup table and can be modified to tune the NLP model. For any comments with COVID-19 search terms, assign "Missed visit" or "Virtual visit" as follows:

i. If COVID-19 terms are identified through NLP and the visit date is missing, then result is "Missed Visit"

ii. If COVID-19 and Virtual terms are identified through NLP for a visit, then result is "Virtual Visit". When there are multiple records for the same subject and the same visit, NLP will be based on multiple records to ensure 1 unique category per subject per visit

iii. Otherwise result is missing

Examples of Search Terms for "COVID-19" and "Virtual" Used to Identify Missed and Virtual Visits

Search Terms for "COVID-19"	Search Terms for "Virtual"
COVID19	VIRTUAL
CORONA	TELEMED
CORONAVIRUS	TELEHEALTH
PANDEMIC	TELEPHONE
OUTBREAK	REMOTE
CRISIS	TELEMEDICINE
LOCKDOWN	TELECONSULTATION
QUARANTINE	TELEPHONICALLY
SHELTER	PHONE
	HOME VISIT
	ZOOM
	SKYPE

Appendix 4. List of laboratory Tests for Safety Summary

Chemistry	Urinalysis	Hematology	Other
Albumin Alkaline phosphatase ALT AST Bicarbonate BUN/total urea Calcium Chloride Serum Creatinine[a] CRP GGT Glucose LDH Lipase Cholesterol Tryglycerides Amylase Magnesium Phosphorus/phosphates Potassium Sodium Total bilirubin[b] Direct bilirubin Total protein Uric acid	Color and appearance Specific gravity pH Occult blood Protein Glucose Bilirubin Leukocyte esterase Nitrite Urobilinogen Ketones Microscopic[b]	WBC and differential absolute count Eosinophils Lymphocytes Monocytes ANC Hemoglobin Hematocrit Platelet count MCV RBC **Coagulation** Prothrombin time (INR) aPTT	Serum β-hCG or urine pregnancy test[c] Endocrine Function Tests (TSH and freeT4[d]) Basal cortisol Hepatitis Serology[b]

β-hCG = beta-human chorionic gonadotropin; ALT = alanine aminotransferase; ANC = total absolute neutrophil count; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CRP = C-reactive protein; Free T4 = free thyroxine; GGT = gamma-glutamyltransferase; INR = international normalized ratio; LDH = lactate dehydrogenase; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; RBC = red blood cell; PT = prothrombin time; TSH = thyroid-stimulating hormone; WBC = white blood cell

a Estimated creatinine clearance (CL_{cr})/glomerular filtration rate will be calculated based on the Cockcroft-Gault formula using actual body weight: CL_{cr} (mL/min) = (140 – age [years])* weight (kg) / (serum creatinine [mg/dL]*72). If the subject is female, multiply the quantity by 0.85.

b Reflex testing based on other abnormalities

c Females of childbearing potential only. Serum pregnancy will be conducted at screening within 72 hours of first treatment dose (if performed earlier in screening period then a urine pregnancy test may be performed prior to first dose); urine pregnancy test at all other indicated visits.

d TSH and free T4 will be tested by the central laboratory. T4 will be tested reflexively based on abnormal TSH results.

GS-US-505-5452 SAP

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Research eSigned	16-Jul-2021 14:59:14
PPD	Biostatistics eSigned	20-Jul-2021 07:05:40