STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 1b/2 Dose Escalation/Expansion Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of GS-4224 in Subjects with Advanced Solid Tumors
Name of Test Drug:	GS-4224
Study Number:	GS-US-494-5484
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CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

AE	adverse event
BID	twice daily
cHL	Classical Hodgkin lymphoma
CTCAE	Common Terminology Criteria for Adverse Events
CSR	Clinical Study Report
CPS	combined positive score
DLT	dose limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
HCC	Hepatocellular carcinoma
HLGT	high-level group term
HLT	high-level term
irAE	immune-related adverse event
LLT	lower-level term
LOQ	limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MSI-H	microsatellite instability-high
MTD	maximum tolerated dose
NSCLC	non-small cell lung cancer
PD-1	programmed cell death protein 1
PK	pharmacokinetics
PT	preferred term
Q1	first quartile
Q3	third quartile
QD	once daily
RCC	renal cell carcinoma
RECIST v1.1	RECIST v1.1 Response Evaluation Criteria in Solid Tumors Version 1.1
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SE	standard error
SOC	system organ class
SRT	safety review team
StD	standard deviation
TPS	Tumor proportion score

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
CLss/F	apparent oral clearance after administration of the drug: at steady state: CLss/F = Dose/AUC_{tau} , where "Dose" is the dose of the drug
$t_{1/2}$	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}
λ_z	terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the concentration of drug versus time curve

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 clinical study report (CSR) for Study GS-US-494-5484. This SAP is based on the study protocol amendment 5.0 dated 02 October 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 originally designed to evaluate the safety, tolerability, Pharmacokinetics (PK), and efficacy of GS-4224 monotherapy in 2 stages: (1) Phase 1b dose-escalation in advanced solid tumors; and (2) Phase 2 dose expansion in select advanced solid tumors expressing ligand 1 of programmed cell death protein 1 (PD-L1) [tumor proportion score (TPS) $\geqslant$ 1% or combined positive score (CPS) $\geq$ 1 or $\geq$ 10] or MSI-H cancers. The study was early terminated during Phase 1b dose escalation part due to lack of objective clinical efficacy in patients dosed in Phase 1b dose-escalation. The Phase 2 part of the study was not be initiated. Subjects currently on study will continue to be treated and/or followed until the end of study criteria are met. The SAP describes the analyses based on the Phase 1b data collected in the study only for a synoptic CSR.

1.1. Study Objectives

1.1.1. Primary Objectives

Phase 1b Dose Escalation

- To characterize the safety and tolerability of GS-4224 in subjects with advanced solid tumors
- To determine the maximum tolerated dose (MTD) or recommended Phase 2 dose (RP2D) of GS-4224 in subjects with advanced solid tumors

1.1.2. Secondary Objectives

Phase 1b Dose Escalation

- To evaluate the pharmacokinetics (PK) of GS-4224 in subjects with advanced solid tumors

Phase 2 Dose Expansion

- To evaluate the safety and tolerability of GS-4224 in subjects with advanced solid tumors

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1.2. Study Design

GS-US-494-5484 is an open-label, multicenter, sequential dose-escalation and dose expansion study to evaluate the safety, tolerability, PK, and efficacy of GS-4224 in subjects with advanced solid tumors. The study will consist of 2 parts: the dose escalation portion, followed by dose expansion in subjects with tumors for which programmed cell death protein 1 (PD-1)/PD-L1 treatments are approved or are known to be active.

1.2.1. Dose Escalation (Phase 1b)

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 of oral GS-4224 as monotherapy.

Dose escalation will proceed using a standard 3+3 design. The starting dose is 400 mg once daily (QD), with subsequent doses of 700 mg QD, 1000 mg QD, 1500 mg QD, and 1000 mg twice daily (BID). Dose level increases are 3-fold or less.

Dose Level Schema

GS-4224 (mg)	Fold Increase
400 QD	-
700 QD	≤ 3×
1000 QD	≤ 3×
1500 QD	≤ 3×
1000 BID	≤ 3×

In the 1000 mg BID dose cohort, at least 6 (as part of the initial 3+3 design) and up to an additional 14 subjects (for a total of 20 subjects) with locally advanced, inoperable or metastatic cancer expressing PD-L1 (tumor proportion score [TPS] ⩾ 10% or combined positive score [CPS] ⩾ 10) and who have not previously been treated with anti-PD-1/L1 antibodies will be enrolled. The additional 14 subjects will not be enrolled at the 1000 mg BID dose level if the subject incidence of DLTs is > 1 in the first 6 subjects. If the subject incidence of DLTs is > 1 in the first 6 subjects at 1000 mg BID, then 20 additional subjects with locally advanced, inoperable or metastatic cancer expressing PD-L1 [TPS ⩾ 10% or CPS ⩾ 10] and who have not previously been treated with anti-PD-1/L1 antibodies will enroll at the MTD.

The initial block of each dose consists of 3 subjects. Dose escalation may occur if no subjects experience DLTs during the first 21 days of study drug dosing. If 1 subject within the initial cohort of 3 subjects experiences a DLT during the first 21 days of study drug dosing, an additional 3 subjects will be enrolled at the same dose level. If no DLTs are observed in the additional 3 subjects, dose escalation will occur. If 2 or more of the 6 subjects experience DLTs within the first 21 days, dose de-escalation to an intermediate dose will occur. The MTD is the highest dose level with a subject incidence of DLTs during the first 21 days of study drug dosing of 0 or 1 out of 6. 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 is withdrawn from the study before the completion of the first 21 days for a reason other than a DLT will be replaced.

If 2 or more delayed DLT-type adverse events (AEs) are noted after the first 21 day observation period within a dose escalation cohort, further accrual at all sites will be held pending safety analysis of the event, and will be restarted only with Investigator and Sponsor approval.

The SRT will review safety and relevant clinical data and make the dose escalation/stay/de-escalation decision. Source Data Verification (SDV) is not required to be performed prior to SRT meetings, as there will be alternative quality control checks implemented. These checks will be described in the SRT Charter.

At dose levels equal to or below the MTD, up to 6 additional subjects per dose level with biopsy accessible, PD-L1-positive (TPS ⩾ 10% or CPS ⩾ 10) tumor lesions may be enrolled in the Dose Escalation Biopsy Substudy to evaluate the tumor target occupancy of GS-4224 in posttreatment tumor biopsy samples. Up to a total of 12 subjects may be enrolled at one of the dose levels in the biopsy substudy. The biopsy substudy cohort may be opened once the dose level has been cleared by the SRT for safety.

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-4224-related toxicities and efficacy. The study is planned to enroll approximately 120 subjects.

Approximately 44 subjects will be enrolled in the dose escalation phase (Phase 1b) and approximately 36 subjects will be enrolled in the Dose Escalation Biopsy Substudy (Phase 1b).

Approximately 40 subjects will be enrolled into the Dose Expansion Cohort B1.

2. PLANNED ANALYSIS

2.1. Interim Analysis

2.1.1. Analyses for Dose Escalation Decisions

To support dose escalation decision, safety data, including DLTs and other AEs will be listed and summarized, if appropriate. Supportive data including demographic, disease history, concomitant medication, and drug administration will be listed. The analysis will occur when all subjects enrolled in a dose level have been followed for at least 21 days after the first dose of GS-4224 or two DLTs have been observed, whichever is earlier.

2.1.2. Analyses for Dose Expansion Decisions

To support dose expansion decision, available and relevant clinical data from all subjects treated in the escalation phase may be listed and summarized, if appropriate. This analysis was originally planned in the study protocol; however, it will not be done due to study early termination.

2.1.3. Primary Analysis

The study primary analysis will be conducted when all enrolled subjects have discontinued the study or have been on treatment of GS-4224 for at least 48 weeks and completed response assessment of Week 48.

This analysis was originally planned in the study protocol; however, it will not be done due to study early termination.

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.

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 dose cohort, 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 cohort to which subjects were initially assigned will be used in the listings. Age, sex at birth, race, and ethnicity information for each subject will be presented in the listings, as space permits.

3.1. Analysis Sets

Analysis sets define which subjects are 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.

3.1.1. All Enrolled Analysis Set

The 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 includes all subjects who received at least 1 dose of study treatment. It will be used in the analyses of efficacy endpoints.

3.1.3. Safety Analysis Set

The Safety Analysis Set includes all subjects who received at least 1 dose of study treatment, with treatment assignments designated according to the actual treatment received. This is the primary analysis set for the safety analyses as well as study treatment administration.

3.1.4. DLT-Evaluable Analysis Set

The DLT-Evaluable Analysis Set includes all subjects in the Safety Analysis Set who enroll to the dose escalation cohort (excluding the Dose Escalation Biopsy Substudy), complete ≥ 75% of the prescribed study treatment (ie., at least 16 of 21 doses) and have safety assessments through the protocol specified DLT assessment window (first 21 days of study dosing, inclusive) or have experienced a DLT prior to the completion of first 21 days of study dosing. Safety assessment relevant to the DLT-Evaluable Analysis Set definition will include laboratory serum chemistry tests and hematology tests as specified in the protocol. Determination of the MTD will be based on the DLT-Evaluable Analysis Set.

3.1.5. Pharmacokinetics (PK) Analysis Set

The PK Analysis Set includes subjects in the Safety Analysis Set who have received the study drug and have at least 1 sample with detectable drug concentration.

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 randomized. 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 randomized treatment only when their actual treatment differs from randomized treatment for the entire treatment duration.

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

For a subject with intra-patient dose escalation per study protocol, the subject will be grouped under the original enrolled cohort in summary tables, unless otherwise specified.

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 participant subgroupings for efficacy and safety analyses.

3.5. Multiple Comparison

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, 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 AE onset is described in Section 7.1.5.2, and for prior and concomitant medications in Section 7.4.2.

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

The following conventions will be used for the imputation of date of birth when it is partially missing or not collected:

- If only month and year of birth is collected, then "15" will be imputed as the day of birth
- If only year of birth is collected, then "01 July" will be imputed as the day and month of birth
- If year of birth is missing, then date of birth will not be imputed

In general, 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. Age required for longitudinal and temporal calculations and analyses (eg, estimates of creatinine clearance, age at date of AE) will be based on age derived from date of birth and the date of the measurement or event, unless otherwise specified

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 transformed data {or specify the transformation method, e.g., log-transformed data} or nonparametric analysis methods may be used, as appropriate.

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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 administration.

For subjects with intra-patient dose escalation per study protocol, days relative to first dose date under each dose level will be calculated and presented respectively in a listing of AEs for such subjects.

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.
- For subjects who prematurely discontinue from the study treatment, the EOT visit data will be assigned to what would have been the next scheduled visit where the respective data were scheduled to be collected.

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 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 electrocardiogram [ECG] findings) for categorical data.
- For postbaseline values:
  - The record closest to the nominal day for that visit will be selected.
  - If there are 2 records that are equidistant from the nominal day, the later record will be selected.
  - If there is more than 1 record on the selected day, 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 cohort for each country and overall based on all enrolled subjects. 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 cohort based on All Screened Subjects. This summary will present the number and percentage of subjects in the following categories:

- Screened Subjects
- All Enrolled Subjects
- Safety Analysis Set
- PK Analysis Set
- DLT-Evaluable Analysis Set
- Study Drug Completion Status
  - Completed Study Drug
  - Discontinued Study Drug
- Reasons for Discontinuation of Study Drug
- Study Completion Status
  - Completed Duration of Study
  - Discontinued Study
- Reasons for Discontinuation of Study

For the status of 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 All Enrolled Analysis Set corresponding to that column.

The following by-subject listings will be provided by cohort and subject identification (ID) number in ascending order to support the above summary table:

- Reasons for study drug or study discontinuation.

4.2. Extent of Study Drug Exposure and Adherence

Extent of exposure to study drug (GS-4224) will be examined by assessing the total duration of exposure to study drug GS-4224, the actual duration of exposure to GS-4224, and prescribed adherence to study drug. The summaries will be based the Safety Analysis Set.

4.2.1. Extent of Exposure to Study Drug

Total duration of exposure to study drug GS-4224 will be defined as last dosing date of study drug minus first dosing date plus 1, 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,

- If the study drug is permanently withdrawn, 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 for subjects included in the final analyses or the last available date in the database snapshot for subjects who were still on treatment at the time of an interim analysis.

- If the study drug completion status is unknown, the earlier of the date of death or data cut-off date for analysis will be used.

The actual duration of exposure to GS-4224 during the DLT assessment window is defined as the last dosing date minus first dosing date plus 1 within the DLT assessment window (first 21 days of study drug dosing), taking into account investigator-prescribed dose interruptions in study drug administration within the DLT assessment window. The level of prescribed adherence to the study drug GS-4224 during the DLT assessment window will be determined by the actual duration of exposure to GS-4224 relative to the total duration of exposure specified by study protocol during a subject's DLT assessment window.

4.2.2. Adherence to Study Drug

The level of prescribed adherence during the DLT assessment window will be expressed as a percentage using the following formula:

Prescribed Adherence During DLT Assessment Window (%) =

$$= \frac{\text{Actual Duration of Exposure to Study Drug During DLT Assessment Window}}{\text{Total Duration of Exposure Specified by Protocol During DLT Assessment Window}} \text{ x } 100$$

Descriptive statistics for the level of prescribed adherence with the number and percentage of subjects belonging to adherence categories (eg, $< 75\%$, $\geq 75\%$) will be provided by cohort for the Safety Analysis Set.

A by-subject listing of study drug (GS-4224) administration will be provided by cohort and subject ID number (in ascending order), including dosing date, total duration of exposure to GS-4224, actual duration of exposure, the prescribed adherence during the DLT assessment window, and reason for dose interruption.

The total duration of exposure to study drug will be summarized using descriptive statistics and using the number (ie, cumulative counts) and percentage of subjects exposed through the following time periods: 1 day, 3 weeks, 6 weeks, 9 weeks, 12 weeks, 18 weeks, and 24 weeks. Summaries will be provided by cohort for the Safety Analysis Set.

4.3. Protocol Deviations

Subjects who did not meet the eligibility criteria for study entry, but enrolled in the study will be identified regardless of whether they were exempted by the sponsor or not. 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. 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 (2019 nCOV [COVID-19]) pandemic, and the COVID-19 pandemic has caused a disruption in the regular visit schedules for this study. Some subjects were unable to attend onsite visits due to shelter in place guidelines, site closures, or other reasons. This section provides guidance on how to handle special situations due to COVID-19 in the analysis.

Adverse events (AEs) due to COVID-19 will be included in AE analyses if applicable. A by-subject listing of Adverse Events due to COVID-19 may be provided. The COVID-19

Standardized MedDRA Queries (SMQ) with Broad Scope in Appendix 1 will be implemented.

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 2.

5. BASELINE CHARACTERISTICS

5.1. Demographics

Subject demographic variables (ie, age, sex, race, and ethnicity) will be summarized for Safety Analysis Set using descriptive statistics for age, and using number and percentage of subjects for sex, race, and ethnicity.

A by-subject demographic listing, including the informed consent date, will be provided by subject ID number in ascending order for All Enrolled Analysis Set.

5.2. Other Baseline Characteristics

Other baseline characteristics include body weight (in kg), height (in cm), body mass index (BMI; in kg/m2), and ECOG status. BMI will be calculated by the formula:

$$\text{BMI (kg/m}^2\text{)} = \text{weight} / (\text{height}^2) \text{ (round to 1 decimal point).}$$

Other baseline characteristics will be summarized by cohort and overall using descriptive statistics for continuous variables and using number and percentage of subjects for categorical variables. The summary of demographic and baseline characteristics data will be provided for the Safety Analysis Set.

A by-subject listing of other baseline characteristics will be provided by subject ID number in ascending order for All Enrolled Analysis Set.

5.3. Medical History

Medical history will be collected at screening for disease-specific conditions including solid tumor malignancy status, and general conditions (i.e. conditions not specific to the disease being studied).

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

5.4. Prior Anti-Cancer Therapy

The details of prior anti-cancer therapy will be listed by cohort and subject ID number in ascending order.

5.5. Prior and On Study Radiotherapy

The details of all radiotherapy will also be listed by cohort and subject ID number in ascending order.

5.6. Surgeries and Procedures

A by-subject listing of prior and on-study surgeries and procedures will be provided by cohort and subject ID number in ascending order.

[redacted]

7. ANALYSIS OF ADVERSE EVENTS AND LABORATORY EVALUATIONS

All Adverse Events (AEs) will be listed. The focus of AE summarization will be on treatment-emergent adverse events (TEAEs). Safety analyses will be conducted using Safety Analysis Set, unless otherwise specified.

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 Medical Dictionary for Regulatory Activities (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 Terminology Criteria for Adverse Events (CTCAE) Version 5.0. 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 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 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.

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 are specified in the study protocol. SAEs captured and stored in the clinical database will be reconciled with the SAE database from then Gilead Global 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 permanent discontinuation of study drug.

7.1.5.2. Incomplete Dates

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

- The AE onset is the same as or after the month and year (or year) of the first dosing date of study drug, and
- The AE onset date is the same as or before the month and year (or year) of the date corresponding to 30 days after the date of the last dose of study drug.

An AE with completely missing onset and stop dates, or with the onset date missing and a stop date later than the first dosing date of study drug, will be considered 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.

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

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

7.1.6. Summaries of Adverse Events and Deaths

TEAEs will be summarized by cohort/dose level based on the Safety Analysis Set.

7.1.6.1. Summaries of Adverse Events Incidence by Severity

The number and percentage of subjects who experienced at least 1 TEAE will be provided and summarized by PT and severity in descending order of total frequency:

- Treatment-Emergent Adverse Events by PT and Severity

For the AE categorizes described below, summaries will be provided by PT in descending order of total frequency:

- Grade 3 or Higher Treatment-Emergent Adverse Events
- Treatment-Emergent GS-4224 related Adverse Events
- Treatment-Emergent Serious Adverse Events
- Treatment-Emergent GS-4224 related Serious Adverse Events
- Treatment-Emergent Adverse Events leading to discontinuation of GS-4224
- Treatment-Emergent Adverse Events leading to temporary interruption of GS-4224
- Treatment-Emergent Adverse Events leading to Death
- Treatment-Emergent Adverse Events leading to study discontinuation

A brief, high-level summary of AEs described above will be provided by cohort and by the number and percentage of subjects who experienced the above AEs.

For summaries of TEAEs by PT, multiple events will be counted only once per subject in each summary. Adverse events will be summarized and listed by PT in descending order of total frequency. 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, by-subject data listings will be provided by cohort and subject ID number in ascending order for the following:

- All AEs, indicating whether the event is treatment emergent
- All SAEs
- All Deaths
- All Adverse Events with Grade 3 or Higher
- All Adverse Events leading to discontinuation of GS-4224
- All Adverse Events leading to temporary interruption of GS-4224
- Adverse Events for Subject(s) with Intra-Subject Dose Escalation
- All Adverse Events leading to study discontinuation

A flag will be included in the listings to indicate whether the event is treatment emergent.

7.1.6.2. Summary of Deaths

A summary (number and percentage of subjects) of deaths will be provided by cohort. The summary will include the following categories:

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

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 date will be the 1st day of the month or the last known alive date + 1, whichever is later.

A by-subject listing of all deaths occurred during this study will be provided by cohort and subject ID number in ascending order.

7.1.7. Definition and Analysis of Dose Limiting Toxicity

Toxicity will be graded according CTCAE Version 5.0. A DLT is any toxicity specified in the study protocol occurring during the DLT assessment window (Day 1 through Day 21).

DLTs occurred within the 21-Day DLT observation period will be summarized by PT in descending order of total frequency for the DLT-Evaluable Analysis Set. Toxicities that meet the criteria of DLTs and occur beyond the first 21 days observation period (ie. DLT-type AEs) will also be summarized for the Safety Analysis Set by PT only in descending order of total frequency.

In addition, by-subject data listings will be provided by cohort and subject ID number in ascending order for the following:

- Dose Limiting Toxicities
- DLT-type AEs: toxicities that met the criteria of DLTs and occurred beyond the first 21 days observation period during study

7.2. Laboratory Evaluations

Laboratory data collected during the study will be analyzed and summarized using both quantitative and qualitative methods. Summaries of laboratory data will be provided for the Safety Analysis Set and will include data collected up to the last dose of study drug plus 30 days. 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 3.5.

A by-subject listing for all lab test results will be provided by cohort, subject ID number and time point in chronological order for hematology, serum chemistry, coagulation, endocrine function tests and urinalysis 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 formal statistical testing is planned.

7.2.1. Graded Laboratory Values

CTCAE Version 5.0 will be used to assign 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. For laboratory tests with criteria for both increased and decreased levels, analyses for each direction (ie, increased, decreased) will be presented separately.

Local labs will be graded based on central lab normal ranges with in-house macro. Baseline grade will be based on central laboratory results, unless only local labs are collected prior to the first dosing of study drug. For post-baseline grade, the worst toxicity grade considering both central and local lab results will be used for the summary of lab toxicities. All central and local laboratory values will be listed for All Enrolled Subjects.

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 postbaseline time point, up to and including the date of last dose of study drug plus 30 days for subjects who permanently discontinued study drug, or the last available date in the database snapshot for subjects who were still on treatment at the time of an analysis. A baseline laboratory value will be defined as the last measurement obtained on or prior to the date/time of first dose of 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.

7.2.1.2. Summaries of Laboratory Abnormalities

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

- TE laboratory abnormalities

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

7.3. Body Weight and Vital Signs

A by-subject listing of body weight and vital signs will be provided for All Enrolled Subjects by cohort subject ID number and visit in chronological order.

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 Drug dictionary.

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.

All prior medications (other than per-protocol study drugs) will be provided in a by-subject listing sorted by cohort, subject ID number and administration date in chronological order based on All Enrolled Analysis Set.

7.4.2. Concomitant Medications

For the purposes of analysis, concomitant medications are defined as any medications

- started 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.

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 not be considered as concomitant medication.

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

All concomitant medications (other than per-protocol study drugs) will be provided in a by-subject listing sorted by cohort, subject ID number and administration date in chronological order based on All Enrolled Analysis Set.

7.5. Electrocardiogram Results

A standard 12-lead electrocardiogram (ECG) will be performed using local standard procedures at screening and at subsequent visits as specified in Appendix 2 of the protocol.

For ECG data, 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.

A by-subject listing of 12-lead ECG will be provided for All Enrolled Subjects by cohort, subject ID number and visit in chronological order.

7.6. Other Safety Measures

Eastern Cooperative Oncology Group (ECOG) performance status is an investigator assessment of the impact of the disease on the subject's activities of daily living. ECOG assessments will be performed at the time points listed in the Study Procedures Table (Appendix 2 of the protocol).

By-subject listings will be generated for the All Enrolled Analysis Set by cohort and subject ID number in ascending order for the following safety parameters and comments:

- ECOG performance scores
- General Comments

7.7. Changes from Protocol-Specified Safety Analyses

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

8. PHARMACOKINETIC ANALYSES

GS-4224 plasma concentrations will be determined by a validated method. The PK parameters to be estimated and reported may include, but may not be limited to, maximum observed drug concentration at steady-state (C_{max}), observed concentration at the end of the dosing interval at steady-state (Ctrough), area under the concentration-time curve from time zero to the end of the dosing interval (AUC_{tau}), time to maximum observed concentration (T_{max}), systemic clearance after oral administration (CL/F), and volume of distribution after oral administration (V/F), etc. Noncompartmental (NCA) techniques will be used to analyze the PK. Compartmental modeling (eg, population pharmacokinetics [PopPK]) analysis may be conducted.

GS-4224 plasma concentrations and PK parameters (T_{max}, C_{max}, C_{trough}, AUC_{tau}, CL/F, V/F, C_{max}/Dose C_{trough}/Dose and AUC_{tau}/Dose, if applicable) for GS-4224 will be listed and summarized using descriptive statistics (eg, sample size, arithmetic mean, geometric mean, % coefficient of variation, standard deviation, median, minimum, and maximum). PK parameters will be generated based on the PK profiles observed at Cycle 1 day 1 and 15 and presented separately. CCI [redacted]

9. REFERENCES

Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. J Clin Oncol 2014.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New Response Evaluation Criteria in Solid Tumours: Revised RECIST Guideline (Version 1.1). Eur J Cancer 2009;45 (2):228-47.

10. SOFTWARE

SAS® (SAS Institute Inc. Version 9.4, Cary, NC) is to be used for all programming of tables, figures, and listings (TFLs).

11. SAP REVISION

Revision Date (DD MMM YYYY)	Section	Summary of Revision	Reason for Revision

12. APPENDICES

Appendix 1. 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 2. 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

GS-US-494-5484 SAP

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Clinical Research eSigned	01-Jul-2021 03:18:41
PPD	Clinical Pharmacology eSigned	02-Jul-2021 17:55:35
PPD	Biostatistics eSigned	12-Jul-2021 08:15:22