STATISTICAL ANALYSIS PLAN

Study Title:	Dose Optimization Study of Idelalisib in Follicular Lymphoma
Name of Test Drug:	Idelalisib
Study Number:	GS-US-313-1580
Protocol Version (Date):	Version 1.0 (Original) 12 June 2015 Version 2.0 (Amendment 1) 28 March 2016 Version 3.0 (Amendment 2) 07 June 2016 Version 4.0 (Amendment 3) 08 September 2016 Version 5.0 (Amendment 4) 25 September 2017 Version 6.0 (Amendment 5) 13 March 2019 Version 7.0 (Amendment 6) 18 March 2021
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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
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
HLGT	high-level group term
HLT	high-level term
LLT	lower-level term
LOQ	limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
ORR	Overall Response Rate
PK	pharmacokinetics
PT	preferred term
Q1	first quartile
Q3	third quartile
QD	once daily
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
PD	Progressive Disease
DOR	Duration of Response
PFS	Progression Free Survival
OS	Overall Survival
FL	follicular lymphoma

1. INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and defines key elements including variable definitions for analysis of data of Study *GS-US-313-1580* in support of the clinical study report (CSR). This SAP is based on the study protocol *amendment 6* dated *18 March 2021*. Any changes made after the finalization of the SAP will be documented in the CSR.

This study was designed to evaluate a safe and effective dosing regimen of idelalisib in subjects with relapsed or refractory Follicular Lymphoma (FL) who have no other therapeutic options. It is a randomized, open-label, multi-center global study with three treatment arms in total of 266 subjects planned. The study was terminated early due to slow enrollment, with rapidly evolving treatment options for FL as the primary reasons.

Analysis methods specified in this document take precedence over those described in protocol should there be any difference.

1.1. Study Objectives

1.1.1. Primary Objectives

- Establish a safe and effective dosing regimen of idelalisib in subjects with relapsed or refractory FL who have no other therapeutic options

1.1.2. Secondary Objectives

- Evaluate the overall response rate (ORR)
- Evaluate the progression-free survival (PFS), duration of response (DOR), and overall survival (OS)
- Evaluate the overall safety profile of idelalisib
- Determine the PK of idelalisib and its major metabolite (GS-563117)

1.2. Study Endpoints

1.2.1. Primary Endpoints

- ORR, defined as the proportion of subjects who achieve a partial response (PR) or complete response (CR) by independent review committee (IRC)
- Incidence of Grade ≥ 4 treatment-emergent adverse events (TEAEs)

1.2.2. Secondary Endpoints

- DOR, defined as the interval from the first documentation of CR or PR to the earlier of the first documentation of disease progression by independent review committee (IRC or death from any cause
- ORR by Week 24, defined as the proportion of subjects who achieve a PR or CR by Week 24
- Overall safety profile of idelalisib, including the incidence of AEs and clinically significant laboratory abnormalities, severity, timing, and relationship to idelalisib of any AEs; SAEs; or AEs leading to interruption, reduction, or discontinuation of idelalisib Time to onset of AEs of interest (AEIs) defined as the interval from the start of idelalisib treatment to the first documentation of start of AEI
- PFS, defined as the interval from randomization to the earlier of the first documentation of disease progression by IRC or death from any cause
- OS, defined as the interval from randomization to death from any cause
- Idelalisib trough (predose) and peak (1.5-hour samples) plasma concentrations assessed by validated bioanalytical method

1.3. Study Design

This is a randomized, open-label, multi-center study that will be conducted globally.

Subjects will be randomized in a 1:1 ratio, until the enrollment target per arm is met, to the following treatment arms:

- Arm A: 150 mg twice daily idelalisib administered continuously
- Arm C: 150 mg twice daily idelalisib administered in 28-day cycles (21 days on-treatment, 7 days off-treatment)

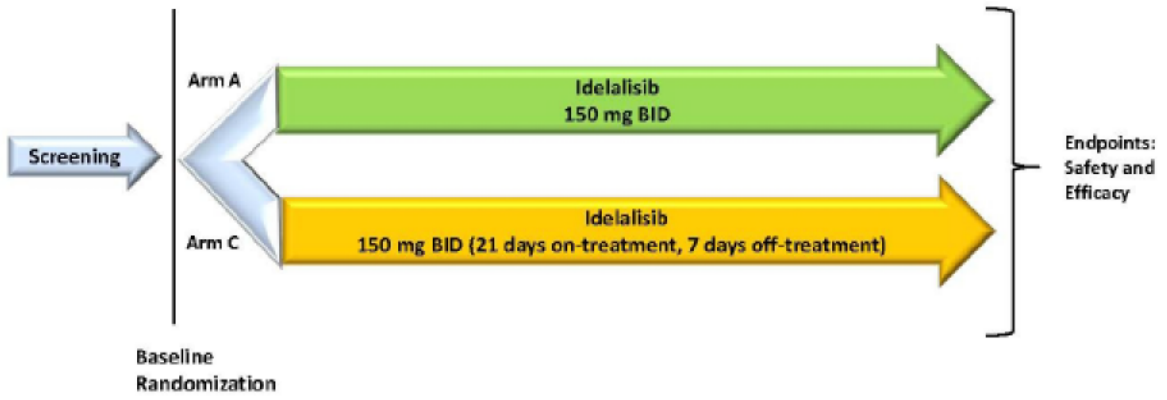
The original protocol for this study included an Arm B, which was closed to enrollment as of Protocol Amendment 5.

- Arm B (*closed to enrollment as of Protocol Amendment 5*): 100 mg twice daily idelalisib administered continuously

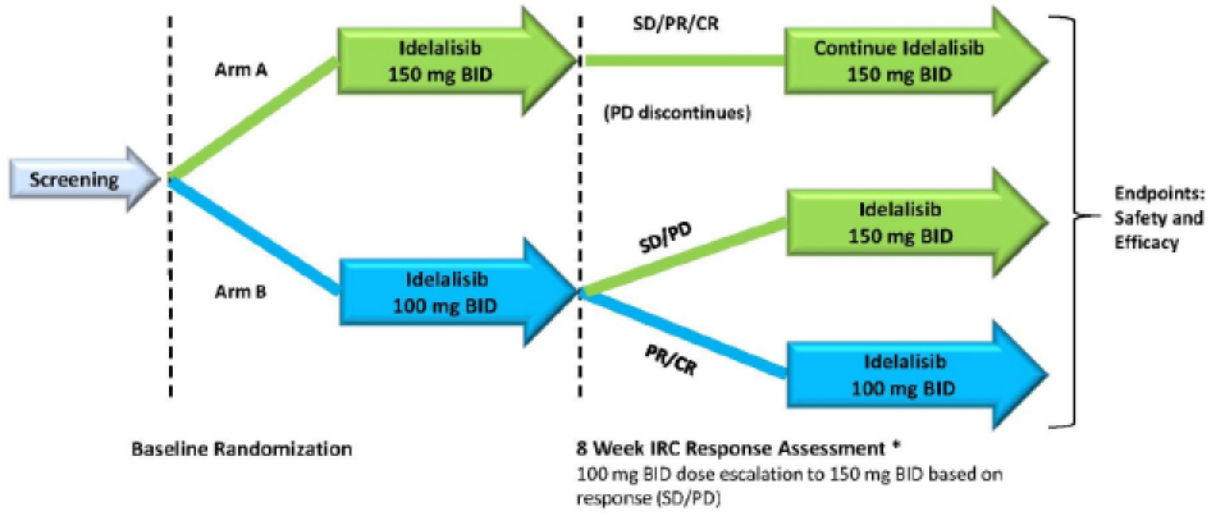
Clinic visits will occur at Screening, Day 1, every 2 weeks through Week 12, every 4 weeks through Week 24, at Weeks 32, 36, 40, 48, and every 12 weeks thereafter through end of study (EOS). Subjects will be assessed for safety at each visit. Additional visits will be required between clinic visits for laboratory testing only.

Subjects will be assessed for FL disease status by continuous utilization of a single modality including positron emission tomography–computed tomography (PET-CT), CT, or MRI. If permanent discontinuation of idelalisib occurs prior to IRC documented progression of FL, subjects shall remain on study until progression of FL or withdrawal from the study for reasons specified in Section 3.5.2 of the Protocol Amendment 6.

Figure 1-1. Study Schema



Subjects enrolled prior to implementation of Protocol Amendment 5 followed the previous study design as shown here.



* Unblinding and dose modifications may occur at any time during study participation if the IRC Assessment confirms progressive disease.

In accordance with Protocol Amendment 6, subjects enrolled prior to implementation of Protocol Amendment 5 and still blinded will be unblinded at the time of Protocol Amendment 6 implementation; these subjects will continue at the randomized dose level if they are still on treatment. These subjects were previously randomized in a blinded manner to either 150 mg twice daily or 100 mg twice daily idelalisib. Based on the 8-week blinded IRC response assessment, subjects with SD or PD were unblinded in both arms. Subjects with a PR or CR maintained the blind and continued at the randomized dose level. Subjects randomized to 100 mg twice daily with SD or PD had the option to be dose escalated to 150 mg twice daily. Subjects randomized to 150 mg twice daily with SD will continue open-label idelalisib at 150 mg twice daily. Subjects randomized to 150 mg twice daily with PD will be discontinued from study treatment. These same unblinding and dose modification principles were applied at any time throughout study participation when disease progression was suspected and confirmed by IRC assessment.

Subjects should follow study procedures as outlined in Section 6 and Appendix 2 Study Procedures Table of the Protocol Amendment 6. Idelalisib will be administered until meeting criteria for discontinuation of study drug as described in Section 3.5.1 of the protocol Amendment 6.

1.4. Sample Size

The planned sample size is approximately 266 subjects: approximately 120 subjects in Arm A, approximately 26 subjects in Arm B, and approximately 120 subjects in Arm C. As of Protocol Amendment 5, Arm B enrollment was closed after enrollment of approximately 26 subjects into Arm B and approximately 26 subjects into Arm A.

As of Protocol Amendment 5, subjects will be randomized to 2 arms (Arms A and C) with a 1:1 ratio until the enrollment target of 120 subjects in each arm is met. The ORR was approximately 56% for subjects with FL in Study 101-09. If the underlying true ORR is 56% for subjects in this study, the chance to observe 60 or more responders out of 120 subjects (observed ORR $\geq$ 50%) is 92%. With 120 subjects in each arm, the half-width of a two-sided 95% CI of ORR is $\leq$ 10% for an observed ORR in the range of 40%-60%, and the half-width of a two-sided 95% CI of $\geq$ Grade 4 TEAEs incidence rate is $\leq$ 10% for an observed AE rate in the range of 20%-40%.

The sample size was originally planned to include 240 subjects randomized to Arm A and Arm B with a 1:1 ratio. The previous sample size calculation is based on the rate of Grade $\geq$ 3 diarrhea/colitis at approximately 15% in the prior idelalisib studies. A sample size of 120 subjects per arm would provide 73% chance to detect a reduction of 10% (ie, 15% incidence in the 150 mg twice daily arm versus 5% incidence in the 100 mg twice daily arm) using a 2-sided Chi-square test with alpha level of 0.05.

2. PLANNED ANALYSIS

2.1. Data Monitoring Committee (DMC) Analysis

An external multidisciplinary DMC will review the progress of the study and perform interim reviews of safety data at regular intervals until all blinded subjects are either unblinded or off the study. The DMC will provide recommendations to Gilead as to whether the nature, frequency, and severity of adverse effects associated with study treatment warrant the early termination of the study in the best interests of the study participants, whether the study should continue as planned, or whether the study should continue with modifications.

The DMC's specific activities will be defined by a mutually agreed charter, which will define the DMC's membership, conduct, and meeting schedule.

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2.2. Primary Analysis

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

2.3. 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. Intent-to-Treat (ITT) Analysis Set

The ITT Analysis Set includes all subjects who are randomized regardless of whether subjects receive any study drug. Treatment assignment will be designated according to a subject's initial randomization. This analysis set will be used in the analysis of efficacy.

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. 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 ITT Analysis Set, 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.

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 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. 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.

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 (in years) collected at screening visit will be used for analyses and presented in listings. If age at screening is not available for a subject, then age derived based on date of birth and the screening visit date will be used instead. If an enrolled subject was not dosed with any study drug, the randomization date will be used instead of the screeing 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 lower 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 upper 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 lower or upper 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).

Natural logarithm transformation will be used for analyzing concentrations 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 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 concentrations that are BLQ will be excluded before log transformation or statistical model fitting.

3.8. Analysis Visit Windows

3.8.1. Definition of Study Day

Study day will be calculated from the 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.

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 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 treatment arms 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 treatment arms based on All Screened Subjects. This summary will present the number and percentage of subjects in the following categories:

- Screened Subjects
- All Enrolled Subjects
- ITT Analysis Set
- Safety Analysis Set
- PK Analysis Set
- Study Drug Completion Status
  - — Discontinued Study Drug
- Reasons for Discontinuation of Study Drug
- Study Completion Status
  - — Discontinued Study
- Reasons for Discontinuation of Study

For the status of study completion and reasons for study drug and study 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 treatment arms 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

Extent of exposure to study treatment will be summarized by treatment arms using descriptive statistics for total duration of exposure to study drug (idelalisib) including the number (ie, cumulative counts) and percentage of subjects exposed through the certain time periods. Summaries will be provided by treatment arms for the Safety Analysis Set.

Total duration of exposure to study drug (idelalisib) 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 months using up to 1 decimal place (eg, 4.5 months). 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 for subjects included in the final analyses.

A by-subject listing of study drug administration will be provided by treatment arms and subject ID number (in ascending order), including dosing date, total duration of exposure to study drug and reason for dose interruption.

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 deviations.

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. 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.

4.4.2. 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 treatment arms 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 medical history will be provided by treatment arms and subject ID number in ascending order for All Enrolled Analysis Set.

5.4. Prior Anti-Cancer Therapy

The details of prior anti-cancer therapy will be listed by treatment arms and subject ID number in ascending order for All Enrolled Analysis Set.

5.5. Prior and On Study Radiotherapy

The details of all radiotherapy will also be listed by treatment arms and subject ID number in ascending order for All Enrolled Analysis Set.

5.6. Surgeries and Procedures

A by-subject listing of prior and on-study surgeries and procedures will be provided by treatment arms and subject ID number in ascending order for All Enrolled Analysis Set.

6. EFFICACY ANALYSIS

Efficacy parameters will be summarized and listed by treatment arms based on the ITT Analysis Set. The analyses will be conducted using the IRC assessments based on standard response criteria applying Cheson 2007.

6.1. Definition and Analysis of Efficacy Endpoints

6.1.1. Primary and Supportive Analysis for Primary Endpoint

For the primary efficacy analysis, ORR will be evaluated by treatment arms using the IRC assessments in the ITT Analysis Set. Subjects who do not have sufficient baseline or on-study tumor assessment to characterize response status will be counted as non-responders. Estimates and the corresponding 95% CIs based on the Clopper-Pearson exact method will be provided.

A by-subject listing of overall response will be provided by treatment arms and subject ID number in ascending order.

6.1.2. Analysis for Secondary Endpoints

The ORR by Week 24 and corresponding 95% CIs will be evaluated by treatment arm using the IRC assessments in the ITT Analysis Set.

The time-to-event efficacy endpoints including PFS, DOR, and OS will be analyzed using the Kaplan-Meier method in the ITT Set, and the analysis of DOR will include subjects who achieve a PR or CR. Analyses may also be performed for subgroups defined by potential predictors of response. The Kaplan-Meier plot will be provided for PFS and OS.

PFS and DOR Censoring rules:

1) Subjects who discontinued study prior to PD or death will be censored on the last tumor assessment date.

2) Subjects who missed >= 2 consecutive tumor assessments, and did not have a PD prior to missing >= 2 consecutive tumor assessments will be censored on the last tumor assessment date prior to missing >=2 consecutive assessments.

3) Subjects who received new anti-cancer therapy will be censored on the last assessment date prior to receiving new anti-cancer therapy.

4) Subjects who are alive and do not have any on-study tumor assessments will be censored on the randomization date (applicable only for PFS)

OS censoring rules:

1) Subjects who do not have a recorded death date will be censored on the last known alive date.

7. ANALYSIS OF ADVERSE EVENTS AND LABORATORY EVALUATIONS

All AEs will be listed. The focus of AE summarization will be on treatment-emergent AEs. 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 01 Jan 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 treatment arms 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 SOC and PT.

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:

- All Treatment-Emergent Adverse Events
- Grade 4 or Higher Treatment-Emergent Adverse Events
- Grade 3 or Higher Treatment-Emergent Adverse Events
- Treatment-Emergent Idelalisib related Adverse Events
- Treatment-Emergent Serious Adverse Events
- Treatment-Emergent Idelalisib related Serious Adverse Events
- Treatment-Emergent Adverse Events leading to discontinuation of Idelalisib
- Treatment-Emergent Adverse Events leading to temporary interruption of Idelalisib
- Treatment-Emergent Adverse Events leading to study discontinuation
- Treatment-Emergent Adverse Events leading to Death

A brief, high-level summary of AEs described above will be provided by treatment arms 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 treatment arms 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 leading to Death
- All Adverse Events with Grade 3 or Higher
- All Adverse Events with Grade 4 or Higher

- All Adverse Events leading to discontinuation of Idelalisib
- All Adverse Events leading to temporary interruption of Idelalisib
- 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 treatment arms. 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 treatment arms and subject ID number in ascending order.

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 treatment arms, subject ID number and time point in chronological order for hematology and serum chemistry, 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 treatment arm; 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 treatment arms 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. Listings will be provided for All Enrolled Analysis Set.

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 treatment arms, 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 treatment arms, subject ID number and administration date in chronological order based on All Enrolled Analysis Set.

7.5. 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 treatment arms and subject ID number in ascending order for the following safety parameters and comments:

- ECOG performance scores
- General Comments

7.6. Changes from Protocol-Specified Safety Analyses

Protocol defined a secondary endpoint of Time to onset of AEs of interest (AEIs). This analysis was not performed.

8. PHARMACOKINETIC ANALYSES

Plasma concentrations of idelalisib/GS-563117 will be listed and summarized by treatment arm and visit using descriptive statistics (eg, sample size, arithmetic mean, geometric mean, % coefficient of variation, StD, median, minimum, and maximum).

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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
27OCT2022	1.2.1, 1.2.2, 6.1.2	Added primary endpoints, Added secondary endpoints Added censoring rules	Added these sections for completeness
27OCT2022	Throughout the document	Minor edits	For clarification

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-313-1580 SAP v1.0

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy hh:mm:ss)
PPD	Biostatistics eSigned	22-Nov-2022 18:47:30
PPD	Clinical Research eSigned	30-Nov-2022 06:17:51