STATISTICAL ANALYSIS PLAN

Study Title:	An Open-Label, Roll-Over Study to Provide Idelalisib to Subjects Previously Treated with the Investigational PI3Kδ Inhibitor, GS-9820
Name of Test Drug:	Idelalisib
Study Number:	GS-US-313-2120
Protocol Version (Date):	Amendment 3 (04 November 2016)
Analysis Type:	Final Analysis
Analysis Plan Version:	1.0
Analysis Plan Date:	21 March 2018
Analysis Plan Author(s):	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BMI	body mass index
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DMC	data monitoring committee
eCRF	electronic case report form
HLGT	high-level group term
HLT	high-level term
LLT	lower-level term
LOQ	limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
StD	standard deviation
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
ULN	upper limit of normal

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-313-2120. This SAP is based on Protocol GS-US-313-2120 Amendment 3 dated 4 November 2016 and the electronic case report form (eCRF). The SAP will be finalized before database finalization. Any changes made after finalization of the SAP will be documented in the CSR.

1.1. Study Objectives

The primary objective of this study is as follows:

- To provide idelalisib, a marketed PI3Kδ inhibitor, in lieu of GS-9820, an investigational second generation PI3Kδ inhibitor, to subjects receiving GS-9820 in Study GS-US-315-0102 at the time of study closure who have had objective evidence of clinical benefit defined as at least stable disease on imaging assessed by the IRC and no toxicities prior to enrollment in this study that would preclude initiating therapy with idelalisib. Idelalisib and GS-9820 are both in the class of agents that inhibit PI3Kδ and as such this exchange of class for class agent is warranted and acceptable.

1.2. Study Design

This study is an open-label, rollover study to provide idelalisib to subjects receiving GS-9820 in Study GS-US-315-0102 at the time of study closure.

1.3. Sample Size and Power

There is no formal hypothesis to be tested in this study; therefore, no formal sample size calculation was performed.

A total of 3 subjects were enrolled in Study GS-US-313-2120.

2. TYPE OF PLANNED ANALYSIS

2.1. Interim Analyses

This study does not have a data monitoring committee (DMC). Therefore, no analyses will be conducted for the DMC.

2.2. Final Analysis

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

3. GENERAL CONSIDERATIONS FOR DATA ANALYSES

By-subject listings will be presented for all subjects in the Safety Analysis Set and sorted by subject identification (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. Age, sex at birth, race, and ethnicity will be included in the listings, as space permits.

3.1. Analysis Sets

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

3.1.1. Safety Analysis Set

The Safety Analysis Set includes all subjects who took at least 1 dose of study drug. This is the primary analysis set for safety analyses.

3.2. Subject Grouping

Not Applicable.

3.3. Strata and Covariates

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

3.4. Examination of Subject Subgroups

There are no prespecified subject subgroupings for safety analyses.

3.5. Multiple Comparisons

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

3.6. Missing Data and Outliers

3.6.1. Missing Data

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

3.6.2. Outliers

All data will be included in the data analysis.

3.7. Data Handling Conventions and Transformations

In general, age (in years) on the date of the first dose of study drug will be used for analyses and presentation in listings. For screen failures, the date the informed consent was signed will be used for age calculation. If only the birth year is collected on the CRF, "01 July" will be used for the unknown birth day and month for the purpose of age calculation. If only birth year and month are collected, "01" will be used for the unknown birth day.

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 eCRF will be used.

4. SUBJECT DISPOSITION

4.1. Subject Enrollment and Disposition

The following by-subject listing will be provided by subject ID number in ascending order:

- Reasons for premature study drug discontinuation

4.2. Extent of Study Drug Exposure

A by-subject listing of study drug administration will be provided by subject ID number (in ascending order) and visit (in chronological order).

4.3. Protocol Deviations

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.

5. BASELINE CHARACTERISTICS

5.1. Demographics

A by-subject demographic listing, including age, sex, race, and ethnicity, will be provided by subject ID number in ascending order.

5.2. Medical History

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

General medical history data will not be coded, but will be listed only.

6. EFFICACY ANALYSES

No efficacy analyses will be conducted for this study.

7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

Clinical and laboratory adverse events (AEs) will be coded using the current version of 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 Toxicity Criteria for Adverse Events (CTCAE) Version 4.03. The severity grade of events for which the investigator did not record severity will be categorized as "missing" for data listings.

7.1.3. Relationship of Adverse Events to Study Drug

Related AEs are those for which the investigator selected "Related" on the AE eCRF 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 shown as missing in by-subject data listings.

7.1.4. Serious Adverse Events

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

7.1.5. Treatment-Emergent Adverse Events

7.1.5.1. Definition of Treatment-Emergent Adverse Events

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

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

7.1.5.2. Incomplete Dates

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.

7.1.6. Summaries of Adverse Events and Deaths

All AEs will be listed based on the Safety Analysis Set.

7.2. Laboratory Evaluations

By-subject listings of laboratory data will be provided by subject ID number and visit in chronological order for serum chemistry based on the Safety Analysis Set. When values are below the LOQ, they will be listed as such, and hemolized test results will be included. 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.

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.

7.2.1. Graded Laboratory Values

CTCAE, Version 4.03, 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.

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. If the relevant baseline laboratory value is missing, any abnormality of at least Grade 1 observed within the time frame specified above will be considered treatment emergent.

7.2.2. Liver-related Laboratory Evaluations

Liver-related abnormalities after initial study drug dosing will be examined using the following laboratory test values for postbaseline measurements:

- Aspartate aminotransferase (AST): (a) > 3 times of the upper limit of reference range (ULN); (b) > 5 x ULN; (c) > 10 x ULN; (d) > 20 x ULN
- Alanine aminotransferase (ALT): (a) > 3 x ULN; (b) > 5 x ULN; (c) > 10 x ULN; (d) > 20 x ULN
- Total bilirubin: (a) > 1.5 x ULN, (b) > 2 x ULN
- AST or ALT > 3 x ULN: (a) total bilirubin> 1.5 x ULN; (b) total bilirubin > 2 x ULN

For individual laboratory tests, subjects will be counted once based on the most severe postbaseline values. For both the composite endpoint of AST or ALT and total bilirubin, subjects will be counted once when the criteria are met at the same postbaseline visit date. A listing of subjects who met at least 1 of the above criteria will be provided.

7.3. Prior and Concomitant Medications

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

7.3.1. Prior Medications

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

For the purposes of analysis, any medication with a start date prior to the first dosing date of study drug will be included in the prior medication summary regardless of when the stop date is. If a partial start date is entered, the medication will be considered prior unless the month and year (if day is missing) or year (if day and month are missing) of the start date are after the first dosing date.

7.3.2. Concomitant Medications

For the purposes of analysis, any medications with a start date prior to or on the first dosing date of study drug and continued to be taken after the first dosing date, or started after the first dosing date but prior to or on the last dosing date of study drug will be considered concomitant medications. Medications started and stopped on the same day as the first dosing date or the last dosing date of study drug will also be considered concomitant. Medications with a stop date prior to the date of first dosing date of study drug or a start date after the last dosing date of study drug will be excluded from the concomitant medication summary. If a partial stop date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) prior to the date of first study drug administration will be excluded from the concomitant

medication summary. If a partial start date is entered, any medication with the month and year (if day is missing) or year (if day and month are missing) after the study drug stop date will be excluded from the concomitant medication summary. Medications with completely missing start and stop dates will be considered as a concomitant medication.

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

7.4. Other Safety Measures

7.4.1. Pregnancy

A data listing will be provided for subjects who became pregnant during the study.

7.5. Changes From Protocol-Specified Safety Analyses

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

8. SOFTWARE

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

9. SAP REVISION

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

10. APPENDIX 1 SCHEDULE OF ASSESSMENTS

Period	Screen	Treatment															
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15+**		
Week	**-4**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**			
Study Day	**Within -28 days**	**1**	**14**	**28**	**42**	**52**	**70**	**84**	**98**	**112**	**126**	**140**	**154**	**168**	**Q4 weeks**	**Q12 weeks**	**End of study**
Visit Window			**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±2**	**±7**	**±7**	
Informed consent	X																
Serum β-HCG[a]	X																
Pneumococcal, Hib, Tetanus titers	X																
ALT/AST/total bilirubin	X	X		X		X		X		X				X		X	X
Urine pregnancy test[a]		X		X		X		X		X				X		X	X
ANC[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
CMV surveillance	X			X		X		X		X		X		X	X[c]		
Immune Monitoring	X			X				X						X		X	X
Assess adverse events and SAEs[d]		X		X		X		X		X				X		X	X
Record concomitant medications[e]		X		X		X		X		X				X		X	X
Idelalisib dispensing/accounting		X		X		X		X		X				X		X	X
Investigator response assessment[f]	X			X		X		X		X				X		X	X

Abbreviations: β-HCG=beta human chorionic gonadotropin, ALT=alanine aminotransferase, AST=aspartate aminotransferase, Hib = Haemophilus Influenzae Type B

a For women of child bearing potential; Serum β-HCG to be collected to be collected at screening, urine pregnancy test to be collected at visits from first dose of idelalisib to EOS

b Absolute neutrophil count (ANC) will be monitored at least every two weeks for the first 24 weeks of idelalisib treatment

c CMV surveillance must be conducted approximately every 4 weeks throughout the course of idelalisib treatment

d For an AE of Diarrhea/Colitis: 1) Obtain history of onset and duration of diarrhea, including description of number of stools and stool composition, travel history, dietary changes and a medication review to identify possible diarrheogenic agents and 2) Perform physical examination including assessment for fever, dizziness, abdominal pain/cramping, and weakness

e Concomitant medications only collected if it is related to an AE

f Record investigator response assessment if obtained per standard of care