STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 1b/2 Study of Idelalisib in Combination with BI 836826 in Subjects with Chronic Lymphocytic Leukemia
Name of Test Drug:	Idelalisib
Study Number:	GS-US-312-1579
Protocol Version (Date):	Amendment 4 (15 June 2017)
Analysis Type:	Final Analysis
Analysis Plan Version:	1.0
Analysis Plan Date:	28 November 2017
Analysis Plan Author(s):	PPD

CONFIDENTIAL AND PROPRIETARY INFORMATION

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LIST OF ABBREVIATIONS

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BID	twice daily
BLQ	below the limit of quantitation
BLRM	Bayesian logistic regression analysis
BMI	body mass index
CLL	chronic lymphocytic leukemia
CR	complete response
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DCR	duration of complete response
DLT	dose limiting toxicity
DMC	data monitoring committee
DOR	duration of response
DSPH	Drug Safety and Public Health
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
highRP2D	high recommended Phase 2 dose
HLGT	high-level group term
HLT	high-level term
IV	intravenous
LLT	lower-level term
LOQ	limit of quantitation
lowRP2D	low recommended Phase 2 dose
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
n	number of subjects
ORR	overall response rate
OS	overall survival
PFS	progression-free survival
PT	preferred term
Q1, Q3	first quartile, third quartile
QRS	electrocardiographic deflection between the beginning of the Q wave and termination of the S wave representing time for ventricular depolarization

QT	electrocardiographic interval between the beginning of the Q wave and termination of the T wave representing the time for both ventricular depolarization and repolarization to occur
R/R	relapsed/refractory
SAE	serious adverse event
SAP	statistical analysis plan
SE	standard error
SOC	system organ class
SRT	Safety Review Team
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-312-1579. This SAP is based on the study protocol amendment 4 dated 15 June 2017 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.

This study has been terminated. Enrollment to this study was closed on 26 April 2017 based on an updated feasibility assessment in relation to changes in the chronic lymphocytic leukemia (CLL) treatment landscape. Two subjects were enrolled in the Phase 1b portion of the study and no subjects were enrolled in the Phase 2 portion of the study.

1.1. Study Objectives

The primary objectives of this study are as follows:

- Phase 1b: To determine the safety and tolerability of the combination of idelalisib with BI 836826 in subjects with relapsed and refractory (R/R) CLL, and to establish the high recommended Phase 2 combination dose (highRP2D) as well as an alternate lower recommended Phase 2 combination dose (lowRP2D) regimen.

- Phase 2: To determine the rates of complete response (CR) and of minimal residual disease (MRD) negativity with the combination at the highRP2D and the lowRP2D.

The secondary objectives of this study are as follows:

- Phase 1b and 2: To evaluate overall response rate (ORR), progression-free survival (PFS), duration of complete response (DCR), duration of response (DOR), and overall survival (OS).

- Phase 2: To further characterize the safety and tolerability of the combination using the highRP2D as well as the lowRP2D regimen.

Due to the early study termination, the study objectives will not be met and the 2 subjects that were enrolled will be assessed for safety only.

1.2. Study Design

The Phase 1b portion of the study will evaluate various dose combinations of idelalisib and BI 836826 in sequential cohorts following an initial 7-day idelalisib monotherapy run-in period. The safety data from each cohort will be used as input into the bayesian logistic regression model (BLRM). The output from this model will be used by the safety review team (SRT) to choose the dose combination for evaluation in the subsequent cohort. At completion of Phase 1b, 2 dose

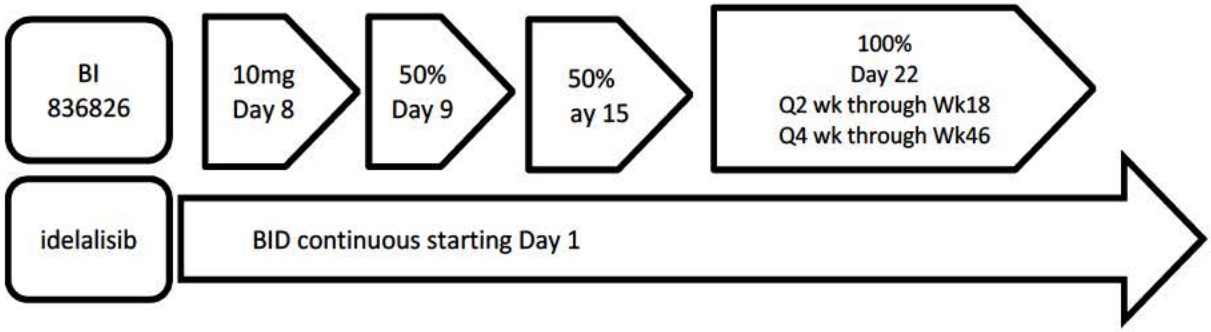
combinations will be selected for further evaluation in Phase 2. In the Phase 2 portion of the study, subjects with R/R CLL will be randomly assigned in a 1:1 manner to receive 1 of the 2 dose combinations selected from Phase 1b following an initial 7-day idelalisib monotherapy run-in period.

Approximately 42 evaluable subjects will be enrolled in the Phase 1b portion of the study and 50 evaluable subjects will be randomized in the Phase 2 portion of the study.

Idelalisib tablets will be administered orally twice daily (BID) continuously until disease progression or intolerable toxicity. During the Phase 1b portion of the study, the following dose levels will be tested: 50 mg BID, 100 mg BID, and 150 mg BID; the starting dose level will be 50 mg BID. BI 836826 will be administered as a rate-controlled intravenous (IV) infusion, with a total of 18 doses, from Week 2 through Week 46. During the Phase 1b portion of the study, the starting dose level will be 100 mg, and the highest possible dose tested will be 600 mg.

In both Phase 1b and Phase 2, idelalisib will be administered starting on Week 1, Day 1. Following 7 days of idelalisib, BI 836826 administration will start during Week 2 with an initial dose of 10 mg on Day 8; 50% of the assigned dose will be given on Days 9 and 15, and 100% of the assigned dose will be given on Day 22. Thereafter, 100% of the assigned dose will be administered every 2 weeks through Week 18, and every 4 weeks through Week 46.

Dosing Schema:



The schedule of assessments is in Appendix 1 of this SAP.

Following enrollment of 2 subjects in the Phase 1b portion of the study, the study was terminated and therefore, Phase 2 will not occur. Subjects may remain on study through approximately Week 50 (to include 30-day follow up after last dose of BI 836826). Study procedures have been modified accordingly.

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.

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.

2.3. Follow-up Analysis

Not applicable

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 adverse events (AEs), will be presented in chronological order within the subject. The dose cohort to which subjects were initially assigned will be used in the listings. Age, sex at birth, race, and ethnicity will be included in the listings.

Due to the early study termination, planned analyses will not be performed and only safety-related endpoints will be reported for the subjects enrolled in the study.

3.1. Analysis Sets

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

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 first dosing date 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 eCRF, "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 listings will be provided by subject ID number in ascending order:

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

4.2. Extent of Study Drug Exposure and Adherence

Extent of exposure to study drug will be examined by assessing the total duration of exposure to study drug.

4.2.1. Duration of Exposure to Study Drug

Total duration of exposure to idelalisib will be defined as last dosing date minus first dosing date plus 1, regardless of any temporary interruptions in idelalisib administration, and will be expressed in days. If the last idelalisib 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.

A by-subject listing of study drug administration will be provided for both idelalisib and BI 836826 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 an important protocol deviation.

5. BASELINE CHARACTERISTICS

5.1. Demographics

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

5.2. Other Baseline Characteristics

Other baseline characteristics include body weight (in kg), height (in cm), body mass index (BMI; in kg/m^2), and Eastern Cooperative Oncology Group (ECOG) performance status at screening.

A by-subject listing of other baseline characteristics will be provided by subject ID number in ascending order.

5.3. Medical History

General medical history data collected at screening will be listed only. Medical history data will not be coded. A by-subject listing of general and disease-specific medical history will be provided by subject ID number in ascending order.

Time since CLL diagnosis (years) will be calculated by (first dosing date of study drug – date of CLL diagnosis). In deriving the time since CLL diagnosis, all partial dates of diagnosis will be identified, and the partial dates will be imputed as follows:

- If both the day and month are missing but the year is available, then the imputed day and month will be 01 Jan.
- If only the day is missing but the month and year are available, then the imputed day will be the first day of the month.
- If the year is missing, a partial date will not be imputed.

5.4. Prior Anticancer Therapy

The regimens and prior therapies that the subjects received and time since the completion of last regimen will be listed based on the Safety Analysis Set. A partial completion date will be imputed using the following algorithm for the last regimen:

- If both the day and month are missing but the year is available, then the imputed day and month will be 01 Jan or the starting date of the last regimen, whichever is later.
- 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 starting date of the last regimen, whichever is later.
- If the year is missing, no imputation will be done and the completion date will be treated as missing.

Prior radiation therapy and prior surgery/procedure will be listed.

6. EFFICACY ANALYSES

This study was terminated in Phase 1b based on an updated feasibility assessment in relation to changes in the CLL treatment landscape. Since only 2 subjects were enrolled at the time of study termination, efficacy endpoints will not be evaluated and available data will only be listed.

6.1. Primary Efficacy Endpoint

Not applicable

6.2. Secondary Efficacy Endpoints

Not applicable

6.3. Exploratory Efficacy Endpoints

Not applicable

7. SAFETY ANALYSES

7.1. Adverse Events and Deaths

7.1.1. Adverse Event Dictionary

Clinical and laboratory 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 (DSPH) 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.

If 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

All AEs and SAEs 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 time point in chronological order for hematology, serum chemistry, and urinalysis separately 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:

- AST: > 3 times of the upper limit of reference range (ULN)
- ALT: > 3 x ULN
- Total bilirubin: (a) > 1.5 x ULN; (b) > 2 x ULN
- ALP > 1.5 x ULN
- ALP < 2 x ULN and total bilirubin > 2 x ULN

The listing will include laboratory data from all postbaseline visits up to 30 days after the last dose of study drug. For individual laboratory tests, subjects will be counted once based on the most severe postbaseline values. For the composite endpoint, subjects will be counted once when the criteria are met at the same postbaseline visit date.

7.3. Body Weight , Height, and Vital Signs

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

7.4. Prior and Concomitant Medications

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

7.4.1. Prior Medications

Prior medications are defined as any medications taken 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 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.

7.4.2. 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.

7.5. Electrocardiogram Results

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

7.5.1. QT Intervals

The QT interval (measured in millisecond [msec]) is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. The QT interval represents electrical depolarization and repolarization of the ventricles.

7.5.2. PR and QRS Intervals

The PR interval (measured in msec) is a measure of the time between the start of the P wave (the onset of atrial depolarization) and the beginning of the QRS complex (the onset of ventricular depolarization). The QRS interval measures the duration of the QRS complex.

7.6. Other Safety Measures

Since only 2 subjects were enrolled at time of study termination, the dose limiting toxicity (DLT) will not be evaluated.

7.7. Changes From Protocol-Specified Safety Analyses

Due to the early study termination, only safety-related endpoints will be listed for the subjects enrolled in the study.

8. PHARMACOKINETIC (PK) ANALYSES

8.1. PK Sample Collection

This study was terminated in Phase 1b based on an updated feasibility assessment in relation to changes in the CLL treatment landscape. Since only 2 subjects were enrolled at the time of study termination, PK samples will not be evaluated.

8.2. PK Analyses Related to Intensive PK Sampling

Not Applicable

8.3. PK Analyses Related to Sparse PK Sampling

Not Applicable

9. REFERENCES

10. SOFTWARE

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

11. SAP REVISION

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

12. APPENDICES

Appendix 1. Schedule of Assessments

Appendix Table 1. Study Procedures Table

Shaded columns indicate laboratory draws only occur on these days

Visit	Screen	Idelalisib Run-in and Combination Treatment through Week 18															
Week	**-4**	**1**	**2**	**2**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**12**	**14**	**16**	**18**
Study Day	**-28**	**1**	**8**	**9**		**15**	**22**		**36**		**50**		**64**	**78**	**92**	**106**	**120**
Visit Window		**NA**				**± 1 day**					**± 3 days**						
Informed Consent	X																
Medical History	X																
Medication History	X																
Physical Examination	X	X	X	X		X	X		X		X		X	X	X	X	X
Vital Signs	X	X	X	X		X	X		X		X		X	X	X	X	X
ECOG Performance Status	X																
12-lead ECG	X																
Chemistry & Hematology [1]	X	X	X	X	XXX	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation	X																
Urinalysis	X								X								
HBV, CMV, HCV, HIV Screening	X																
CMV monitoring [2]	X						X				X			X		X	X
β 2 microglobulin		X															
Immune monitoring (CD4)[3]		X					X							X			
ADA testing [4]			X						X				X		X		X
CCI																	
Investigator Assessment	X														X		
Idelalisib & PJP Prophylaxis Dispensing		X					X				X			X		X	X
Idelalisib Accountability							X				X			X		X	
Idelalisib Administration [6]		→	→	→	→	→	→	→	→	→	→	→	→	→	→	→	→
BI 836826 Administration [7]			10 mg	50%		50%	100%		X		X		X	X	X	X	X
Adverse Events		X	X	X		X	X		X		X		X	X	X	X	X
Concomitant Medication	X	X	X	X		X	X		X		X		X	X	X	X	X

ALL FOOTNOTES APPEAR AT END OF PART 2

Visit	Combination Treatment and Post- Combination Treatment									30-Day Follow-up End of Study[8]
Week	**20**	**22**	**24**	**26**	**30**	**34**	**38**	**42**	**46**	
Study Day	**134**	**148**	**162**	**176**	**204**	**232**	**260**	**288**	**316**	
Visit Window	**± 3 days**									**±7 days**
Informed Consent										
Medical History										
Medication History										
Physical Examination		X		X	X	X	X	X	X	X
Vital Signs		X		X	X	X	X	X	X	X
ECOG Performance Status										X
12-lead ECG				X						X
Chemistry & Hematology [1]	X	X	X	X	X	X	X	X	X	X
Coagulation										
Urinalysis				X						X
CMV monitoring [2]		X		X	X	X	X	X	X	X
β 2 microglobulin										
Immune monitoring (CD4) [3]		X					X		X	X
ADA testing [4]				X		X		X		X
CCI										
Investigator Assessment				X			X			X
Idelalisib & PJP Prophylaxis Dispensing		X		X	X	X	X	X	X	
Idelalisib Accountability		X		X	X	X	X	X	X	
Idelalisib Administration [6]		→		→	→	→	→	→	→	
BI 836826 Administration [7]		X		X	X	X	X	X	X	
Adverse Events		X		X	X	X	X	X	X	X
Concomitant Medication		X		X	X	X	X	X	X	X

1 Chemistry & hematology will be obtained a minimum of 3 times in the first week following completion of the first 50% dose of BI 836826 on Day 9; and once after the first full dose of BI 836826 on Day 22, then a minimum of weekly x 6 weeks, then prior to each BI 836826 infusion. All subjects should have blood counts monitored at least every two weeks for the first 6 months of idelalisib treatment. For subjects who develop ANC 0.5 to < 1.0 Gi/L, blood counts should be monitored at least weekly

2 CMV surveillance for active disease must be conducted approximately every 4 weeks throughout the course of idelalisib treatment.

3 Samples for immune monitoring were drawn at Baseline prior to the first dose of idelalisib. With the implementation of Amendment 4, only CD4 will be collected at the time points specified.

4 With the implementation of Amendment 4, PK and biomarker samples are no longer being collected and subjects are past Week 16. Samples for BI 836826 anti-drug antibody testing will be drawn at the time points indicated. For additional information see the protocol Appendix Table 2 PK and Anti-Drug Antibody Sampling and the Laboratory Manual.

[redacted]

6 Idelalisib is taken BID; on BI 836826 dose days the morning dose is taken in the clinic approximately 60 minutes prior to starting the BI 836826 infusion
7 BI 836826 given via IV infusion at the indicated time points, beginning with 10 mg and ramping up through 50% to 100% of the intended dose over 4 weeks
8 The 30-day Follow-up assessment will be done following last dose of BI 836826 (no later than Week 50).