1.0 Title Page

Statistical Analysis Plan

Study M14-032

A Phase 2 Open-Label Study of the Efficacy and Safety of ABT-199 (GDC-0199) in Chronic Lymphocytic Leukemia Subjects with Relapse or Refractory to B-Cell Receptor Signaling Pathway Inhibitor Therapy

Date: 09 Nov 2018

Version 5.0

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3.0 Introduction

This statistical analysis plan (SAP) describes the fifth interim statistical analyses for venetoclax (ABT-199/GDC-0199) Protocol M14-032 Amendment 4 dated 13 September 2016. It will provide details of statistical methods and describe analysis conventions to guide the statistical programming work.

Unless noted otherwise, all analyses will be performed using SAS® version 9.3 (SAS Institute Inc., Cary, NC 27513) under the UNIX operating system.

4.0 Study Objectives, Design and Procedures

4.1 Objectives

Primary Objective:

The primary objective of this study is to evaluate the efficacy and safety of venetoclax monotherapy in subjects with chronic lymphocytic leukemia (CLL) relapsed after or refractory to treatment with B-cell receptor signaling pathway inhibitors. Efficacy will be measured by overall response rate (ORR).

Secondary Objectives:

The secondary objectives are to evaluate the duration of overall response, time to progression (TTP), progression free survival (PFS), event free survival (EFS), time to first response, and overall survival (OS).

Exploratory Objectives:

- Time to next anti-CLL treatment (TTNT)
- Minimal residual disease (MRD) will be assessed in the peripheral blood and bone marrow (BM) by flow cytometry and PCR
- Health Economic and Patient-Reported Outcome Measures will include the EORTC QLQ-C30 and EORTC QLQ CLL16 (a measure of health-related

quality of life specific to CLL) and the EQ-5D-5L (measure of general health status) including EQ-5D-VAS.

Study Design and Plan

This is an open-label, non-randomized, two arm, and multicenter study to determine the efficacy and safety of venetoclax monotherapy in subjects with CLL relapsed/refractory to treatment with B-cell receptor signaling pathway inhibitors and is sponsored by AbbVie in collaboration with Genentech/Roche.

This study is designed to enroll approximately 120 subjects, who have CLL that is refractory to treatment with ibrutinib and/or idelalisib, has relapsed on treatment or experienced progression after discontinuation of either one of these agents.

Two arms and an expansion cohort will be implemented to enroll as follows:

- Arm A with approximately 40 subjects that have ibrutinib-resistant with relapsed or refractory CLL.
- Arm B with approximately 20 subjects that have idelalisib-resistant with relapsed or refractory CLL.
- Expansion Cohort with approximately 60 subjects that have either ibrutinib-resistant or idelalisib-resistant with relapsed or refractory CLL. Subjects who have received both agents and any additional interim therapy will be enrolled into the corresponding arm based on their most recent treatment.

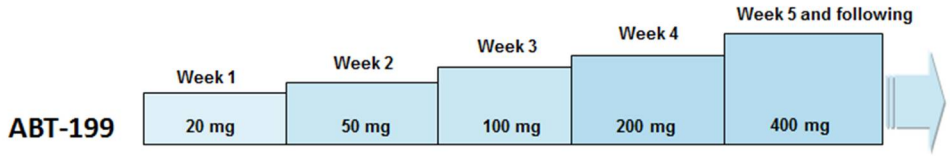
Subjects in this study will be enrolled at approximately 15 research sites.

The study was designed to enroll approximately 120 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. Therefore, if the target number of subjects has been enrolled, there is a possibility that additional subjects in screening will not be enrolled.

Dosing Schedule Overview

Venetoclax was administered orally once daily (QD), continuously. To mitigate the risk for tumor lysis syndrome (TLS), a lead-in period (up to 5 weeks) was employed to evaluate a step wise dose escalation as specified in the protocol, and Figure 1.

Figure 1. Dosing Schematic



4.2 Sample Size

There are no planned hypotheses testing on the primary endpoint overall response rate (ORR). ORR will be presented by a point estimate and its corresponding 95% confidence interval. A sample size of 20 subjects ensures that the distance of true rate will be within 23% of the observed rate with 95% confidence and a sample size of 60 subjects ensures that the distance of true rate will be within 14% of the observed rate with 95% confidence.

Table 1. Sample Size Calculation

Number of Subjects (N)	Distance of True Rate from Observed Rate
20	23%
40	17%
60	14%

4.3 Interim Analysis

To support regulatory submission of venetoclax with indication of relapsed/refractory CLL, the interim analyses were conducted with the corresponding data cutoff dates illustrated in Table 2.

4.4 Efficacy Analyses and Safety Evaluations

Table 2. Summary of Interim Analyses with Cutoff Dates and Data Included

Analysis Number/ Database Version	Cutoff Date	Efficacy Data Included	Safety Data Included
1/M14032E	30 April 2015	Subjects with Investigator assessed response/progression data: N = 28. Subjects with IRC assessed response/progression data: N = 0.	All subjects: N = 28.
2/M14032O	10 June 2016	Subjects with Investigator assessed response/progression data: N = 64. Subjects with IRC assessed response/progression data: N = 64.	All subjects: N = 109.
3/M14032Q	31 January 2017	Subjects with Investigator assessed response/progression data: N = 127. Subjects with IRC assessed response/progression data: N = 64.	All subject: N = 127.
4/M14032T	31 January 2017	Subjects with Investigator assessed response/progression data: N = 127. Subjects with IRC assessed response/progression data: N = 97.	All subjects: N = 127.
5/M14032AA	26 July 2017	Subjects with Investigator assessed response/progression data: N = 127. Subjects with IRC assessed response/progression data: N = 127.	All subjects: N = 127.
6/M14032AE	30 March 2018	Subjects with Investigator assessed response/progression data: N = 127. Subjects with IRC assessed response/progression data: N = 127.	All subjects: N = 127.

Database versions for previous and current interim CSRs are summarized below:

- M14032E for the 1st interim CSR (R&D/14/1069), which was used for venetoclax Submission in U.S.
- M14032O for the 2nd interim CSR (R&D/16/0802), which was used for venetoclax Submission in Russia and Switzerland.
- M14032Q for the 3rd interim CSR (R&D/17/0383), which was used for venetoclax Submission in Canada.

- M14032T for the 4th interim CSR (R&D/17/0573), which was used for venetoclax supplemental Submission in U.S.
- M14032AA for the 5th interim CSR (R&D/17/1058), which was used for venetoclax Commitment in EU.
- M14032AE for the 6th interim CSR (R&D/18/0885), which will be used for venetoclax Post Marketing Commitment for FDA using updated IRC data as of 30 March 2018.

All data specified in Table 2 from dosed subjects up to the corresponding cutoff date will be included in the corresponding interim analysis. Efficacy and safety analyses will be performed for the subjects in the Main and Expansion Cohort. Efficacy and safety data up to and including the cutoff date will be collected. During this data collection period, active subjects will continue to receive venetoclax, as applicable. When data collection is complete and all data management quality assurance (QA) and quality control (QC) procedures are performed, the clinical database data will be extracted for documentation and statistical analyses. Any active subjects will continue to receive venetoclax until they discontinue or for up to 2 years from the date of the last subject enrolled in study. Once the last enrolled subject discontinues/completes the study, the study will be considered complete and all remaining data will be collected and entered into the clinical database.

5.0 Analysis Populations

5.1 Definition for Analysis Populations

Efficacy and safety analyses will be performed for all subjects in the Main and Expansion Cohort who received at least one dose of venetoclax. Subjects in the Expansion Cohort will be categorized to either Arm A Expansion or Arm B Expansion based on their last received BCRi regimens. Both efficacy and safety analyses will be performed for ibrutinib and idelalisib failure subjects with the following 9 groups: Arm A, Arm B, Main Cohort Total, Arm A Expansion, Arm B Expansion, Expansion Cohort Total, Arm A Total, Arm B Total, and All Subjects.

5.2 Variables Used for Stratification of Randomization

There is no randomization for this trial.

6.0 Analysis Conventions

Definition of Baseline

The baseline value (except for laboratory variables) is defined as the last non-missing measurement collected before the first dose of venetoclax. The baseline value for laboratory variables will be defined as:

- For subject hospitalized for TLS prophylaxis, the baseline value will be the lab value taken at hospital admission prior to the subject receiving hydration for TLS prophylaxis (the day prior to the first dose of venetoclax).

For subject not hospitalized for TLS prophylaxis, the baseline value will be the 0 hour lab draw prior to the first dose of study drug on Day 1.

Definition of Final Observation

The final observation (Final Visit) is defined as the last non-missing observation collected within 30 days following the last dose of venetoclax.

Definition of Treatment Days (Days Relative to the First Dose of Venetoclax)

Treatment (Rx) days are calculated for each time point relative to the first dose date of venetoclax. They are defined as the number of days between the day of the first dose of venetoclax and the specific time point. Rx days are negative values when the time point of interest is prior to the first venetoclax dose day. Rx days are positive values when the time point of interest is after the first venetoclax dose day. The day of the first dose of venetoclax is defined as Rx Day 1, while the day prior to the first venetoclax dose is defined as Rx Day –1 (there is no Rx Day 0).

Definition of Analysis Windows

For quality of life, the time window is specified in Table 3.

Table 3. Time Windows for Quality of Life

Scheduled Visit	Nominal Day	Time Window (Study Rx Day Range)
Week 1 Day 1	Baseline	See the baseline definition
Week 24 Day 1	162	[149, 176]
Week 36 Day 1	246	[233, 288]
Every 12 Weeks from Week 36 Day 1	Rx day of Week X Day 1	[Rx day of Week (X) Day 1 – 6 weeks to Rx day of Week (X) Day 1 + 6 weeks]
Final Observation		Last value within 30 days of last dose of Venetoclax

Note: EQ-5D-5L and EQ-5D-VAS will be assessed at Week 1 Day 1, Week 24 Day 1, every 12 weeks starting with Week 36, and at the Final Visit. EORTC QLQ-C30 and EORTC QLQ-CLL16 will be assessed at Week 1 Day 1, Week 24 Day 1, every 12 weeks starting with Week 36, at the Final Visit.

7.0 Subject Disposition

The number and percentage of subjects will be summarized for each of the following categories, for overall and by country:

- Subjects enrolled into the study.
- Subjects who discontinued the study – overall and for each reported primary reason.
- Subjects who discontinued venetoclax – overall and for each reported primary reason.

8.0 Demographics, Baseline Characteristics, Medical History, and Previous Concomitant Medications

8.1 General Consideration

All demographic, baseline characteristics, medical history, prior and concomitant medication summaries will be performed on the analysis sets specified in Section 8.2.

8.2 Demographic and Baseline Characteristics

All baseline summary statistics and analyses are based on characteristic prior to the first dose of venetoclax. The following demographic and baseline characteristics will be summarized:

- Age
- Gender
- Race
- Region (US, EU, ROW)
- Tobacco use
- Alcohol use
- ECOG performance status
- LDH
- Prior number of oncology therapies
- 17p deletion status
- Rai staging at diagnosis
- Binet staging at diagnosis
- IGVH status
- ZAP-70
- CD-38
- Beta 2-microglobulin
- TP53 mutation
- 11q
- 13q
- 12q trisomy
- ALC ($< 25 \times 10^9$/L, $\geq 25 \times 10^9$/L)
- ALC ($< 100 \times 10^9$/L, $\geq 100 \times 10^9$/L)
- Nodal size (≥ 5 cm, < 5 cm)
- Nodal size (≥ 10 cm, < 10 cm)

- TLS risk category (low, medium, or high)

The distributions of the continuous demographic and baseline variables will be summarized with the number of non-missing observations, mean, standard deviation, and median, as well as the minimum and maximum values.

For the categorical variables, the frequency and percentages of subjects within each outcome will be summarized. The number of subjects with missing information will also be summarized.

8.3 Medical History

Medical history data will be summarized and presented using body systems and conditions/diagnoses as captured on the CRF. The body systems will be presented in alphabetical order and the conditions/diagnoses will be presented in alphabetical order within each body system. The number and percentage of subjects with a particular condition/diagnosis will be summarized. Subjects reporting more than one condition/diagnosis within a body system will be counted only once for that body system.

8.4 Previous Treatment and Concomitant Medications

A prior medication is defined as any medication taken prior to the first dose of venetoclax. A concomitant medication is defined as any medication that started prior to the first dose of venetoclax and continued to be taken after the first dose of venetoclax or any medication that started after the first dose of venetoclax, but not after the last dose of venetoclax. The number and percentage of subjects who have taken medications will be summarized by generic drug name for prior medications, concomitant medication, and prior oncology therapies. In addition, the number and percentage of subjects who have taken zero, one, two, three, four, and five or more drugs will be summarized for prior medications, concomitant medications, and prior oncology therapies.

For summaries of concomitant medications, if an incomplete start date was collected for a medication, the medication will be assumed to be a concomitant medication unless there is evidence that confirms that the medication was not a concomitant medication (e.g., the medication end date was prior to the first dose of venetoclax).

A subject who reports the use of two or more medications will be counted only once in the summary of "Any Concomitant Medication." A subject who reports two or more uses of the same medication will be counted only once in the total for the associated generic drug name. Similar rules apply to prior medications as well.

9.0 Venetoclax Exposure and Compliance

The duration of exposure to venetoclax will be summarized. Duration of exposure is defined for each subject as (last dose date – first dose date) + 1. Duration of exposure will be summarized using the following statistics: sample size (N), mean, standard deviation, median, and range. In addition, the number and percentage of subjects exposed to venetoclax will be summarized for the following categories of exposure duration: 0 to 5 weeks (1 day to ≤ 35 days), > 5 weeks to 8 weeks (> 35 days to 56 days), > 8 weeks to 12 weeks (> 56 days to 84 days), > 12 weeks to 16 weeks (> 84 days to 112 days), > 16 weeks to 20 weeks (> 112 days to 140 days), > 20 weeks to 24 weeks (> 140 days to 168 days), > 24 weeks to 28 weeks (> 168 days to 196 days), > 28 weeks to 32 weeks (> 196 days to 224 days), > 32 weeks to 36 weeks (> 224 days to 252 days), > 36 weeks to 48 weeks (> 252 days to 336 days), > 48 weeks to 60 weeks (> 336 days to 420 days), and > 60 weeks (> 420 days).

The compliance based on investigator opinion for each subject will be provided in the listing.

10.0 Efficacy Analysis

10.1 General Considerations

No statistical testing will be performed for the efficacy endpoints. Further details on the analysis sets used will be specified in efficacy analyses described below.

10.2 Efficacy Analyses per Investigators' Review

10.2.1 Primary Efficacy Analyses

The primary efficacy endpoint will be overall response rate (ORR) – the proportion of subjects with an overall response (per the investigator assessment) will be calculated for all subjects based on 2008 Modified IWCLL NCI-WG criteria.

In addition, the ninety-five percent (95%) confidence interval based on binomial distribution (Clopper-Pearson exact method) will be constructed for the calculated ORR.

The assessment of ORR will be performed for subjects in the Main Cohort (by Arm A and Arm B) and the Expansion Cohort (by Arm A Expansion and Arm B Expansion as defined in Section 5.1) separately, and combined (by Main Cohort Total, Expansion Cohort Total, Arm A total, Arm B total, and all subjects). Subjects who have not had a confirmed response prior to the data "cutoff" date defined in Section 4.4 will be considered to be non-responders.

10.2.2 Secondary Efficacy Analyses

Key secondary efficacy endpoints will include duration of overall response, time to progression, progression-free survival, and overall survival.

Duration of overall response will be defined as the number of days from the date of first response (CR or PR) to the earliest recurrence or PD. If a subject is still responding, then the subject's data will be censored at the date of the subject's last available disease assessment. For subjects who never experience response, the subject's data will be censored on the date of first dose. Duration of overall response will be analyzed by

Kaplan Meier methodology using data for all subjects. Median duration of overall response will be calculated and the corresponding 95% confidence interval will be presented.

Time to progression (TTP) will be defined as the number of days from the date of first dose to the date of earliest disease progression. All disease progression will be included regardless whether the event occurred while the subject was taking the study drug or had previously discontinued the study drug. If the subject does not experience disease progression, then the data will be censored at the date of last available disease assessment. Data for patients who receive non-protocol, CLL therapy prior to disease progression will be censored at the last disease assessment prior to receiving non-protocol therapy. Data for subjects without any disease assessments performed after the baseline visit will be censored at the time of dosing plus 1 day. TTP will be analyzed by Kaplan-Meier methodology using data for all dosed subjects. Median time TTP will be calculated and 95% confidence interval for median time TTP will be presented.

Progression-free survival (PFS) will be defined as the number of days from the date of first dose to the date of earliest disease progression or death. All disease progression will be included regardless whether the event occurred while the subject was taking the study drug or had previously discontinued the study drug. If the subject does not experience disease progression or death, then the data will be censored at the date of last disease assessment. Data for patients who receive non-protocol, CLL therapy prior to disease progression will be censored at the last disease assessment prior to receiving non-protocol therapy. Data for subjects without any disease assessments performed after the baseline visit will be censored at the time of dosing plus 1 day. PFS will be analyzed by Kaplan-Meier methodology using data for all dosed subjects. Median time PFS will be calculated and 95% confidence interval for median time PFS will be presented.

Event-free survival (EFS) is defined as the number of days from the date of first dose to the date of earliest confirmation of disease progression, death, or start of a new anti-leukemic therapy. If the specified event (disease progression, death, start of a new anti-leukemic treatment) does not occur, patients will be censored at the date of last disease

assessment. Data for subjects without any disease assessments performed after the baseline visit will be censored at the date of first dose plus 1 day. EFS will be analyzed by Kaplan-Meier methodology. EFS will be calculated and 95% confidence interval for median EFS will be presented.

Time to first response will be defined as the number of days from the date of first dose to the date of the first sign of response (CR, CRi, nPR, or PR) given the subject has had a confirmed CR, CRi, nPR, or PR per the 2008 Modified IWCLL NCI-WG criteria. The first response can be an assessment by physical exam as long as the results are later confirmed per the 2008 Modified IWCLL NCI-WG criteria. For subjects who never experience a response, the subject's data will not be included in the analysis. Descriptive statistics (mean, standard deviation, median, and range) and the 95% confidence interval of the mean will be presented.

Overall survival (OS) will be defined as number of days from the date of first dose to the date of death for all dosed subjects. For subjects who did not die, their data will be censored at the date of last study visit or the last known date to be alive, whichever is later. OS will be analyzed by Kaplan-Meier methodology using data from all dosed subjects. Median time survival will be estimated and 95% confidence interval for the median time survival will be presented.

10.3 Efficacy Analyses per Independent Review Committee

An Independent Review Committee (IRC) will evaluate disease progression and response. The following efficacy endpoints, described in details in Section 10.2, overall response rate, duration of response, time to progression, and progression-free survival based on this IRC review, will be analyzed.

10.4 Additional Exploratory Efficacy Analyses

Additional efficacy endpoints to be analyzed for the Main and Expansion Cohort subjects are time to next anti-leukemia treatment, MRD response rate, and Health Economic and Patient Reported Outcome measures.

Time to next anti-leukemia treatment will be defined as the number of days from the date of the first dose to the date of first dose of any non-protocol anti-leukemia therapy (NPT) or death from any cause. For subjects who did not take NPT, the data will be censored at the last known date to be free of NPT. TTNT will be analyzed by Kaplan-Meier methodology. Median TTNT time will be calculated and 95% confidence interval for median TTNT time will be presented.

The rate of MRD response in subjects will be defined as the proportion of subjects who had MRD negative status. All dosed patients will be included in the calculation of MRD response rate, indeterminate or missing samples will be considered MRD positive for the calculation. Ninety-five percent (95%) confidence intervals based on the binomial distribution (Clopper-Pearson exact method) will be provided.

Health Economic and Patient Reported Outcome measures will include the EORTC QLQ-C30, QLQ-CLL16 (a measure of health related quality of life specific to CLL), and the EQ-5D-5L (measure of general health status) and EQ-5D-VAS.

The EORTC QLQ-C30 consists of a Global Health Status/QoL scale,
five Functional scales (Cognitive Functioning, Social Functioning, Physical Functioning, Emotional Functioning, and Role Functioning), and nine Symptom scales/items (Fatigue, Insomnia, Appetite Loss, Pain, Constipation, Diarrhea, Dyspnea, Financial Difficulties, and Nausea and Vomiting).

Each of these scales will be calculated as per the EORTC scoring manual, and summarized (mean, standard deviation, median) at each assessment; in addition mean change in each of these values (final assessment versus baseline) will be calculated to identify any statistically significant differences versus baseline.

The five EORTC QLQ-CLL16 domains (Fatigue, Treatment Side Effects and Disease Symptoms, Infection, Social Activities, Future Health Worries) will be summarized (mean, standard deviation, and median) at each assessment; in addition mean change in

each of these values (final assessment versus baseline) will be calculated to identify any statistically significant differences versus baseline.

The EORTC QLQ-C30 and EORTC QLQ-CLL16 will also be administered through post treatment. To explore the trend of time, a repeated measures analysis will be performed for the scheduled times of measurement without imputation of missing values.

The EuroQol 5 Dimensions (EQ-5D-5L) is a generic preference instrument that has been validated in numerous populations. The EQ-5D-5L has five dimensions: mobility, self care, usual activities, pain/discomfort and anxiety/depression. These dimensions are measured on a five level scale: no problems, slight problems, moderate problems, severe problems, and extreme problems. The EQ-5D-5L also contains a visual analog scale (VAS) to assess the subject's overall health.

For each of the five dimensions of the EQ-5D-5L, the number and percentage of subjects at each level will be summarized at each assessment. The Visual Analog Scale (VAS) will also be summarized (mean, standard deviation, median) at each assessment; in addition mean change in VAS values (final assessment versus baseline) will be calculated to identify any statistically significant differences versus baseline.

10.5 Subgroup Analyses of Efficacy

ORR will be assessed by the following subgroups:

- Age (< 65 years versus ≥ 65 years, < 75 years versus ≥ 75 years)
- Gender (Male, Female)
- Race (White, Black, Asian, and other)
- ECOG performance status (0, 1, 2)
- Prior number of oncology therapies (1, 2, 3, 4, ≥ 5)
- Prior number of BCRi regimens (< 2, ≥ 2)
- Fludarabine refractory (yes, no)
- Prior chemoimmunotherapy (yes, no)

- 17p deletion (Deleted, Not deleted)
- TP53 mutation status (Yes, No)
- TP53 mutation and/or 17p del (yes, no)
- Rai staging at diagnosis (Stage 0, Stage 1, Stage 2, Stage 3 or Stage 4)
- Binet staging at diagnosis (Stage A, Stage B, or Stage C)
- ALC ($< 25 \times 10^9$/L, $\geq 25 \times 10^9$/L)
- ALC ($< 100 \times 10^9$/L, $\geq 100 \times 10^9$/L)
- Nodal size (≥ 5 cm, < 5 cm)
- Nodal size (≥ 10 cm, < 10 cm)

ORR and their 95% CIs will be reported for each level of subgroups in a forest plot. DOR, PFS, EFS, TTP, OS, and TTNT will also be assessed by 17p deletion, *TP53* mutation status, and *TP53* mutation and/or 17p deletion.

10.6 Handling of Multiplicity

There will be no multiplicity adjustments performed.

11.0 Safety Analysis

Safety assessments will only include subjects who have received at least one dose of venetoclax in the Main Cohort (by Arm A and Arm B) and the Expansion Cohort (by Arm A Expansion and Arm B Expansion), and total (Main Cohort Total, Expansion Cohort Total, Arm A Total, Arm B Total, and all subjects).

11.1 Analysis of Treatment-Emergent Adverse Events

All summaries/analyses involving AEs will include treatment-emergent adverse events (TEAE) only, unless otherwise specified. TEAE are defined as any event with onset after the first dose of venetoclax and no more than 30 days after the last dose of venetoclax. Events where the onset date is the same as the venetoclax start date are assumed to be treatment-emergent, unless the venetoclax start time and the AE start time are collected and the AE start time is prior to the venetoclax start time. If an incomplete onset date was

collected for an AE, the AE will be assumed to be treatment-emergent unless there is evidence that confirms that the AE was not treatment-emergent (e.g., the AE end date was prior to the date of the first dose of venetoclax).

Adverse event data will be summarized and presented using primary MedDRA system organ classes (SOCs) and preferred terms (PTs) according to the MedDRA coding dictionary version 17.1 or higher.

The number and percentage of subjects experiencing treatment-emergent adverse events will be summarized for the following adverse event summaries:

- Any treatment-emergent adverse event.
- Any treatment-emergent adverse event with reasonable possibility related to venetoclax by the investigator.
- Any treatment-emergent NCI toxicity (CTCAE V4.0) grade 3, 4, or 5 adverse events.
- Any treatment-emergent NCI toxicity (CTCAE V4.0) grade 3 or 4 adverse event.
- Adverse events broken down by NCI toxicity grade (Severity).
- Any treatment-emergent serious adverse event.
- Any treatment-emergent adverse event leading to discontinuation of venetoclax.
- Any treatment-emergent adverse event leading to discontinuation of venetoclax due to progression.
- Any treatment-emergent adverse event leading to discontinuation of venetoclax not due to progression.
- Any treatment-emergent adverse event leading to venetoclax interruption.
- Any treatment-emergent adverse event leading to venetoclax reduction.
- Any treatment-emergent adverse event leading to death.

In addition, adverse events of special interest will be summarized. The list of adverse events of special interest that will be presented is shown in Table 4.

Table 4. Adverse Events of Special Interest

Adverse Event of Special Interest/Lab Abnormality	Search Criteria
Tumor Lysis Syndrome (AE) Tumor Lysis Syndrome (Howard Criteria)	SMQ – "Tumor Lysis Syndrome" (narrow); ≥ 2 of the following metabolic abnormalities within 24 hours of each other (applicable to post-dose lab values only): Uric Acid > 476 µmol/L or 8.0 mg/dL; Potassium > 6.0 mmol/L; Inorganic Phosphorus > 1.5 mmol/L or 4.5 mg/dl; Calcium < 1.75 mmol/L or 7.0 mg/dl
Grade ≥ 3 neutropenia	PT terms – "neutropenia," "neutrophil count decreased," "febrile neutropenia," "agranulocytosis," "neutropenic infection," and "neutropenic sepsis"
Grade ≥ 3 infection, including opportunistic infections	SOC of "infections and infestations"
Second primary malignancy	SMQ – "malignant tumours" (narrow) and "myelodysplastic syndromes" (narrow)
Drug-Induced Liver Injury	PT Term – Drug induced liver injury;
Grade ≥ 3 thrombocytopenia	PT terms – "thrombocytopenia" and "platelet count decreased"

ALT = alanine aminotransferase; AST = aspartate aminotransferase; PT = preferred term; SMQ = Standardised MedDRA Query; SOC = system organ class; ULN = upper limit of normal

11.2 Deaths

The number of deaths will be summarized (1) for deaths occurring while the subject is still receiving venetoclax in this study, (2) for deaths occurring off treatment within 30 days after the last dose of venetoclax.

11.3 Analysis of Laboratory and Vital Signs Data

The value for baseline used in laboratory and vital sign analyses is defined in Section 6.0.

11.3.1 Analyses of Shift from Baseline in Clinical Laboratory Data

For shifts relative to National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE version 4.0), baseline and post-baseline laboratory observations

(maximum and final) will be categorized as grade 0, grade 1, grade 2, grade 3, or grade 4 according to NCI CTCAE grade version 4.

The baseline and final grades will be defined respectively as the grade of the last measurement collected prior to the first dose of venetoclax unless specified differently in Section 6.0, and as the last post-baseline measurement collected no more than 30 days after the last dose of venetoclax. An exception will be used for those subjects enrolled with a baseline value of neutrophils less than 1000/μL requiring G-CSF support to meet entry criteria. For these subjects, the last value pre-G-CSF administration will be the baseline.

The maximum NCI toxicity grade value is the value with highest NCI toxicity grade collected after the first dose of venetoclax and within 30 days following the last dose of venetoclax. In cases where multiple values are collected on the same day, the maximum grade value will be selected as the value for that day.

For each variable, shift tables will be generated that cross tabulate the number of subjects with baseline values of grade 0, grade 1, grade 2, grade 3, or grade 4 versus maximum or final observations of grade 0, grade 1, grade 2, grade 3, or grade 4.

Detailed listings of data for subjects experiencing NCI CTCAE grade 3 to 4 blood chemistry and hematology values will be provided. All measurements collected, regardless of the number of days after the last dose of venetoclax, will be included in these listings.

Potential Drug-Induced Liver Injury (DILI)

Potential DILI will be determined by searching post-dose laboratory ALT or AST > 3 × ULN in combination with total bilirubin > 2 × ULN that occur within 72 hours of each other.

Laboratory Search Strategy for TLS

To determine if subjects' laboratory values qualify for TLS, the Howard criteria[1] will be used. The Howard criteria for TLS comprise of ≥ 2 of the following electrolyte abnormalities within 24 hours of each other and are specified in Table 5.

Table 5. Howard Criteria for TLS

Element	Value
Uric Acid	< 476 µmol/L or 8 mg/dL
Potassium	< 6.0 mmol/L or 6 mEq/L
Inorganic Phosphorus	< 1.5 mmol/L
Calcium	< 1.75 mmol/L

The following summaries of laboratory TLS as assessed by Howard criteria will be provided:

- Number and percentage of subjects meeting the Howard criteria for laboratory TLS (at least two values meeting the criteria in Table 5, occurring within 24 hours of each other).
- Listing of all the lab test values for each subject meeting the Howard criteria for laboratory TLS.

11.3.2 Assessment of Potentially Clinically Significant Vital Signs Values

For selected vital signs variables, a listing of all observations collected will be generated for subjects that had at least one post-baseline observation meeting pre-defined criteria for potentially clinically significant values. The number and percentage of subjects who have at least one post-baseline observation meeting the pre-defined criteria for potentially clinically significant values will be provided for each variable.

Pre-defined criteria for potentially clinically significant vital signs values are given in Table 6 below based on CTCAE criteria:

Table 6. Criteria for Potentially Clinically Significant Laboratory Values – Vital Signs Variables

Vital Signs Variables	Criterion	Definition of Potentially Clinically Significant
Systolic blood pressure	High	Value ≥ 160 mmHg
Diastolic blood pressure	High	Value ≥ 100 mmHg
Heart rate	Low	Value < 50 bpm
	High	Value ≥ 120 bpm
Temperature	Low	Value < 36°C
	High	Value ≥ 38.5°C

12.0 Pharmacokinetic Analyses

Plasma concentrations of venetoclax and possible metabolites(s) will be listed for each subject by scheduled visit. Summary statistics will also be computed for each scheduled visit.

13.0 Summary of Changes

For the 6th interim clinical study report, the following changes have been implemented into the current statistical analysis plan V5, compared with SAP V4:

- The cutoff date 30 March 2018 for Interim CSR #6 was added in Table 2 for updated Investigator and IRC assessed data.

14.0 References

1. Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. N Engl J Med. 2011;364(19):1844-54.

Appendix A. List of Abbreviations

AE	Adverse Event
BM	Bone Marrow
CLL	Chronic Lymphocytic Leukemia
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DILI	Drug-Induced Liver Injury
DOR	Duration of Overall Response
ECOG	Eastern Cooperative Oncology Group
G-CSF	Granulocyte-colony stimulating factor
IWCLL	International Workshop for Chronic Lymphocytic Leukemia
MedDRA	Medical Dictionary for Regulatory Activities
MRD	Minimal Residual Disease
NCI	National Cancer Institute
NCI-WG	National Cancer Institute-Working Group
NPT	Non-protocol Anti-leukemia Therapy
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-free Survival
QA	Quality Assurance
QC	Quality Control
QD	Once Daily
SAP	Statistical Analysis Plan
SMQ	Standard MedDRA Query
TEAE	Treatment-emergent Adverse Event
TLS	Tumor Lysis Syndrome
TTNT	Time to next anti-CLL treatment
TTP	Time to Progression
ULN	Upper Limit of Normal