1.0 Title Page

Statistical Analysis Plan

Study M13-982

A Phase 2 Open-Label Study of the Efficacy of ABT-199 in Subjects with Relapsed or Refractory Chronic Lymphocytic Leukemia Harboring the 17p Deletion

Date: 27 April 2018

Version 3.0

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3.0 Introduction

This statistical analysis plan (SAP) describes the full statistical analyses for Venetoclax (ABT-199) original protocol and all protocol amendments for Study M13-982. The latest Protocol Amendment 6 is dated 28 February 2017. 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

Main Cohort

The primary objective of this cohort is to evaluate the efficacy of Venetoclax monotherapy in subjects with relapsed or refractory chronic lymphocytic leukemia (CLL) harboring the 17p deletion. Efficacy will be measured by overall response rate (ORR) based on an independent review committee (IRC) assessment.

The secondary objectives are to evaluate the ORR by investigator assessment, complete remission rate (CR rate), partial remission rate (PR rate), duration of overall response (DoR), progression-free survival (PFS), event free survival (EFS), time to progression (TTP), time to first response, time to 50% reduction in absolute lymphocyte count (ALC), overall survival (OS) and percent of subjects who move on to stem cell transplant. The safety and tolerability of Venetoclax in subjects with relapsed or refractory CLL harboring 17p deletion will also be evaluated.

Safety Expansion Cohort

The primary objective of the safety expansion cohort is to evaluate the safety of Venetoclax in approximately 50 subjects with relapsed or refractory CLL harboring 17p deletion treated per the updated TLS prophylaxis and management measures based on

the analysis conducted on 58 subjects utilizing the TLS prophylaxis and management procedures.

The secondary objectives are to evaluate ORR, CR rate, PR rate, DoR, PFS, EFS, TTP, time to first response, time to 50% reduction in absolute lymphocyte count (ALC), OS, and percent of subjects who move on to stem cell transplant.

Exploratory Objectives

The exploratory objectives which will be evaluated in both cohorts include time to next anti-leukemia treatment (TTNT) and minimal residual disease (MRD) response rate, assessed in the peripheral blood and/or bone marrow (BM). Pharmacokinetics, pharmacogenetics and biomarkers will also be evaluated as exploratory objectives. Health Economic and Patient-Reported Outcome Measures will include the MDASI (measure of subject reported symptoms), 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) and EQ-5D-VAS.

4.2 Study Design and Plan

This is an open-label, single arm, multicenter, global study to determine the efficacy and safety of Venetoclax monotherapy in subjects with relapsed or refractory chronic lymphocytic leukemia harboring 17p deletion sponsored by AbbVie in collaboration with Genentech/Roche.

Subjects in this study were enrolled at 56 research sites.

After the first 21 subjects had completed 12 weeks of study treatment in the Main Cohort, a safety analysis was conducted by an Independent Data Monitoring Committee (IDMC). In the safety expansion cohort, interim safety analysis results will be reviewed by the IDMC after approximately 20 subjects have completed approximately 5 weeks of the lead-in period.

Dosing Schedule Overview

Venetoclax was administered orally once daily (QD), continuously. To mitigate the risk for 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 and Figure 2.

Figure 1. Dosing Schematic – Main Cohort

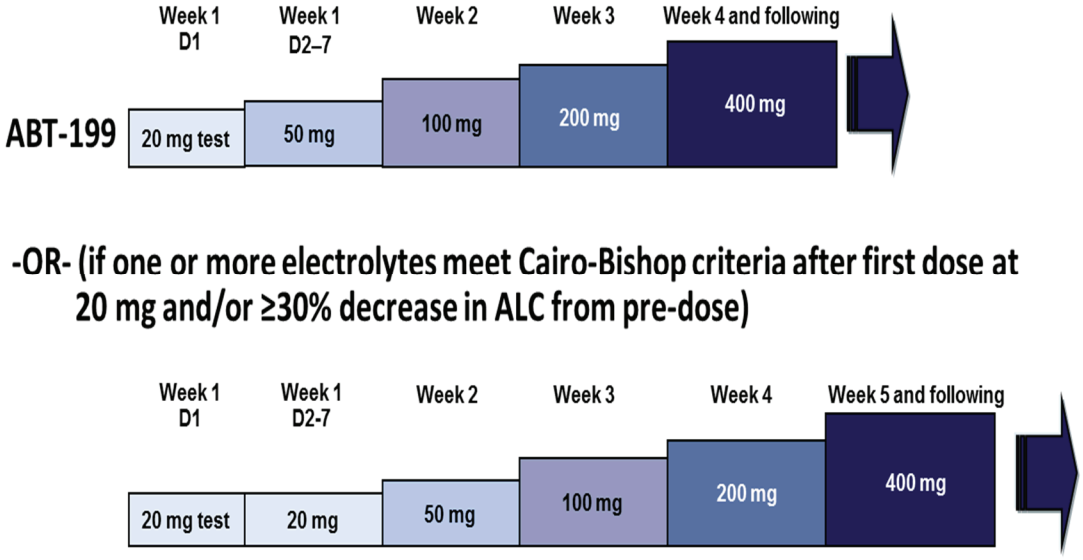
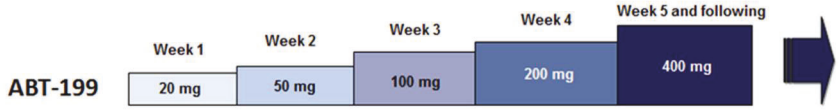


Figure 2. Dosing Schematic – Safety Expansion Cohort



4.3 Sample Size

Approximately 100 subjects were planned to be enrolled in the main cohort to assess the safety and efficacy of Venetoclax in subjects with relapsed or refractory chronic lymphocytic leukemia (CLL) harboring the 17p deletion. With this sample size, if a rare

adverse event occurs at a rate of 2%, then the probability of observing at least 1 event in a trial with 100 subjects is 86%.

Reported overall response rates (ORR) for CLL subjects with 17p deletion range from approximately 7% to 77% with the higher responses in more novel but also more toxic regimens such as alemtuzumab + steroids.[1] Conventional therapies such as FCR and BR, demonstrated ORRs of 35% and 7%, respectively. Therefore, a therapy providing a significant benefit in overall response rate over a standard rate of 40% would be considered clinically meaningful.

Performing the efficacy analyses at 70 subjects provides at least 90% power (at two-sided alpha of 5%) to reject the null hypothesis of 40% ORR in favor of an alternative hypothesis of 60% ORR. The power calculations for a range of different sample sizes are presented in Table 1.

Table 1. Sample Size Calculation

Subjects (N)	Power (%)
50	76
60	82
70	90
80	93
90	96

For the safety expansion cohort, an additional 50 subjects will be enrolled to assess the modifications made to the initial dosing of Venetoclax for the management of TLS. With this sample size, if a TLS event occurs at a rate of 2%, then the probability of observing at least 1 event in this cohort of 50 subjects is 64%.

4.4 Interim Analysis

4.4.1 Independent Data Monitoring Committee (IDMC)

In the Main Cohort, the safety data from the first 21 subjects who had completed at least 12 weeks of study treatment was reviewed by an Independent Data Monitoring Committee (IDMC). A separate charter was created to provide detailed descriptions of the anticipated schedule of the interim analyses and the IDMC meetings. The IDMC membership, responsibilities and the description of the data coordinating center were documented in the charter. The IDMC received a data summary, which included enrollment data, subject baseline characteristics and safety data.

The IDMC recommended the continuation of the study.

An additional interim analysis of safety data will be reviewed by the IDMC after approximately 20 subjects have completed approximately 5 weeks of the lead-in period in the safety expansion cohort.

4.5 Timing of Efficacy Analyses and Safety Evaluations

To support regulatory submissions and post-approval requirements of Venetoclax for the treatment of relapsed/refractory CLL, interim CSRs were written using efficacy and safety analyses based on the database version and data cutoff dates illustrated in below Table 2, Table 3, and Table 4. Descriptions of the analysis datasets for the analyses are provided in Section 5.1.

There were two IRC assessments in the study. The first IRC assessment was done for the 107 subjects in the main cohort after they completed 36-week disease assessment. The second IRC assessment was done separately at a later date for the 5 frontline subjects from the expansion cohort after they completed 36-week disease assessment. The 107 subjects from the main cohort were not evaluated again in the second IRC assessment.

Table 2. Efficacy and Safety Analyses for the 1st Interim CSR (R&D/14/1067)‡

Cutoff Date[&]		**30APR2015**		
Database Version[&]		**M13982Y**		
Number of Subjects		**N = 107**		**N = 145**
Efficacy Summaries	**Assessment**		**Safety Summaries**	
ORR (CR + CRi + nPR + PR Rates)	IRC	Yes	Adverse Events	Yes (N = 107 + 38**)
	Investigator	Yes	SAEs/Deaths/AEs leading to discontinuation	Yes (N = 107 + 38**)
DoR	IRC	Yes	Labs (Hematology, Chemistry, and Urinalysis)	Yes (N = 107 + 38**)
	Investigator	Yes	Vital Signs	Yes (N = 107 + 38**)
PFS	IRC	Yes		
	Investigator	Yes		
EFS	IRC	Yes		
	Investigator	Yes		
TTP	IRC	Yes		
	Investigator	Yes		
Time to First Response	IRC	Yes		
	Investigator	Yes		
Time to 50% Reduction in ALC		Yes		
OS		Yes		
Percent of Subjects Who Move to Stem Cell Transplant		Yes		
Time to Next Anti-Leukemia Treatment		Yes		
MRD Response Rate	IRC	Yes		
	Investigator	Yes		

Table 2. Efficacy and Safety Analyses for the 1st Interim CSR (R&D/14/1067)‡ (Continued)

Cutoff Date&		**30APR2015**	
Database Version&		**M13982Y**	
Number of Subjects		**N = 107**	**N = 145**
Efficacy Summaries	**Assessment**	**Safety Summaries**	
MDASI, HEOR (EORTC QLQ-C30, EORTC QLQ CLL16, EQ-5D-5L, EQ-5D-VAS)	Yes		

& All data will be included up to the date specified for the identified summaries.

** Subjects from the safety expansion cohort receiving at least one dose of Venetoclax will be included in the safety analyses. The final subject number was determined at the time of the data cutoff.

‡ 1st CSR report was used for the original R/R 17p del CLL NDA. An efficacy and safety analysis will occur when all subjects enrolled in the Main Cohort have completed the 36-week disease assessment.

Table 3. Efficacy and Safety Analyses for the 2nd Interim CSR (R&D/16/0801)‡

Description		**30APR2015 (IRC), 10JUN2016 (INV)***		**10JUN2016**
Database Version&		**M13982Y (IRC), M13982AH (INV)**		**M13982AH**
Number of Subjects		**N = 107 (IRC), 158 (INV)†**		**N = 158†**
Efficacy Summaries	**Assessment**		**Safety Summaries**	
ORR (CR + CRi + nPR + PR Rates)	IRC	Yes (N = 107)	Adverse Events	Yes (N = 107 (main) + 51 (expansion)†
	Investigator	Yes (N = 107 (main) + 51 (expansion)†	SAEs/Deaths/AEs leading to discontinuation	Yes (N = 107 (main) + 51 (expansion)†
DoR	IRC	Yes (N = 107)	Labs (Hematology, Chemistry, and Urinalysis)	Yes (N = 107 (main) + 51 (expansion)†
	Investigator	Yes (N = 107 (main) + 51 (expansion)†	Vital Signs	Yes (N = 107 (main) + 51 (expansion)†
PFS	IRC	Yes (N = 107)		
	Investigator	Yes (N = 107 (main) + 51 (expansion)†		
EFS	IRC	Yes (N = 107)		
	Investigator	Yes (N = 107 (main) + 51 (expansion)†		
TTP	IRC	Yes (N = 107)		
	Investigator	Yes (N = 107 (main) + 51 (expansion)†		
Time to First Response	IRC	Yes (N = 107)		
	Investigator	Yes (N = 107)		
Time to 50% Reduction in ALC		Yes (N = 107)		
OS		Yes (N = 107 (main) + 51 (expansion)†		

Table 3. Efficacy and Safety Analyses for the 2nd Interim CSR (R&D/16/0801)‡ (Continued)

Description		**30APR2015 (IRC), 10JUN2016 (INV)***	**10JUN2016**
Database Version&		**M13982Y (IRC), M13982AH (INV)**	**M13982AH**
Number of Subjects		**N = 107 (IRC), 158 (INV)†**	**N = 158†**
Efficacy Summaries	**Assessment**	**Safety Summaries**	
Percent of Subjects Who Move to Stem Cell Transplant		Yes (N = 107)	
Time to Next Anti-Leukemia Treatment		Yes (N = 107)	No
MRD Response Rate	IRC	Yes (N = 107)	
	Investigator	Yes (N = 107 (main) + 51 (expansion) †	
MDASI, HEOR (EORTC QLQ-C30, EORTC QLQ CLL16, EQ-5D-5L, EQ-5D-VAS)		Yes (N = 107)	

& All data will be included up to the date specified for the identified summaries.

† N = 107 from the main cohort and N = 51 from expansion cohort.

* 10JUN2016 is the Investigator cutoff date; 30APR2015 is the IRC cutoff date.

‡ The 2nd interim CSR was submitted for the FDA expanded monotherapy sNDA for patients with chronic lymphocytic leukemia (CLL) with or without 17p deletion, who have received at least one prior therapy.

Table 4. Efficacy and Safety Analyses for the 3rd Interim CSR (R&D/17/1065)‡

Data Cutoff Date&		**30APR2015 (IRC-Main Cohort) # 29JAN2016 (IRC-5 Frontline Subjects) # 15JUN2017 (INV) #**		**15JUN2017**
(Database Version)&		**M13982Y (IRC-Main Cohort) M13982AE (IRC-5 Frontline Subjects) M13982AL (INV)**		**M13982AL**
Number of Subjects		**N = 112 (IRC)**, 158 (INV)†**		**N = 158†**
Efficacy Summaries	**Assessment**		**Safety Summaries**	
ORR (CR + CRi + nPR + PR Rates)	IRC	Yes (N = 107 + 5)**	Adverse Events	Yes (N = 107 (main) + 51 (expansion)†
	Investigator	Yes (N = 107 (main) + 51 (expansion)†	SAEs/Deaths/AEs leading to discontinuation	Yes (N = 107 (main) + 51 (expansion)†
DoR	IRC	Yes (N = 107 + 5) **	Labs (Hematology, Chemistry, and Urinalysis)	Yes (N = 107 (main) + 51 (expansion)†
	Investigator	Yes (N = 107 (main) + 51 (expansion)†	Vital Signs	Yes (N = 107 (main) + 51 (expansion)†
PFS	IRC	Yes (N = 107 + 5) **		
	Investigator	Yes (N = 107 (main) + 51 (expansion)†		
EFS	IRC	Yes (N = 107 + 5)**		
	Investigator	Yes (N = 107 (main) + 51 (expansion)†	Description	
TTP	IRC	Yes (N = 107 + 5) **		
	Investigator	Yes (N = 107 (main) + 51 (expansion)†		
Time to First Response	IRC	Yes (N = 107 + 5) **		
	Investigator	Yes (N = 107 (main) + 51 (expansion)†		
Time to 50% Reduction in ALC		Yes (N = 107 (main) + 51 (expansion)†		

Table 4. Efficacy and Safety Analyses for the 3rd Interim CSR (R&D/17/1065)‡ (Continued)

Data Cutoff Date[&]		**30APR2015 (IRC-Main Cohort) # 29JAN2016 (IRC-5 Frontline Subjects) # 15JUN2017 (INV) #**	**15JUN2017**
(Database Version)[&]		**M13982Y (IRC-Main Cohort) M13982AE (IRC-5 Frontline Subjects) M13982AL (INV)**	**M13982AL**
Number of Subjects		**N = 112 (IRC) **, 158 (INV)†**	**N=158†**
Efficacy Summaries	**Assessment**	**Safety Summaries**	
OS		Yes (N = 107 (main) + 51 (expansion)†	
Percent of Subjects Who Move to Stem Cell Transplant		Yes (N = 107 (main) + 51 (expansion)†	
Time to Next Anti-Leukemia Treatment		Yes (N = 107 (main) + 51 (expansion)†	
MRD Response Rate	IRC	Yes (N = 107 + 5)**	
	Investigator	Yes (N = 107 (main) + 51 (expansion)†	
MDASI, HEOR (EORTC QLQ-C30, EORTC QLQ CLL16, EQ-5D-5L, EQ-5D-VAS)		Yes (N = 107 (main) + 51 (expansion)†	

& All data will be included up to the date specified for the identified summaries.

† N = 107 from the main cohort and N = 51 from expansion cohort.

** N = 107 from the main cohort and N = 5 from expansion cohort are IRC evaluated.

15JUN2017 is the Investigator cutoff date; 30APR2015 is the IRC cutoff date for the main cohort; 29JAN2016 is the IRC cutoff for the 5 frontline subjects.

‡ The 3rd interim CSR will be submitted to a health authority.

5.0 Analysis Populations

5.1 Definition for Analysis Populations

Efficacy and/or safety analyses will be performed for the following analysis sets. More details about analyses populations for efficacy and safety are shown in Table 5.

All Treated Subjects:

This analysis set contains all subjects who received at least one dose of Venetoclax in either the Main Cohort or Safety Expansion Cohort.

All Treated Subjects in Main Cohort:

This analysis set contains all subjects who received at least one dose of Venetoclax in the Main Cohort.

All Treated Subjects in Main Cohort with 17p Deletion CLL:

This analysis set contains all subjects who received at least one dose of Venetoclax in the Main Cohort and have a confirmation of 17p deletion based on the central laboratory.

Primary Efficacy Subjects:

This analysis set contains the first 70 subjects who received at least one dose of Venetoclax in the Main Cohort and have a confirmation of 17p deletion based on the central laboratory.

Safety Expansion Subjects:

This analysis set contains all subjects who received at least one dose of Venetoclax in the Safety Expansion Cohort.

Frontline CLL Subjects

This analysis set contains all frontline CLL subjects in the study who received at least one dose of Venetoclax. This analysis set will be used for efficacy assessments.

BCRi Failure CLL Subjects

This analysis set contains all BCRi failure subjects who received at least one dose of Venetoclax. This analysis set will be used for efficacy assessments.

Table 5. Analysis Populations for Efficacy and Safety Analyses

Analysis Population	1st Interim CSR		2nd Interim CSR		3rd Interim CSR	
	Efficacy	Safety	Efficacy	Safety	Efficacy	Safety
All Treated Subjects		X*	X	X	X	X
All Treated Subjects in Main Cohort	X		X		X	
All Treated Subjects in Main Cohort with 17p Deletion CLL	X		X		X	
Primary Efficacy Subjects	X		X		X	
Safety Expansion Subjects			X		X	
Frontline CLL Subjects			X		X	
BCRi Failure CLL Subjects	X		X		X	

* Subjects from the safety expansion cohort receiving at least one dose of Venetoclax will be included in the safety analyses. The final subject number was determined at the time of the data cutoff.

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 Rx Days (Days Relative to the First Dose of Venetoclax)

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 visit wise analyses including quality of life and performance status, and visit wise safety analyses, the time windows specified in Table 6, Table 7, and Table 8 describe how efficacy and safety data are assigned to protocol specified visits respectively. Analysis time windows are constructed using the following algorithm:

- Determine the nominal study Rx day for each scheduled visit.
- Determine the window around a specific nominal study Rx day as in Table 6, Table 7 and Table 8.
- If more than one assessment is included in a time window the assessment closest to the nominal day should be used. If there are two observations equal distant to the nominal day the latest one will be used in analyses.
- For laboratory variables with both central and local lab results, the mean change analyses will be performed using the central lab result. For missing central lab results, the local lab will be used to replace the missing value if

available. For the lab parameters of white blood cell (WBC) counts, neutrophil count, platelet count, and hemoglobin an additional analysis of the local result will be provided due to discrepancies observed during the trial between the central and local lab results. These discrepancies between the central result and the local result will be discussed in the CSR. Except for laboratory measurements for TLS, if more than one measurement exists for a subject on a particular day from the central lab, an arithmetic average is calculated and used as the subject's measurement for that day. For TLS laboratory variables where multiple values were collected over the course of a day (4 hours, 8 hours, 12 hours and 24 hours post dose of Venetoclax) all values will be used and no averages will be taken. For the shift tables, all values will be used from both the central and local labs. The highest National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) grade will be used. For potentially clinically significant lab listing, all values from both the central and local labs that meet the NCI CTCAE grade 3 or higher will be reported.

Table 6. Time Windows for Analysis of Hematology, Chemistry Parameters, Vital Signs, and Performance Status

Scheduled Visit	Nominal Day	Time Window (Study Rx Day Range)
Screening	Screening	Screening Visit
Baseline	≤ 1	See the baseline definition (Section 6.0)
Week 1 Day 1	1	[1]*
Week 1 Day 2	2	[2]*
Week 1 Day 3	3	[3]
Week 1 Day 4	4	[4]
Week 1 Day 5	5	[5 – 6]
Week 2 Day 1	8	[7 – 8]*
Week 2 Day 2	9	[9 – 10]
Week 3 Day 1	15	[11 – 15]
Week 3 Day 2	16	[16 – 17]
Week 4 Day 1	22	[18, 22]
Week 4 Day 2	23	[23, 25]
Week 5 Day 1	29	[26, 29]
Week 5 Day 2	30	[30, 39]
Week 8 Day 1	50	[40, 64]
Week 12 Day 1	78	[65, 92]
Week 16 Day 1	106	[93, 120]
Week 20 Day 1	134	[121, 148]
Week 24 Day 1	162	[149, 176]
Week 28 Day 1	190	[177, 204]
Week 32 Day 1	218	[205, 232]
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
Post Treatment		3 month intervals after last study visit

Table 6. Time Windows for Analysis of Hematology, Chemistry Parameters, Vital Signs, and Performance Status (Continued)

* TLS lab draws could occur at 4 hours, 8 hours, 12 hours and 24 hours post dose of Venetoclax for both the 20 mg and 50 mg dosing.

Note: Hematology and chemistry samples will be collected at the Screening Visit, on Week 1 Days –1, 1, 2, 3, 4 and 5 (when applicable), Weeks 2, 3, 4 Days 1 and 2, Week 5 Days 1 and 2 (when applicable), Week 8 Day 1, Week 12 Day 1, Week 16 Day 1, Week 20 Day 1, Week 24 Day 1, Week 28 Day 1, Week 32 Day 1, every 12 weeks starting with Week 36, at least 8 weeks after the CR, CRi or PR criteria for tumor response are first met, at the Final Visit, and every 3 months post treatment. Physical exam will be assessed at the Screening Visit, on Week 1 Day 1, Week 2 Day 1, Week 3 Day 1, Week 4 Day 1, Week 5 Day 1 (when applicable), Week 8 Day 1, Week 12 Day 1, Week 16 Day 1, Week 20 Day 1, Week 24 Day 1, Week 28 Day 1, Week 32 Day 1, every 12 weeks starting with Week 36, at least 8 weeks after the CR, CRi or PR criteria for tumor response are first met, at the Final Visit, and every 3 month post treatment. Vital Signs and ECOG Performance Status will be assessed at the Screening Visit, on Week 1 Day 1, Week 2 Day 1, Week 3 Day 1, Week 4 Day 1, Week 5 Day 1 (when applicable), Week 8 Day 1, Week 12 Day 1, Week 16 Day 1, Week 20 Day 1, Week 24 Day 1, Week 28 Day 1, Week 32 Day 1, every 12 weeks starting with Week 36, and every 3-month post treatment (for vital signs only).

Table 7. Time Windows for Analysis of Urinalysis

Scheduled Visit	Nominal Day	Time Window (Study Rx Day Range)
Screening	Screening	See the baseline definition
Week 24 Day 1	162	[149, 176]
Final Observation		Last value within 30 days of last dose of Venetoclax

Note: Urinalysis will be collected at Screening, on Week 24 Day 1, and at the Final Visit.

Table 8. 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 4 Day 1	22	[17, 25]
Week 12 Day 1	78	[65, 92]
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
Post Treatment		3 month intervals after last study visit

Note: MDASI, EQ-5D-5L and EQ-5D-VAS will be assessed at Week 1 Day 1, Week 4 Day 1, Week 12 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 4 Day 1, Week 12 Day 1, Week 24 Day 1, every 12 weeks starting with Week 36, at the Final Visit, and every 3 months post treatment.

7.0 Patient 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 Venetoclax – overall and for each reported primary reason.

These analyses will be performed on the All Treated Subjects analysis set, All Treated Subjects in the Main Cohort analysis set, and Safety Expansion Subjects analysis set.

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 each section below.

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
- 17p central laboratory testing center
- staging at diagnosis
- IgVH status
- ZAP-70
- CD-38
- Beta 2-microglobulin (≤ 3 mg/L, > 3 mg/L)
- P53 mutation

- 11q
- 13q
- 12q trisomy
- bulky disease [nodes > 5 cm and nodes > 10 cm]
- Absolute Lymphocyte count [$\geq 25 \times 10^9$/L and $\geq 100 \times 10^9$/L]
- Fludarabine refractory
- 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 frequencies and percentages of subjects within each outcome will be summarized. The number of subjects with missing information will also be summarized.

These analyses will be performed on the All Treated Subjects analysis set, All Treated Subjects in the Main Cohort analysis set, All Treated Subjects in the Main Cohort with 17p Deletion CLL analysis set, and Safety Expansion Subjects analysis set.

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.

These analyses will be performed on the All Treated Subjects analysis set, All Treated Subjects in the Main Cohort analysis set, All Treated Subjects in the Main Cohort with 17p Deletion CLL analysis set, and Safety Expansion Subjects analysis set.

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, five and six 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.

These analyses will be performed on the All Treated Subjects analysis set, All Treated Subjects in the Main Cohort analysis set, All Treated Subjects in the Main Cohort with 17p Deletion CLL analysis set, and Safety Expansion Subjects analysis set.

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, > 5 weeks to 8 weeks, > 8 weeks to 12 weeks, > 12 weeks to 16 weeks, > 16 weeks to 20 weeks, > 20 weeks to 24 weeks, > 24 weeks to 28 weeks, > 28 weeks to 32 weeks, > 32 weeks to 36 weeks, > 36 weeks to 48 weeks, > 48 weeks to 60 weeks, and > 60 weeks.

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

These analyses will be performed on the All Treated Subjects analysis set, All Treated Subjects in the Main Cohort analysis set, All Treated Subjects in the Main Cohort with 17p Deletion CLL analysis set, and Safety Expansion Subjects analysis set.

10.0 Efficacy Analysis

10.1 General Considerations

Main Cohort

Further details on the analysis sets used will be specified in each description of efficacy analyses to be performed below.

For the primary efficacy analysis of ORR based on IRC assessment in the first 70 subjects treated in the Main Cohort, statistical significance will be determined by a two-sided *P* value < 0.05 (one-sided < 0.025 where applicable). No other efficacy endpoints will have statistical testing performed. Descriptive statistics and the ninety-five percent (95%) confidence interval will be presented, where applicable.

Safety Expansion Cohort

No statistical testing will be performed for the efficacy endpoints in the Safety Expansion Cohort. Descriptive statistics with 95% confidence intervals will be presented, where applicable.

10.2 Main Cohort Analysis

10.2.1 Primary Efficacy Analysis

The primary efficacy endpoint will be overall response rate (ORR) – the proportion of subjects with an overall response (complete remission [CR] + complete remission with incomplete marrow recovery [CRi] + nodular partial remission [nPR] + partial remission [PR]) per the 2008 Modified IWCLL NCI-CWG criteria as assessed by the Independent Review Committee (IRC) in the first 70 subjects treated in the Main Cohort (Primary Efficacy Subject Analysis Set).

The ORR (based on the IRC assessment) for Venetoclax will be tested to reject the null hypothesis of ORR = 40%. If the null hypothesis is rejected and the ORR is higher than 40%, then Venetoclax has been shown to have an ORR significantly higher than 40%.

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

Among these 70 subjects, those who have not achieved a CR, CRi, confirmed nPR, or confirmed PR prior to the data cutoff date will be considered to be non-responders.

10.2.2 Secondary Efficacy Analyses

Secondary efficacy endpoints will include all 107 subjects for ORR, complete remission rate (CR + CRi), partial remission rate (nPR + PR), duration of overall response (DoR), progression-free survival (PFS), event-free survival (EFS), time to progression (TTP), time to 50% reduction in absolute lymphocyte count (ALC), overall survival (OS) and percent of subjects who move on to stem cell transplant.

Secondary efficacy analyses will be performed for both the IRC assessment of response and the investigator assessment of response, as applicable, for the All Treated Subjects in the Main Cohort analysis set and the All Treated Subjects in the Main Cohort with 17p Deletion CLL analysis set. Description of the secondary efficacy analyses are as follows:

CR rate will be defined as the proportion of subjects who achieved a CR or CRi per the 2008 Modified IWCLL NCI-CWG criteria. In addition, the 95% confidence interval based on the binomial distribution (Clopper-Pearson exact method) will be provided. Subjects who do not achieve a CR or CRi will be considered to be non-responders in the calculation of CR rate.

PR rate will be defined as the proportion of subjects who achieved a nPR or PR per the 2008 Modified IWCLL NCI-CWG criteria. In addition, the 95% confidence based on the binomial distribution (Clopper-Pearson exact method) will be provided. Subjects who do not achieve a nPR or PR will be considered to be non-responders in the calculation of PR rate.

Duration of overall response (DoR) will be defined as the number of days from the date of first response (CR, CRi, nPR, or PR) by either CT scan or physical exam determination to the earliest recurrence (PD) or death per the IRC assessment. For subjects who have a PR before CR, CRi, or nPR in subsequent visits, the DoR is computed from the earliest PR. 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. To be included in the DoR analysis, subjects must have had a response per the 2008 Modified IWCLL NCI-WG criteria (CR, CRi, confirm nPR, or confirmed PR). For subjects who never experience response, the subject's data will not be included in the analysis. Duration of overall response will be analyzed by Kaplan-Meier methodology. Median duration of response will be calculated and the corresponding 95% confidence interval will be presented.

Duration of 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 of whether the event occurred while the subject was taking the Venetoclax or had previously discontinued the Venetoclax. 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 subjects without any disease assessments performed after the baseline visit will be censored at the date of first dose plus 1 day. PFS will be analyzed by Kaplan-Meier methodology. Median duration of PFS will be calculated and 95% confidence interval for median duration of 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 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 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 of whether the event occurred while the subject was taking the Venetoclax or had previously discontinued the Venetoclax. If the subject does not experience disease progression, then the data will be censored at the date of last available 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. TTP will be analyzed by Kaplan-Meier methodology. Median TTP will be calculated and 95% confidence interval for median TTP 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 CR, CRi, confirmed nPR, or confirmed 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.

Time to 50% reduction in ALC will be defined as the number of days (hours if applicable) from the date of first dose to the date when the ALC has reduced to 50% of the baseline value (as defined in Section 6.0). Only subjects with a baseline of ALC > 5×10^9/L will be included in the analysis. For subjects who never achieve a 50% reduction in ALC, 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 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. Median survival time will be estimated and 95% confidence interval for the median survival time will be presented.

The percent of subjects who move on to stem cell transplant will be summarized and the 95% confidence interval based on the binomial distribution (Clopper-Pearson exact method) will be provided.

10.2.3 Additional Exploratory Efficacy Analyses

The additional exploratory efficacy analyses will be performed on the Treated Subjects in the Main Cohort analysis set, and All Treated Subjects in the Main Cohort with 17p Deletion CLL analysis set.

Descriptions of the additional efficacy endpoints are as follows:

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 new 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. Only subjects with an MRD assessment (negative or positive), as required per protocol, will be used in calculation of MRD response rate, indeterminate samples will not be included in the denominator 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 MDASI (measure of patient reported symptoms), the EORTC QLQ-C30 and 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 MDASI is a multi-symptom PRO measure for clinical and research use. The MD Anderson Symptom Inventory Core Items contains 13 symptom severity items (pain, fatigue, nausea, disturbed sleep, distress [emotional], shortness of breath, lack of appetite, drowsiness, dry mouth, sadness, vomiting, difficulty remembering, and numbness or tingling), and 6 symptom interference items (general activity, mood, walking ability, normal work, relations with other people, and enjoyment of life).

Mean symptom severity and symptom interference scores will be calculated for each observation as defined in the MDASI scoring manual and then summarized 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 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.

10.3 Safety Expansion Cohort

10.3.1 Efficacy Analyses

The efficacy analyses for the Safety Expansion Cohort will be performed when the last subject in this cohort has discontinued Venetoclax. The analysis set summarized for the Safety Expansion Cohort will be the Safety Expansion Subjects analysis set. For this efficacy assessment, the investigator assessment of response will be used for all analyses.

The following efficacy analyses will be performed and summarized as specified in Section 10.2.2: ORR, CR rate, PR rate, DoR, PFS, EFS, TTP, time to first response, time to 50% reduction in ALC, OS, and the percent of subjects who move on to stem cell transplant.

10.3.2 Additional Exploratory Efficacy Analyses

Additional efficacy endpoints to be performed on the Safety Expansion Cohort subjects are time to next anti-leukemia treatment, MRD response rate, and Health Economic and Patient Reported Outcome measures and will be summarized as specified in Section 10.2.3.

10.4 Handling of Multiplicity

There will be no multiplicity adjustments performed. The only testing procedure performed will be on the primary endpoint of ORR using a two-sided alpha = 0.05 which will include the first 70 subjects enrolled.

10.5 Efficacy Subgroup Analysis

To evaluate the impact of baseline conditions on efficacy, subgroup summaries will be performed in the All Treated Subjects in the Main Cohort analysis set, the All Treated Subjects in the Main Cohort with 17p Deletion CLL analysis set and All Treated Subjects analysis set.

The subgroups defined below will be used for these analyses:

1. Gender (Male, Female)
2. Age (< 65, or ≥ 65)
3. Age (< 75, or ≥ 75)
4. Race (White, Black, Other)
5. Number of prior therapies (1, 2, 3, 4, ≥ 5)
6. LDH status (0 - 1 × ULN, > 1 × ULN)
7. ECOG (0, ≥ 1)
8. Fludarabine refractory status (Yes, No)
9. IgVH (mutated, unmutated)
10. Bulky disease (nodes < 5 cm, nodes ≥ 5 cm)
11. Bulky disease (nodes < 10 cm, nodes ≥ 10 cm)
12. ALC (< 25×10^9/L, ≥ 25×10^9/L)
13. ALC (< 100×10^9/L, ≥ 100×10^9/L)
14. 17p deletion central laboratory testing center
15. BCRi failure CLL subjects (Yes)

10.6 Efficacy Data Conventions

The following data conventions will be implemented for each of the analysis time points.

- The window for the 8-week CT confirmation for response will allow a 1-week variation post first sign of response (≥ 49 days for a confirmation of response).
- If the subject does not experience disease progression by the cutoff dates specified in Section 4.5, then the data will be censored at the date of last available disease assessment prior (clinical or radiographical) to the cutoff dates.

- A discontinued subject could be a responder if the subject had a CR, CRi, confirmed nPR, or confirmed PR prior to discontinuing Venetoclax. If a subject reaches a PR clinical response (per investigator assessment) but was not confirmed 8 weeks later then the response will be considered to be SD. A CR clinical response (per investigator assessment) must be confirmed with a bone marrow assessment. If no bone marrow was performed, then the response will be considered a PR.
- Data from the IRC assessment will not be combined with the assessment provided by the investigator. These will be two separate analyses.
- For a subject to be determined to have an MRD negative status, the level of CLL cells in the bone marrow or blood sample must be less than 1×10^{-4} (less than one CLL cell per 10,000 leukocytes). For samples with CLL cells greater than or equal to 1×10^{-4}, the MRD status will be considered positive. Only subjects with an MRD assessment, as required per protocol, will be used in calculation of MRD status. If a sample from the central laboratory is determined to be indeterminate, the local laboratory sample will be used instead of the central laboratory, if available.
- For time to event analyses, months will be computed using 30.4 days per month.

11.0 Safety Analysis

Safety assessments will only include subjects who have received at least one dose of Venetoclax.

The safety assessment of Venetoclax will be performed at three time points. The first assessment time point for the safety of Venetoclax will be performed for all subjects as of 30 April 2015 assessment. At this time point, all subjects who have been treated in the study, either in Main Cohort or Safety Expansion Cohort, will be assessed for safety. The analysis sets for this time point will include: All Treated Subjects analysis set, All Treated Subjects in the Main Cohort analysis set, and the Safety Expansion Subjects analysis set.

The second assessment time point for safety will occur when the last subject enrolled into the Safety Expansion Cohort has completed the 5-week step wise dose escalation. For this time point the Safety Expansion Subject analysis set will be used.

The final assessment time point for safety will occur when the last subject discontinues Venetoclax and has complete the 30-day safety follow-up period. The analysis sets for this final time point will include: All Treated Subjects analysis set, All Treated Subjects in the Main Cohort analysis set, and Safety Expansion Subjects analysis set.

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 20.1 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 9.

Table 9. Adverse Events of Special Interest

Adverse Event of Special Interest	Search Criteria
Tumor Lysis Syndrome (AE)	SMQ – "Tumor Lysis Syndrome" (Narrow)
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 (AE)	PT Term – Drug Induced Liver Injury
Grade ≥ 3 Thrombocytopenia	PT Terms – "Thrombocytopenia" and "Platelet Count Decreased"

11.2 Deaths

The number of deaths will be summarized (1) for death occurring during the first day of Venetoclax and within 30 days after the last dose of Venetoclax, (2) for death occurring > 30 days after the last dose of Venetoclax, (3) for all deaths in this study, i.e., 1) and 2).

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. Post baseline visits windows are specified in Table 6 and Table 7.

11.3.1 Analysis of Mean Changes from Baseline in Clinical Laboratory Data

Changes from baseline will be analyzed for each scheduled post-baseline visit and for the final visit (Table 6 and Table 7) for blood chemistry and hematology parameters, as well as urinalysis and vital sign parameters.

Laboratory tests to be summarized are included in Table 10.

Table 10. Clinical Laboratory Tests

Hematology	Chemistry	Urinalysis
Hematocrit Hemoglobin Red Blood Cell (RBC) count White Blood Cell (WBC) count Neutrophils Bands Lymphocytes Monocytes Basophils Eosinophils Platelet count Reticulocyte count Prothrombin time (PT) Activated partial thromboplastin time (aPTT)	Blood Urea Nitrogen (BUN) Creatinine Total bilirubin Serum glutamic-pyruvic transaminase (SGPT/ALT) Serum glutamic-oxaloacetic transaminase (SGOT/AST) Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphorus Uric acid Cholesterol (Screening and Final Visit) Total protein Glucose Triglycerides (Screening and Final Visit) Albumin Lactate dehydrogenase (LDH) Magnesium Chloride Bicarbonate Calculated Creatinine Clearance	Specific gravity pH **Quantitative Immunoglobulins** IgA IgG IgM **Lymphocyte Enumeration** T-cells (CD3) B-cells (CD19) B-cells (CD5 + CD19) Natural Killer Cells (CD16 + CD56) Helper T-cells (CD4) T-Suppressor to T-Cytotoxic cells (CD8)

Mean changes from baseline at each scheduled post-baseline visit and Final Visit will be summarized with the baseline mean, visit mean, change from baseline mean, standard deviation, and median.

11.3.2 Analyses of Shift from Baseline in Clinical Laboratory Data

For shifts relative to NCI CTCAE, baseline and post-baseline laboratory observations 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.

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 final observations of grade 0, grade 1, grade 2, grade 3, or grade 4.

Additionally, for each variable, the number and percentage of subjects that have a baseline observation that is categorized as a grade 0, grade 1, or grade 2 and that also have a grade 3 or 4 final observation will be presented. A similar set of summaries will be produced for the maximum post-baseline laboratory observations.

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.

11.3.3 Assessment of Potentially Clinically Significant Laboratory Values

For selected laboratory 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.

Criteria for potentially clinically significant laboratory values are defined as laboratory grade values ≥ 3 per the NCI CTCAE version 4. The NCI CTCAE grade 3 criteria are given in Table 11 and Table 12 below.

Table 11. Criteria for Potentially Clinically Significant Laboratory Values – Chemistry Variables

		Definition of Potentially Clinically Significant Current (Version 4) Grade 3	
Chemistry Variables	**Units**	**Very Low**	**Very High**
Total bilirubin	mcmol/L		> 3.0 × ULN
Albumin	g/L	< 20	
Aspartate amino transaminase (AST/SGOT)	U/L		> 5.0 × ULN
Alanine amino transferase (ALT/SGPT)	U/L		> 5.0 × ULN
Alkaline phosphatase	U/L		> 5.0 × ULN
Creatinine	mcmol/L		> 3.0 × ULN
Sodium	mmol/L	< 130	> 155
Potassium	mmol/L	< 3.0	> 6.0
Total calcium	mmol/L	< 1.75	> 3.1
Glucose	mmol/L	< 2.2	> 13.9
Inorganic Phosphate	mmol/L	< 0.6	
Bicarbonate	mmol/L	< 11	
Cholesterol	mmol/L		> 10.34
Triglycerides	mmol/L		> 5.0 × ULN
Magnesium	mmol/L	< 0.4	> 1.23

Table 12. Criteria for Potentially Clinically Significant Laboratory Values – Hematology Variables

		Definition of Potentially Clinically Significant Current (Version 4) Grade 3
Hematology Variables	**Units**	**Very Low**
Hemoglobin	g/L	< 80
White blood cell count	10^9/L	< 2
Neutrophils	10^9/L	< 1
Lymphocytes	10^9/L	< 0.5
Platelets	10^9/L	< 50

A listing of subjects who meet Hy's law to assess drug-induced liver injury (DILI) will be provided. The listing will contain subjects with ALT or AST > 3 × ULN who also show elevation of total bilirubin > 2 × ULN on laboratory samples taken within 72 hours of each other.

Laboratory Search Strategy for TLS

To determine if a subjects laboratory values qualify for TLS, the Howard criteria[2] will assessed. The Howard criteria for TLS comprises of ≥ 2 of the following electrolyte abnormalities within 24 hours of each other and are specified in Table 13.

Table 13. 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 Howard criteria will be provided:

- Number and percentage of subjects meeting Howard criteria in Table 12 (at least two values meeting the criteria, occurring within 24 hours of each other).

- Listing of all the Howard criteria lab test values for each subject meeting Howard criteria.
- Number of subjects meeting single Howard criteria in Table 13 (at least one value meeting the criteria).
- Listing of all the Howard criteria lab test values for each subject who meets single Howard criteria Table 13.

11.3.4 Assessment of Mean Changes from Baseline in Vital Signs Variables

Analyses of mean change from baseline in continuous vital signs variables which are measured longitudinally will be performed (systolic blood pressure, diastolic blood pressure, heart rate, and temperature). Similar analyses may be performed for the mean change from baseline to the minimum, maximum, and final observations.

For each change from baseline analysis, the following summary statistics will be presented: sample size, baseline mean, visit mean, and the mean, standard deviation, and median of the changes from baseline. The baseline and visit means will be calculated for each visit for subjects who have both a baseline and visit value.

11.3.5 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 14 below based on CTCAE criteria:

Table 14. 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

11.4 ECG/2D Echocardiogram

For ECG testing, subjects were only required to have a screening and a final visit assessment. If an ECG was clinically indicated, additional measurement could have been performed. Only ECG results that were abnormal were collected in the database.

For 2D echocardiogram testing, subjects had a screening assessment if clinically indicated. If an echocardiogram was clinically indicated, additional measurement could have been performed.

Data from ECG or 2D Echocardiogram that were collected will be provided in data listings.

No analyses are planned given the limited collection of data.

12.0 Pharmacokinetic Analyses

12.1 Tabulations and Summary Statistics

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 dose level by scheduled visit. Samples with significant sampling time deviations will be excluded from summary statistics calculations. Binning will also be performed for trough samples of subjects receiving 400 mg Venetoclax with respect to the difference between the

sample collection date and time and their last dose date and time of Venetoclax. Summary statistics will also be computed for each bin.

12.2 Attainment of Steady State

Exploratory analyses of trough (pre-dose) concentrations for Weeks 8 (first visit), 12 (second visit), 16 (third visit) and 24 (fourth visit) will be done to characterize the achievement of steady state pharmacokinetics. The model will include Visit as a fixed effect and will account for both intra- and inter-subject variability. Trough concentrations from subjects receiving 400 mg Venetoclax for which samples were taken between 22 and 26 hours after their last dose at each above visit will be included in the analysis.

Within the framework of the model, trend analyses will be performed on the contrasts in the visit effects to determine the earliest visit after which there is no statistically significant change. The trend analyses will begin with a test of hypothesis on the orthogonal linear contrast for all the specified visits. If the test result is not statistically significant for this linear contrast, the trend analysis will be stopped to suggest that steady state was reached on the first visit identified in the linear contrast. If the test result is statistically significant, the next trend analysis will be performed on the orthogonal linear contrast re-established for the visits from the second visit through the last visit. This process will be repeated with a elimination of the visits one by one from the beginning until the trend test is not statistically significant, or until only two visits (the second to the last and the last visits) remain for the trend analysis.

13.0 Summary of Changes

13.1 Summary of Changes Between the Latest Version of Protocol and the Current SAP

- Updated the data cutoff date for the 36-week disease assessment for the 107 subjects in the main cohort to 30 April 2015. Bone marrow assessments required by the NCI-WG criteria to confirm the complete remission responses were to be completed by 30 April 2015.

- Updated the Adverse of special interest to be more relevant for clinical significance determination.
- Clarification of the laboratory values to be summarized.
- Updated the pharmacokinetics analyses section.
- Corrected typographical errors and minor language or word revisions throughout the document.
- The Appendix B - AE Search Criteria for AE of Special Interest is removed.
- The SAP was updated to include analyses for the 3rd Interim CSR

14.0 References

1. Pettitt AR, Jackson R, Carruthers S, et al. Alemtuzumab in combination with methylprednisolone is a highly effective induction regimen for patients with chronic lymphocytic leukemia and deletion of TP53: final results of the National Cancer Research Institute CLL206 trial. J Clin Oncol. 2012;30(14):1647-55.
2. 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
ALT	Alanine aminotransferase
ALC	Absolute Lymphocyte Count
AST	Aspartate aminotransferase
aPTT	Activated Partial Thromboplastin Time
Bcl	B-Cell Lymphoma
BM	Bone Marrow
BR	Bendamusitne plus Rituximab
BUN	Blood Urea Nitrogen
CLL	Chronic Lymphocytic Leukemia
cm	Centimeter
CR	Complete Remission
CRi	Complete Remission with Incomplete Marrow Recovery
CrCL	Creatinine Clearance
CSR	Clinical Study Report
CT	Computed Tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DILI	Drug-Induced Liver Injury
DoR	Duration of Overall Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free Survival
FCR	Fludarabine, cyclophosphamide, and rituximab
G-CSF	Granulocyte-colony stimulating factor
IDMC	Independent Data Monitoring Committee
IRC	Independent Review Committee
IWCLL	International Workshop for Chronic Lymphocytic Leukemia
IxRS	Interactive Response System
LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
mm	Millimeter
MPV	Mean Platelet Volume

MRD	Minimal Residual Disease
MUGA	Multi Gated Acquisition Scan
NCI	National Cancer Institute
NCI-WG	National Cancer Institute-Working Group
nPR	Nodular Partial Remission
NPT	Non-protocol Anti-leukemia Therapy
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-free Survival
PR	Partial Remission
PT	Prothrombin Time
QA	Quality Assurance
QC	Quality Control
QD	Once Daily
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SGOT	Serum Glutamic-oxaloacetic Transaminase
SGPT	Serum Glutamic-pyruvic Transaminase
SLL	Small Lymphocytic Lymphoma
SMQ	Standard MedDRA Query
SPD	Sum of the products of the greatest diameters
TEAE	Treatment-emergent Adverse Event
TLS	Tumor Lysis Syndrome
TTNT	Time to next anti-CLL treatment
TTP	Time to Tumor Progression
ULN	Upper Limit of Normal
VAS	Visual Analog Scale
WBC	White Blood Cell