1.0 Title Page

Statistical Analysis Plan

Study M15-889

Open-Label, Single Arm, Phase 3b, Multi-Center Study Evaluating the Impact of Venetoclax on the Quality of Life of Relapsed/Refractory Subjects with Chronic Lymphocytic Leukemia (CLL) (VENICE II)

Date: 09 May 2018

Version 1.0

2.0 Table of Contents

List of Tables

List of Figures

List of Appendices

3.0 Introduction

This statistical analysis plan (SAP) describes the full statistical analyses for venetoclax (ABT-199) Protocol M15-889. Study M15-889 evaluates the quality of life of subjects with relapsed or refractory chronic lymphocytic leukemia (CLL). Quality of life is assessed based on patient-reported outcome (PRO) measures, including the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30), the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Chronic Lymphocytic Leukemia Module (EORTC QLQ-CLL16), and the EuroQoL 5 Dimension 5 Level Questionnaire (EQ-5D-5L).

This statistical analysis plan (SAP) provides details to elaborate the statistical methods outlined in Study Protocol M15-889 Amendment 1 dated 11 July 2016 and Amendment 2 dated 30 January 2018. 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 or newer (SAS Institute Inc., Cary, NC USA).

The SAP will not be updated in case of future administrative or minor amendments to the protocol unless the changes have any impact on the analysis of the study data.

4.0 Study Objectives, Design and Procedures

4.1 Objectives

Primary Objective

The primary objective of this study is to evaluate the impact of venetoclax monotherapy on the quality of life of subjects with relapsed or refractory chronic lymphocytic leukemia (CLL). Quality of life will be assessed by the Global Health Status/Quality of Life (GHS/QoL) subscale of the EORTC QLQ-C30.

Secondary Objectives

The secondary objectives are to

- evaluate the impact of venetoclax monotherapy on quality of life based on the EORTC QLQ-CLL16, EQ-5D-5L, and the remaining subscales from the EORTC QLQ-C30
- complete remission rate (CR + CRi)
- overall response rate (ORR)
- duration of overall response (DOR)
- time to progression (TTP)
- duration of progression-free survival (PFS)
- overall survival (OS)
- complete remission rate (CR + CRi) in BCRi treated subjects

The safety and tolerability of venetoclax in subjects with relapsed/refractory CLL will also be evaluated.

4.2 Study Design and Plan

This is an open-label, single arm, Phase 3b, multi-center study evaluating the impact of venetoclax monotherapy on the quality of life in relapsed/refractory CLL.

This study is designed to enroll approximately 200 subjects to meet scientific objectives without enrolling an undue number of subjects in alignment with ethical considerations.

Subjects meeting the eligibility criteria will be treated with venetoclax once daily (QD), continuously up to 2 years provided they continue to tolerate the drug, have no evidence of disease progression (based on Investigator's assessment), do not have unacceptable toxicity, and do not meet any of the protocol specified criteria for discontinuation.

Dosing Schedule Overview

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

Figure 1. 5-Week Dose-Titration Schedule

Week	VENETOCLAX Daily Dose
1	20 mg
2	50 mg
3	100 mg
4	200 mg
5 and beyond	400 mg

4.3 Sample Size

An improvement in the EORTC QLQ-C30 GHS/QoL subscale of 5 units is considered to be a clinically meaningful difference to subjects. From a prior study of venetoclax monotherapy in 17p del R/R CLL subjects (Study M13-982), the standard deviation was approximately 20.5 for the GHS/QoL subscale. Using a one-sided alpha of 0.025, 90% power, and a standard deviation of 20.5; 177 subjects are required to reject the null hypothesis in favor of the alternative hypothesis that venetoclax improves GHS/QoL by at least 5 units. To account for potential drop-outs at Week 48, a total of 200 subjects to be dosed.

4.4 Interim Analysis

Data Monitoring Committee (DMC)

A Data Monitoring Committee (DMC) has been independently organized to support the review of safety data associated with venetoclax monotherapy dosing. The DMC will

review the safety data with an initial review to occur when approximately 20 subjects have completed a minimum of 12 weeks of treatment.

A separate charter will be created to provide detailed descriptions of the schedule of analyses and the DMC meetings. DMC membership, responsibilities and the description of the data coordinating center are documented in the charter.

4.5 Timing of Quality of life and Efficacy Analyses and Safety Evaluations

Table 1. Summary of Analyses with Cutoff Dates and Data Included

Reason	Database Version	Cutoff Date	QoL/Efficacy Data Included	Safety Data Included
DMC	A	24 Apr 2017	Not included	All safety data[a]
DMC	F	03 Nov 2017	Not included	All safety data[a]
DMC	G	30 Apr 2018	Included	All safety data[a]

a. Safety population is defined in Section 5.1.1.

Quality of life, efficacy, and safety analysis occur when all subjects participating in the study have completed the 48-week disease assessment or have discontinued venetoclax (including early termination of the study). Quality of life, efficacy, and safety data up to the cutoff date specified in Table 1 will be considered. During this data collection period, active subjects 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 should be extracted for documentation and statistical analyses. The study will be considered completed when the last enrolled subject discontinues or completes the dosing regimen.

5.0 Analysis Populations

5.1 Definition for Analysis Populations

5.1.1 Quality of Life, Efficacy, and Safety Populations

All enrolled subjects who receive at least one dose of venetoclax will be included in this analysis unless otherwise specified.

5.2 Variables Used for Stratification of Randomization

There is no randomization for this open-label single-arm study.

6.0 Analysis Conventions

6.1 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 the laboratory variables is defined as:

- For subject with IV hydration for TLS prophylaxis, the baseline value is the lab value taken before the subject receiving IV hydration for TLS prophylaxis prior to the first dose of venetoclax.
- For subject without IV hydration for TLS prophylaxis, the baseline value is the lab value taken before the first dose of venetoclax on Day 1.

6.2 Treatment Days

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 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, unless otherwise specified.

6.3 Definition of Analysis Windows

For visit wise analyses including quality of life and safety analyses, the time windows specified in Table 2 and Table 3, describe how the data will be assigned to protocol specified visits. Analysis time windows will be constructed using the following algorithm:

- Determine the nominal study Rx day for each scheduled visit.
- Determine the time window around a specific nominal study Rx day as in Table 2.
- If more than one assessment is included in a time window the most conservative value (i.e., the smallest score) should be used for the analysis of quality of life measures. A sensitivity analysis should be performed based on considering the most favorable (i.e., the largest value) assessment of the quality of life measures. Except the quality of life measures, if there are two observations with equal distance to the nominal day, the latest one will be used in analyses.

Table 2. Time Windows for Quality of Life Measures

Scheduled Visit	Nominal Day	Time Window (study Rx day range)
Baseline (Week 1 Day -1 or Week 1 Day 1)	≤ 1	See the baseline definition (Section 6.0)
Week 4 Day 1	22	2 to 43
Week 8 Day 1	50	44 to 71
Week 12 Day 1	75	72 to 153
Week 24 Day 1	162	154 to 237
Week 36 Day 1	246	238 to 321
Week 48 Day 1	330	322 to 405
Week 60 Day 1	414	406 to 489
Week 72 Day 1	498	490 to 573
Week 84 Day 1	582	574 to 657
Week 96 Day 1	666	658 to 743
Week 108 Day 1	750	742 to 825
Final Observation	Last non-missing value within 30 days of last dose of Venetoclax	

6.4 Missing Data Imputation

Subjects with missing disease progression date, missing death date, or missing last known alive date will be considered as censored subjects for time to progression, progression free survival analysis, and survival analysis. And the subject will be censored at the interim data cutoff date.

If a respondent answers at least 50% of the items in quality of life measures, the missing items will be imputed with the average score of the answered items in the same scale. In cases where the respondent did not answer at least 50% of the items, the score for that domain will be considered missing.

7.0 Subject Disposition

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

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

The number and percentage of subjects who discontinued venetoclax will be summarized by reason (all reasons) and by primary reason (per eCRF). Similar summaries will be provided for discontinuations from the study.

The number and percentage of subjects with reported venetoclax interruptions will be summarized. Reasons for venetoclax interruptions will be presented in the listings.

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

8.1 General Consideration

The safety population will be used to summarize baseline variables. The safety population also will be used to summarize medical history and previous, concomitant, and post-treatment medications.

8.2 Demographic and Baseline Characteristics

Categorical baseline variables will be summarized with the number and percentage of subjects in each category. Continuous baseline variables will be summarized with descriptive statistics (number of non-missing observations, mean, standard deviation, median, maximum and minimum).

Categorical baseline variables include:

- Sex (male, female)
- Race (White, Black or African American, Asian, and Other)
- Geographic region (EUROPE, and ROW)

- Ethnicity (Not Hispanic or Latino, and Hispanic or Latino)
- Age (< 65, ≥ 65, < 75, and ≥ 75)
- Tobacco use (current, former, never, and unknown)
- Alcohol use (current, former, never, and unknown)
- ECOG performance status (grade: 0, 1, 2)
- LDH (≤ ULN, > ULN)
- Prior number of oncology therapies (1, 2, ≥ 3)
- Previous line of Ibrutinib failure (1, > 1)
- Previous line of Idelalisib failure (1, > 1)
- 17p deletion status (deleted, not deleted, indeterminate)
- Rai stage (0, 1, 2, 3, 4)
- Binet stage (A, B, C)
- IgVH status (mutated, unmutated)
- ZAP-70 (positive, negative, indeterminate)
- CD-38 (positive, negative, indeterminate)
- Beta 2-microglobulin (< 3 mg/L, ≥ 3 mg/L)
- TP53 mutation (yes, no, unknown)
- 11q (deleted, not deleted, indeterminate)
- 13q (deleted, not deleted, indeterminate)
- 12q trisomy (present, not present, indeterminate)
- Absolute lymphocyte count (ALC) (< 25×10^9/L, ≥ 25×10^9/L; < 100×10^9/L, ≥ 100×10^9/L)
- Bulky disease nodes (< 5 cm, 5 cm To 10 cm, ≥ 10 cm)
- Prior BCRi treated (yes, no)
- TLS risk category (low/medium, high)
- Hospitalized for TLS prophylaxis before venetoclax (yes, no)

Continuous baseline variables include:

- Age (year)

- Weight (kg) by male and female
- Height (cm)
- Number of prior oncology therapy
- Beta-2 microglobulin (MG/L)
- Lactate dehydrogenase (LDH)
- Absolute lymphocytes count (10^9/L)
- Bulky disease nodes (cm)
- Duration of BCRi therapy before venetoclax

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, 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, > 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.

10.0 Quality of Life and Efficacy Analyses

10.1 General Considerations

Details on the analysis sets used will be specified in quality of life and efficacy analyses described below.

10.1.1 Definitions for Quality of Life Assessments

EORTC QLQ-C30

Quality of life and symptoms will be assessed with the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30) version 3[1]. The QLQ-C30 is a 30-item subject self-report questionnaire composed of both multi-item and single scales, including five functional scales (physical, role, emotional, social, and cognitive), three symptom scales (fatigue, nausea and vomiting, and pain), a global health status/quality of life (GHS/QoL) scale, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Subjects rate items on a four-point scale, with 1 as "not at all" and 4 as "very much." The EORTC QLQ-C30 was developed and validated for use in a cancer subject population, and its reliability and validity is highly consistent across different language cultural groups. A change of 5 – 10 points is considered a small change, and the lower bound (5) is being used to define the minimum important difference (MID). A change of 10 – 20 points is considered a moderate change.

The EORTC-QLQ-C30 domains (global health status/quality of life, physical, role, emotional, social, cognitive, fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) will be summarized (mean, standard deviation, and median) at each assessment. In addition the mean change in each of these values (visit-level assessment versus baseline) will be calculated to identify any statistically significant differences. The ninety-five percent (95%) confidence interval of the mean change will be constructed based on (a) without model assumption and (b) with model assumption. A linear model will be used for the analysis of repeated measures where the covariance pattern will be assumed as compound symmetry (CS).

EORTC QLQ-CLL16

The EORTC QLQ-CLL16 was designed specifically for subjects with stage 0 to stage 4 CLL[2]. It is comprised of sixteen questions that address five domains of HRQoL important in CLL. There are three multi-item scales assessing Fatigue (2 items), Disease

and Treatment Effects (7 items), and Infection (5 items), and two single-item scales assessing Social Activities and Future Health Worries. Subjects rate items on a four-point scale, with 1 as "not at all" and 4 as "very much." A negative change in score from baseline represents an improvement in symptoms. A change of 5 – 10 points is considered a small change, and the lower bound (5) is being used to define the minimum important difference (MID). A change of 10 – 20 points is considered a moderate change.[3]

The 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 the mean change in each of these values (visit-level assessment versus baseline) will be calculated to identify any statistically significant differences. The ninety-five percent (95%) confidence interval of the mean change will be constructed based on (a) without model assumption and (b) with model assumption. A linear model will be used for the analysis of repeated measures where the covariance pattern will be assumed as compound symmetry (CS).

EQ-5D-5L

The EuroQol EQ-5D-5L is a generic preference instrument that has been validated in numerous populations[4-5].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 scores for the 5 dimensions are used to compute a single utility index score ranging from zero (0.0) to 1 (1.0) representing the general health status of the individual. The EQ-5D-5L also contains a visual analog scale (VAS) to assess the subject's overall health. The MID for the EQ-5D utility index score in cancer subjects is 0.08, and the MID for EQ-5D VAS is 7[6].

Each of the five dimensions of the EQ-5D-5L, the VAS and overall utility score will be calculated using the EuroQol scoring manual, and summarized (mean, std. dev., median)

at each assessment. The impact of treatment over time will be assessed by calculating the change in score from baseline at each assessment time point. The ninety-five percent (95%) confidence interval of the mean score change will be constructed based on (a) without model assumption and (b) with model assumption. A linear model will be used for the analysis of repeated measures where the covariance pattern will be assumed as compound symmetry (CS).

10.1.2 Definitions for Efficacy Endpoints

Complete Remission Rate (CR + CRi)

Complete response rate, complete remission (CR) or complete remission with incomplete marrow recovery (CRi), will be defined as the proportion of subjects who achieved per the 2008 Modified IWCLL NCI-WG criteria as assessed by investigator using the best response at any time during the study. In addition, the 95% confidence interval for complete response rate (CR) rate 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 complete response rate.

Overall Response Rate (ORR)

ORR (CR + CRi + nPR + PR) will be defined as the proportion of subjects who achieved complete remission (CR), complete remission with incomplete marrow recovery (CRi), nodular partial remission (nPR), or confirmed partial remission (PR) based on the 2008 Modified IWCLL NCI-WG criteria as assessed by investigator using the best response at any time during the study. The corresponding exact 95% confidence interval for the proportion (Clopper-Pearson exact method) will be constructed. Subjects who do not respond will be considered non-responders.

Duration or Response (DOR)

The DOR for a given subject will be defined as the number of days from the day the criteria are met for CR, CRi, nPR, or PR (whichever is recorded first) to the earliest date that progressive disease (PD) is objectively documented (radiographic or clinical) or death

(i.e., DoR = PD/death/censoring date – earliest CR/CRi/nPR/PR date + 1 day). 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 last available disease evaluation or at the cut-off date for the interim analysis if the subject has a disease evaluation that is after the cut-off date. Only subjects with the iWCLL response criteria will be included in the analysis of DOR. The distribution of the duration of overall response will be estimated using the Kaplan-Meier methodology. Median duration of response will be calculated and the corresponding 95% confidence interval will be presented.

Time to Progression (TTP)

Time to progression for a given subject will be defined as the number of days from the date the subject started venetoclax to the date of earliest PD (radiographic or clinical) (i.e., TTP = PD/censoring date – first dose date + 1 day). All PD will be included regardless of whether the event occurred while the subject was taking venetoclax or had previously discontinued venetoclax. If the subject does not experience PD, then the subject's data will be censored at the date of the last available disease evaluation or at the cut-off date for the interim analysis if the subject has a disease evaluation that is after the cut-off date. If a subject does not have any post baseline disease assessments, the data will be censored at the first dose date plus 1 day. The distribution of the time to progression will be estimated using Kaplan-Meier methodology. Median time to progression and the corresponding 95% confidence interval will be estimated.

Progression Free Survival (PFS)

Progression-free survival (PFS) will be defined as the number of days from the date of first dose of venetoclax to the date of earliest PD (radiographic or clinical) or death (i.e., PFS = PD/death/censoring date – first dose date + 1 day). All disease progression will be included regardless of whether the event occurred while the subject was taking venetoclax or had previously discontinued the study drug. If the subject does not experience disease progression or death, then the subject's data will be censored at the

date of the last available disease evaluation, last known alive date, or at the cut-off date for the interim analysis if the subjects has a disease evaluation or death that is after the cut-off date. If a subject does not have any post baseline tumor assessment or clinical assessment for progression, the data will be censored at the date of first dose plus 1 day. Progression-free survival 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.

Overall Survival (OS)

Overall survival (time to death) for a given subject will be defined as the number of days from the date the subject started venetoclax to the date of the subject's death (i.e., OS = death/censoring date – first dose date + 1 day). All events of death will be included, regardless of whether the event occurred while the subject was still taking venetoclax, or after the subject discontinued venetoclax. If a subject has not died, then the data will be censored at the date of the last study visit, the last contact date, the date the subject was last known to be alive, or at the cut-off date for the interim analysis if the subject has a death that is after the cut-off date. The date of the last study visit will be determined by selecting the last available date of the following study procedures for a subject: tumor assessment, clinical disease progression, physical examination, vital signs assessment, clinical laboratory collection, study drug, adverse event and concomitant medication assessment, performance status, quality of life evaluation, survival form, and drug and study completion form. The distribution of the time to death will be estimated using Kaplan-Meier methodology. Median survival time and the corresponding 95% confidence interval will be estimated.

10.2 Quality of Life and Efficacy Analyses

Data collected at any point prior to the specified interim cutoff date during the study will be used in the analyses, unless otherwise specified. The population of these analyses is defined in Subsection 5.1.1.

10.2.1 Primary Endpoint Analysis

The primary endpoint will be assessed by the GHS/QoL subscale of the EORTC QLQ-C30. Summary stats will be on mean change. The endpoint (at subject level) will be mean change from baseline to Week 48. Scores will be calculated based on the scoring manual. Mean score for baseline visit and post-baseline visit (Week 4, Week 12, Week 24, Week 36, Week 48, Week 60, Week 72, Week 84, Week 96, and Week 108/Final visit) will be reported with standard deviation (SD). The 95% confidence interval for mean change additionally will be provided for each post-baseline versus baseline.

10.2.2 Secondary Efficacy Analyses

ORR and CR will be assessed as the proportion of subjects with an overall response based on the IWCLL NCI-WG criteria. The 95% confidence interval based on the Clopper-Pearson exact method for binomial distribution will be constructed for the calculated ORR and CR rates.

DOR, TTP, PFS, and OS will be analyzed by Kaplan-Meier methodology using data for all subjects defined in Section 5.1.1. Median time of each endpoint will be calculated and 95% confidence interval for median time of each endpoint will be presented.

Secondary quality of life endpoints will include all multi-item scales and single-item scales from the EORTC QLQ-C30, EORTC QLQ-CLL16, and EQ-5D-5L. Scores will be calculated based on the scoring manual for each instrument. The mean change score from baseline to post-baseline (Week 4, Week 12, Week 24, Week 36, Week 48, Week 60, Week 72, Week 84, Week 96, and Week 108/Final visit) will be summarized with the 95% confidence interval. Mean score with SD of baseline and each post-baseline visit also will be presented.

10.3 Subgroup Analyses of Quality of Life and Efficacy

To evaluate the impact of baseline conditions on quality of life subgroup analyses will be performed on the analysis population defined in Section 5.1.1. The following subgroups below will be used for quality of life analyses:

- 17p deletion status (deleted, not deleted)
- TP53 mutation (yes, no)
- Prior BCRi treated (yes, no)
- Prior number of oncology therapies (1, 2, ≥ 3)
- Baseline ALC (< 25×10^9/L, ≥ 25×10^9/L; < 100×10^9/L, ≥ 100×10^9/L)
- Baseline node size (< 5 cm, 5 cm to 10 cm, ≥ 10 cm)
- Hospitalized for TLS prophylaxis before venetoclax (yes, no)

The following subgroups below will be used for ORR and CR analyses on the analysis population defined in Section 5.1.1 and on previously untreated BCRi subjects, and on previously treated BCRi subjects:

- Sex (male, female)
- Race (White, Non-White)
- Age (< 65, ≥ 65; < 75, ≥ 75)
- ECOG status (0, 1, 2)
- 17p deletion status (deleted, not-deleted)
- TP53 mutation status (yes, no)
- Prior number of oncology therapies (1, 2, ≥ 3)
- Baseline ALC (< 25×10^9/L, ≥ 25×10^9/L; < 100×10^9/L, ≥ 100×10^9/L)
- Baseline node size (< 5 cm, 5 cm To 10 cm, ≥ 10 cm)

ORR and CR and their 95% CIs will be reported for each level of subgroups in a forest plot. KM plot for DOR and PFS will be also be provided for 17p deleted versus non-17p

del., TP53 mutation versus TP53 non-mutation, and prior BCRi treated versus prior BCRi naïve.

10.4 Handling of Multiplicity

There will be no multiplicity adjustments performed in this open arm study.

11.0 Safety Analysis

11.1 General Considerations

Safety data will be summarized for the safety population, and the population is defined in Subsection 5.1.1.

11.2 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).

Treatment-emergent adverse events will be summarized by maximum severity grade level of each preferred term. Each adverse event will be assigned a grade level (grade 1, 2, 3, 4, or 5) by the investigator. If a subject has an AE with unknown severity, then the subject will be counted in the severity grade level category of "unknown," even if the subject has another occurrence of the same event with a severity present. The only exception is if the subject has another occurrence of the same AE with the highest grade level (grade 5). In this case, the subject will be counted under the "Grade 5" category.

Treatment-emergent adverse events will be summarized by relationship of each preferred term to venetoclax, as assessed by the investigator. If a subject has an adverse event with unknown relationship, then the subject will be counted in the relationship category of "unknown," even if the subject has another occurrence of the same event with a relationship present. The only exception is if the subject has another occurrence of the same adverse event with a relationship assessment of "Reasonable Possibility." In this case, the subject will be counted under the "Reasonable Possibility" category.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The actual version of the MedDRA coding dictionary will be noted in the clinical study report.

The number and percentage of subjects with treatment-emergent adverse events will be tabulated by primary MedDRA System Organ Class (SOC) and preferred term (PT). The system organ classes will be presented in alphabetical order, and the preferred terms will be presented in alphabetical order within each system organ class.

Adverse Event

An overview of AEs will be presented consisting of the number and percentage of subjects experiencing at least one event for each of the following AE categories:

- 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, or 4 adverse events;
- Any treatment-emergent NCI toxicity (CTCAE V4.0) grade 3, 4, or 5 adverse events;
- 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 venetoclax interruption;
- Any treatment-emergent adverse event leading to venetoclax dose reduction;
- Any treatment-emergent adverse event leading to death;
- Deaths.

The deaths in the overview summary include all deaths that occurring while the subject is still receiving venetoclax in this study and occurring off treatment within 30 days after the last dose of venetoclax.

For summary tables of AE by PT, subjects reporting more than one AE for a given PT will be counted only once for that term (most severe/highest grade incident for the severity tables and most related incident for the relationship tables). Subjects reporting more than one AE within an SOC will be counted only once for that SOC. Subjects reporting more than one AE will be counted only once in the overall total.

Adverse Events of Special Interest

Adverse events of special interest will be summarized. The list of adverse events of special interest is shown in Table 3.

For each of the adverse event of interest, the number and percentage of subjects experiencing at least one treatment-emergent adverse event will be presented overall and by SOC and PT. In addition, a listing of treatment-emergent adverse events for subjects meeting each of the search criterions will be provided.

Table 3. Adverse Events of Special Interest

Risk	Search Criteria
Tumor Lysis Syndrome (three searches)	1) SMQ – "Tumour lysis syndrome" (Narrow-scope) 2) SMQ – "Tumuor lysis syndrome" (Narrow) plus PT terms of "Hyperkalaemia," "Hyperuricaemia," "Hyperphosphataemia," "Hypocalaemia," "Blood potassium increased," "Blood uric acid increased," "Blood phosphorus increased," "Blood calcium decreased" 3) SMQ – "Tumuor lysis syndrome" (Narrow) plus broad-scope terms with algorithm applied (ie., two events from category B and one event from category C required for a subject to be counted as having a TLS event)
Neutropenia	PT terms – "Neutropenia," "Neutrophil count decreased," "Febrile neutropenia," "Agranulocytosis," "Neutropenic infection," and "Neutropenic sepsis"
Serious Infection, Including Opportunistic Infections	SAEs in the SOC of "Infections and Infestations"
Second Primary Malignancy	SMQ – "Malignant tumours" (Narrow) and "Myelodysplastic syndromes" (Narrow)
Lymphopenia	PT terms – "Lymphopenia" and "Lymphocyte count decreased"
Anemia	PT terms – "Anaemia" and "Haemoglobin decreased"
Thrombocytopenia	PT terms – "Thrombocytopenia" and "Platelet count decreased"
Drug Induced Liver Injury (DILI)	SMQ – "Drug related hepatic disorders – comprehensive search"
Medication Error	SMQ – "Medication error" (broad)

SMQ = Standardised MedDRA Query;

11.3 Analysis of Laboratory and Vital Signs Data

Data collected from the central and local laboratories, including additional laboratory testing due to an SAE, will be used in all analyses.

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 3.

Hematology variables include: hematocrit, hemoglobin, red blood cell (RBC) count, white blood cell (WBC) count, neutrophils, lymphocytes, platelet count, and reticulocyte count.

Chemistry variables include: blood urea nitrogen (BUN), creatinine, total bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, sodium, potassium, calcium, inorganic phosphorus, uric acid, glucose, albumin, Lactate dehydrogenase (LDH).

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

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 4.0.

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 maximum or final observations of grade 0, grade 1, grade 2, grade 3, grade 4 or grade 5.

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.

11.3.2 Assessment of Potentially Clinically Significant Vital Signs Values

Vital sign variables are systolic blood pressure, diastolic blood pressure, heart rate, and body temperature.

Pre-defined criteria for potentially clinically significant vital signs values are given in Table 4:

Table 4. 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

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 vital sign. 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.

11.3.3 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 References

1. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365-76.
2. EORTC. Chronic lymphocytic leaukemia (QLQ-CLL16). Available from: http://groups.eortc.be/qol/chronic-lymphocytic-leaukemia-qlq-cll16. Accessed on: February 2016.
3. Hoffmann-La Roche, German CLL Study Group. CLL11: a study of obinutuzumab (RO5072759 [GA101]) with chlorambucil in patients with previously untreated chronic lymphocytic leukemia (stage 2). ClinicalTrials.gov website. Available from: https://clinicaltrials.gov/ct2/show/NCT02053610. Accessed on: February 2016.
4. Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual Life Res. 2011;20:1727-36.

5. Oppe M, Devlin NJ, van Hout B, et al. A program of methodological research to arrive at the new international EQ-5D-5L valuation protocol. Value Health. 2014(4);17:445-53.
6. Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. Health Qual Life Outcomes. 2007;5:70-8.

Appendix A. List of Abbreviations

AE	Adverse Event
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
EORTC QLQ C30	European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire
EORTC QLQ CLL 16	European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire Chronic Lymphocytic Leukemia Module
EQ-5D-5L	EuroQoL 5 Dimension 5 Level Questionnaire
IWCLL	International Workshop for Chronic Lymphocytic Leukemia
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NCI-WG	National Cancer Institute-Working Group
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
TTP	Time to Progression
ULN	Upper Limit of Normal