1.0 Title Page

Statistical Analysis Plan

Study M15-550

Open-Label, Single Arm, Phase 3b, Multi-Center Study Evaluating the Efficacy of Venetoclax (ABT-199) in Relapsed/Refractory Subjects with Chronic Lymphocytic Leukemia (CLL) (VENICE I)

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3.0 Introduction

This statistical analysis plan (SAP) describes the statistical analyses to be performed for Study M15-550. Study M15-550 evaluates the efficacy of venetoclax monotherapy in subjects with relapsed or refractory chronic lymphocytic leukemia (CLL).

This statistical analysis plan (SAP) provides details to elaborate the statistical methods outlined in Clinical Study Protocol M15-550 Amendments 0.01 (US Only), 0.01.01 (US Only), and 0.0.1.01.01 (US Only) and Amendments 0.02 (ROW), 0.02.01 (ROW), and 0.02.01.01 (ROW). 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 9.4 (SAS Institute Inc., Cary, NC 27513) or later under the UNIX operating system.

4.0 Study Objectives, Design and Procedures

4.1 Objectives

Primary Objective

The primary objective of this study is to evaluate the efficacy of venetoclax monotherapy in subjects with relapsed or refractory CLL. Efficacy will be measured by complete remission rate (complete remission, CR, and complete remission with incomplete bone marrow recovery, CRi) of the subjects who have not been previously treated with BCRi therapy, as assessed by the investigator.

Secondary Objectives

The secondary objectives are to evaluate other efficacy parameters including the overall response rate (ORR), duration of overall response (DOR), time to progression (TTP), progression-free survival (PFS), overall survival (OS), and complete remission rate in BCRi treated subjects.

Additional secondary objectives are to evaluate the quality of life measures using the following patient reported outcomes (PRO) questionnaires: the EuroQoL 5 Dimensions (EQ-5D-5L), the Functional Assessment of Cancer Therapy – Leukemia Questionnaire (FACT-Leu), and the Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F). Safety and tolerability of venetoclax in subjects with relapsed/refractory CLL will also be evaluated.

Exploratory Objective

The exploratory objective is to evaluate the level of Minimal Residual Disease (MRD) and the rate of MRD negativity in the peripheral blood.

4.2 Study Design and Plan

This is a Phase 3b, open-label, single arm, and multicenter study evaluating the efficacy of venetoclax monotherapy in subjects with relapsed/refractory CLL.

This study is designed to enroll approximately 250 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 two years.

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/Dose Ramp-up 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

Using the CR rate of 6% reported for current therapies,[1] 250 subjects would provide approximately 90% power (based on an exact test for single proportions using a two-sided alpha of 5%) to reject the null hypothesis of 6% in favor of an alternative hypothesis that the CR rate for venetoclax monotherapy is 12% (doubling of the CR rate).

In order to provide approximately 80% power (based on an exact test for single proportions using a two-sided alpha of 5%) to reject the null hypothesis of 6% CR rate in favor of an alternative hypothesis that the CR rate for venetoclax monotherapy is 12% (doubling of the CR rate), the study will enroll 190 subjects who have not been previously treated with BCRi therapy. Since there are approximately a total of 250 subjects, up to 60 subjects previously treated with BCRi therapy can be enrolled.

The power calculation was performed in nQuery Version 7.

4.4 Interim Analysis

Data Monitoring Committee (DMC)

An Independent Data Monitoring Committee (DMC) will review the safety data when approximately 20 subjects have completed a minimum of 12 weeks of treatment. Subsequent reviews may be conducted based on recommendations from the DMC or

requests from the Sponsor. Details of the DMC review will be presented in the DMC charter.

4.5 Timing of Efficacy Analyses and Safety Evaluations

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

	Analysis Number/Database Version	Cutoff Date	Efficacy/PRO Data Included	Safety Data Included
DMC	C	24 Apr 2017	Not included	All safety data[a]
DMC	I	03 Nov 2017	Not included	All safety data[a]
DMC	J	30 Apr 2018	Included	All safety data[a]

a. Safety population is defined in Section 5.1.2.

Efficacy and safety data up to and including the cutoff date specified in Table 1 will be analyzed. During this data collection period, active subjects will continue to receive venetoclax, as applicable. When data collection is complete and all data management quality assurance (QA) and quality control (QC) procedures are performed, the clinical database data will be extracted for documentation and statistical analyses. Any active subjects will continue to receive venetoclax until they discontinue or for up to 2 years. Subjects that continue to derive clinical benefit after 2 years of treatment and where venetoclax is not commercially available may continue with treatment with venetoclax for up to 2 additional years. AbbVie will work with investigator on case by case basis to consider the potential continuation of the treatment. Once the last enrolled subject discontinues/completes the study, the study will be considered complete and all remaining data will be collected and entered into the clinical database.

All analyses will be conducted at AbbVie (or their designees) according to the methodologies specified in this SAP.

5.0 Analysis Populations

5.1 Definition for Analysis Populations

5.1.1 Efficacy Populations

5.1.1.1 Intent-to-Treat (ITT) Population

All enrolled subjects treated with at least one dose of venetoclax will be included in the ITT population. Efficacy analyses will be performed on the ITT population, unless otherwise specified.

5.1.1.2 ITT BCRi-Naive (ITT-BN) Population

ITT-BN population includes subjects who have not been previously treated with BCRi therapy in the ITT population.

5.1.1.3 ITT BCRi-Experienced (ITT-BE) Population

ITT-BE population includes subjects who were previously treated with BCRi therapy in the ITT population.

5.1.2 Safety Population

All ITT subjects will be included in the safety population.

5.2 Variables Used for Stratification of Randomization

No stratification is used for this open-label single-arm study.

6.0 Analysis Conventions

6.1 Baseline

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 with IV hydration for TLS prophylaxis, the baseline value will be the non-missing lab value taken before the subject receiving IV hydration prior to the first dose of venetoclax.
- For subject without IV hydration for TLS prophylaxis, the baseline value will be the non-missing lab value taken before the first dose of venetoclax.

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 (Qol), the time windows specified in Table 2 describe how the data are assigned to protocol specified visits. 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 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

Scheduled Visit	Nominal Day	Time Window (Study Day Range)
Week 1 Day 1/Baseline	≤ 1	See the baseline definition (Section 6.0)
Week 4 Day 1	22	2 to 56
Week 12 Day 1	78	57 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	744 to 835
Final Observation	Last non-missing value within 30 days of last dose of Venetoclax	

6.4 Missing Data Imputation

If a respondent answers at least 50% of the items in FACIT-F, 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. Similarly, the missing items of the FACIT-Leu questionnaire will be imputed with the average score of the answered items in the same scale as long as more than 50% of the items in the scale are answered. For EQ-5D-5L index, no imputation will be performed for missing items.

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.

7.0 Subject Disposition

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

- Subjects enrolled into the study.
- Subjects who discontinued 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 study drug interruptions will be summarized. Reasons for study drug interruptions will be presented in the CSR listings.

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

8.1 General Consideration

The ITT population, ITT-BE, and ITT-BN population will be used to summarize demographics and baseline characteristics. The safety population 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 (US, EUROPE)
- 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 ($\leq$ 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-US (low, medium, high)
- TLS risk category-ROW (yes, no)
- 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 (month)

8.3 Medical History

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

8.4 Previous Treatment and Concomitant Medications

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

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

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

9.0 Venetoclax Exposure and Compliance

The duration of exposure to Venetoclax will be summarized. Duration of exposure is defined for each subject as (last dose date – first dose date) + 1. Duration of exposure will be summarized using the following statistics: sample size (N), mean, standard deviation, median, and range. In addition, the number and percentage of subjects exposed to Venetoclax will be summarized for the following categories of exposure duration: 0 to 5 weeks, > 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 Efficacy Analysis

10.1 General Considerations

No statistical testing will be performed for the efficacy endpoints. Further details on the analysis sets used will be specified in efficacy analyses described below. All efficacy responses were assessed per investigator review.

10.1.1 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 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. Confirmatory PR response will be determined by not less than 49 days from the first PR was observed. 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 confirmed 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 assessment prior to the data cutoff 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). If the subject does not experience disease progression then the subject's data will be censored at the date of the last available disease assessment prior to the data cutoff 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). 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 assessment prior to the data cutoff 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 first dose date of 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 any study drug, or after the subject discontinued any study drug. If a subject has not died, then the data will be censored at the date when the subject was last known to be alive prior to the cutoff date. The date of the last known to be alive will be determined by selecting the last available date of the following study procedures for a subject: study visit/contact date, tumor assessment, clinical disease progression, physical examination, vital signs assessment, clinical laboratory collection, study drug, adverse event assessment, concomitant medication assessment, drug or study completion, survival visit, and post treatment therapy assessment. 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.

Minimal Residual Disease (MRD) Response Rate

The rate of MRD response in CLL subjects will be defined as the proportion of CLL subjects who achieved MRD negative status with less than one CLL cell per 10,000 leukocytes (or below 10^{-4}). All subjects with an MRD assessment will be included in the denominator for the calculation of MRD response rate. Minimal residual disease response will be summarized by categories: MRD negative, MRD positive, or MRD unknown/missing. The 95% confidence intervals based on the binomial distribution (Clopper-Pearson exact method) will be provided.

10.2 Efficacy Analyses

Data collected at any point prior to the specified cutoff date during the study will be used in efficacy analyses, unless otherwise specified.

10.2.1 Primary Efficacy Analysis

The primary efficacy endpoint will be complete remission rate (CR + CRi) of the subjects in ITT-BN population defined in Section 5.1.1.

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

10.2.2 Secondary Efficacy Analyses

ORR will be assessed as the proportion of subjects with an overall response (CR + CRi + nPR + PR) based on the IWCLL NCI-WG criteria. The ninety-five percent (95%) confidence interval based on the Clopper-Pearson exact method for binomial distribution will be constructed for the calculated ORR rate.

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.

The analyses of ORR, DOR, TTP, PFS, and OS will be performed on ITT, ITT-BN, and ITT-BE population.

The complete remission (CR + CRi) rate in will be assessed based on the 2008 Modified IWCLL NCI-WG criteria for ITT and ITT-BE population. The ninety-five percent (95%) confidence interval based on binomial distribution will be constructed for the calculated complete remission rate.

10.2.3 Exploratory Efficacy Analysis

The rate of MRD negativity in subjects will be summarized. This rate will be defined as the proportion of subjects who had MRD negativity status in peripheral blood. Ninety-five percent (95%) confidence intervals based on the Clopper-Pearson exact method for binomial distribution will be provided.

10.3 Additional Secondary Efficacy Analyses

Additional efficacy endpoints to be analyzed for the ITT, ITT-BN, and ITT-BE populations are Health Economic and Patient Reported Outcome measures, which include the FACT-Leu, FACIT-F, and the EQ-5D-5L (measure of general health status) and EQ-5D-VAS (Visual Analog Scale).

For the FACT-Leu, scores will be summarized descriptively at each assessment. The impact of treatment on quality of life over time will be assessed by calculating the change in scores from baseline at each assessment time point. Scores will be calculated according to the FACT-Leu scoring manual. The scores will also be summarized (mean, standard deviation, median) at each assessment. In addition mean change in scores (each assessment versus baseline) will be estimated. The 95% confidence interval of the mean change will be constructed based on (a) paired t-test and (b) with model assumption. A

linear mixed effect model will be used for the analysis of repeated measures where the covariance pattern will be assumed as compound symmetry (CS).

For the FACIT-F, scores will be summarized descriptively at each assessment. The impact of treatment on fatigue over time will be assessed by calculating the change in score from baseline at each assessment time point. Scores will be calculated according to the FACIT-F scoring manual. The scores will also be summarized (mean, standard deviation, median) at each assessment. In addition mean change in scores (each assessment versus baseline) will be estimated. The 95% confidence interval of the mean change will be constructed based on (a) paired t-test and (b) with model assumption. A linear mixed effect model will be used for the analysis of repeated measures where the covariance pattern will be assumed as compound symmetry (CS).

The 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 VAS values and the score of the EQ-5D-5L will also be summarized (mean, standard deviation, median) at each assessment; in addition mean change in VAS values and the score of the EQ-5D-5L (each assessment versus baseline) will be estimated. The 95% confidence interval of the mean change will be constructed based on (a) paired t-test and (b) with model assumption. A linear mixed effect model will be used for the analysis of repeated measures where the covariance pattern will be assumed as compound symmetry (CS).

10.4 Subgroup Analyses of Efficacy and Quality of Life

To evaluate the impact of baseline conditions on efficacy, subgroup analyses will be performed for complete remission (CR + CRi) in the ITT, ITT-BN, and ITT-BE population.

The following subgroups below will be used for efficacy analyses:

- 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. MRD response rate will be additionally summarized by overall response category (CR/PR/non-responders) and the BCRi failure status (yes, no).

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)

10.5 Handling of Multiplicity

There will be no multiplicity adjustments performed.

11.0 Safety Analysis

11.1 General Considerations

Safety data will be summarized for the ITT population.

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.

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.

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 V4.03) grade 3, 4, or 5 adverse events;
- Any treatment-emergent NCI toxicity (CTCAE V4.03) 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 venetoclax interruption
- Any treatment-emergent adverse event leading to venetoclax reduction

- Any treatment-emergent adverse event leading to death;

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 (i.e., 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 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).

11.4 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.

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, LDH.

11.4.1 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 4.03), 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 4.03.

For laboratory tests for which a normal range limit is one end of the grade 1 range, then values that are either within the normal range or outside of it in direction opposite, the test will be classified as grade 0 values. For other tests, values outside of the grade 1 range in the direction opposite of that the test will be classified as grade 0.

The baseline and final grades will be defined respectively as defined in Section 6.1.

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

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

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

Potential Drug-Induced Liver Injury (DILI)

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

11.4.2 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 below:

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.

11.4.3 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 Pharmacokinetic Analyses

Plasma concentrations of venetoclax and possible metabolites(s) will be listed for each subject by scheduled visit. Summary statistics will also be computed for each scheduled visit. Samples not taken pre-dose will be excluded from summary statistics calculation.

13.0 Summary of Changes

- Updated secondary endpoints and added exploratory endpoint
- Updated censoring rules for the analysis of time to event
- Updated the safety data analysis

14.0 References

1. Resonate Trial. ASH. 2014. Abstract 3331.

Appendix A. List of Abbreviations

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

Document Approval

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