

Statistical Analysis Plan for Study M20-353

A Phase 2 Study of the Safety and Efficacy of Venetoclax in Combination with Obinutuzumab or Ibrutinib in Japanese Subjects with Previously Untreated Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)

Date: 07 May 2024

Version 2.0

Table of Contents

1.0	Introduction.....	5
2.0	Study Design and Objectives	5
2.1	Objectives, Hypotheses and Estimands	5
2.2	Study Design Overview	6
2.3	Treatment Assignment and Blinding.....	8
2.4	Sample Size Determination	9
3.0	Endpoints	9
3.1	Primary Endpoint	9
3.2	Secondary Endpoints	9
3.3	Other Efficacy Endpoints	10
3.4	Safety Endpoints	11
3.5	Pharmacokinetic Endpoints	11
3.6	Biomarker Research Endpoints.....	11
4.0	Analysis Populations	12
5.0	Subject Disposition	12
6.0	Study Drug Duration and Compliance	13
7.0	Demographics, Baseline Characteristics, Medical History, and Prior/Concomitant Medications	14
7.1	Demographics and Baseline Characteristics	15
7.2	Medical History.....	17
7.3	Prior and Concomitant Medications.....	17
8.0	Handling of Potential Intercurrent Events for the Primary and Secondary Endpoints	18
9.0	Efficacy Analyses.....	19
9.1	General Considerations.....	19
9.2	Handling of Missing Data.....	19
9.3	Primary Efficacy Endpoint and Analyses.....	19
9.3.1	Primary Efficacy Endpoint	19
9.3.2	Analysis of Primary Efficacy Endpoint.....	20
9.4	Secondary Efficacy Endpoints and Analyses	21
9.4.1	Secondary Efficacy Endpoints	21

9.4.2	Analyses of Secondary Efficacy Endpoints.....	21
9.5	Additional Efficacy Analyses	25
10.0	Safety Analyses	26
10.1	General Considerations.....	26
10.2	Adverse Events.....	26
10.2.1	Treatment-Emergent Adverse Events.....	27
10.2.2	Adverse Event Overview	27
10.2.3	Treatment-Emergent Adverse Events by SOC and/or PT	29
10.2.4	SAEs (Including Deaths) and Adverse Events Leading to Study Drug Discontinuation	29
10.2.5	Adverse Events of Special Interest.....	29
10.3	Analysis of Laboratory Data	29
10.4	Analysis of Vital Signs	31
11.0	Pharmacokinetic Analyses	32
12.0	Biomarker Research Analyses	32
13.0	Interim Analyses.....	33
14.0	Overall Type-I Error Control.....	33
15.0	Version History	33
16.0	References	34

List of Tables

Table 1.	Venetoclax Dose Ramp-Up Levels (Cohort 1).....	8
Table 2.	Venetoclax Dose Ramp-Up Levels (Cohort 2).....	8
Table 3.	Summary of the Estimand Attributes Corresponding to the Primary Efficacy Endpoint	20
Table 4.	Summary of the Estimand Attributes Corresponding to the Secondary Efficacy Endpoint	23
Table 5.	SAP Version History Summary	33

List of Figures

Figure 1.	Study Schematic	7
-----------	-----------------------	---

List of Appendices

Appendix A.	Protocol Deviations	35
Appendix B.	Definition of Adverse Events of Special Interest.....	36
Appendix C.	Potentially Clinically Important Criteria for Safety	38

1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses for venetoclax Study M20-353: "A Phase 2 Study of the Safety and Efficacy of Venetoclax in Combination with Obinutuzumab or Ibrutinib in Japanese Subjects with Previously Untreated Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)." This version of the plan has been developed using protocol dated 19 March 2024 (version 5.0).

Study M20-353 examines the efficacy and safety of Venetoclax in Combination with Obinutuzumab or Ibrutinib in Japanese Subjects with Previously Untreated CLL/SLL.

The SAP will not be updated in case of administrative changes or amendments to the protocol unless the changes impact the analysis.

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.

2.0 Study Design and Objectives

2.1 Objectives, Hypotheses and Estimands

The primary objective of the study is to evaluate the efficacy of venetoclax in combination with obinutuzumab (V+G, Cohort 1) or with ibrutinib (V+I, Cohort 2) in Japanese subjects with previously untreated CLL/SLL.

The corresponding estimands of interest for evaluating the primary objective are:

- The complete remission (CR)/ complete remission with an incomplete marrow recovery (CRi) rate for subjects treated with V+G (Cohort 1) based on objective assessment by an Independent Review Committee (IRC).
- The CR/CRi rate for subjects treated with V+I (Cohort 2) based on objective assessment by an IRC.

For each of these regimens, efficacy will be considered "established" if the lower bound of the corresponding 95% confidence interval (CI) for CR/CRi rate is greater than the pre-set threshold of 10%.

The secondary objectives are to evaluate the safety of the V+G and V+I combinations, and to further characterize their efficacy. For the V+G combination only, the tolerability will also be evaluated in Japanese subjects.

Please see Section 9.3 for further details on corresponding estimands.

2.2 Study Design Overview

This is a Phase 2, open-label, multicenter, non-comparator, two-cohorts study of previously untreated CLL/SLL subjects. Subjects will be assigned to one of two treatment groups via 1:1 variable alternating assignment. The study will explore safety and efficacy of two treatment arms:

- Venetoclax + obinutuzumab (V+G; Cohort 1)
- Venetoclax + ibrutinib (V+I; Cohort 2)

The study will enroll 20 subjects (10 subjects per cohort) across 20 sites in Japan.

The study will consist of Screening, Treatment, and Follow-up periods. The schematic of the study is shown in Figure 1.

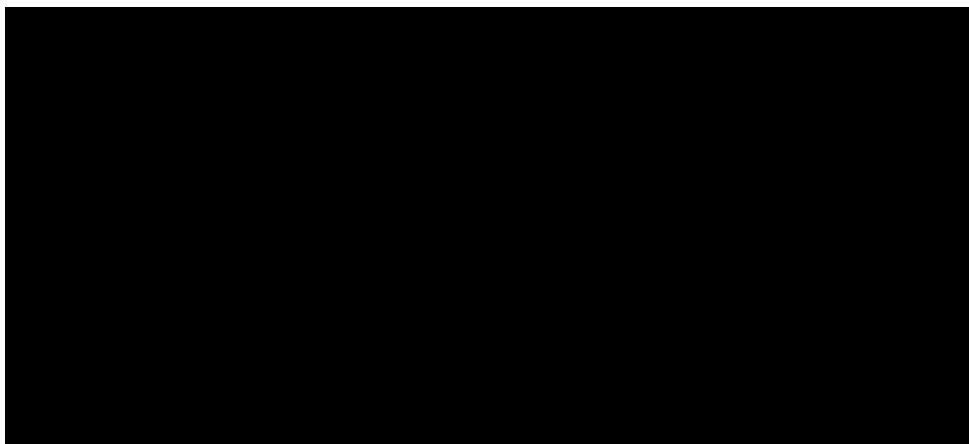
Efficacy will be examined as follows:

- Cohort 1 (V+G) Cycle 4 Day 1, Cycle 7 Day 1, and Cycle 9 Day 1, and end of treatment and follow up visits.
- Cohort 2 (V+I) - Cycle 4 Day 1, Cycle 9 Day 1, and Cycle 15 Day 1, and end of treatment and follow up visits.

In Cohort 1, dose-limiting toxicities (DLTs) will be evaluated in the first 6 subjects, from Cycle 1 Day 22 for a minimum of 5 weeks and at least 1 week of venetoclax dosing at

■■■■ mg, in order to confirm the initial safety and tolerability in Japanese subjects. After the completion of the DLT evaluation period in the first 6 subjects, the Sponsor will review all available safety data to evaluate the tolerability of venetoclax in combination with obinutuzumab in Japanese subjects. If there are 0 or 1 DLTs in the first 6 subjects, enrollment will proceed. If DLTs are observed in 2 or more of the first 6 subjects, further enrollment in Japan will be interrupted and additionally, a detailed safety assessment will be conducted.

Figure 1. Study Schematic



Note: A cycle will be defined as 28 days in both cohorts.

Cohort 1 (V+G)

Subjects assigned to Cohort 1 (V+G) will receive obinutuzumab ■■■■ mg or ■■■■ mg, depending on splitting rules, intravenously (IV) on Cycle 1 Day 1 (if ■■■■ mg administered on Day 1, then ■■■■ mg will be administered on Day 2) and then ■■■■ mg on ■■■■ of Cycle 1. For all subsequent cycles (up through the end of Cycle 6) subjects will receive obinutuzumab ■■■■ mg on Day 1. Venetoclax will be administered with a 5-step dose ramp up beginning with a ■■■■ mg dose (Cycle 1 ■■■■) to reach the final dose of ■■■■ mg (Cycle 2 ■■■■) ([Table 1](#)) to reduce the risk of TLS. Venetoclax will be continued at ■■■■ mg daily thereafter through Cycle 12.

Table 1. Venetoclax Dose Ramp-Up Levels (Cohort 1)

Daily Venetoclax Dose (mg)					
Week 1	Week 2	Week 3	Week 4	Week 5	Subsequent Cycles
					Cycles 3 through

Cohort 2 (V+I)

Subjects assigned to Cohort 2 (V+I) will receive ibrutinib [REDACTED] mg orally (PO) once a day (QD) for 15 cycles, starting with 3 cycles of ibrutinib monotherapy. Venetoclax will be administered with a 5-step dose ramp-up beginning at Cycle 4 (Table 2). The combination of V+I will be given for 12 cycles (through Cycle 15).

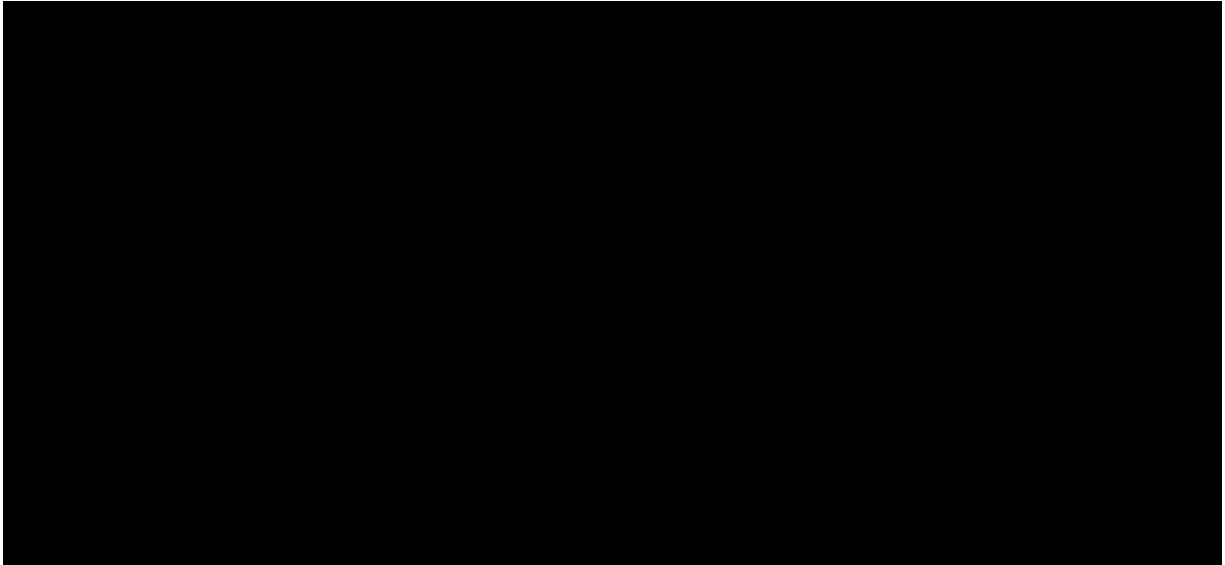
Table 2. Venetoclax Dose Ramp-Up Levels (Cohort 2)

Daily Venetoclax Dose (mg)					
Week 1	Week 2	Week 3	Week 4	Week 5	Subsequent Cycles
					Cycle 5 [REDACTED] and Cycles 6 through Cycle 15
Cycle 4	Cycle 4	Cycle 4	Cycle 4	Cycle 5	

2.3 Treatment Assignment and Blinding

Subjects will be assigned to one of two treatment groups via 1:1 variable alternating assignment.

2.4 Sample Size Determination



3.0 Endpoints

3.1 Primary Endpoint

The primary efficacy endpoint is the CR/CRi rate, as assessed by an IRC per modified 2008 International Workshop on Chronic Lymphocytic Leukemia Working Group (iwCLL) criteria for tumor response.

3.2 Secondary Endpoints

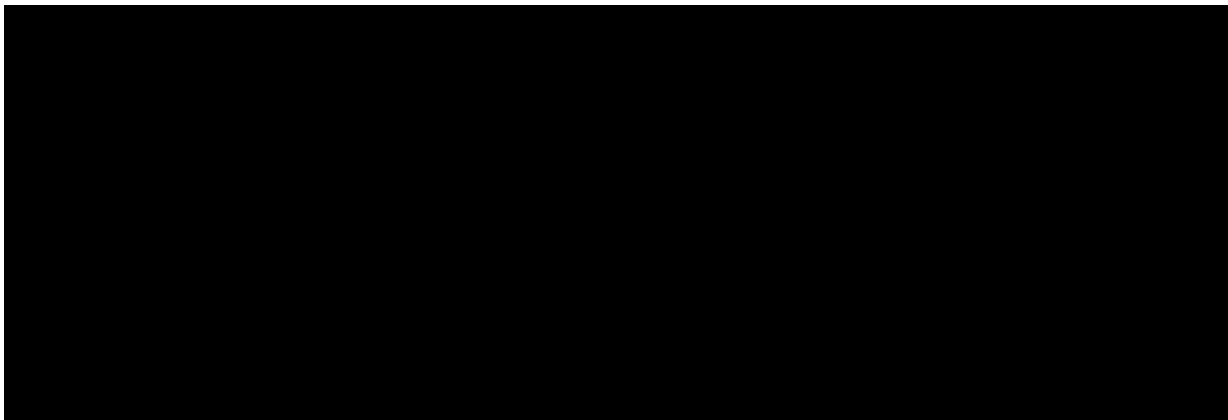
The secondary endpoints are the following:

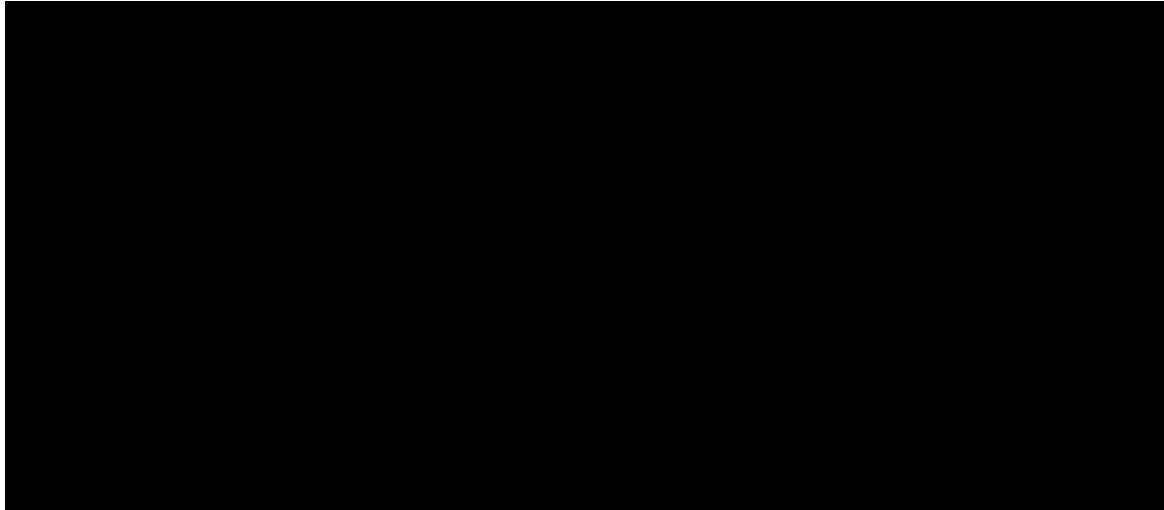
- CR/CRi rate as assessed by investigator per 2008 iwCLL.
- Overall response rate (ORR), defined as the proportion of subjects with a best overall response of CR, CRi, nodular partial remission (nPR), or partial remission (PR) per 2008 iwCLL criteria as assessed by an IRC.
- ORR, defined as the proportion of subjects with a best overall response of CR, CRi, nPR, or PR per 2008 iwCLL criteria as assessed by investigator.
- Progression-free survival (PFS), defined as the time from the date of first dose of any study drug until the date of disease progression as determined by an

IRC according to iwCLL criteria or death due to any cause, whichever occurs first.

- PFS, defined as the time from the date of first dose of any study drug until the date of disease progression as determined by the investigator according to iwCLL criteria or death due to any cause, whichever occurs first.
- Duration of response (DOR), defined as the time from the first occurrence of verall response (CR, CRi, nPR or PR) until disease progression as determined by an IRC according to iwCLL criteria or death due to any cause, whichever occurs first.
- DOR, defined as the time from the first occurrence of overall response (CR, CRi, nPR or PR) until disease progression as determined by the investigator according to iwCLL criteria or death due to any cause, whichever occurs first.
- Overall survival (OS), defined as the time from the date of the first dose of any study drug until death due to any cause.
- Time to progression (TTP), defined as the time from the date of first dose of any study drug until the date of disease progression, as determined by an IRC according to iwCLL criteria.
- TTP, defined as the time from the date of first dose of any study drug until the date of disease progression, as determined by the investigator according to iwCLL criteria.

3.3 Other Efficacy Endpoints





3.4 Safety Endpoints

Safety evaluations include AE monitoring, physical examinations, vital sign measurements, and clinical laboratory testing (hematology and chemistry) as measures of safety and tolerability for the entire study duration.

3.5 Pharmacokinetic Endpoints

Blood samples to assess plasma concentration of venetoclax and ibrutinib and serum concentration of obinutuzumab will be obtained at specified time points as indicated in Appendix L of the protocol.

3.6 Biomarker Research Endpoints

Biomarker values are exploratory endpoints in this study.

Prespecified biomarker endpoints include:

- undetectable minimal residual disease (uMRD) rates 3 months after end of treatment (EOT)
- Overall uMRD rate

Undetectable minimal residual disease is defined as less than one CLL cells detected among 10,000 leukocytes.

4.0 Analysis Populations

The following population sets will be used for the analyses.

For Cohort 1, the Full Analysis Set (FAS) includes all subjects who received at least 1 dose of venetoclax and/or obinutuzumab. For Cohort 2, the FAS includes all subjects who received at least 1 dose of venetoclax and/or ibrutinib. The FAS will be used for all efficacy (except the endpoints assessed by IRC), safety, pharmacokinetic (PK), and baseline analyses. All analyses will be performed independently for each of the two enrolled cohorts.

The IRC assessed endpoints will be analyzed using the per-protocol (PP) population for the primary and secondary efficacy endpoints data assessed by IRC. The PP population includes FAS subjects who have evaluable disease at baseline, i.e., excludes FAS subjects who have been determined as having non-evaluable disease at baseline, as determined by IRC: e.g., a subject with no disease at baseline and/or malignancies other than CLL/SLL at baseline identified.

5.0 Subject Disposition

Analysis for subject disposition will be based on FAS and PP population.

A summary of subject accountability will be provided where the number of subjects in each of the following categories will be summarized for each cohort:

Both cohorts

- Subjects enrolled in the study
- Subjects who completed protocol-specified treatment
- Subjects who discontinued venetoclax (primary reason)
- Subjects who discontinued study (primary reason)

- Subjects in each analysis population, FAS and PP population.

Cohort 1

- Subjects who took at least one dose of study drug (venetoclax / obinutuzumab)
- Subjects who discontinued obinutuzumab (primary reason)

Cohort 2

- Subjects who took at least one dose of study drug (venetoclax / ibrutinib)
- Subjects who discontinued ibrutinib (primary reason)

Descriptive statistics will be provided for time on study in FAS. Time on study is defined as the time from the date of the first dose of any study drug to last day known to be alive. If a subject has died, then the data will be censored at death date. The Kaplan-Meier method will be used to estimate the median time on study.

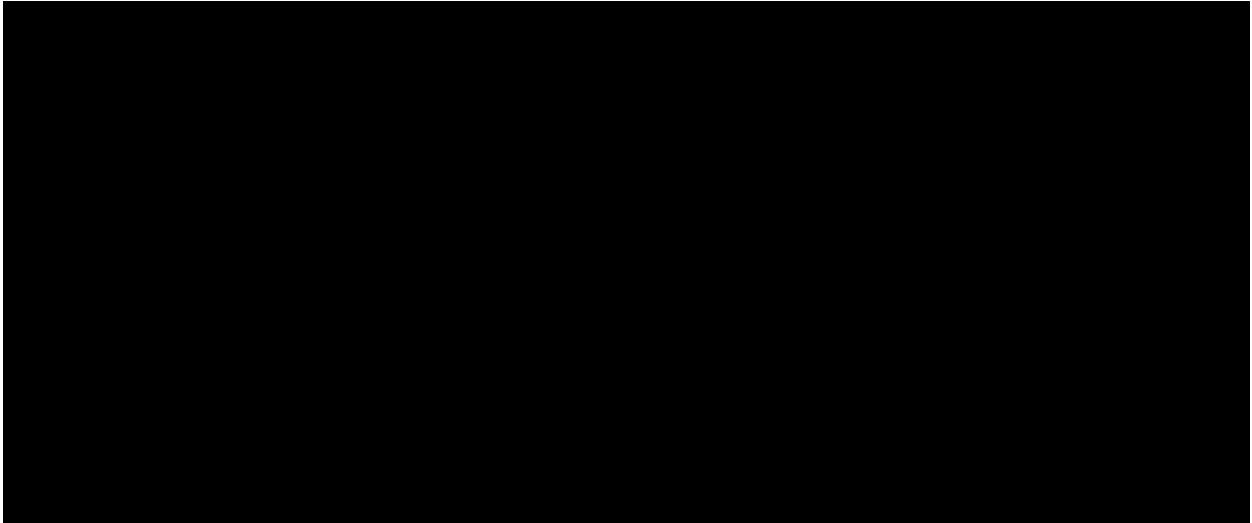
6.0 Study Drug Duration and Compliance

Duration of treatment / number of cycles

For venetoclax and ibrutinib, duration of treatment will be summarized for each study drug separately for the FAS population. Duration of treatment will be defined for each subject as last dose date minus first dose date + 1. Duration of each study drug (venetoclax / ibrutinib) will be summarized using the number of subjects treated, mean, standard deviation, median, minimum and maximum. In addition, the number and percentage of subjects in each treatment duration interval will be summarized for venetoclax and ibrutinib separately.

For obinutuzumab, the number of cycles that subjects are exposed will be summarized for the FAS population using the number of subjects treated, mean, standard deviation, median, minimum and maximum.

Dose modification



Dose intensity / total cumulative dose

Total cumulative dose will be summarized for venetoclax / obinutuzumab / ibrutinib separately.

The relative dose intensity (RDI) will be summarized for venetoclax / obinutuzumab / planned dose intensity (PDI): ODI/PDI.

Details derivations on ODI and PDI are documented in Statistical Programming Plan (SPP).

7.0 Demographics, Baseline Characteristics, Medical History, and Prior/Concomitant Medications

Demographics, baseline or disease characteristics, medical history, and prior and concomitant medications will be summarized by cohort on the FAS. Categorical variables will be summarized with the number and percentage of subjects; percentages will be calculated based on the number of non-missing observations. Continuous variables will be summarized with descriptive statistics (number of non-missing observations, mean and standard deviation, median, minimum and maximum).

7.1 Demographics and Baseline Characteristics

All baseline characteristic summary statistics and analyses are based on characteristics prior to the first dose of study drug.

Distributions of the continuous demographic and baseline characteristic variables will be summarized by cohort with the number of non-missing observations, mean, standard deviation, and median, as well as the minimum and maximum values. For the categorical demographic and baseline characteristic variables, the frequency and percentages of subjects within each category will be summarized. The number of subjects with missing information will also be summarized.

The following demographic and baseline characteristics will be summarized:

Demographics:

Categorical baseline variables include:

- Age (< 65, ≥ 65 years)
- Gender (Male, Female)
- Race (Asian, Others)
- If Asian (Japanese, Chinese, Korean, Taiwanese and others)
- Tobacco user (current, former, never, unknown)
- Alcohol user (current, former, never, unknown)

Continuous baseline variables include:

- Age (years)
- Height (cm)
- Weight (kg)

Baseline and Disease-Related Characteristics:

Categorical baseline variables include:

- Diagnosis (CLL, SLL)
- Rai staging: CLL only (Stage 0, Stage I, Stage II, Stage III, Stage IV)
- Binet staging: CLL only (Stage A, Stage B, Stage C)
- Lugano classification modified by the Ann Arbor Staging System: SLL only (Stage I, Stage IE, Stage II, Stage IIE, Stage II bulky, Stage III, Stage IV)
- 13q deletion (Present, Absent, Indeterminate, Not done)
- Trisomy 12 (Present, Absent, Indeterminate, Not done)
- 11q deletion (Present, Absent, Indeterminate, Not done)
- 17p deletion (Present, Absent, Indeterminate)
- TP53 mutation status (Mutated, Unmutated, Indeterminate, Not done)
- TP53 mutated and / or 17p deletion (Yes, No)
- IgHV mutation status (Mutated, Unmutated, Indeterminate, Not done)
- Child-Pugh Classification (A, B, C)
- ECOG performance status (Grade 0, Grade 1, Grade 2, Grade > 2)
- TLS risk category (High, Medium, Low)
- Antiglobulin Test, Direct (Negative, Positive)
- Antiglobulin Test, Indirect (Negative, Positive)
- B-Symptoms (Yes, No)
- B-Symptoms Weight loss (Yes, No)
- B-Symptoms Fevers (Yes, No)
- B-Symptoms Night sweats (Yes, No)
- B-Symptoms Significant fatigue (Yes, No)
- Beta-2 microglobulin (≤ 3.5 mg/L, > 3.5 mg/L)
- Cumulative Illness Rating Scale score (≤ 6 , > 6)
- Bulky disease (< 5 cm, ≥ 5 cm)
- Bulky disease (< 10 cm, ≥ 10 cm)

- Creatinine clearance (< 70 mL/min, ≥ 70 mL/min)
- Absolute Lymphocyte count ($< 25 \times 10^9/L$, $\geq 25 \times 10^9/L$)

Continuous baseline variables include:

- Time from first diagnosis (years)
- Beta-2 microglobulin (mg/L)
- Cumulative Illness Rating Scale score
- Creatinine clearance (mL/min)
- Absolute lymphocytes count ($10^9/L$)

7.2 Medical History

Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The actual version of the MedDRA coding dictionary will be noted in the statistical tables and clinical study report. The number and percentage of subjects in each medical history category (by MedDRA system organ class and preferred term) will be summarized by cohort. The system organ class (SOC) will be presented in alphabetical order, and the preferred terms will be presented in alphabetical order within each SOC. Subjects reporting more than one condition/diagnosis will be counted only once in each row (SOC or preferred term).

7.3 Prior and Concomitant Medications

Prior and concomitant medications will be summarized by generic name. A prior medication is defined as any medication taken prior to the date of the first dose of study drug. A concomitant medication is defined as any medication that started prior to the date of the first dose of study drug and continued to be taken after the first dose of study drug or any medication that started on or after the date of the first dose of study drug, but not after the date of the last dose of study drug plus 30 days. The number and percentage of subjects taking medications will be summarized by generic drug name based on the World Health Organization (WHO) Drug Dictionary for both prior and concomitant medications.

In addition, the number and percentage of subjects who received TLS prophylaxis will be summarized.

In addition, post-treatment anti-leukemic therapies will be summarized.

8.0 Handling of Potential Intercurrent Events for the Primary and Secondary Endpoints

Potential intercurrent events will be handled as described in Section 9.3.2 and Section 9.4.2.

For all efficacy endpoints unless otherwise mentioned, the following potential intercurrent events (ICEs) will be considered:

- ICE1: Subjects with premature discontinuation of combination study drug due to any cause.
- ICE2: Subjects with the use of subsequent new anti-leukemic therapy

For CR/CRi rate and ORR, the intercurrent events will be handled based on the following strategies:

- ICE1: The disease assessments after ICE1 will be used for the derivation of efficacy endpoints.
- ICE2: The disease assessments after ICE2 will not be used for the derivation of efficacy endpoints.

For PFS, DOR, OS and TTP, the intercurrent events will be handled based on the following strategies:

- ICE1: The disease assessments after ICE1 will be used for the derivation of efficacy endpoints.
- ICE2: The disease assessments after ICE2 will be used for the derivation of efficacy endpoints.

9.0 Efficacy Analyses

9.1 General Considerations

All efficacy analyses will be conducted in the FAS except for primary and secondary efficacy endpoints analysis assessed by IRC. The investigator's assessment will use the FAS population for the primary and secondary efficacy endpoints data. The IRC assessment will use the PP population for the primary and secondary efficacy endpoints data.

For binary endpoint (CR/CRi rate, ORR), the estimated proportion and corresponding 95% CI will be provided based on the Clopper-Pearson exact method.

Time-to-event endpoints (PFS, DOR, OS and TTP) will be summarized using the Kaplan-Meier methodology. The median and the corresponding 95% CI will be provided.

The primary analysis will be performed when all subjects have completed two tumor response assessments or discontinued.

9.2 Handling of Missing Data

Details on the handling of missing data are described in the analysis section corresponding to each endpoint.

9.3 Primary Efficacy Endpoint and Analyses

9.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint will be CR/CRi rate, as assessed by IRC per modified 2008 iwCLL criteria for tumor response. CR/CRi rate is defined as the proportion of subjects with a best response of CR or CRi.

V+G (Cohort 1) and V+I (Cohort 2) will be considered effective for Japanese patients with previously untreated CLL/SLL if the lower bound of the corresponding 95% CI for CR/CRi rate is greater than the threshold of 10%.

9.3.2 Analysis of Primary Efficacy Endpoint

Analysis of the primary endpoint will be performed on the PP population.

Subjects who are enrolled but have no post-baseline disease assessment will be considered as non-responders. Subjects who have not achieved best response of CR/CRi at the time of analysis will be considered as non-responders in the calculation of CR/CRi rate. If a subject receives a new anti-leukemic therapy, the disease assessment collected after a new anti-leukemic therapy will be excluded.

The attributes of the estimand corresponding to the primary efficacy endpoint are summarized in [Table 3](#).

Table 3. Summary of the Estimand Attributes Corresponding to the Primary Efficacy Endpoint

Estimand Label	Attributes of the Estimand				
	Treatment	Endpoint	Population	Handling of Intercurrent Events	Statistical Summary
CR/CRi rate	V+G (Cohort 1) or V+I (Cohort 2)	IRC-assessed best overall response of CR/CRi.	PP population	1) Study drug discontinuation: Treatment policy strategy - Ignore the intercurrent events. 2) Use of new anti-leukemic therapy: While on treatment strategy - Only use assessments prior to the initiation of new anti-leukemic therapies.	CR/CRi rate and 95% CI

9.4 Secondary Efficacy Endpoints and Analyses

9.4.1 Secondary Efficacy Endpoints

All IRC assessed secondary endpoints will use PP population for primary analysis and all investigator assessed secondary endpoints will use FAS. The secondary endpoints will be assessed per modified 2008 iwCCLL criteria for tumor response.

9.4.2 Analyses of Secondary Efficacy Endpoints

CR/CRi rate:

The same methodology as for the analysis of CR/CRi rate assessed by IRC will be applied to the analysis of CR/CRi rate assessed by investigator.

ORR:

ORR is defined as the proportion of subjects with a best response of CR, CRi, nPR or PR, assessed by IRC. Subjects who are enrolled but have no post-baseline disease assessment will be considered as non-responders. Subjects who have not achieved best response of CR, CRi, nPR or PR at the time of analysis will be considered as non-responders in the calculation of ORR. If a subject receives a new anti-leukemic therapy, the disease assessment collected after a new anti-leukemic therapy will be excluded.

Similarly, analysis of ORR will be performed using investigator assessed data.

PFS:

PFS is defined as the time from the date of the first dose of any study drug to the date of disease progression, as assessed by an IRC, or death from any cause, whichever occurs first. All events (disease progression or death from any cause) will be included, regardless of whether the event occurred while the subject was still taking study drug or after the subject discontinued study drug or the subject started of new anti-leukemic therapy. For subjects that do not experience disease progression or death, then the data will be censored at the date of the last adequate disease assessment. Data for subjects without any

disease assessments performed after the baseline visit will be censored at the date of the first dose plus 1 day.

Similarly, analysis of PFS will be performed using investigator assessed data.

DOR:

DOR is defined as the time from the first occurrence of overall response (CR, CRi, nPR or PR) to disease progression, as assessed by an IRC, or death due to any cause, whichever occurs first. All events (disease progression or death from any cause) will be included, regardless of whether the event occurred while the subject was still taking study drug or after the subject discontinued study drug or the subject started of new anti-leukemic therapy. If a subject is still responding, subjects will be censored at the date of the last adequate disease assessment. The DOR will be analyzed for subjects who achieve a best overall response of CR, CRi, nPR or PR.

Similarly, analysis of DOR will be performed using investigator assessed data.

OS:

OS is defined as the time from the date of the first dose of any study drug to death from any cause. All events of death will be included, regardless of whether the event occurred while the subject was still taking study drug or after the subject discontinued study drug or the subject started of new anti-leukemic therapy. If a subject has not died, then the data will be censored at the date the subject was last known to be alive. The analysis will be performed on FAS.

TTP:

TTP is defined as the time from the date of first dose of any study drug to the date of disease progression, as assessed by an IRC. All events of disease progression will be included, regardless of whether the event occurred while the subject was still taking study drug or after the subject discontinued study drug or the subject started of new

anti-leukemic therapy. For subjects that do not experience disease progression, then the data will be censored at the date of the last adequate disease assessment. Data for subjects without any disease assessments performed after the baseline visit will be censored at the date of the first dose plus 1 day.

Similarly, analysis of TTP will be performed using investigator assessed data.

The attributes of the estimands corresponding to the secondary efficacy endpoints are summarized in [Table 4](#).

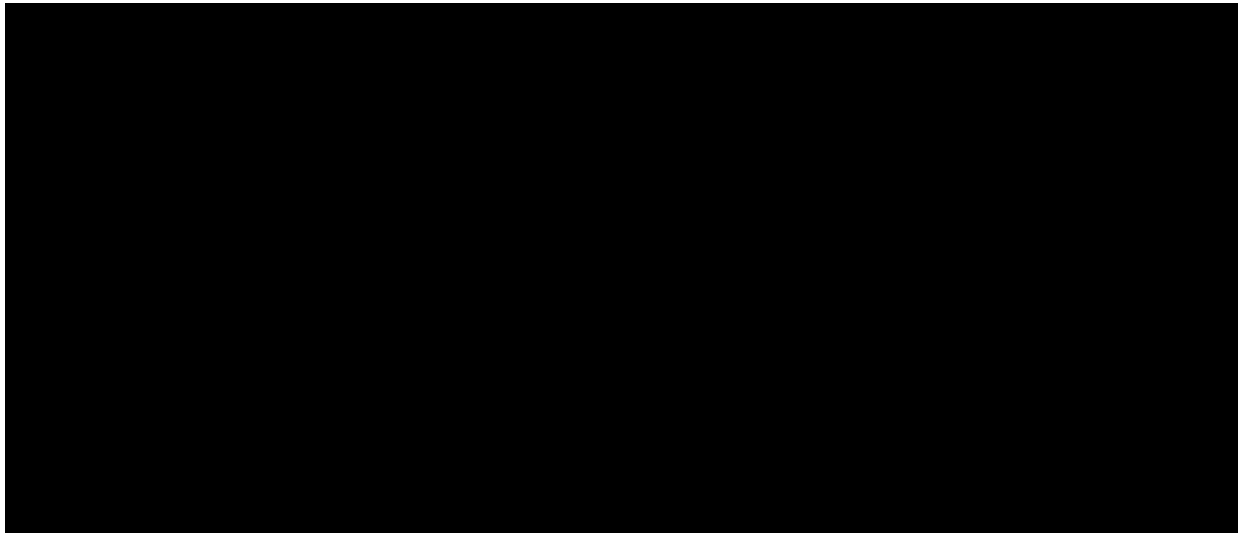
Table 4. Summary of the Estimand Attributes Corresponding to the Secondary Efficacy Endpoint

Estimand Label	Attributes of the Estimand				Statistical Summary
	Treatment	Endpoint	Population	Handling of Intercurrent Events	
CR/CRi rate	V+G (Cohort 1) or V+I (Cohort 2)	Investigator-assessed best overall response of CR/CRi.	FAS population	1) Study drug discontinuation: Treatment policy strategy - Ignore the intercurrent events. 2) Use of new anti-leukemic therapy: While on treatment strategy - Only use assessments prior to the initiation of new anti-leukemic therapies.	CR/CRi rate and 95% CI

Attributes of the Estimand					
Estimand Label	Treatment	Endpoint	Population	Handling of Intercurrent Events	Statistical Summary
ORR	V+G (Cohort 1) or V+I (Cohort 2)	IRC-assessed best overall response of CR, CRi, nPR or PR.	PP population	1) Study drug discontinuation: Treatment policy strategy - Ignore the intercurrent events.	ORR and 95% CI
		Investigator-assessed best overall response of CR, CRi, nPR or PR.	FAS population	2) Use of new anti-leukemic therapy: While on treatment strategy - Only use assessments prior to the initiation of new anti-leukemic therapies.	
PFS	V+G (Cohort 1) or V+I (Cohort 2)	IRC-assessed PFS	PP population	1) Study drug discontinuation: Treatment policy strategy - Ignore the intercurrent events.	1) K-M plot 2) K-M estimates 3) Median PFS
		Investigator-assessed PFS	FAS population	2) Use of new anti-leukemic therapy: Treatment policy strategy - Ignore the intercurrent events.	
DOR	V+G (Cohort 1) or V+I (Cohort 2)	IRC-assessed DOR of CR, CRi, nPR or PR.	Achieving CR, CRi, nPR or PR in PP population	1) Study drug discontinuation: Treatment policy strategy - Ignore the intercurrent events.	1) K-M plot 2) K-M estimates 3) Median DOR
		Investigator - assessed DOR of CR, CRi, nPR or PR.	Achieving CR, CRi, nPR or PR in FAS population	2) Use of new anti-leukemic therapy: Treatment policy strategy - Ignore the intercurrent events.	

Attributes of the Estimand					
Estimand Label	Treatment	Endpoint	Population	Handling of Intercurrent Events	Statistical Summary
OS	V+G (Cohort 1) or V+I (Cohort 2)	OS	FAS population	1) Study drug discontinuation: Treatment policy strategy - Ignore the intercurrent events. 2) Use of new anti-leukemic therapy: Treatment policy strategy - Ignore the intercurrent events.	1) K-M plot 2) K-M estimates 3) Median OS
TTP	V+G (Cohort 1) or V+I (Cohort 2)	IRC-assessed TTP Investigator - assessed TTP	PP population FAS population	1) Study drug discontinuation: Treatment policy strategy - Ignore the intercurrent events. 2) Use of new anti-leukemic therapy: Treatment policy strategy - Ignore the intercurrent events.	1) K-M plot 2) K-M estimates 3) Median TTP

9.5 Additional Efficacy Analyses



10.0 Safety Analyses

10.1 General Considerations

Safety data will be summarized for the Full Analysis Set defined in Section [4.0](#).

10.2 Adverse Events

Adverse events (AEs) will be summarized and presented using primary MedDRA System Organ Classes (SOCs) and preferred terms (PTs) according to the version of the MedDRA coding dictionary used for the study at the time of database lock. The actual version of the MedDRA coding dictionary used will be noted in the AE tables and in the clinical study report. Specific adverse events will be counted once for each subject for calculating percentages, unless stated otherwise. In addition, if the same adverse event occurs multiple times within a subject, the highest severity and level of relationship to investigational product will be reported.

10.2.1 Treatment-Emergent Adverse Events

Treatment-emergent AEs are defined as any AE with the onset that is after the first dose of study drug until 30 days after the last dose of the study drug for subjects. Events where the onset date is the same as the study drug start date are assumed to be treatment-emergent. 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 study drug).

For summaries of AEs related (reasonable possibility) to study drug, at each level of summation (overall, SOC, and PT) each subject is counted only once. If a subject has an AE 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 of "no reasonable possibility" present. The only exception is if the subject has another occurrence of the same AE with the relationship of "reasonable possibility." In this case, the subject will be counted under the reasonable possibility category.

All treatment-emergent AEs will be summarized overall, as well as by primary MedDRA SOC and Preferred Term. The SOCs will be presented in alphabetical order, and the PTs will be presented in alphabetical order within each SOC.

The number and percentage of subjects experiencing treatment-emergent AEs will be summarized.

10.2.2 Adverse Event Overview

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 NCI toxicity (CTCAE V4.03) Grade 3, Grade 4 or Grade 5 adverse event

- Any treatment-emergent NCI toxicity (CTCAE V4.03) Grade 3 or Grade 4 adverse event
- Any treatment-emergent adverse events broken down by NCI toxicity (CTCAE V4.03) grade
- 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 that is rated at least possibly related to venetoclax by the investigator (Reasonable Possibility Related)
- Any treatment-emergent adverse event leading to discontinuation of obinutuzumab
- Any treatment-emergent adverse event leading to obinutuzumab interruption
- Any treatment-emergent adverse event that is rated at least possibly related to obinutuzumab by the investigator (Reasonable Possibility Related)
- Any treatment-emergent adverse event leading to discontinuation of ibrutinib
- Any treatment-emergent adverse event leading to ibrutinib interruption
- Any treatment-emergent adverse event leading to ibrutinib reduction
- Any treatment-emergent adverse event that is rated at least possibly related to ibrutinib by the investigator (Reasonable Possibility Related)
- Any serious treatment-emergent AE
- Any treatment-emergent adverse events leading to DLT
- Any treatment-emergent adverse events related to COVID-19 infection
- Any treatment-emergent AE leading to death
- All deaths
- Deaths occurring ≤ 30 days after last dose of study drug
- Deaths occurring > 30 days after last dose of study drug.

10.2.3 Treatment-Emergent Adverse Events by SOC and/or PT

Treatment-emergent adverse events will be summarized by SOC and PT; by maximum severity and SOC and PT; Specific adverse events will be counted once for each subject for calculating percentages, unless stated otherwise. In addition, if the same adverse event occurs multiple times within a subject, the highest severity and level of relationship to investigational product will be reported.

10.2.4 SAEs (Including Deaths) and Adverse Events Leading to Study Drug Discontinuation

SAEs (including deaths) and AEs leading to study drug discontinuation will be summarized by SOC and PT and in listing format.

The number of subject deaths will be summarized.

- All deaths in this study regardless of the number of days after the last dose of study drug
- Deaths occurring ≤ 30 days after the last dose of study drug
- Deaths occurring > 30 days after the last dose of study drug

10.2.5 Adverse Events of Special Interest

Adverse events of special interest will be summarized by SOC and PT and will be based on standardized or company MedDRA queries (SMQs or CMQs). Adverse events of special interest along with the detailed information about the search criteria are provided in [Appendix B](#). Tabular listings of selected adverse events of special interest will be provided.

10.3 Analysis of Laboratory Data

Data collected from local laboratories, including additional laboratory testing due to an SAE, will be used in all analyses, except for Baseline where SAE-related laboratory assessments on or before the first dose of study drug will be excluded. The clinical

laboratory tests defined in the protocol operations manual (e.g., hematology and clinical chemistry) will be summarized.

Baseline is defined as the last non-missing observation before the first administration of study drug or randomization if no study drug is given.

Mean change from baseline to each applicable post-baseline visit will be summarized for selected laboratory variables, with the number of observations, baseline mean, and visit mean. The change from baseline mean, standard deviation, median, minimum, and maximum will be presented for the mean change from baseline within each cohort.

For shifts relative to National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE version 4.03), 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 4.03. The baseline and final grades will be defined respectively as the grade of the last measurement collected on or prior to the first dose of study drug, and as the last post-baseline measurement collected no more than 30 days after the last dose of study drug. In cases where multiple values are collected on the same day, the maximum grade value will be selected as the value for that day. If a subject had missing baseline and non-missing post-baseline for a given lab, the baseline grade will be assumed to be Grade 0. The maximum NCI toxicity grade value is the value with highest NCI toxicity grade collected after the first dose of study drug.

For each lab test, cross tabulate will be generated for the number of subjects with baseline values of Grade 0, Grade 1, Grade 2, Grade 3, Grade 4, or missing grade versus maximum post-baseline values of Grade 0, Grade 1, Grade 2, Grade 3, Grade 4, or missing grade.

The separate laboratory shifts tables based on the two criteria below will be generated for each laboratory tests related to CTCAE:

1. Shifts from Grade 0 (normal) at baseline to Grade 1 – Grade 4 post-baseline (maximum) and worsening from an abnormal baseline value of at least one grade up post-baseline (maximum)

2. Shifts from Grade 0 – Grade 2 at baseline to Grade 3 or Grade 4 post-baseline (maximum) and from Grade 3 at baseline value to Grade 4 post-baseline (maximum).

For above shift tables, baseline grade of 0 (normal) will be imputed for all subjects with at least one post-baseline but missing a baseline value for each lab test.

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

Number and percentage of subjects meeting the Howard criteria for tumor lysis syndrome (TLS) will be presented.

The Howard Criteria¹ for TLS is defined as two or more of the following treatment-emergent lab changes within a 24-hour period. The evaluation period for TLS is from first dose date of study drug up to 30 days after last dose date of study drug.

- Uric Acid > 475.8 mcmmol/L,
- Potassium > 6 mmol/L,
- Inorganic Phosphorus > 1.5 mmol/L
- Calcium < 1.75 mmol/L.

Number and percentage of subjects with liver Enzyme value meeting the criteria for potential drug-induced liver injury (ALT > 3 × ULN or AST > 3 × ULN and TBILI > 2 × ULN within 72 hours of each other) will be presented.

10.4 Analysis of Vital Signs

Vital sign measurements of systolic and diastolic blood pressure, heart rate, respiratory rate, body temperature and body weight will be summarized.

Mean change from baseline to each applicable post-baseline visit will be summarized for each vital sign variable, with the number of observations, baseline mean, and visit mean. The change from baseline mean, standard deviation, median, minimum, and maximum will be presented for the mean change from baseline within each cohort.

Vital sign variables will be evaluated based on potentially clinically important (PCI) criteria ([Appendix C](#), Table C-1). For each vital sign PCI criterion, the number and percentage of subjects who have a vital sign value meeting the criteria will be summarized. Listings will be provided to summarize subject-level vital sign data for subjects meeting PCI criteria.

11.0 Pharmacokinetic Analyses

For Cohort 1, plasma concentrations of venetoclax and serum concentrations of obinutuzumab will be summarized by sampling time. For Cohort 2, plasma concentrations of venetoclax and ibrutinib will be summarized by sampling time.

12.0 Biomarker Research Analyses

uMRD at 3 months after EOT:

uMRD rate will be defined as the proportion of subjects who had MRD negative status. MRD negativity is defined as the presence of less than one CLL cell per 10,000 leukocytes in the peripheral blood. All subjects in the FAS will be included in the calculation of MRD response, indeterminate or missing samples will be considered MRD positive for the calculation. If a subject receives a new anti-leukemic therapy, samples collected after a new anti-leukemic therapy will be excluded.

The number and percentage of subjects with uMRD will be summarized along with 95% CI. Confidence intervals for uMRD rate will be constructed using the exact binomial distribution (Clopper-Pearson methodology).

Overall uMRD rate:

The same methodology as for the analysis of uMRD at 3 months after EOT will be applied. Overall uMRD rate is based on all post-baseline MRD assessment.

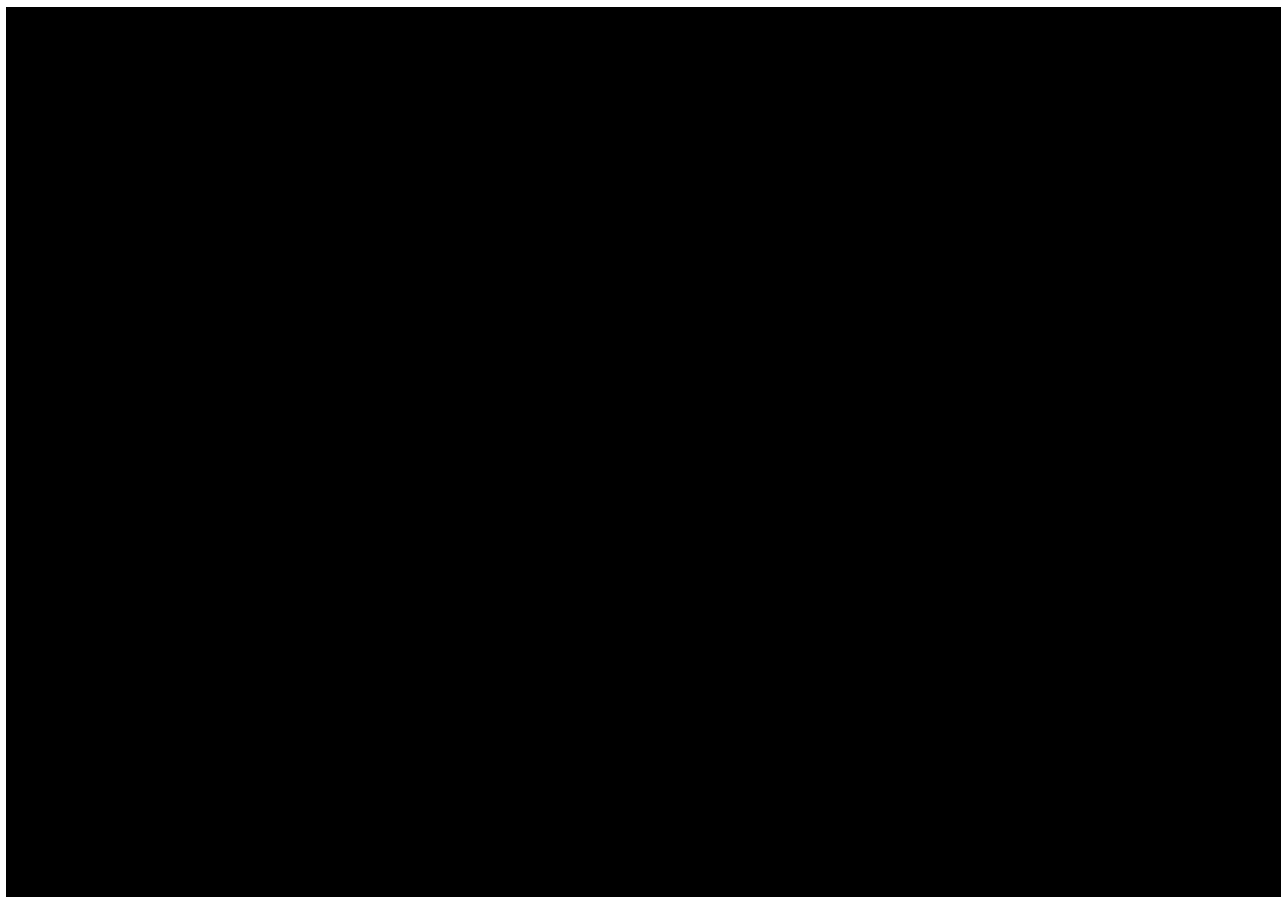
13.0 Interim Analyses

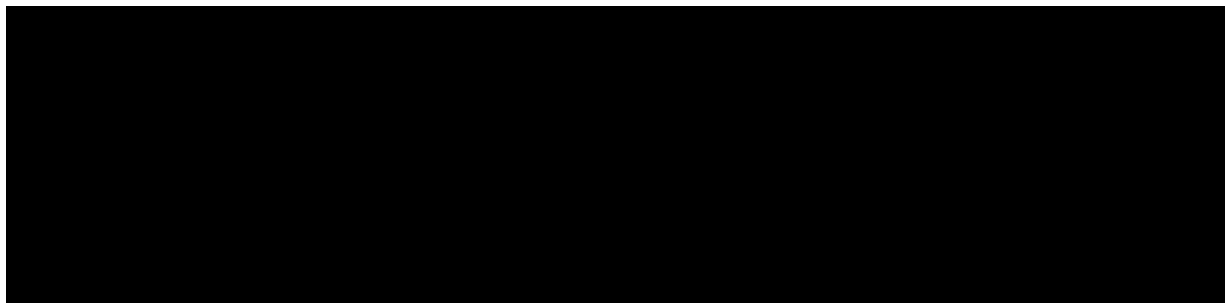
No interim analysis is pre-planned for this study.

14.0 Overall Type-I Error Control

Not applicable for this study.

15.0 Version History





16.0 References

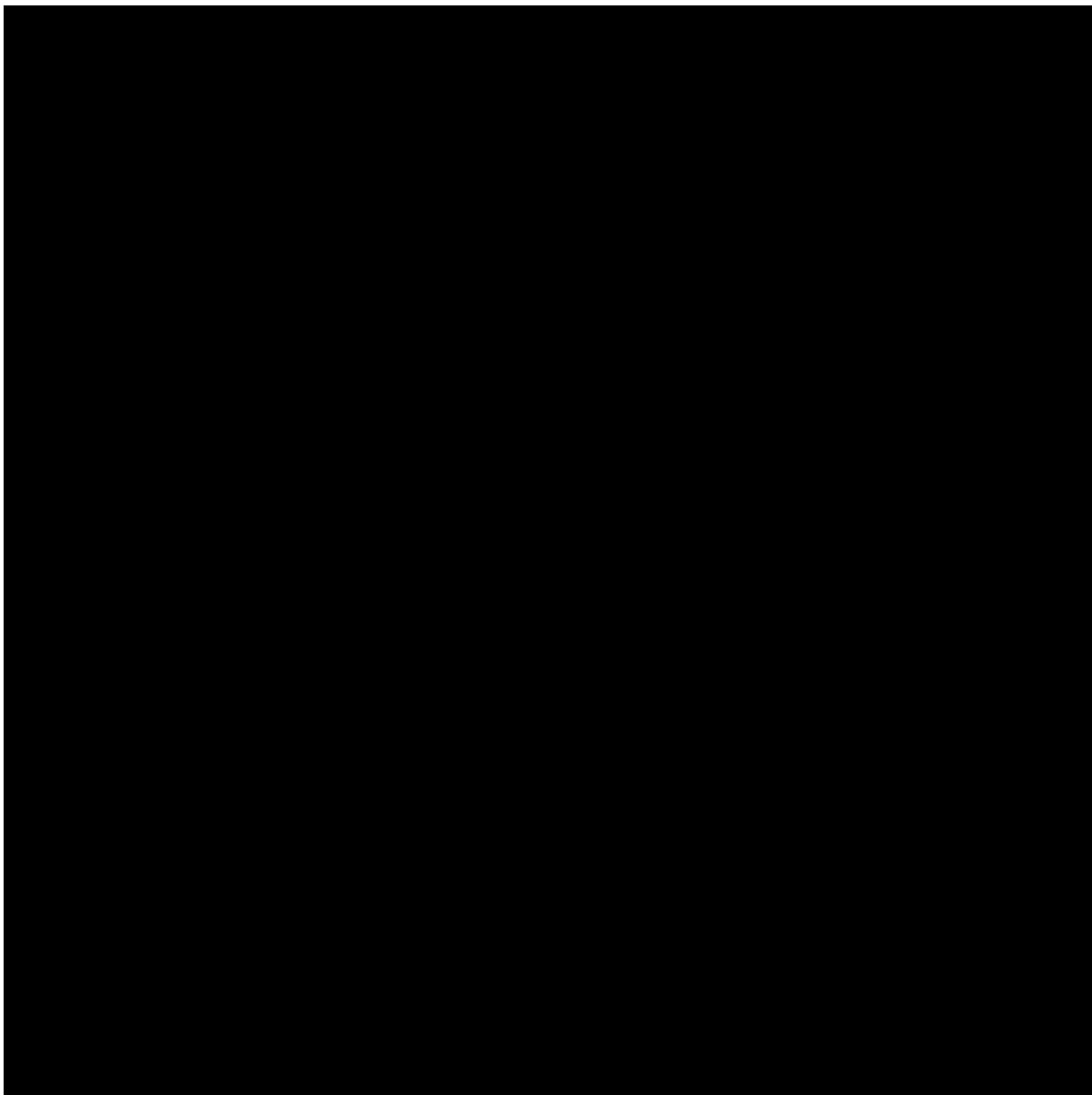
1. Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. N Engl J Med. 2011;364(19):1844-54.

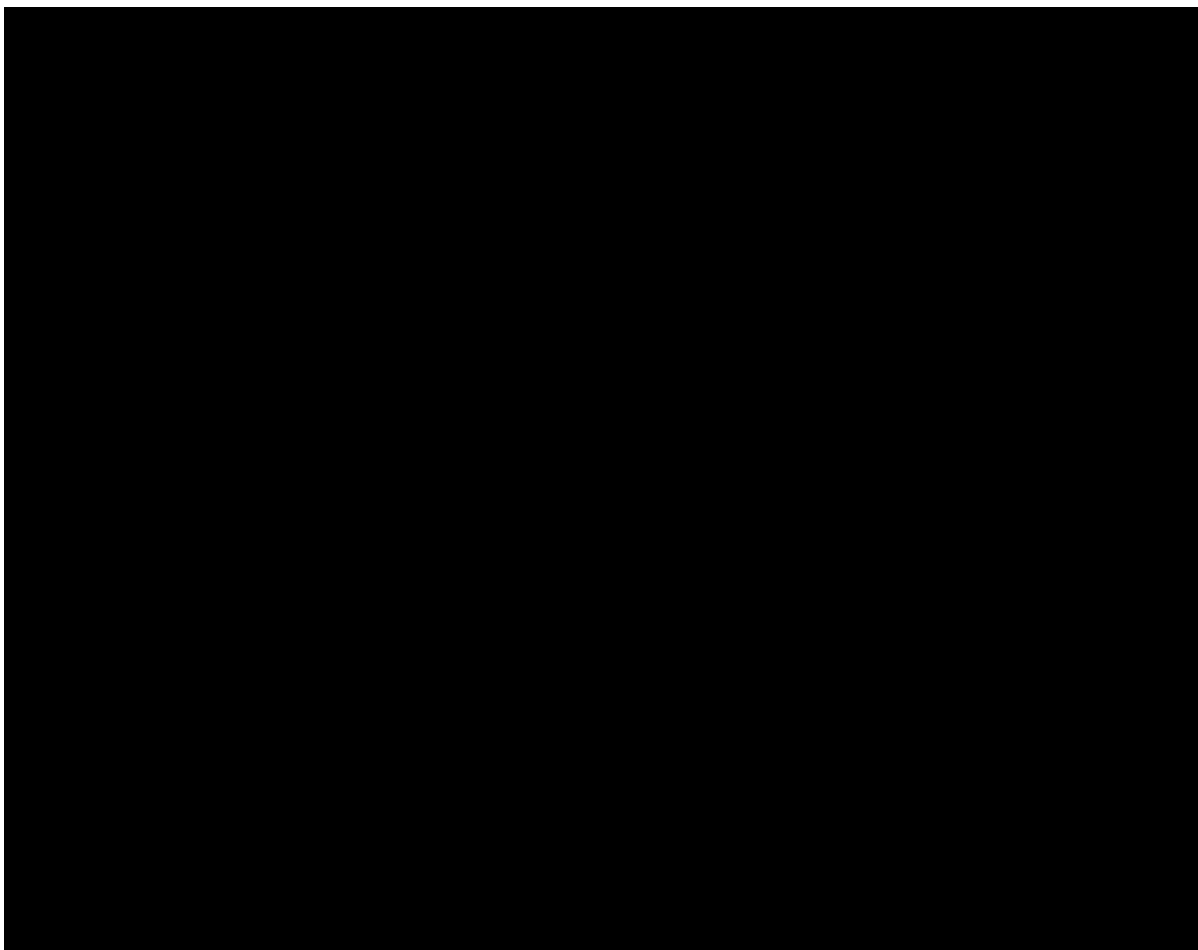
Appendix A. Protocol Deviations

A listing of subjects who reported at least one of the following protocol deviation categories will be provided.

- Subject entered into the study even though s/he did not satisfy entry criteria.
- Subject developed withdrawal criteria during the study and was not withdrawn.
- Subject received wrong treatment or incorrect dose of study.
- Subject took prohibited concomitant medication.

Appendix B. Definition of Adverse Events of Special Interest





Appendix C. Potentially Clinically Important Criteria for Safety

Table C-1. Criteria for Potentially Clinically Important Vital Sign Values

Vital Signs Variables	Criterion	Definition of Potentially Clinically Significant
Systolic blood pressure	High	Value $\geq$ 160 mmHg
Diastolic blood pressure	High	Value $\geq$ 100 mmHg
Heart rate	Low	Value $<$ 50 beats/min
	High	Value $\geq$ 120 beats/min
Temperature	Low	Value $<$ 36°C
	High	Value $\geq$ 38.0°C