Statistical Analysis Plan for Study M20-075

Phase 2 Study of the Efficacy and Safety of Venetoclax in Combination with Ibrutinib in Japanese Subjects with Relapsed/Refractory Mantle Cell Lymphoma

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Version 2.0

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1.0 Introduction

This Statistical Analysis Plan (SAP) describes the statistical analyses for venetoclax Study M20-075: "Phase 2 Study of the Efficacy and Safety of Venetoclax in Combination with Ibrutinib in Japanese Subjects with Relapsed/Refractory Mantle Cell Lymphoma," protocol amendment 3.0 dated February 17, 2022.

Study M20-075 examines the efficacy and safety of venetoclax and ibrutinib in subjects with relapsed/refractory (R/R) mantle cell lymphoma (MCL).

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 effect on best overall response of complete response (CR) of the concurrent administration of venetoclax and ibrutinib in Japanese subjects with R/R MCL.

The hypothesis corresponding to the primary objective is to demonstrate superiority of venetoclax in combination with ibrutinib against a historical reference of 12.5% complete response rate (CRR) in Japanese subjects with R/R MCL treated with ibrutinib only.

The estimand corresponding to the primary objective is:

Proportion of best overall response of CR as assessed by IRC, for subjects receiving venetoclax in combination with ibrutinib (with approximately 104 weeks on combination therapy, followed by ibrutinib monotherapy until disease progression [PD]), regardless of

whether or not the subject is receiving study drugs and regardless the use of other anti-MCL treatments, in the R/R MCL subjects.

The secondary objectives of the study are:

- To evaluate the effect on best overall response of CR or partial response (PR), duration of response (DOR), MRD, PFS, and OS of the concurrent administration of venetoclax and ibrutinib in Japanese subjects with R/R MCL.
- To evaluate the safety and tolerability of the concurrent administration of venetoclax and ibrutinib in Japanese subjects with R/R MCL.
- To evaluate the pharmacokinetics of venetoclax and ibrutinib in Japanese subjects with R/R MCL.

Hypotheses corresponding to the secondary objectives, are to achieve positive results with venetoclax in combination with ibrutinib (i.e., greater proportion of subjects achieving favorable outcomes or longer duration of positive benefits, etc.).

The estimands corresponding to the secondary objectives are:

- Proportion of subjects achieving:
  - Best overall response of CR or PR (as assessed by Independent Review Committee [IRC]/investigator)
  - Best overall response of CR (as assessed by investigator)
  - Undetectable MRD (disease assessed by IRC/investigator)

    With venetoclax in combination with ibrutinib (with approximately 104 weeks on combination therapy, followed by ibrutinib monotherapy until PD), regardless of whether or not the subject is receiving study drugs and regardless of the use of other anti-MCL treatments, in the R/R MCL subjects.
- The median time-to-event (if estimable) will be estimated for the following endpoints:
  - Duration of response (as assessed by IRC/investigator)
  - PFS (as assessed by investigator)

- OS

  with venetoclax in combination with ibrutinib (with approximately 104 weeks on combination therapy, followed by ibrutinib monotherapy until PD), regardless of whether or not the subject is receiving study drugs and regardless of the use of other anti-MCL treatments, in the R/R MCL subjects.

2.2 Study Design Overview

This Phase 2, open-label, single-arm study is designed to evaluate the efficacy and safety of the combination of venetoclax and ibrutinib in Japanese subjects with R/R MCL.

Approximately 12 subjects will receive ibrutinib at 560 mg once daily until progression and venetoclax starting at 20 mg once daily and gradually ramped up to a target dose of 400 mg once daily over a 5-week period for a maximum period of 104 weeks.

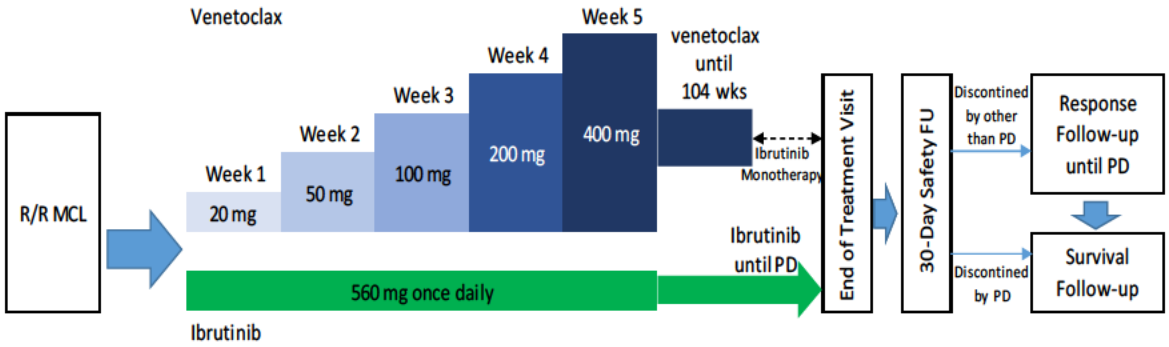
Dose-limiting toxicities will be evaluated in the first 6 subjects, from Day 1 for a minimum of 5 weeks and at least 1 week of venetoclax dosing at 400 mg, in order to confirm the initial safety and tolerability in Japanese subjects. After the completion of the DLT evaluation period in the first 6 subjects, the AbbVie Study Team and investigators who enrolled the 6 treated subjects will review all available safety and PK data to evaluate the tolerability of venetoclax in combination with ibrutinib in Japanese subjects with R/R MCL. If there are zero or 1 DLTs in the first 6 subjects, enrollment of the additional 6 subjects will proceed. If DLTs are observed in 2 or more of the first 6 subjects, further enrollment in Japan will be interrupted and additional, a detailed safety assessment will be conducted.

A DLT is defined as any Grade ≥ 3 adverse events considered to be at least possibly related to study drug (ibrutinib and/or venetoclax) and occurring during the DLT assessment period as defined in protocol Section 6.3. Under certain circumstances as defined in protocol Section 6.3, a subject is not evaluable for DLT, that subject will be replaced but are included for efficacy analysis.

Subjects who discontinue study treatment for any reason will be followed for progression (if no progression before treatment discontinuation), subsequent anti-cancer therapy, and survival status until study closure, as appropriate

The schematic of the study is shown in Figure 1.

Figure 1. Study Schematic



FU = follow up; MCL = mantle cell lymphoma; PD = disease progression; R/R = relapsed/refractory; wks = weeks

Note: After approval of venetoclax and ibrutinib combination therapy for R/R MCL in Japan, Study M20-075 will be discontinued, and subjects will transition to commercial drug.

2.3 Treatment Assignment and Blinding

The treatment is venetoclax in combination with ibrutinib for up to 104 weeks starting Week 1 Day 1. Venetoclax will discontinued after a maximum of 104 weeks of treatment followed by ibrutinib monotherapy until PD. The study will be discontinued after approval of the venetoclax and ibrutinib combination for R/R MCL in Japan and subjects continuing to derive benefit at that time will transition to commercial supplies.

As this is an open label study, so blinding is not applicable.

2.4 Sample Size Determination

Approximately 12 subjects will be enrolled in the study. The tolerability of the combination of venetoclax and ibrutinib will be assessed after the first 6 subjects enrolled

in the study have received the combination for a minimum of 5 weeks and at least 1 week of venetoclax dosed at 400 mg.

Using exact binomial test, with an expected complete response rate (CRR) of 50% for venetoclax in combination with ibrutinib and a threshold CRR of 12.5%, 12 subjects will provide 80% power to demonstrate superiority of venetoclax in combination with ibrutinib against a historical reference of 12.5% CRR in the ibrutinib only Japanese study with R/R MCL, at a 1-sided overall significance level of 0.025. A significant test result is achieved when at least 5 CRs are observed among 12 subjects, corresponding to a minimal observed CRR of 41.7%.

If the first 12 subjects include one or more subjects who are assessed by the IRC as non-evaluable at baseline, then additional subject(s) will be enrolled at the Sponsor's discretion to ensure that there are 12 evaluable subjects per IRC assessment for primary endpoint analysis.

3.0 Endpoints

3.1 Primary Endpoint

The primary endpoint is best overall response of CR according to the Revised Criteria for Response Assessment (Cheson 2014)[1] as assessed by the Independent Review Committee (IRC). The best overall response of CR is defined as achieving an overall response of CR at any time point during the study.

3.2 Secondary Endpoints

The secondary efficacy endpoints are listed below:

- Investigator-assessed best overall response of CR, according to the Revised Criteria for Response Assessment (Cheson 2014).[1]
- IRC-assessed best overall response of CR or PR (defined as achieving partial metabolic and/or radiologic response at any time point during the study according to the Revised Criteria for Response Assessment (Cheson 2014).[1]

- Investigator-assessed best overall response of CR or PR, according to the Revised Criteria for Response Assessment (Cheson 2014).[1]
- Investigator-assessed DOR, defined for subjects who achieve a best overall response, as the time from the first occurrence of response to disease progression or death, whichever occurs first, according to the Revised Criteria for Response Assessment (Cheson 2014).[1]
- IRC-assessed DOR, defined for subjects who achieve a best overall response, as the time from the first occurrence of response to disease progression or death, whichever occurs first, according to the Revised Criteria for Response Assessment (Cheson 2014).[1]
- Undetectable MRD in subjects who achieve a best overall response of CR as assessed by investigator, according to the Revised Criteria for Response Assessment (Cheson 2014).[1]
- Undetectable MRD in subjects who achieve a best overall response of CR as assessed by IRC, according to the Revised Criteria for Response Assessment (Cheson 2014).[1]
- Progression-free survival (PFS), defined as the time from the date of the first dose of any study drug (venetoclax or ibrutinib) to the date of investigator-assessed disease progression, using the Revised Response Criteria for Response Assessment (Cheson 2014),[1] or death from any cause, whichever occurs first.
- Overall Survival, defined as the time from the date of the first dose of any study drug (venetoclax or ibrutinib) to death from any cause.

3.3 Other Efficacy Endpoints

Not applicable.

3.4 Safety Endpoints

Safety and tolerability will be assessed by evaluating DLTs, adverse events, physical examinations, and changes in laboratory data (hematology, chemistry, and urinalysis) and vital signs for the entire study treatment duration.

3.5 Pharmacokinetic Endpoints

Intensive blood samples for analysis of venetoclax and ibrutinib PK will be collected at Week 6 Day 1. Values for the pharmacokinetic parameters of venetoclax and ibrutinib will be determined at steady state using noncompartmental methods. The maximum observed plasma concentration (C_{max}), the time to C_{max} (peak time, T_{max}), the area-under-the-plasma concentration-time curve (AUC) over the dosing interval (AUC_{tau}) will be determined. Additional analyses may be performed as appropriate based on data availability.

4.0 Analysis Populations

The following population set will be used for the analyses:

The full analysis set (FAS) includes all subjects who received at least 1 dose of study drug. The FAS will be used for all efficacy (except the endpoints based on IRC assessment), safety, pharmacokinetic, and baseline analyses.

The per protocol (PP) population excludes FAS subjects who have been determined as having non-evaluable disease at baseline, based on IRC assessment. PP population will be used for IRC assessed endpoints. PP population will be used to compare the sensitivity of IRC endpoints with investigator assessed endpoints.

5.0 Subject Disposition

The total number of subjects who were screened, enrolled, and treated will be summarized. Reasons for exclusion, including screen failure, will be listed. Analysis for subject disposition will be based on FAS.

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

- Subjects enrolled in the study
- Subjects in each analysis population, FAS, and PP population.

- Subjects who discontinued study drug (venetoclax and ibrutinib) (all reasons and primary reason)
- Subjects who discontinued study.

6.0 Study Drug Duration and Compliance

For the FAS, duration of treatment will be summarized for each study drug (venetoclax/ibrutinib) and for venetoclax and ibrutinib combination. Duration of treatment is defined for each subject as last dose date minus first dose date +1. Duration of study drug (venetoclax/ibrutinib) and the combination 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 study drug and the combination duration interval will be summarized as below:

- 0 to 4 weeks
- > 4 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 52 weeks
- 52 weeks

The number and percentage of subjects with dose reduction and dose interruption of venetoclax/ibrutinib will be summarized by the number of occurrences of dose reduction or interruption as no, 1 time, 2 times, or > 2 times.

Relative dose intensity (RDI) will be calculated for venetoclax/ibrutinib using observed dose intensity (ODI) and planned dose intensity (PDI):

- ODI: Actual total dose/ Actual total duration of treatment exposure (days)
- PDI:
  - PDI (mg/day) for venetoclax is calculated as the total amount of the planned dose (mg) during the maximum treatment period allowed (104 weeks) divided by the duration of the maximum treatment period allowed (104 weeks). Venetoclax started at 20 mg once daily and gradually ramped up to a target dose of 400 mg once daily over a 5-week period for a maximum period of 104 weeks.
  - PDI for Ibrutinib is based on fixed daily dosing of 560 mg/day.
- RDI (%) will be calculated as ODI/PDI *100 %.

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 for the PP population and 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 treatment arm 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:

- Age (years) and age categories age (< 40, 40 – 65, ≥ 65 years)
- Gender (Male, Female)
- Race (Asian, Others)
- If Asian (Japanese, non-Japanese)
- Height (cm)
- Weight (kg)
- Tobacco user (current, former, never, unknown)
- Alcohol user (current, former, never, unknown).

Baseline and Disease-Related Characteristics:

- ECOG performance status (Grade 0, 1, 2)
- Relapsed or refractory
- Prior bone marrow involvement (Yes/No)
- Prior GI involvement (Yes/No)
- TLS risk category (High, Low)
- B-symptoms (Yes, No)
- Child-Pugh Classification (A, B, C)
- Number of prior regimens (1, 2, ≥ 3)
- MIPI score (Low, Intermediate, High)
- Bulky disease (< 5 cm, ≥ 5 cm)

7.2 Medical History

Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA 23.0). 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. 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. The number and percentage of prior medication will be summarized. 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. The number and percentage of subjects who received CYP3A inhibitors and/or P-gp inhibitors, and/or antiplatelet agents and anticoagulants will be summarized by moderate/strong CYP3A inhibitors, moderate P-gp inhibitors and antiplatelet agents and anticoagulants.

In addition, post-treatment oncology medications will be summarized and/or listed. A post-treatment oncology medication is defined as any oncology medications taken after the discontinuation of study drug.

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

The primary endpoint of best overall response of CR will be analyzed based on the PP population and the secondary endpoints will be analyzed based on the PP/FAS population, as appropriate, the following potential intercurrent events (ICEs) will be considered:

- ICE1: Subjects with study drug discontinuation
- ICE2: Subjects with the use of other anti-MCL treatment

And will be handled for both primary and secondary endpoints based on the following strategy:

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

9.0 Efficacy Analyses

9.1 General Considerations

PP population will be used for primary endpoint. PP population/FAS will be used for other efficacy endpoints, as appropriate.

All tests will be 1-sided at an alpha level of 0.025.

In the DLT assessment period, the first 6 study subjects enrolled was evaluated for the tolerability of the venetoclax and ibrutinib combination for a minimum of 5 weeks and at least 1 week of venetoclax dosing at 400 mg. DLT assessment committee along with ISM recommended that 'the study to be continued for full enrollment'.

The primary analysis will be performed after all subjects enrolled in the study have completed Week 13 disease assessment or have discontinued study, whichever is early.

The best overall response will be derived for each subject based on timepoint-wise disease assessments, according to the response categories ordered as CR > PR > SD > PD > NE (Not evaluable). Each subject will be assigned a "best overall response" based on the above-mentioned rule.

Unless otherwise specified, "Baseline" refers to the last non-missing observation before the first administration of study drug.

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 is the best overall response of CR based on IRC assessment and will be evaluated using complete response rate (CRR), defined as proportion of subjects achieving best overall response of CR.

Subjects in PP population but have no post-baseline disease assessment will be considered as non-responders in the calculation of CRR. Subjects who have not achieved best overall response of CR at the time of analysis will be considered as non-responders in the calculation of CRR.

9.3.2 Main Analysis of Primary Efficacy Endpoint

The attributes of the estimand corresponding to the primary efficacy endpoint are summarized in Table 1.

Table 1. Summary of the Estimand Attributes of the Primary Efficacy Endpoint

Attributes of the Estimand					
Estimand Label	**Treatment**	**Population**	**Endpoint**	**Handling of Intercurrent events**	**Statistical Summary**
CRR	Venetoclax + Ibrutinib combination for a maximum of 104 weeks followed by Ibrutinib monotherapy until PD	PP population	IRC-assessed best overall response of CR	ICE1: Study drug discontinuation ICE2: Use of other anti-MCL treatment All data will be used regardless of ICE1 or ICE2.	CRR and 95% CI

The analysis of CRR will be based on exact binomial distribution.

9.3.3 Sensitivity and Supplementary Analyses of the Primary Efficacy Endpoint

A sensitivity analysis of best overall response of CR will be performed based on investigator's assessment.

9.4 Secondary Efficacy Endpoints and Analyses

9.4.1 Secondary Efficacy Endpoints

The secondary endpoints (except for MRD and OS) will be assessed according to the Revised Criteria for Response Assessment (Cheson 2014)[1]. Endpoint of best overall response of CR or PR will be evaluated using overall response rate (ORR). ORR is defined as the proportion of subjects with a best overall response of CR or PR. This endpoint is assessed separately per IRC and investigator's assessment.

DOR of CR is defined as the time from the first occurrence of response of best overall response of CR to disease progression or death, whichever occurs first. If a subject is still responding, subjects will be censored at the date of the last adequate disease assessment.

DOR of CR or PR is defined as the time from the first occurrence of best overall response of CR or PR to disease progression or death, whichever occurs first. If a subject is still responding, subjects will be censored at the date of the last adequate disease assessment.

DOR (of CR, of CR or PR) analyses will be performed separately for IRC and investigator assessed responses.

Endpoint of undetectable MRD (uMRD) is defined as subject achieving uMRD (defined as subjects having < 0.05% MCL cells per 10,000 leukocytes) and a best overall response of CR. MRD will be assessed by flow cytometry of peripheral blood sample per central laboratory for all subjects. The proportion of subjects with undetectable MRD who achieve a best overall response of CR will be provided, separately for IRC and investigator assessed CR.

Progression-free survival is defined as the time from the date of the first dose of any study drug (venetoclax or ibrutinib) to the date of investigator-assessed disease progression, or death from any cause, whichever occurs first. 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. If the subject does 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.

Overall survival is defined as the time from the date of the first dose of any study drug (venetoclax or ibrutinib) 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 was on other anti-MCL treatment. If a subject has not died, then the data will be censored at the date the subject was last known to be alive.

9.4.2 Main Analyses of Secondary Efficacy Endpoints

The attributes of the estimands corresponding to the secondary efficacy endpoints are summarized in Table 2.

Table 2. Summary of the Estimand Attributes of the Key Secondary Efficacy Endpoints

Attributes of the Estimand					
Estimand Label	**Treatment**	**Population**	**Endpoint**	**Handling of Intercurrent Events**	**Statistical Summary**
Best overall response	Venetoclax + Ibrutinib combination for a maximum of 104 weeks followed by Ibrutinib monotherapy until PD	PP population/FAS, as appropriate	Investigator-assessed best overall response of CR. IRC-assessed best overall response of CR or PR	ICE1: Study drug discontinuation ICE2: Use of other anti-MCL treatment All data will be used regardless of ICE1 or ICE2.	CRR and 95% CI ORR and 95% CI
uMRD		PP population/FAS, as appropriate	Undetectable MRD for a subject with IRC-assessed BOR of CR Undetectable MRD for a subject with investigator-assessed BOR of CR		uMRD rate and 95% CI
DOR		PP population/FAS, as appropriate	IRC-assessed DOR of CR, DOR of CR or PR Investigator-assessed DOR of CR, DOR of CR or PR		K-M estimate at specified time-points and their corresponding 95% CI Median DOR and 95% CI KM curve

Attributes of the Estimand					
Estimand Label	**Treatment**	**Population**	**Endpoint**	**Handling of Intercurrent Events**	**Statistical Summary**
PFS		PP population/FAS, as appropriate	Investigator-assessed PFS		K-M estimate at specified time-points and their corresponding 95% CI Median PFS and 95% CI KM curve
OS		FAS	OS		K-M estimate at specified time-points and their corresponding 95% CI Median OS and 95% CI KM curve

The analysis of CRR, ORR and uMRD rates will be based on exact binomial distribution.

The analysis of DOR, PFS and OS will be based on Kaplan-Meier methodology.

9.4.3 Supportive Secondary Efficacy Analyses

Not applicable.

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 adverse event with NCI toxicity (CTCAE version 4.03) grade 3, adverse events
- Any treatment-emergent adverse event with NCI toxicity (CTCAE version 4.03) grade 4 adverse events
- Any treatment-emergent adverse event with NCI toxicity (CTCAE version 4.03) grade 5 adverse events
- Any treatment-emergent adverse event with NCI toxicity (CTCAE version 4.03) grade 3 or 4 adverse events
- Any treatment-emergent adverse events leading to DLT
- Any treatment-emergent adverse events related to COVID-19 infection
- 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 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 treatment-emergent serious adverse event
- Any treatment-emergent adverse event leading to death

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 relationship to study drug as assessed by the investigator (e.g., reasonable possibility or no reasonable possibility) and SOC and PT; by maximum grade and SOC and PT; and by subject number 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 grade and level of relationship to investigational product will be reported.

In addition, treatment-emergent adverse events will be summarized by PT and sorted by decreasing frequency.

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/listed:

- 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

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 if no study drug is given.

Changes from baseline will be analyzed for each chemistry, hematology parameters. The change from baseline mean, standard error, min, median, max and 95% confidence interval will be presented for the mean change from baseline for the post-baseline maximum value.

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.

An upward shift table from grade 0 – 2 at baseline to grade 3 or 4 post-baseline (maximum) will be provided.

Treatment emergent laboratory abnormalities 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– 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 – 2 at baseline to grade 3 or 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 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 Criteria 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 the first 7 days from the date of the first dose:

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

TLS events are defined as:

- Clinical TLS: any event that meets Howard criteria with the following exceptions:
  - For the purpose of TLS assessment during the DLT evaluation period, only those increases in serum creatinine > 1.0 mg/dL from pre-treatment baseline will be considered clinical TLS.
  - In subjects with renal dysfunction at baseline (CrCl < 60 mL/min), clinical TLS is defined as the presence of laboratory TLS plus either seizures, cardiac dysrhythmia, or death.
- Laboratory TLS: any event that meets Howard criteria for laboratory TLS, that does not resolve within 72 hours despite protocol required management.

A listing of possible Hy's Law cases, defined as those who meet all of the following conditions simultaneously, will be provided: ALT > 3 × ULN or AST > 3 × ULN that is associated with an increase in bilirubin > 2 × ULN within 72 hours of each other.

10.4 Analysis of Vital Signs

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

11.1 Tabulations and Summary Statistics

Summary statistics of plasma concentrations of venetoclax and ibrutinib will be computed for each sampling time. Pharmacokinetic parameter values of venetoclax and ibrutinib will be summarized as applicable. Additional analyses will be performed if useful and appropriate.

12.0 Interim Analyses

There is no planned interim efficacy analysis for this study. However, a safety analysis of tolerability of the venetoclax and ibrutinib combination will be performed after the first 6 evaluable subjects have been on the combination for a minimum of 5 weeks and at least 1 week of venetoclax dosed at 400 mg.

12.1 Independent Safety Monitor

For DLT assessments of the first 6 evaluable subjects enrolled, sponsor will appoint an Independent Safety Monitor (ISM), who will be a Japan medical oncologist with experience in clinical studies and who is familiar with the safety assessment of antitumor agents. The Sponsor will consult the Independent Safety Monitor (ISM) with results of the safety evaluation and Sponsor's conclusion on tolerability, then receive the answer from ISM. The Sponsor will recommence subject enrolment based on the safety review and only if agreed by the ISM. Depending on the results of the safety review by ISM, revising the protocol will be considered where necessary. Detailed procedures for safety assessments will be described in a separately prepared document for operational purposes.

Since only safety and PK data (if available at the time of tolerability assessment meeting) are to be assessed for DLT, so no alpha adjustment is needed.

13.0 Overall Type-I Error Control

The overall type I error rate of 1-sided 0.025 will be used to determine the statistical significance of the primary endpoint at the time of primary analysis. All other analyses will be done for descriptive purpose. Hence, no multiplicity adjustment of type I error is needed.

14.0 Version History

Table 3. SAP Version History Summary

Version	Date	Summary
1.0	12 Nov 2020	Original version
2.0	16 Apr 2022	Amendment 1

15.0 References

1. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32(27):3059-68.

Appendix A. Protocol Deviations

A listing of subjects who reported at least one (but not limited to) 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

Adverse Events of Special Interest (AESI) and Selected AEs will be identified using the following search criteria:

Risk	Search Criteria
Tumor Lysis Syndrome	SMQ 20000219 – "Tumour lysis syndrome" (Narrow-scope)
Neutropenia – expanded search	Neutropenia CMQ 80000171
Neutropenia	PT terms – "Neutropenia" and "Neutrophil count decreased"
Serious Infection	SAEs in the SOC of "Infections and Infestations"
Second Primary Malignancy	SMQ 20000194 – "Malignant tumours" (Narrow) and SMQ 20000217 - "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"
Major Hemorrhage	SMQ – "Haemorrhagic disorders" (narrow)
Cardiac arrhythmia	1. Atrial fibrillation: PT= Atrial fibrillation 2. Cardiac arrhythmias: Cardiac arrhythmias SMQ broad (excluding PT of Atrial fibrillation) 3. Ventricular tachyarrhythmias (as a sub-analysis under Cardiac arrhythmias recognizing there is overlap): Ventricular tachyarrhythmias SMQ narrow

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 ≥ 160 mmHg
Diastolic blood pressure	High	Value ≥ 100 mmHg
Heart rate (bpm)	Low	Value < 50 bpm
	High	Value ≥ 120 bpm
Temperature	Low	Value < 36°C
	High	Value ≥ 38.0°C