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Protocol for Study M20-075

Relapsed/Refractory Mantle Cell Lymphoma: Venetoclax and Ibrutinib in Japanese Subjects

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FULL TITLE: 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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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

1 SYNOPSIS

Title: Phase 2 Study of the Efficacy and Safety of Venetoclax in Combination with Ibrutinib in Japanese Subjects with Relapsed/Refractory Mantle Cell Lymphoma	
Background and Rationale:	Mantle cell lymphoma (MCL) is a distinct, clinical-pathologic entity within the non-Hodgkin's lymphomas (NHL). It accounts for about 3% of all NHL cases in Japan. Ibrutinib is approved for relapsed/refractory (R/R) MCL but new treatment strategies are needed that may substantially improve outcomes for R/R MCL patients and may in the long-term obviate intensive chemotherapy and/or transplantation in younger MCL patients and chemotherapy in older patients with MCL. Based on data from a venetoclax monotherapy study in subjects with R/R MCL and prior ibrutinib studies, the AIM study is evaluating the combination of ibrutinib at 560 mg and venetoclax at a target dose of 400 mg in subjects with R/R MCL. Based on the early data showing a best CR rate of 71% with an acceptable safety profile, coupled with the durability of responses observed with ibrutinib monotherapy and venetoclax monotherapy in patients with relapsed or refractory MCL who achieved CR, the combination of ibrutinib and venetoclax is expected to induce deep and durable responses in patients with R/R MCL. This Phase 2 study of venetoclax in combination with ibrutinib in Japanese subjects with R/R MCL is based on the ongoing SYMPATICO study (ibrutinib 560 mg and venetoclax target dose 400 mg, in R/R MCL).
Objective(s) and Endpoint(s):	**Objectives** The primary objective 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 secondary objectives are: • To evaluate the effect on best overall response of CR or partial response (PR), duration of response (DOR), minimal residual disease (MRD), progression-free survival (PFS), and overall survival (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. **Endpoints** <u>Primary Efficacy Endpoint</u> The primary endpoint is the best overall response of CR, according to the Revised Criteria for Response Assessment as assessed by the Independent Review Committee (IRC).

	Secondary Efficacy Endpoints • IRC-assessed best overall response of CR or PR, according to the Revised Criteria for Response Assessment. • Investigator-assessed best overall response of CR, according to the Revised Criteria for Response Assessment. • Investigator-assessed best overall response of CR or PR, according to the Revised Criteria for Response Assessment. • 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. • 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. • Undetectable MRD in subjects who achieve a best overall response of CR as assessed by investigator, according to the Revised Criteria for Response Assessment. • Undetectable MRD in subjects who achieve a best overall response of CR as assessed by the IRC, according to the Revised Criteria for Response Assessment. • 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, 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. 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. Pharmacokinetic Endpoints 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. Intensive pharmacokinetic blood samples will be collected. Biomarker Endpoints Biospecimens (blood and bone marrow aspirate) will be collected at specified time points throughout the study to evaluate known and/or

	novel disease-related or drug-related biomarkers. Types of biomarkers may include nucleic acids, proteins, lipids, and/or metabolites, either free or in association with particular cell types. The biomarker research may be exploratory in nature and the results may not be included with the clinical study report. Provision of biospecimens for biomarker research is mandatory, but they will not be collected from sites where local regulations do not allow for the collection, use, and storage of samples as described in the protocol.
Investigator(s):	Multicenter
Study Site(s):	Approximately 12 sites in Japan
Study Population and Number of Subjects to be Enrolled:	Approximately 12 adult Japanese subjects with R/R MCL
Investigational Plan:	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 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.

Key Eligibility Criteria:	• Adult **male or female**, at least 20 years old.
	• Pathologically confirmed MCL (tumor tissue) by local testing, with documentation of either overexpression of cyclin D1 in association with other relevant markers (e.g., CD19, CD20, PAX5, CD5) or evidence of the t(11;14) translocation, as assessed by cytogenetics, fluorescent in situ hybridization (FISH), or polymerase chain reaction (PCR).
	• At least 1 measurable site of disease on cross-sectional imaging that is ≥ 2.0 cm in the longest diameter and measurable in 2 perpendicular dimensions per CT.
	• At least 1, but no more than 5, prior treatment regimens for MCL including at least 1 prior rituximab/anti-CD20 containing regimen.
	• Failure to achieve at least PR with, or documented disease progression after, the most recent treatment regimen.
	• No history of other malignancies, except:
	  • Malignancy treated with curative intent and with no known active disease present for ≥ 3 years before the first dose of study drug and felt to be at low risk for recurrence by treating physician.
	  • Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
	  • Adequately treated carcinoma in situ without evidence of disease.
	• No history or current evidence of central nervous system lymphoma.

	• No treatment with any of the following within 7 days prior to the first dose of study drug:
	  • moderate or strong cytochrome P450 3A (CYP3A) inhibitors
	  • moderate or strong CYP3A inducers.
	• No anticancer therapy, including chemotherapy, radiotherapy, small molecule, and investigational agents, and/or monoclonal antibody ≤ 21 days prior to the first dose of study drug.

Study Drug and Duration of Treatment:	Venetoclax tablets (10 mg, 50 mg, and 100 mg) and ibrutinib capsules (140 mg) will be provided by the Sponsor for oral administration once daily. Venetoclax and ibrutinib may be administered for up to 104 weeks, followed by ibrutinib monotherapy, until study discontinuation, disease progression, unacceptable toxicity, or withdrawal of consent.
Date of Protocol Synopsis:	17 November 2023

2 INTRODUCTION

2.1 Background and Rationale

Why This Study Is Being Conducted?

Disease Background

Mantle cell lymphoma (MCL) is a distinct, clinical-pathologic entity within the non-Hodgkin's lymphomas (NHL). Initially termed "centrocytic lymphoma" in the Kiel Classification system,[1] MCL has subsequently been shown to harbor the translocation t(11;14)(q13;q32), which results in constitutive overexpression of cyclin D1.[2] These features are now considered requisite for the diagnosis of the disease.

Mantle cell lymphoma accounts for about 6 to 9% of all NHL cases in the Western world. The annual incidence of MCL has increased during recent decades to 1 to 2/100,000. In Japan, MCL accounts for about 3% of all NHL cases. Mantle cell lymphoma occurs more frequently in older adults.[3] Most patients with MCL are men (median age 65 years) who present with advanced stage disease (i.e., Stage III or IV), and most cases follow an aggressive clinical course.[4] The typical presentation is with generalized lymphadenopathy, and extranodal involvement frequently occurs in the gastrointestinal (GI) tract, spleen, bone marrow, and liver; less common extranodal sites are skin, lungs, and breast or soft tissues. Though the clinical course of MCL may be somewhat indolent at diagnosis, the course invariably becomes aggressive over time. Unlike other NHLs, MCL is considered incurable with standard therapies and is associated with a poor prognosis and a relatively short median overall survival (OS).[5] There is no curative therapy for MCL. A few patients may achieve long-term, disease-free survival after allogeneic stem cell transplantation,[6] but in general, the disease is characterized by a series of relapses with a median OS of 4 to 5 years. A number of MCL prognostic variables have been identified, including the presence or absence of extranodal disease, age, lactate dehydrogenase levels, performance status, Mantle Cell Lymphoma International Prognostic Index (MIPI), and Ki-67 proliferative index.[7]

Current Treatment Options

Current initial therapy for the treatment of MCL includes cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), or hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and cytarabine (Hyper-CVAD), often in combination with rituximab (R-CHOP or R-Hyper CVAD). In recent years, treatment with bendamustine and rituximab has gained increasing use following studies showing that this combination significantly prolongs progression-free survival (PFS), while maintaining a favorable safety profile among patients with previously untreated MCL.[8,9] For patients who relapse after initial therapy, chemoimmunotherapy treatment options involve the use of rituximab in combination with one or more of the following: bendamustine, cladribine, fludarabine, cyclophosphamide, mitoxantrone, etoposide, and procarbazine.[10,11] Also in Japan, the use of bendamustine, bortezomib, fludarabine, ibrutinib, and cladribine monotherapy, the use of rituximab or other antineoplastic drug combinations with the above drugs, and radioimmunotherapy (90 Y ibritumomab tiuxetan) monotherapy are recommended. In cases of early relapses or in patients with refractory disease, newer targeted approaches should be strongly considered. Three non-cytotoxic drugs, ibrutinib, bortezomib, and lenalidomide, are Food and Drug Administration (FDA)-approved for previously treated patients with MCL in the United States (US). In the European Union, approved treatment in the relapsed and refractory (R/R) MCL setting was limited

to temsirolimus until the approval of ibrutinib in 2014. In Japan, ibrutinib is approved for R/R MCL and bortezomib is approved for MCL. Based on registration trials, the overall response rate (ORR) for these drugs are 87.5% (12.5% complete response [CR]) in the Japanese population with ibrutinib, 33% (8% CR) with bortezomib, 28% (8% CR) with lenalidomide, and 22% (2% CR) with temsirolimus, with a median PFS of 13.9, 6.5, 4, and 4.8 months, respectively.[12] Despite the fact that results from ibrutinib showed marked improvement over temsirolimus,[13] the median PFS of approximately 14 months underscores the need to improve further on the dismal outcome for relapsed MCL patients. New treatment strategies are needed that may substantially improve outcomes for R/R MCL patients and may in the long-term obviate intensive chemotherapy and/or transplantation in younger MCL patients and chemotherapy in older patients with MCL.[12]

Several in vitro studies have shown ibrutinib and venetoclax to be an active combination. In one study, MCL cell lines and leukemic patient cells were exposed to ibrutinib, venetoclax, and the combination for 72 hours. The combination substantially increased induction of apoptosis compared to each agent alone (combination: 23%, ibrutinib: 3.8%, venetoclax: 3.0%).[14] A separate study using MCL cell lines confirmed the synergistic effect of ibrutinib and venetoclax on proliferation inhibition and apoptosis through perturbation of the BTK, AKT and B-cell lymphoma-2 (BCL2) pathways[15] providing further mechanistic rationale for co-targeting of these two oncogenic pathways.

Supportive in vivo data is derived from a CCMCL1/NSG mouse model where the ibrutinib and venetoclax combination was tested. The combination produced apoptosis of MCL tumor cells, which was associated with a down-regulation of SOX11 and PAX5. Simultaneous down regulation of MCL1 via ibrutinib and targeting of BCL2 was hypothesized to contribute to the in vitro synergism and in vivo activity observed in this report.[16]

With respect to venetoclax monotherapy activity, in clinical Study M12-175, venetoclax was tested in 28 subjects with R/R MCL at target doses of 200 to 1200 mg. The ORR was found to be 75% with a CR rate of 21%.[17] Based on these data and prior ibrutinib studies, the AIM study (ibrutinib and venetoclax in MCL) is evaluating the combination of ibrutinib at 560 mg and venetoclax at a target dose of 400 mg in subjects with R/R MCL. This study is using a 4-week venetoclax ramp-up after 4 weeks of ibrutinib monotherapy. The CR according to computed tomography (CT) scan at Week 16 was 42%. The CR rate as assessed by positron emission tomography (PET) was 62% at Week 16. Sixteen subjects with relapsed or refractory MCL[18] were dosed and have completed the ramp-up with tumor lysis syndrome (TLS) events reported in 2 subjects with high tumor burden, leading to revision of the protocol venetoclax starting dose from 50 mg to 20 mg per day. Subsequently, 8 additional subjects have been treated using the revised schedule with no cases of TLS encountered.[19] These data suggest that the combination had an acceptable safety profile without unexpected toxicities and resulted in high rates of deep remission. In addition, the flow minimal residual disease- (MRD) negative and allele-specific oligonucleotide-polymerase chain reaction (ASO-PCR) MRD-negative rates were 67% and 38%, respectively, and for the current analysis, the median duration of response (DOR) and time to progression (TTP) had not been reached and were estimated to be 74% and 60% at 30 months, respectively. The median PFS was 29 months (95% confidence interval [CI] of 13-negative estimates [NE]), and the median OS was 32 months (95% CI of 27-NE).[20]

Two other studies evaluating the combination of ibrutinib and venetoclax (one of which will also explore the addition of anti-CD20 therapy to the doublet) in subjects with R/R MCL have started enrollment, though no toxicity or safety data have yet been reported.[21,22] Based on the early data in the AIM study

of ibrutinib and venetoclax in patients with relapsed or refractory MCL[23] showing a best CR rate of 71% with an acceptable safety profile, coupled with the durability of responses observed with ibrutinib monotherapy and venetoclax monotherapy in patients with relapsed or refractory MCL who achieved CR observed with each,[17,24,25] the combination of ibrutinib and venetoclax is expected to induce deep and durable responses in patients with R/R MCL.

The ongoing SYMPATICO Study (ibrutinib and venetoclax in R/R MCL), which is the basis of Study M20-075, is evaluating the combination of ibrutinib at 560 mg and venetoclax at a target dose of 400 mg in subjects with R/R MCL. The study started with an open-label safety run-in period to evaluate the occurrence of TLS and dose-limiting toxicities (DLTs) with the concurrent administration of ibrutinib and venetoclax. The safety run-in period of the study included 21 patients with R/R MCL, 15 patients at high-risk for TLS, and 6 patients at low risk for TLS. One laboratory TLS event occurred in a patient at high-risk for TLS. No clinical TLS events occurred. No TLS event occurred in patients at low risk for TLS. Dose-limiting toxicities were observed in 3 patients at high-risk for TLS; Grade 4 neutropenia (n = 1), Grade 4 infection (n = 1), and Grade 3 atrial fibrillation plus grade 3 hypotension (n = 1). No DLT event occurred in patients at low risk for TLS. As pre-specified in the protocol, the combination dosing schedule of ibrutinib 560 mg + venetoclax 400 mg was recommended for both subjects at high and low risk for TLS, and the randomization part of the study is ongoing with the same schedule as the safety run-in period. The CR rate was 48% in all patients, 67% in patients at low risk for TLS, and 40% in patients at high-risk for TLS, with a longer follow-up time for patients at low risk for TLS than high-risk for TLS (median follow-up, 14 versus 8 months).[26]

Study M20-075 will evaluate the safety and efficacy of the combination of venetoclax at a target dose of 400 mg and ibrutinib at 560 mg in Japanese subjects with R/R MCL.

Clinical Hypothesis

The combination of venetoclax and ibrutinib can be safely administered and will result in high CRs in Japanese subjects that is similar to that observed in non-Japanese subjects.

2.2 Benefits and Risks to Subjects

Mantle cell lymphoma is considered incurable with standard therapies and is associated with a poor prognosis and a relatively short median OS. New strategies are needed that may substantially improve outcomes for R/R MCL patients and may in the long-term obviate intensive chemotherapy and/or transplantation in younger MCL patients and chemotherapy in older patients with MCL.

The combination of venetoclax and ibrutinib is being evaluated in subjects with R/R MCL in 3 ongoing studies. Early data from the AIM study suggest the combination has an acceptable safety profile without unexpected toxicities and results in high rates of deep remission. Data from the safety run-in period of the SYMPATICO study evaluating the occurrence of TLS and DLTs support the same dosing schedule of ibrutinib 560 mg + venetoclax 400 mg in the ongoing randomization phase and initiation of this Phase 2 study in Japanese subjects at both high and low risk of TLS with R/R MCL.

The benefit of potentially high rates of response and prolonged PFS are favorable when compared to a potentially increased rate of adverse events (AEs) that remains acceptable and is without unexpected toxicities for both venetoclax and ibrutinib.

Protocol instructions and information related to Coronavirus Disease - 2019 (COVID-19) are listed in Appendix I.

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives, Hypotheses, and Estimands

Primary Objective

1. To evaluate the effect on best overall response of 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 the ibrutinib only Japanese study with R/R MCL.[27]

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 as long as the subject's disease assessment occurs, and regardless of the use of other anti-MCL treatments, in the R/R MCL subjects.

Secondary Objectives

1. 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.
2. To evaluate the safety and tolerability of the concurrent administration of venetoclax and ibrutinib in Japanese subjects with R/R MCL.
3. To evaluate the pharmacokinetics of venetoclax and ibrutinib in Japanese subjects with R/R MCL.

Hypotheses corresponding to the secondary objectives, are to achieve superior 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 as long as subject's disease assessment occurs, and regardless of the use of other anti-MCL treatments, in the R/R MCL subjects.

- The median survival time measured from subject's:
  - 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 as long as the subject's disease assessment occurs, and regardless of the use of other anti-MCL treatments, in the R/R MCL subjects.

3.2 Primary Endpoint

The primary endpoint is best overall response of CR according to the Revised Criteria for Response Assessment as assessed by the Independent Review Committee (IRC) (Appendix D).[28]

3.3 Secondary Efficacy Endpoints

The secondary endpoints are:

- IRC-assessed best overall response of CR or PR, according to the Revised Criteria for Response Assessment (Appendix D).
- Investigator-assessed best overall response of CR, according to the Revised Criteria for Response Assessment (Appendix D).
- Investigator-assessed best overall response of CR or partial response (PR), according to the Revised Criteria for Response Assessment (Appendix D).
- 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 (Appendix D).
- 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 (Appendix D).
- Undetectable MRD in subjects who achieve a best overall response of CR as assessed by investigator, according to the Revised Criteria for Response Assessment (Appendix D).
- Undetectable MRD in subjects who achieve a best overall response of CR as assessed by the IRC, according to the Revised Criteria for Response Assessment (Appendix D).

- Progression-free survival, 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 (Appendix D), 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.

3.4 Safety Endpoints

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

3.5 Pharmacokinetic Endpoints

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. Intensive pharmacokinetic blood samples will be collected.

3.6 Biomarker Research Endpoints

Biospecimens (blood and bone marrow aspirate) will be collected at specified time points (Appendix E) throughout the study, to evaluate known and/or novel disease-related or drug-related biomarkers. Types of biomarkers may include nucleic acids, proteins, lipids, and/or metabolites, either free or in association with particular cell types. The biomarker research may be exploratory in nature and the results may not be included with the clinical study report. Further details regarding the biomarker research rationale and collection time points are located in the Operations Manual, Section 3.7.

Provision of biospecimens for biomarker research is mandatory, but they will not be collected from sites where local regulations do not allow for the collection, use, and storage of samples as described in the protocol.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

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 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.

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, enrolment 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. 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.

To mitigate the risk of TLS, a ramp-up period of approximately 5 weeks will be employed with a stepwise increase of the venetoclax dose (Figure 1). Subjects will receive a venetoclax dose of 20 mg on Week 1 Day 1 of the ramp-up period and continue with dose increases every 7 days as tolerated. Ramp-up doses of venetoclax include 20 mg, 50 mg, 100 mg, 200 mg, and 400 mg. Subjects will receive ibrutinib at 560 mg once daily starting on Week 1 Day 1.

If one or more electrolyte changes suggestive of TLS occur within 24 hours of the 20 mg dose, no additional venetoclax doses will be administered until resolution. If correction of electrolytes abnormalities is performed, the subsequent dose of venetoclax can only be given when electrolytes have been stable without any more treatment for at least 24 hours. Refer to Table 2, Recommended Dose Modifications for Venetoclax-Related Toxicities, for additional TLS management guidelines. Upon resolution of laboratory abnormalities, the subject will resume at the ramp-up dose. When venetoclax dose interruptions are required during the ramp-up period, the next highest dose level may be initiated 7 days from the start of the current dose level, once the toxicity has resolved to Grade 1 or baseline level and at the investigator's discretion. At the investigator's discretion, the duration of a single dose level during the ramp-up period may be longer than 7 days before increasing to the next highest dose level.

For all ramp-up doses, laboratory values for subject management must be reviewed in real time by the investigator or designee, and prior to the subject's next dose, to ensure appropriate subject management. Based on the laboratory values, the subject may continue dosing, may need to hold dose until resolution, may require hospitalization for further monitoring, or may need additional post-dose laboratory checks.

Initially, subjects at high-risk for TLS will be hospitalized at the start of the venetoclax 20 mg ramp-up dose and again at the start of the 50 mg ramp-up dose for monitoring and prophylaxis of TLS. Subjects will be considered as high-risk for TLS if they have a high tumor burden (at least one lesion > 10 cm; or at least one lesion > 5 cm and circulating lymphocytes > 25,000 cells/mm^3) and/or with baseline creatinine clearance (CrCl) < 60 mL/min. Subjects not meeting the high-risk criteria will be considered low risk for TLS. Subjects will be discharged from hospital if there is no evidence of TLS. AbbVie will review the safety data during the course of the study to determine whether continued hospitalization of subjects at high-risk for TLS during ramp-up remains warranted.

Subjects may be treated with venetoclax and ibrutinib for up to 104 weeks, starting with the Week 1 Day 1 venetoclax dose of 20 mg dose during the ramp-up period, followed by ibrutinib monotherapy until disease progression, unacceptable toxicity, or withdrawal of consent. Venetoclax will discontinued

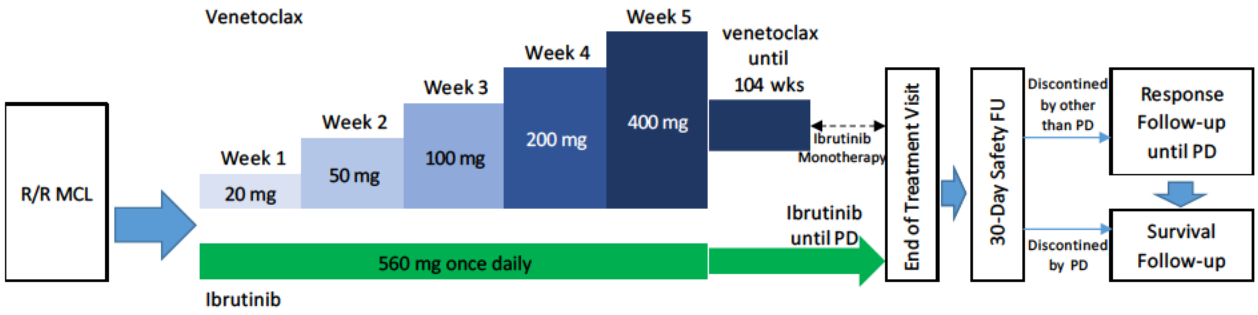
after a maximum of 104 weeks of treatment. The study will be discontinued after approval of the venetoclax and ibrutinib combination for R/R MCL in Japan and subjects continuing to derive benefit at that time will transition to commercial supplies.

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.

The schematic of the study is shown in Figure 1. Further details regarding study procedures are included in the Operations Manual.

See Section 5 for information regarding eligibility criteria.

Figure 1. Study Schema



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.

4.2 Discussion of Study Design

Choice of Control Group

This study does not include a control group.

Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. All efficacy and safety-related measurements in this study are standard for assessing disease activity in subjects with MCL. All clinical and laboratory procedures in this study are standard and generally accepted.

Suitability of Subject Population

Preliminary data from the Phase 2 studies evaluating the combination of venetoclax and ibrutinib in subjects with R/R MCL suggest an acceptable safety profile and high rates of deep remission, including subjects with both high and low risk of TLS.[18,23,26]

For subjects in Japan with R/R MCL, the use of bendamustine, bortezomib, fludarabine, ibrutinib, and cladribine monotherapy, the use of rituximab or other antineoplastic drug combinations with the above

drugs, and radioimmunotherapy (90 Y ibritumomab tiuxetan) monotherapy are recommended. However, new strategies are needed that may substantially improve outcomes and may in the long-term obviate intensive chemotherapy and/or transplantation in younger MCL patients and chemotherapy in older patients with MCL.[12]

This study is designed to confirm the safety and tolerability of the combination of ibrutinib 560 mg + venetoclax 400 mg in Japanese subjects with R/R MCL.

Selection of Doses in the Study

The dose selection in this study is based on data from the safety run-in period of the SYMPATICO study, evaluating the combination of ibrutinib at 560 mg once daily and venetoclax at a target dose of 400 mg once daily in subjects at high and low risk of TLS with R/R MCL. In this study, venetoclax will be ramped up starting at 20 mg with weekly increases to 50 mg, 100 mg, 200 mg, to the target daily dose of 400 mg, per the SYMPATICO safety run-in regimen. In the AIM study, venetoclax was initiated at 50 mg which resulted in TLS in 13% of subjects. This resulted in reduction of venetoclax initiation to 20 mg, after which TLS was not observed.[18,23]

This dose regimen is expected to be efficacious with an acceptable safety profile in Japanese subjects.

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

Subjects must meet all of the following criteria in order to be included in the study. Anything other than a positive response to the questions below will result in exclusion from study participation.

Consent

- 1. Subjects or their legally authorized representative must voluntarily **sign and date an informed consent** (and assent for minors as required by applicable regulation), approved by an independent ethics committee (IEC)/institutional review board (IRB), prior to the initiation of any screening or study-specific procedures.

Demographic and Laboratory Assessments

- 2. Adult **male or female**, at least 20 years old.
- 3. Adequate hematologic function independent of transfusion and growth factor support for at least 7 days prior to first dose with the exception of pegylated granulocyte-colony stimulating factor (G-CSF; pegfilgrastim) which requires at least 14 days prior to the first dose, defined as:
  - Absolute neutrophil count (ANC) > 1000 cells/mm^3 (1.0×10^9/L)
  - Platelet count > 50,000 cells/mm^3 (50×10^9/L)
  - Hemoglobin > 8.0 g/dL.

At the discretion of the investigator: Subjects with bone marrow involvement may be enrolled without meeting the above hematologic function criteria after documented discussion with the AbbVie Therapeutic Area Medical Director (TA MD).

- 4. Adequate hepatic and renal function defined as:
  - Serum aspartate transaminase (AST) or alanine transaminase (ALT) ≤ 3.0 × upper limit of normal (ULN).
  - Bilirubin ≤ 1.5 × ULN; Subjects with documented Gilbert's syndrome may be allowed with a total bilirubin of < 5 × ULN.
  - Estimated CrCl ≥ 30 mL/min (Cockcroft-Gault or 24 hour urine collection).
- 5. Prothrombin time (PT)/international normal ratio (INR) < 1.5 × ULN and PTT (partial thromboplastin time, activated partial thromboplastin time [aPTT]) < 1.5 × ULN (unless abnormalities are unrelated to coagulopathy or bleeding disorder). When treated with warfarin or other vitamin K antagonists, then INR ≤ 3.0.
- 6. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2.
- 7. Able to swallow capsules or tablets.
- 8. Are willing and able to comply with procedures required in this protocol.

Disease Activity

- 9. Pathologically confirmed MCL (tumor tissue) by local testing, with documentation of either overexpression of cyclin D1 in association with other relevant markers (e.g., CD19, CD20, PAX5, CD5) or evidence of the t(11;14) translocation, as assessed by cytogenetics, fluorescent in situ hybridization (FISH), or polymerase chain reaction (PCR).
- 10. At least 1 measurable site of disease on cross-sectional imaging that is ≥ 2.0 cm in the longest diameter and measurable in 2 perpendicular dimensions per CT.
- 11. At least 1, but no more than 5, prior treatment regimens for MCL including at least 1 prior rituximab/anti-CD20 containing regimen.
- 12. Failure to achieve at least PR with, or documented disease progression after, the most recent treatment regimen.

Subject History

- 13. No history or current evidence of central nervous system (CNS) lymphoma.
- 14. No history of other malignancies, except:
  - Malignancy treated with curative intent and with no known active disease present for ≥ 3 years before the first dose of study drug and felt to be at low risk for recurrence by treating physician.
  - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
  - Adequately treated carcinoma in situ without evidence of disease.

- 15. No uncontrolled active systemic infection.
- 16. No unresolved toxicities from prior anticancer therapy, defined as having not resolved to Common Terminology Criteria for Adverse Event (CTCAE, v5.0), Grade 0 or 1, or to the levels dictated in the inclusion/exclusion criteria with the exception of alopecia.
- 17. No known bleeding disorders (e.g., von Willebrand's disease or hemophilia).
- 18. No history of stroke or intracranial hemorrhage within 6 months prior to the first dose of study drug.
- 19. Subject has not undergone an allogeneic stem cell transplant within the last 6 months or currently does not have active graft-versus-host disease requiring the use of immunosuppressants.
- 20. No history of human immunodeficiency virus (HIV) infection (due to potential drug-drug interactions between antiretroviral medications and venetoclax); HIV testing will only be performed at Screening if required per local guidelines or institutional standards.
- 21. No active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection.
  - History of HCV may enroll if their HCV RNA level is undetectable after antiviral therapy.
  - History of HBV infection (without active infection at Screening) may enroll if there is no evidence of active HBV infection. Subjects with hepatitis B surface antigen (HBsAg) negative and anti-HBs antibody positive or anti-HBc antibody positive may participate if HBV DNA quantitative is < 20 IU/ml. Refer to the latest Japan Society of Hepatology guideline.[29]
- 22. No major surgery within 4 weeks of the first dose of study drug.
- 23. No life-threatening illness, medical condition, or organ system dysfunction that, in the investigator's opinion, could compromise the subject's safety or put the study outcomes at undue risk.
- 24. No clinically significant cardiovascular disease, such as:
  - Currently or a history of uncontrolled arrhythmia.
  - Currently Class 3 or 4 congestive heart failure as defined by the New York Heart Association Functional Classification.
  - History of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to the first dose of study drug.
- 25. No history of malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction. Note: a subject with gastrointestinal infiltration by MCL may be enrolled in the study if study drug can be taken and gastrointestinal absorption is possible.
- 26. No history of interstitial lung disease or pneumonitis that required treatment with systemic corticosteroids, or any current evidence of active interstitial lung disease or pneumonitis.
- 27. No contraindications of xanthine oxidase inhibitors and rasburicase.
- 28. No history of chronic liver disease with hepatic impairment Child-Pugh class B or C (refer to Table 7).

- 29. No known hypersensitivity to the active ingredient or other components of one or more study drugs.
- 30. No known active COVID-19 infection. Subject must not have signs/symptoms associated with COVID-19 infection or known exposure to a confirmed case of COVID-19 infection during 14 days prior to Screening.
- Subjects who do not meet COVID-19 eligibility criteria must be screen failed and, may only rescreen after they meet the following COVID-19 viral clearance criteria:
  - Symptomatic subjects: At least 2 negative viral tests in a row, ≥ 24 hours apart after at least 10 days have passed since resolution of symptoms, defined as resolution of fever without use of antipyretics and improvement in respiratory symptoms (e.g., cough, shortness of breath)
  - Asymptomatic subjects (if acceptable locally): At least 2 negative viral tests in a row, ≥ 24 hours apart after at least 10 days have passed since prior positive result (Note: subjects who develop symptoms will follow guidance above for symptomatic subjects)

  Frequency or timing of COVID-19 testing and interval between testing for the above viral clearance criteria may be adjusted to account for epidemiological trends, updated information regarding infectivity and local/institutional guidelines.

Contraception

- 31. If female, subject must not be pregnant, breastfeeding, or considering becoming pregnant during the study or for approximately 90 days after the last dose of study drug.
- 32. Male and female subjects of reproductive potential who agree to use both a highly effective method of birth control (e.g., implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], complete abstinence, or sterilized partner) and a barrier method (e.g., condoms, cervical ring, sponge, etc.) during the period of therapy and for 90 days after the last dose of study drug.
- 33. For all females of child-bearing potential; a **negative serum pregnancy test** at the Screening Visit and a negative urine pregnancy test at baseline prior to the first dose of study drug.
- 34. If male, subject must not be considering fathering a child or donating sperm during the study or for approximately 90 days after the last dose of study drug
- 35. **If male**, and subject is **sexually active with female partner(s) of childbearing potential**, he must agree, from Study Day 1 through 90 days after the last dose of study drug, to practice the protocol-specified contraception.

Concomitant Medications

- 36. No concurrent enrollment in another therapeutic investigational study or prior therapy with ibrutinib or other BTK inhibitors.
- 37. No prior treatment with venetoclax or other BCL2 inhibitors.

- 38. No anticancer therapy, including chemotherapy, radiotherapy, small molecule, and investigational agents, and/or monoclonal antibody ≤ 21 days (or at least 5 drug half-lives, whichever is shorter) prior to the first dose of study drug.
- 39. No corticosteroids for treatment of the underlying malignancy ≤ 21 days (or at least 5 drug half-lives, whichever is shorter) prior to the first dose of study drug.
- 40. Not vaccinated with live, attenuated vaccines within 4 weeks of the first dose of study drug.
- 41. No clinically significant infection requiring intravenous (IV) systemic treatment that was completed ≤ 14 days before the first dose of study drug.
- 42. No treatment with any of the following within 7 days prior to the first dose of study drug:
  - moderate or strong cytochrome P450 3A (CYP3A) inhibitors
  - moderate or strong CYP3A inducers.
- 43. No administration or consumption of any of the following within 3 days prior to the first dose of study drug:
  - grapefruit or grapefruit products
  - Seville oranges (including marmalade containing Seville oranges)
  - star fruit.

5.2 Contraception Recommendations

Contraception Requirements for Females

Subjects must follow the following contraceptive guidelines as specified:

- Females of Non-Childbearing Potential

  Females do not need to use birth control during or following study drug treatment if considered of non-childbearing potential due to meeting any of the following criteria:

  1. Premenopausal female with permanent sterility or permanent infertility due to one of the following:
     - Permanent sterility due to a hysterectomy, bilateral oophorectomy, bilateral salpingectomy.
     - Non-surgical permanent infertility due to Mullerian agenesis, androgen insensitivity, or gonadal dysgenesis; investigator discretion should be applied to determining study entry for these individuals.
  2. Postmenopausal female:
     - Age > 55 years with no menses for 12 or more months without an alternative medical cause.
     - Age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND a follicle-stimulating hormone (FSH) level > 30 IU/L.

- Females of Childbearing Potential
  - Females of childbearing potential must avoid pregnancy while taking study drug(s) and for at least 90 days after the last dose of study drug(s).
  - Females must commit to one of the following methods of birth control:
    - Combined (estrogen and progestogen containing) hormonal birth control (oral) associated with inhibition of ovulation initiated at least 30 days prior to study baseline Day 1.
    - Progestogen-only hormonal birth control (oral) associated with inhibition of ovulation initiated at least 30 days prior to study baseline Day 1.
    - Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure).
    - Intrauterine device (IUD).
    - Intrauterine hormone-releasing system (IUS).
    - Vasectomized partner (provided the partner has received medical confirmation of the surgical success of the vasectomy and is the sole sexual partner of the trial subject).
    - Practice true abstinence, defined as: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).
- If required per local practices, male condom with or without spermicide should be used in addition to one of the birth control methods listed above (excluding true abstinence).

Contraception recommendations related to use of concomitant therapies prescribed should be based on the local label.

Contraception Requirements for Males

Male subjects who are sexually active with a female partner of childbearing potential must agree **to use male condoms, even if the male subject has undergone a successful vasectomy**, from Study Day 1 through at least 90 days after the last dose of study drug:

- His female partner(s) must also use at least 1 of the following methods of birth control:
  - Combined (estrogen and progestogen containing) hormonal birth control (oral) associated with inhibition of ovulation initiated at least 30 days prior to study Baseline Day 1.
  - Progestogen-only hormonal birth control (oral) associated with inhibition of ovulation initiated at least 1 month prior to study Baseline Day 1.
  - Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure).
  - Intrauterine device (IUD).
  - Intrauterine hormone-releasing system (IUS).

- Vasectomized partner (provided the partner has received medical confirmation of the surgical success of the vasectomy, and is the sole sexual partner of the trial subject).

5.3 Prohibited/Cautionary Medications and Therapy

Prohibited Concomitant Medications and Products

Any non-study protocol-related chemotherapy, anticancer immunotherapy, experimental therapy, or radiotherapy are prohibited while the subject is receiving study treatment.

Corticosteroids for the treatment of the underlying malignancy are prohibited with the exception of inhaled steroids for asthma, topical steroids, or replacement/stress corticosteroids.

The Sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

Subjects may not consume grapefruit or grapefruit products, Seville oranges (including marmalade containing Seville oranges), or star fruit within the 3 day period prior to the first venetoclax and ibrutinib administration and until the last day of treatment is completed due to possible CYP3A mediated metabolic interaction.

Do not administer live attenuated vaccines prior to, during, or up to 4 weeks after treatment with venetoclax. The safety and efficacy of immunization with live or attenuated viral vaccines during or following venetoclax therapy have not been studied. Advise subjects that vaccinations may be less effective.

Cautionary Medications and Products

The following concomitant medications are cautionary during study treatment:

- **P-gp substrate:**
  - To avoid a potential interaction in the GI tract, coadministration of narrow therapeutic index P-glycoprotein (P-gp) substrates such as digoxin with venetoclax should be avoided. If a narrow therapeutic index P-gp substrate must be used, it should be taken at least 6 hours before venetoclax.
  - To avoid a potential interaction in the GI tract, narrow therapeutic range P-gp substrates such as digoxin should be taken at least 6 hours before or after ibrutinib.
- **Antiplatelet Agents and Anticoagulants:**
  - To avoid potential interaction with warfarin, which is a narrow therapeutic index drug, it is recommended that the INR be monitored closely in subjects receiving warfarin.
  - Use ibrutinib with caution in subjects requiring anticoagulants or medications that inhibit platelet function, and supplements such as fish oil and vitamin E preparations should be avoided during treatment with ibrutinib. In subjects requiring the initiation of anticoagulation therapy (e.g., atrial fibrillation), consider the risks and benefits of continuing ibrutinib treatment.

- **CYP3A Inhibitors and Inducers:** Table 1 summarizes the recommended dose modifications with moderate and strong CYP3A inhibitors. Avoid concomitant use of systemic strong CYP3A inducers (e.g., carbamazepine, rifampin, phenytoin, and St. John's Wort). Consider alternative agents with less CYP3A induction.

Table 1. Management of Potential Ibrutinib and Venetoclax Interactions with CYP3A Inhibitors

	Venetoclax[a]		Ibrutinib
Inhibitors	**Initiation and Ramp-Up Period**	**Target Daily Dose (After Ramp-Up)**	**At Any Time**
Strong CYP3A inhibitor	Contraindicated (from 7 days prior to first dose)	Avoid inhibitor use, consider alternative agent. If must be used, reduce the venetoclax dose by at least 75%	Avoid inhibitor use, consider alternative agent. If must be used, withhold ibrutinib for duration of inhibitor use, or reduce ibrutinib to 140 mg
Moderate CYP3A inhibitor	Avoid inhibitor use, consider alternative agent. If must be used, reduce the venetoclax dose by at least 50%		Avoid inhibitor use, consider alternative agent. If must be used, reduce ibrutinib to 140 mg

CYP 3A = cytochrome P450 3A

a. Resume the venetoclax dose that was used prior to initiating the CYP3A inhibitor, 2 to 3 days after discontinuation of the inhibitor.

A sample list of cautionary medications that fall into the categories within section can be found in Appendix F. Since it is not possible to provide an exhaustive list of medications that fall into these categories, please refer to the appropriate local product label and/or FDA website.[30]

5.4 Prior and Concomitant Therapy

Concomitant medications are collected from 14 days before the first dose through 30 days after the last dose of study drug.

Any medication (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) or vaccine (note that live attenuated vaccines are prohibited during study treatment) that the subject is receiving at the time of enrollment or receives during the study must be recorded.

Supportive medications in accordance with standard practice (such as for emesis, diarrhea, etc.) are permitted.

Usage of antimicrobial prophylaxis in accordance with standard practice (e.g., ASCO guidelines)[31] is permitted and should be considered in subjects who are at increased risk for opportunistic infections.

Use of neutrophil growth factors (filgrastim and pegfilgrastim) and transfusion is permitted in accordance with institutional policy (e.g., ASCO Guidelines).[32]

In addition, short courses (≤ 14 days) of steroid treatment for non-cancer related medical reasons (e.g., joint inflammation, asthma exacerbation, rash, antiemetic use, and infusion reactions) at doses that are clinically indicated are permitted.

Any questions regarding concomitant or prior therapy should be raised to the AbbVie emergency contact. Information regarding potential drug interactions with venetoclax and ibrutinib can be located in the venetoclax Investigator's Brochure and ibrutinib package insert, respectively.

Subjects must be able to safely discontinue any prohibited medications prior to initial study drug administration. Subjects must be consented for the study prior to discontinuing any prohibited medications for the purpose of meeting study eligibility.

Protocol instructions and information related to COVID-19 and COVID-19 vaccination are listed in Appendix I.

5.5 Guidelines for Ibrutinib Management with Surgeries or Procedures

Ibrutinib may increase risk of bleeding with invasive procedures or surgery. The following guidance should be applied to the use of ibrutinib in the perioperative period for subjects who require surgical intervention or an invasive procedure while receiving ibrutinib.

Minor Surgical Procedures

For minor procedures (e.g., a central line placement, skin or needle biopsy, lumbar puncture [other than shunt reservoir access], thoracentesis, or paracentesis), ibrutinib should be held for at least 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure. For bone marrow biopsies that are performed while the subject is on ibrutinib, it is not necessary to hold ibrutinib.

Major Surgical Procedures

For any surgery or invasive procedure requiring sutures or staples for closure, ibrutinib should be held at least 7 days prior to the intervention (except for emergency procedures) and should be held at least 7 days after the procedure and restarted at the discretion of the investigator when the surgical site is reasonably healed without serosanguineous drainage or the need for drainage tubes.

5.6 Withdrawal of Subjects and Discontinuation of Study

Venetoclax and ibrutinib will be discontinued in the event of any of the following events:

- Progressive disease including clinical progression
- Unacceptable toxicity: an intercurrent illness or AE that prevents further ibrutinib or venetoclax administration regardless relatedness of study drugs as determined by the investigator or Sponsor.
- Withdrawal of consent for treatment by subject
- Investigator decision (such as chronic noncompliance, significant protocol deviation, or best interest of the subject)

- Subject becomes pregnant
- Study discontinuation at the time that the venetoclax and ibrutinib combination becomes commercially available in Japan for R/R MCL
- Study termination by Sponsor.

Withdrawal from study (including all follow-up) will occur under the following circumstances:

- Withdrawal of consent for follow-up observation by the subject
- Lost to follow-up
- Death
- Study termination by Sponsor.

For subjects to be considered lost to follow-up, reasonable attempts must be made to obtain information on the subject's final status. At a minimum, 2 telephone calls must be made and 1 certified letter must be sent, and documented in the subject's source documentation.

AbbVie may terminate this study prematurely, either in its entirety or at any site. The investigator may also stop the study at their site if they have safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will promptly notify the investigator.

Coronavirus Disease - 2019-related acceptable protocol modifications and COVID-19 interruption/discontinuation instructions are discussed in Appendix I.

5.7 Follow-Up after Subject Discontinuation of Study Drug or from Study

To minimize missing data for efficacy and safety assessments, subjects who prematurely discontinue study drug treatment should continue to be followed for all regularly scheduled visits, unless subjects have decided to discontinue the study participation entirely (withdrawal of informed consent). Subjects should be advised on the continued scientific importance of their data even if they discontinue treatment with study drug early.

If a subject prematurely discontinues study treatment (withdrawal of informed consent), the procedures outlined for the end-of-treatment visit should be completed as soon as possible. In addition, a 30-day safety follow-up visit should be completed to ensure all treatment-emergent AEs/serious adverse events (SAEs) have been resolved.

Subjects who discontinue for reasons other than disease progression will continue disease assessment as follow-up response assessments every 12 weeks for the first year; every 16 weeks during the second and third years, and every 24 weeks thereafter until disease progression.

If a subject withdraws from study follow-up or withdraws permission for the collection of their personal data, the study staff may still use available public records to obtain information about survival status only, as appropriate per local regulations.

In the event a subject withdraws consent from the clinical study and confirms research should no longer be conducted upon biomarker samples, research will continue unless the subject explicitly requests analyses to be stopped. When AbbVie is informed that samples are withdrawn from research, samples will not be analyzed, and no new biomarker analysis data will be collected for the withdrawn subject or added to the existing data or database(s). Data generated for biomarker research before a subject's withdrawal of consent will remain part of the study results.

5.8 Survival Follow-Up

For all subjects, after disease progression, survival status, other malignancies, and subsequent anticancer therapy will be collected approximately every 12 weeks after the 30-day safety follow-up or the last visit when 30-day safety follow-up is not implemented until death by clinic visit or telephone call, withdrawal by the subjects, lost to follow-up, study discontinuation, or study termination by the Sponsor, whichever comes first.

5.9 Study Drug

Study drugs refer to drugs that are used (or can be used) in this study to assess the safety and the efficacy of the Investigational Product. Investigators will assess the relationship of adverse events to the use of study drugs (refer to Operations Manual Section 5.2, Table 2) for the list of study drugs.

Venetoclax tablets (10 mg, 50 mg, and 100 mg) and ibrutinib capsules (140 mg) will be provided by the Sponsor for oral administration once daily beginning on Day 1 and should be taken at approximately the same time each day with water within 30 minutes after the completion of a meal, preferably breakfast. Venetoclax tablets and ibrutinib capsules should be swallowed whole and not chewed, crushed, or broken prior to swallowing. If subjects should forget to take their venetoclax and/or ibrutinib dose at their regularly scheduled dosing time, they should take the forgotten dose as soon as they remember within 8 hours with a return to the normal schedule the following day. In cases of vomiting after taking study drug, no additional dose (tablets) should be taken that day.

Subject dosing will be recorded on a subject dosing diary. The subject will be instructed to return all drug containers (even if empty) to the study site personnel at each study visit. The study site personnel will document compliance.

Venetoclax and ibrutinib will be packaged in bottles with quantities sufficient to accommodate study design. Each kit will be labeled per local requirements and this label must remain affixed to the kit. Upon receipt, study drug should be stored as specified on the label and kept in a secure location. Each kit will contain a unique kit number. This kit number is assigned to a subject via interactive response technology (IRT) and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit. Site staff will complete all blank spaces on the label before dispensing to subjects. Study drug will only be used for the conduct of this study.

Further information on study drug, packaging, labeling, etc. is provided in the Operation Manual, Section 6. Protocol instructions and information related to COVID-19, including direct-to-patient study drug shipment, are discussed in Appendix I.

5.10 Drug Assignment

All subjects will be assigned a unique identification number by IRT at the screening visit. For subjects who rescreen, the screening number assigned by the IRT at the initial screening visit should be used. Subjects who are enrolled will retain their subject number assigned by IRT at the screening visit throughout the study and receipt of study drug will be acknowledged in the IRT system.

5.11 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol except when necessary to eliminate an immediate hazard to study subjects. The investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. If a protocol deviation occurs (or is identified, including those that may be due to the COVID-19 pandemic), the investigator is responsible for notifying IEC/IRB, regulatory authorities (as applicable), and AbbVie.

5.12 Independent Safety Monitor

The ISM will be a Japan medical oncologist with experience in clinical studies and who is familiar with the safety assessment of antitumor agents. To avoid any conflict of interest, the ISM must not be associated with or be an employee of the participating study institutions. 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. The ISM must be available for the AbbVie Clinical Team to contact for urgent evaluation of any safety issues. Detailed procedures for safety assessments will be described in a separately prepared document for operational procedures.

6 SAFETY CONSIDERATIONS

6.1 Complaints and Adverse Events

Complaints

A complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device. Complaints associated with any component of this investigational product must be reported to AbbVie.

Product Complaint

A product complaint is any complaint related to the biologic or drug component of the product or to the medical device component(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the

labeling/instructions (e.g., printing illegible), missing components/product, device damage or not working properly, or packaging issues.

Product complaints concerning the investigational product and/or device must be reported to AbbVie within 24 hours of the study site's knowledge of the event.

Reporting will be done via electronic data capture (EDC). The date the product complaint details are entered into EDC and the form is saved represents the date reported to AbbVie. A back-up paper form will be provided for reporting complaints related to unassigned product or in the event of an EDC system issue. If a back-up paper form is used, the date the form is emailed to RD_PQC_QA@abbvie.com represents the date reported to AbbVie.

All follow-up information is to be reported to the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. Product complaints associated with AEs will be reported in the study summary. All other complaints will be monitored on an ongoing basis. Product complaints occurring during the study will be followed up to a satisfactory conclusion.

Medical Complaints/Adverse Events and Serious Adverse Events

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from "special situations" such as accidental or intentional overdose, medication error, occupational or accidental exposure, off-label use, drug abuse, drug misuse, or drug withdrawal, all which must be reported whether associated with an AE or not. Any worsening of a pre-existing condition or illness is considered an AE. Worsening in severity of a reported AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, meet protocol-specific criteria (see Section 6.2 regarding toxicity management), and/or if the investigator considers them to be AEs.

The investigators will monitor each subject for clinical and laboratory evidence of AEs on a routine basis throughout the study. All AEs will be followed to a satisfactory conclusion.

An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and/or the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

If any TLS AEs are reported, the TLS supplemental report (electronic case report form [eCRF]) must be completed.

If an AE, whether associated with study drug or not, meets any of the following criteria, it is to be reported to AbbVie clinical pharmacovigilance as a serious adverse event (SAE) within 24 hours of the

site being made aware of the SAE (refer to Section 4.2 of the Operations Manual for reporting details and contact information):

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All AEs reported from the time of study drug administration until 30 days after discontinuation of study drug administration will be collected, whether solicited or spontaneously reported by the subject. After 30 days following the last dose of study drug or completion of study treatment only spontaneously reported SAEs will be collected (nonserious AEs will not be collected). In addition, study procedure-related serious and nonserious AEs will be collected from the time the subject signs the study-specific informed consent.

Adverse Events of Special Interest

The following AEs of special interest will be monitored during the study:

- Tumor lysis syndrome
- Major hemorrhage

Tumor lysis syndrome events are defined as:

- Clinical TLS: any event that meets Howard criteria (Appendix G) 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 (Appendix G) for laboratory TLS, that does not resolve within 72 hours despite protocol required management.

Major hemorrhage events are defined as:

- Any treatment-emergent Grade ≥ 3 hemorrhage AEs (all hemorrhagic events requiring transfusion of red blood cells should be reported as Grade 3 or higher AE per National Cancer Institute (NCI) CTCAE v5.0).
- Any treatment-emergent SAEs of bleeding of any grade
- Any treatment-emergent CNS hemorrhage/hematoma of any grade.

Adverse Event Severity and Relationship to Study Drug

The investigator will rate the severity of each AE according to the NCI CTCAE Version 5.0. If a reported AE increases in severity, the initial event should be given an outcome date and a new AE must be reported to reflect the change in severity. For all reported SAEs that increase in severity, the supplemental eCRFs also need to be updated to reflect any changes due to the increase in severity.

For AEs not captured by the NCI CTCAE, the following criteria should be used:

Grade 1	Mild; asymptomatic or mild symptoms; clinical diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self- care activities of daily living.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to adverse event.

The investigator will use the following definitions to assess the relationship of the AE to the use of study drug (venetoclax and ibrutinib):

Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is sufficient evidence (information) to suggest a causal relationship.
No Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is insufficient evidence (information) to suggest a causal relationship.

Pregnancy

While not an AE, pregnancy in a study subject must be reported to AbbVie within 24 hours after the site becomes aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.6). If a pregnancy occurs in a study subject or in the partner of a study subject, information regarding the pregnancy and the outcome will be collected.

In the event of pregnancy occurring in a subject's partner during the study, written informed consent from the partner must be obtained prior to collection of any such information. AbbVie will provide a separate consent form for this purpose. Pregnancy in a subject's partners will be collected from the date of the first dose through 90 days following the last dose of study drug.

The pregnancy outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a SAE and must be reported to AbbVie within 24 hours after the site becomes aware of the event.

6.2 Toxicity Management

Venetoclax

Dose Modification for Adverse Reactions

Venetoclax dosing interruption and/or dose reduction may be required. See Table 2 for dose modifications for hematologic and other toxicities related to venetoclax. For subjects who have had a dosing interruption greater than 1 week during the ramp-up period or greater than 2 weeks when at target dose, reassess for risk of TLS to determine if re-initiation with a reduced dose is necessary. Venetoclax dose reduction is not allowed during the DLT assessment period.

Table 2. Recommended Dose Modifications for Venetoclax-Related Toxicities

Event	Occurrence	Action
Tumor Lysis Syndrome Blood chemistry changes or symptoms suggestive of TLS	Any	Withhold the next day's dose. If resolved within 24 to 48 hours of last dose, once the toxicity has resolved to Grade 1 or baseline level, resume at the same dose.
		For any blood chemistry changes requiring more than 48 hours to resolve, once the toxicity has resolved to Grade 1 or baseline level, resume at a reduced dose[a] (see Table 3)
		For any events of clinical TLS, once the toxicity has resolved to Grade 1 or baseline level, resume at a reduced dose following resolution (see Table 3)
Non-Hematologic Toxicities Grade 3 or 4 non-hematologic toxicities	First	Interrupt venetoclax Once the toxicity has resolved to Grade 1 or baseline level, venetoclax therapy may be resumed at the same dose. No dose modification is required.
	Second and subsequent	Interrupt venetoclax Once the toxicity has resolved to Grade 1 or baseline level, resume at a reduced dose following resolution (see Table 3). A larger dose reduction may occur at the discretion of the investigator.
Hematologic Toxicities Grade 3 or 4 neutropenia with infection or fever; or Grade 4 hematologic toxicities (except lymphopenia)	First	Interrupt venetoclax. To reduce the infection risks associated with neutropenia, G-CSF may be administered with venetoclax if clinically indicated. Once the toxicity has resolved to Grade 1 or baseline level, venetoclax may be resumed at the same dose.[a]
	Second and subsequent occurrence	Interrupt venetoclax. Consider using G-CSF as clinically indicated. Once the toxicity has resolved to Grade 1 or baseline level, resume at a reduced dose following resolution[a] (see Table 3). A larger dose reduction may occur at the discretion of the investigator.

DLT = dose limiting toxicity; G-CSF = granulocyte-colony stimulating factor; TLS = tumor lysis syndrome

a. Venetoclax dose reduction is not allowed during the DLT assessment period.

Consider discontinuing venetoclax for subjects who require dose reductions to less than 100 mg for more than 2 weeks.

If the dose of venetoclax is reduced, at the investigator's discretion, the dose of venetoclax may be re-escalated after 2 months of a dose reduction in the absence of a recurrence of the toxicity that led to the reduction. Subsequent dose re-escalations should be discussed with the AbbVie TA MD.

Table 3. Dose Modification for Toxicity During Venetoclax Treatment

Dose at Interruption	Restart Dose[a]
400 mg	300 mg
300 mg	200 mg
200 mg	100 mg

a. Continue the reduced dose for at least 1 week before increasing the dose.

Prophylaxis and Management of Tumor Lysis Syndrome

Venetoclax can cause rapid reduction in tumor and thus poses a risk for TLS in the ramp-up period. Changes in electrolytes consistent with TLS that require prompt management can occur as early as 6 to 8 hours following the first dose of venetoclax and at each dose increase. The risk of TLS is a continuum based on multiple factors, including comorbidities. Subjects with high tumor burden are at greater risk of TLS when initiating venetoclax. Reduced renal function further increases the risk. The risk may decrease as tumor burden decreases with continued venetoclax treatment.

Tumor burden assessments, including radiographic evaluation (e.g., CT scan) should be performed at Screening as well as blood chemistry assessments (potassium, phosphorus, calcium, uric acid, creatinine, lactate dehydrogenase, and, if available, albumin, corrected calcium, and ionized calcium) in all subjects. Pre-existing abnormalities should be corrected prior to initiation of treatment with venetoclax.

- High risk for TLS: Subjects with high tumor burden (at least one lesion > 10 cm; or at least one lesion > 5 cm **and** circulating lymphocytes > 25,000 cells/mm^3) and/or with baseline CrCl < 60 mL/min.
- Low risk for TLS: Subjects not meeting the criteria described above.

The prophylaxis measures listed below should be followed and more intensive measures (including hospitalization) should be employed for subjects at high-risk for TLS based on local guidelines or institutional standards:

- Hydration: Ensure adequate hydration (1.5 L to 2 L) 48 hours prior to initiating therapy with venetoclax and throughout the ramp-up period, especially on the first day of each ramp-up dose. Administer IV fluids as indicated based on the overall risk of TLS or for those who cannot maintain adequate oral hydration.
- Anti-hyperuricemic agents: Administer anti-hyperuricemic agents (e.g., allopurinol) within 72 hours prior to initiation of venetoclax; consider continuing through the ramp-up period. Rasburicase is recommended for subjects at high-risk, especially those with high tumor burden.
- Laboratory Assessments:
  - Pre-dose: Assess blood chemistries prior to initiating venetoclax to evaluate kidney function and correct pre-existing abnormalities. Reassess blood chemistries before starting each subsequent ramp-up dose of venetoclax.

- Post-dose: **For hospitalized subjects**, monitor blood chemistries 4 hours, 8 hours, 12 hours, 24 hours and, as needed, 48 hours after the venetoclax dose. **For outpatient subjects**, monitor blood chemistries at 6 to 8 hours and at 24 hours after the venetoclax dose. Electrolyte abnormalities should be corrected promptly (see Appendix G). **The next dose of venetoclax should not be administered until the 24 hour blood chemistry results have been evaluated.** The monitoring schedule should be followed in the Operations Manual (Appendix K) when starting each subsequent ramp-up dose. Refer to Appendix G for definitions of laboratory and clinical TLS.
- Subjects at low risk of TLS may have laboratory assessments conducted on an outpatient basis. If low risk subjects are hospitalized for logistical reasons, laboratory assessments will be conducted per the outpatient schedule.

- Hospitalization: Based on investigator assessment, subjects with a high-risk of TLS require hospitalization at the 20 mg and the 50 mg ramp-up doses of venetoclax for more intensive prophylaxis and monitoring. The timing of discharge from hospital will be decided based on investigator assessment of available data at that time. Consider hospitalization for subsequent ramp-up doses based on the reassessment of risk. Subjects at low risk of TLS may also be hospitalized, at the investigator's discretion. During the course of the study, the investigators and Sponsor will review TLS data to determine whether continued hospitalization of these subjects is warranted.

Ibrutinib

Dose Modification for Adverse Reactions

Ibrutinib interruption and/or dose reduction may be required for toxicities related to ibrutinib. The dose of study drug must be modified according to the dose modification guidance in Table 4 and Table 5 if any of the following ibrutinib related toxicities occur:

- Grade 3 or greater neutropenia with infection or fever
- Grade 4 neutropenia (ANC < 500/µL) for more than 7 days
- Grade 3 thrombocytopenia (platelets < 50,000/µL) in the presence of Grade ≥ 2 bleeding
- Grade 4 thrombocytopenia (platelets < 25,000/µL)
- Grade 3 or greater non-hematological toxicity (Note: Table 5 recommendations for Grade 3 or greater cardiac failure and cardiac arrhythmias)
- Grade 2 cardiac failure (Table 5)
- Any other Grade 4 or unmanageable Grade 3 toxicity.

If clinically indicated, the use of anticoagulants or antiplatelet agents should be considered for the thromboprophylaxis of atrial fibrillation.

Dose changes must be recorded in the Dose Administration eCRF. Ibrutinib dose reduction is not allowed during the DLT assessment period.

Table 4. Ibrutinib Dose Modifications for Toxicities

Event	Occurrence	Action
Hematologic Toxicities (neutrophil decrease and platelet decrease)	First	Withhold ibrutinib until recovery to an ANC ≥ 750/µL or platelets > 25,000/µL with no evidence of Grade ≥ 2 bleeding; may restart at the same dose level.
	Subsequent	Withhold ibrutinib until recovery to an ANC ≥ 750/µL or platelets > 25,000/µL with no evidence of Grade ≥ 2 bleeding; may restart at 1 dose level lower (refer to Table 6).
Other Hematologic and Non-Hematological Toxicities (for events not specified in Table 5)	First	Withhold ibrutinib until recovery to Grade ≤ 1 or baseline; may restart at the same dose level.[a]
	Second	Withhold ibrutinib until recovery to Grade ≤ 1 or baseline; restart at 1 dose level lower (i.e., 420 mg daily) (refer to Table 6).
	Third	Withhold ibrutinib until recovery to Grade ≤ 1 or baseline; restart at 1 dose level lower (i.e., 280 mg daily) (refer to Table 6).
	Fourth	Discontinue ibrutinib

ANC = absolute neutrophil count; DLT = dose limiting toxicity

a. When resuming treatment, restart at the same or lower dose based on benefit-risk evaluation. If the toxicity reoccurs, reduce daily dose by 140 mg.

Notes:

- Ibrutinib dose reduction is not allowed during the DLT assessment period.
- Do not dose below 280 mg daily except in case of required concomitant administration of strong or moderate CYP3A inhibitors or moderate hepatic impairment.
- Refer to Table 5 for Ibrutinib Dose Modifications for Cardiac Failure or Cardiac Arrhythmias.

Table 5. Ibrutinib Dose Modifications for Cardiac Failure or Cardiac Arrhythmias

Event	Occurrence	Action
Grade 2 cardiac failure	First	Hold ibrutinib until recovery to Grade ≤ 1 or baseline; restart at 1 dose level lower (i.e., 420 mg daily)
	Second	Hold ibrutinib until recovery to Grade ≤ 1 or baseline; restart at 1 dose level lower (i.e., 280 mg daily)
	Third	Discontinue ibrutinib
Grade 3 cardiac arrhythmias	First	Hold ibrutinib until recovery to Grade ≤ 1 or baseline; restart at 1 dose level lower (i.e., 420 mg daily)[a]
	Second	Discontinue ibrutinib
Grade 3 or 4 cardiac failure; Grade 4 cardiac arrhythmias	First	Discontinue ibrutinib

a. Evaluate the benefit-risk before resuming treatment.

Notes:

- Ibrutinib dose reduction is not allowed during the DLT assessment period.
- Refer to Table 4 for additional ibrutinib dose modifications.

Table 6. Ibrutinib Dose Reduction Levels

Starting Dose Level	560 mg
Dose Reduction Level 1	420 mg
Dose Reduction Level 2	280 mg
Dose Reduction Level 3	140 mg
Dose Reduction Level 4	Discontinue

Leukocytosis/Leukostasis

A high number of circulating white blood cells (> 400,000/µL) may confer increased risk of leukostasis; these subjects should be closely monitored. Administer supportive care such as hydration and/or leukapheresis as indicated. Ibrutinib may be temporarily held.

Dose Modification for Hepatic Impaired Subjects

Ibrutinib is metabolized in the liver, and therefore subjects with clinically significant chronic hepatic impairment at Screening (Child-Pugh class B or C) are excluded from study participation.

- For subjects with existing chronic mild hepatic impairment (Child-Pugh class A) at enrollment, the starting dose will be adjusted to a level of 280 mg daily (two capsules).
- For subjects who develop mild hepatic liver impairment while on study (Child-Pugh class A), the recommended dose reduction for ibrutinib is to a level of 280 mg daily (two capsules) unless lower doses had already been implemented.

- Subjects who develop moderate or severe hepatic impairment while on study (Child-Pugh class B or C) must hold study drug(s) until resolved to mild impairment (Child-Pugh class A) or better.
- Subjects who develop acute hepatic toxicity with liver enzymes Grade 3 or higher while on study should be managed per standard dose modification guidelines.

Table 7. Child-Pugh Score for Subjects with Liver Impairment[33,34]

Measure	1 point	2 points	3 points
Total bilirubin, µmol/L (mg/dL)	< 34 (< 2)	34 to 50 (2 to 3)	> 50 (> 3)
Serum albumin, g/L (g/dL)	> 35 (> 3.5)	28 to 35 (2.8 to 3.5)	< 28 (< 2.8)
PT/INR	< 1.7	1.71 to 2.30	> 2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I to II (or suppressed with medication)	Grade III to IV (or refractory)
Points		**Class**	
5 to 6		A	
7 to 9		B	
10 to 15		C	

INR = international normalized ratio; PT = prothrombin time

6.3 Dose-Limiting Toxicity Criteria

Tolerability in the first 6 Japanese subjects (DLT assessment period) will be determined considering all available data, including information on AEs, laboratory results, and PK data. For each of the first 6 subjects, DLTs will be assessed during the venetoclax ramp-up period for a minimum of 5 weeks and at least 1 week of venetoclax dosing at 400 mg.

A DLT is defined as any Grade ≥ 3 AE considered to be at least possibly related to study drug (ibrutinib and/or venetoclax) and occurring during the DLT assessment period with the following clarifications:

Non-Hematologic DLTs:

- Grade ≥ 3 nausea, vomiting, or diarrhea, uncontrolled despite maximum medical supportive care and persisting > 5 days
- Grade 3 fatigue persisting > 7 days
- Grade 3 infection is not a DLT; however, an infection with life-threatening consequences or requiring urgent intervention (Grade 4) will be considered a DLT
- Treatment delay of any study drug of > 7 consecutive days for toxicity.

Hematologic DLTs:

- Grade 3 neutropenia is not a DLT; however, Grade 4 neutropenia (ANC < 500/mm^3) lasting for > 7 days is a DLT
- Grade 3 or 4 neutropenia complicated by fever ≥ 38.5°C or infection
- Grade 4 thrombocytopenia (< 25,000/mm^3) that persists for > 7 days
- Grade 3 or 4 thrombocytopenia associated with Grade 2 or greater bleeding
- Grade 3 anemia is not a DLT; however, Grade 4 anemia is a DLT
- Treatment delay of any study drug > 7 consecutive days for hematologic toxicity.

In addition, clinically important or persistent toxicities that are not included in the above criteria will be considered a DLT following review by the Sponsor and the investigators.

Subjects who miss ≥ 20% of the planned doses of venetoclax or ibrutinib for reasons other than toxicity (e.g., non-compliance, withdrawal of consent, disease progression) during the DLT assessment period, or subjects who do not complete the DLT assessment period for any reason other than a DLT will be considered non-evaluable and will need to be replaced.

A subject must be on study from Day 1 for a minimum of 5 weeks and at least 1 week of venetoclax dosing at 400 mg to be evaluable for DLT assessment. However, in circumstances of an event not related to study drug (e.g., traffic accident, clear disease progression) that leads to study discontinuation before the end of the defined DLT assessment period, the subject might be deemed evaluable if the Sponsor and investigators and agree.

Subjects who are replaced for DLT assessments are also included in the planned total 12 subjects.

Enrollment of subjects will be suspended after the first 6 subjects are enrolled for DLT assessment. The decision around tolerability will be based on data from all subjects who received at least 1 dose of the study drug, regardless of whether the subjects are DLT evaluable or not.

Evaluation of Tolerability:

Dose-limiting toxicities will be evaluated in the first 6 subjects from the planned total of 12 subjects in order to confirm the initial safety and tolerability in Japanese subjects. Enrollment of new subjects will be suspended once the first 6 subjects evaluable for tolerability are enrolled. Dose-limiting toxicities will be evaluated during the venetoclax ramp-up period, from Day 1 for a minimum of 5 weeks and at least 1 week of venetoclax dosing at 400 mg. After the completion of the DLT evaluation period in the first 6 subjects, the AbbVie Study Team and investigators who enrolled the treated subjects will review all available safety and PK data to evaluate whether venetoclax in combination with ibrutinib is tolerable in Japanese subjects with R/R MCL. If there is 0 or 1 DLT in the first 6 subjects, enrolment of the additional 6 subjects will proceed. If DLTs are observed in 2 or more of the first 6 subjects, further enrollment will be interrupted and additional, detailed safety assessment will be conducted, including discussions to determine if other doses should be explored. The Sponsor will consult the ISM with the results of safety evaluation and the Sponsor's conclusion on tolerability, then receive the response from the ISM.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

The statistical methods provided in this protocol will be utilized for primary and secondary analyses. Complete and specific details of the statistical analysis will be described in the Statistical Analysis Plan (SAP).

The primary analysis will be conducted after the last subject has completed the Week 13 disease assessments or all subjects have discontinued the study, whichever is earlier.

In the DLT assessment period, the first 6 study subjects enrolled will be 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.

7.2 Definition for Analysis Populations

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 non-evaluable disease at baseline based on IRC assessment. For endpoints based on IRC assessment, PP population will be used. For investigator assessed endpoints, PP population may be used as appropriate.

Statistical Analyses for Efficacy

Summary and Analysis of the Primary Endpoint

The primary efficacy endpoint will be the best overall response of CR (defined as achieving complete metabolic and/or radiologic response at any time point during the study), according to the Revised Criteria for Response Assessment as assessed by the IRC[28] in the PP population. The primary endpoint will be evaluated using complete response rate (CRR), defined as the proportion of subjects achieving a best overall response of CR for the venetoclax and ibrutinib combination in the PP population, and will be compared to the threshold CRR of 12.5% using the exact binomial test at a 1-sided overall significance level of 0.025. The CRR will be estimated using exact binomial distribution, the estimate and 95% CI for CRR will be constructed.

Subjects who are enrolled but have no disease assessment post-baseline will be considered as non-responders in the calculation of CRR.

Summary and Analysis of Secondary Endpoints

The secondary efficacy analysis will be based on the following endpoints:

- Best overall response of CR by investigator

- Best overall response of CR or PR (defined as achieving partial metabolic and/or radiologic response at any time point during the study), DOR, and undetectable MRD, as assessed by investigator and IRC, respectively.
- PFS by investigator
- OS

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

Endpoint of best overall response of CR or PR will be evaluated using ORR. The ORR will be defined as the proportion of subjects with a best overall response of CR or PR, according to the Revised Criteria for Response Assessment as assessed by the investigator.[28] The estimate and 95% CI for ORR based on exact binomial distribution will be constructed. Similarly, analysis of ORR assessed by IRC will be performed.

DOR will be defined 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 as assessed by the investigator.[28] If a subject is still responding, subjects will be censored at the date of the last adequate disease assessment. DOR will be analyzed for subjects who achieve a best overall response of CR/PR. The distribution of the DOR will be estimated using Kaplan-Meier methodology. If estimable, median DOR and the corresponding 95% CI will be provided. Similarly, analysis of DOR will be performed using IRC-assessed data.

Minimal residual disease (MRD) rate will be defined as the proportion of subjects with undetectable MRD who achieve a best overall response of CR, according to the Revised Criteria for Response Assessment as assessed by the investigator[28] will be estimated and the corresponding 95% CI for the proportion based on exact binomial distribution will be constructed. Similarly, analysis of the proportion of subjects with undetectable MRD who achieve a best overall response of CR, as assessed by the IRC, will be estimated.

Progression-free survival will be 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,[28] 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. The distribution of the PFS events will be estimated using Kaplan-Meier methodology. If estimable, median PFS and the corresponding 95% CI will be provided.

Overall survival will be 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. If a subject has not died, then the data will be censored at the date the subject was last known to be alive. The distribution of the OS will be estimated using Kaplan-Meier methodology. If estimable, median OS and the corresponding 95% CI will be provided.

Details on the secondary efficacy analyses are provided in the SAP.

Summary and Analysis of Additional Efficacy Endpoints

Details on other efficacy analyses are provided in the SAP.

Subgroup Analysis for Efficacy

There is no separate subgroup analysis planned for this study.

7.3 Handling Potential Intercurrent Events for the Primary and Key Secondary Endpoints

The primary endpoint of best overall response of CR (defined in Section 3.2) will be analyzed based on the PP population and the secondary endpoints (defined in Section 3.3) 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 anti-MCL treatment

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

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

7.4 Statistical Analyses for Safety

The safety and tolerability of venetoclax in combination with ibrutinib will be assessed by evaluation of study drug exposure, DLTs, AEs, SAEs, and deaths, as well as changes in laboratory parameters, physical examinations, electrocardiogram (ECG), and vital sign measurements.

Tolerability of venetoclax and ibrutinib combination will be assessed for the first 6 evaluable subjects, where an evaluable subject is defined as a subject who has received the combination for a minimum of 5 weeks and at least 1 week of venetoclax dosed at 400 mg.

Details on the statistical analyses for safety are provided in the SAP.

7.5 Interim Analysis

There is no plan for an interim efficacy analysis. However, an interim 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.

7.6 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.

7.7 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 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,[34] 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 subject(s) 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.

8 ETHICS

8.1 Independent Ethics Committee/Institutional Review Board (IEC/IRB)

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IEC/IRB for review and approval. Approval of both the protocol and the informed consent form(s) must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IEC/IRB before the changes are implemented to the study. In addition, all changes to the consent form(s) will be IEC/IRB approved.

8.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, Operations Manual, International Council for Harmonisation (ICH) guidelines, applicable regulations, and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the investigator are specified in Appendix B.

8.3 Subject Confidentiality

To protect subjects' confidentiality, all subjects and their associated samples will be assigned numerical study identifiers or "codes." No identifiable information will be provided to AbbVie.

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be attributable, legible, contemporaneous, original, accurate, and complete to ensure accurate interpretation of data. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, ICH Good Clinical Practice (GCP), and applicable local regulatory requirement(s). Refer to Appendix I for COVID-19 remote data review/verification details.

10 DATA QUALITY ASSURANCE

AbbVie will ensure that the clinical trial is conducted with a quality management system that will define quality tolerance limits in order to ensure human subject protection and reliability of study results. Data will be generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

11 COMPLETION OF THE STUDY

The end-of-study is defined as the date of the last subject's last visit or date of the last follow-up contact with the subject, whichever is later.

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APPENDIX A. STUDY-SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial prothromboplastin time
ASO	Allele-specific oligonucleotide
AST	Aspartate aminotransferase
AUC	Area-under-the-plasma concentration-time curve
AUC_{tau}	Area-under-the-plasma concentration-time curve over the dosing interval
BCL2	B-cell lymphoma-2
BCRP	Breast cancer resistance protein
CHOP	Cyclophosphamide, doxorubicin, vincristine, and prednisone
CI	Confidence interval
C_{max}	Maximum observed plasma concentration
CMR	Complete Metabolic Response
CNS	Central nervous system
COVID-19	Coronavirus Disease - 2019
CR	Complete response
CrCl	Creatinine clearance
CRR	Complete response rate
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Event
CYP3A	Cytochrome P450 3A
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of response
DTP	Direct-to-patient
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
FAS	Full analysis set

FDA	Food and Drug Administration
FDG	flurodeoxyglucose
FISH	Fluorescent in situ hybridization
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
G-CSF	Granulocyte-colony stimulating factor
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICE	intercurrent event
ICH	International Council for Harmonisation
IEC	Independent ethics committee
IMP	Investigational Medicinal Product
INR	International normalized ratio
IRB	Institutional Review Board
IRC	Independent Review Committee
IRT	Interactive response technology
ISM	Independent safety monitor
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
MCL	Mantle cell lymphoma
MIPI	Mantle Cell Lymphoma International Prognostic Index
MRD	Minimal residual disease
mRNA	messenger Ribonucleic acid [mRNA]
NCI	National Cancer Institute
NE	Negative estimate
NHL	Non-Hodgkin's lymphoma
OAT	Organic ion transporter
ORR	Overall response rate
OS	Overall survival
PCR	Polymerase chain reaction

PD	Disease progression
PET	Positron emission tomography
PFS	Progression-free survival
P-gp	P-glycoprotein
PP	Per-protocol
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
RNA	Ribonucleic acid
R/R	Relapsed/refractory
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
TA MD	Therapeutic Area Medical Director
TLS	Tumor lysis syndrome
T_{max}	Time to maximum observed plasma concentration
TTP	Time to progression
ULN	Upper limit of normal
US	United States

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol 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 Date: 17 November 2023

Clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practices (GCP) and local laws and regulations and guidelines governing the study at the site location. In signing the Investigator Agreement, the investigator is agreeing to the following:

1. Conducting the study in accordance with ICH GCP, the applicable regulatory requirements, current protocol and operations manual, and making changes to a protocol only after notifying AbbVie and the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC), except when necessary to protect the subject from immediate harm.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., IEC or IRB) review and approval of the protocol and its amendments.
4. Reporting complaints that occur in the course of the investigation(s) to AbbVie.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical protocol and all of its amendments.
9. Reporting promptly to AbbVie, the ethics committees/institutional review boards (as required) and other appropriate individuals (e.g., coordinating investigator, institution director):
    - All changes in the research activity and all unanticipated problems involving risks to human subjects or others.
    - Any departure from relevant clinical trial law or regulation, GCP, or the trial protocol that has the potential to affect the following:
        - Rights, safety, physical or mental integrity of the subjects in the clinical trial
        - Scientific value of the clinical trial, reliability or robustness of data generated
10. Providing direct access to source data documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s).

Signature of Principal Investigator	Date

Name of Principal Investigator (printed or typed)	

APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]	[redacted]	Statistics Therapeutic Area Lead Japan TA Oncology and Medical Monitor Japan TA Oncology Clinical Pharmacology Clinical Study Leadership

APPENDIX D. REVISED CRITERIA FOR RESPONSE ASSESSMENT FOR MALIGNANT LYMPHOMA

Site	PET-CT-Based Response Complete Metabolic Response (CMR)	CT-Based Response Complete Radiologic Response (ALL of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS.** It is recognized that in Waldeyer's ring or extranodal sites with high physiological uptake or with activation within spleen or marrow, e.g., with chemotherapy or myeloid colony stimulating factors, uptake may be greater than normal mediastinum and/or liver. In this circumstance, CMR may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiological uptake.	Target nodes/nodal masses must regress to < 1.5 cm in LDi No extralymphatic sites of disease
Non-measured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid diseases in marrow	Normal by morphology; if indeterminate, IHC negative
	Partial Metabolic Response (PMR)	**Partial Remissions (PR) (ALL of the following)**
Lymph nodes and extralymphatic sites	Score 4, 5** with reduced uptake compared with baseline and residual mass(es) of any size. At *interim* these findings suggest responding disease At *end-of-treatment* these findings indicate residual disease	> 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites (When a lesion is too small to measure on CT, assign 5 mm × 5mm as the default value. When no longer visible, 0 × 0 mm For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation.)
Non-measured lesion	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal

Site	PET-CT-Based Response Complete Metabolic Response (CMR)	CT-Based Response Complete Radiologic Response (ALL of the following)
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy, or an interval scan	Not applicable
	No Metabolic Response (NMR)	**Stable Disease**
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline, at interim or end-of-treatment.	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for PD are met
Non-measured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
	Progressive Metabolic Disease (PMD)	**Progressive disease requires at least ONE of the following:**
Individual target nodes/nodal masses, Extranodal lesions	Score 4, 5 with an increase in intensity of uptake from baseline and/or New FDG-avid foci consistent with lymphoma at *interim* or *end-of-treatment* assessment	PPD Progression: An individual node must be abnormal with: LDi > 1.5 cm AND Increase by ≥ 50% from PPD nadir AND an increase in LDi or SDi from nadir 0.5 cm for lesions < 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (e.g., a 15 cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Non-measured lesions	None	New or clear progression of pre-existing non-measured lesions

Site	PET-CT-Based Response Complete Metabolic Response (CMR)	CT-Based Response Complete Radiologic Response (ALL of the following)
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology, e.g., infection, inflammation. If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered.	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis if less than 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma. Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

CT = computed tomography; FDG = flurodeoxyglucose; LDi = longest transverse diameter of a lesions; PD = disease progression; PET = positron emission tomography; PPD = cross product of the LDi and perpendicular diameter; SPD = sum of the product of the perpendicular diameters for multiple lesions; SPDi = shortest axis perpendicular to the LDi

Measured dominant lesions: Up to 6 of the largest dominant nodes, nodal masses and extranodal lesions selected to be clearly measurable in 2 diameters. Nodes should preferably be from disparate regions of the body, and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs, e.g., liver, spleen, kidneys, lungs, etc., GI involvement, cutaneous lesions of those noted on palpation.

Non-measured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant, measurable or which do not meet the requirements for measurability but are still considered abnormal. As well as truly assessable disease which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses and other lesions that cannot be confirmed and followed by imaging.

In Waldeyer's ring or in extranodal sites, e.g., GI tract, liver, and bone marrow, FDG uptake may be greater than mediastinum with CMR, but should be no higher than surrounding normal physiologic uptake, e.g., with marrow activation due to chemotherapy or myeloid growth factors.

* Score 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider score 3 as inadequate response (to avoid under-treatment).

** PET Five Point Scale (5-PS):

1. No update above background
2. Uptake < mediastinum***
3. Uptake > mediastinum, but < liver
4. Uptake moderately > liver
5. Uptake markedly higher than liver and/or new lesions

X. New areas of uptake unlikely to be related to lymphoma

Source: 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 E. ACTIVITY SCHEDULE

The following table shows the required study activities. The individual activities are described in detail in the **Operations Manual**.

Allowed activity schedule modifications due to COVID-19 are detailed within the Operations Manual.

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Study Activities Table

Activity	Screening	Week 1			Week 2			Week 3	Week 4	Week 5	Week 6	Week 8	Week 10	Week 13 & beyond	Response Assessment	End-of-Treatment Visit	30-Day Safety Follow-Up	Scheduled Follow-Up Visits	Survival Follow-Up
	Day –28 to –1	Day 1 (+ 2 days)	Day 2	Day 3	Day 1	Day 2	Day 3	Day 1	Day 1	Day 1	Day 1	Day 1 (± 1 day)	Day 1 (± 1 day)	Day 1 (± 7 days)	Day 1 (± 7 days)		(± 7 days)	(± 14 days)	(± 14 days)
INTERVIEWS & QUESTIONNAIRES																			
Informed consent	✓																		
Eligibility criteria	✓																		
Medical/surgical history	✓	✓																	
Alcohol and nicotine use	✓																		
Adverse event assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓		
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓		
Subsequent anticancer therapy																		✓	✓
Survival status, other malignancies																		✓	✓
LOCAL LABS & EXAMS																			
Physical examination	✓	✓			✓			✓	✓	✓	✓	✓	✓	✓		✓	✓		
ECOG performance status	✓	✓						✓			✓			✓					
Vital signs	✓	✓	✓		✓	✓		✓	✓	✓	✓	✓	✓	✓		✓	✓		
B-Symptoms	✓														✓			✓	
Hematology	✓	✓			✓			✓	✓	✓	✓	✓	✓	✓		✓	✓		
Chemistry	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓		

Activity	Screening	Week 1			Week 2			Week 3	Week 4	Week 5	Week 6	Week 8	Week 10	Week 13 & beyond	Response Assessment	End-of-Treatment Visit	30-Day Safety Follow-Up	Scheduled Follow-Up Visits	Survival Follow-Up
	Day –28 to –1	Day 1 (+ 2 days)	Day 2	Day 3	Day 1	Day 2	Day 3	Day 1	Day 1	Day 1	Day 1	Day 1 (± 1 day)	Day 1 (± 1 day)	Day 1 (± 7 days)	Day 1 (± 7 days)		(± 7 days)	(± 14 days)	(± 14 days)
Child-Pugh score	✓																		
Coagulation studies	✓																		
Serum β2-microglobulin	✓																		
Urinalysis	✓															✓	✓		
Pregnancy test	✓	✓														✓	✓		
HIV test (if required)	✓																		
Hepatitis serology	✓																		
Single 12-lead ECG	✓															✓	✓		
CT/MRI/PET scan (Note: See Appendix K Section 3.14 for details.)	✓														✓			✓	
Endoscopy, if GI involvement	✓														✓				
Bone marrow aspirate	✓														✓				
Bone marrow biopsy	✓														✓				
Response assessment															✓			✓	
Tumor lysis syndrome risk management	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓					
Cytology test (as clinically indicated)	✓														✓				
Pathology test (as clinically indicated)	✓														✓				

Activity	Screening	Week 1			Week 2			Week 3	Week 4	Week 5	Week 6	Week 8	Week 10	Week 13 & beyond	Response Assessment	End-of-Treatment Visit	30-Day Safety Follow-Up	Scheduled Follow-Up Visits	Survival Follow-Up
	Day –28 to –1	Day 1 (+ 2 days)	Day 2	Day 3	Day 1	Day 2	Day 3	Day 1	Day 1	Day 1	Day 1	Day 1 (± 1 day)	Day 1 (± 1 day)	Day 1 (± 7 days)	Day 1 (± 7 days)		(± 7 days)	(± 14 days)	(± 14 days)
CENTRAL LABORATORY TESTS																			
Pharmacokinetic sampling for ibrutinib and venetoclax											✓								
MRD bone marrow aspirate	✓														✓				
MRD assessment in blood		✓													✓	✓			
TREATMENT																			
Dispense study drug & subject dosing diary		✓			✓			✓	✓	✓	✓	✓	✓	✓					
Review subject dosing diary and perform drug reconciliation					✓			✓	✓	✓	✓	✓	✓	✓		✓			

APPENDIX F. SAMPLE LIST OF CAUTIONARY MEDICATIONS

INHIBITORS OR INDUCERS		SUBSTRATES
Strong CYP3A Inhibitors:	**Strong CYP3A Inducers:**	**Substrates of P-gp:**
Boceprevir	Avasimibe	Aliskiren
Clarithromycin	Carbamazepine	Ambrisentan
Cobicistat	Phenobarbital	Colchicines
Conivaptan	Phenytoin	Dabigatran etexilate
Indinavir	Rifabutin	Digoxin
Itraconazole	Rifampicin	Everolimus
Ketoconazole	St John's Wort	Fexofenadine
Lopinavir		Lapatinib
Mibefradil		Loperamide
Nefadozone	**Moderate CYP3A Inducers:**	Maraviroc
Nelfinavir	Bosentan	Nilotinib
Posaconazole	Efavirenz	Ranolazine
Ritonavir	Etravirine	Saxagliptin
Saquinavir	Modafinil	Sirolimus
Telaprevir	Nafcillin	Sitagliptin
Telithromycin	Oxcarbazepine	Talinolol
Troleandomycin	Troglitazone	Tolvaptan
Voriconazole[a]		Topotecan
Moderate CYP3A Inhibitors:	**Weak CYP3A Inducers:**	**Substrates of BCRP (venetoclax only):**
Aprepitant	Amprenavir	Methotrexate
Amprenavir	Aprepitant	Mitoxatrone
Atazanavir	Armodafanil	Irrinotecan
Ciprofloxacin	Clobazamechinacea	Lapatinib
Crizotinib	Glucocorticoids (e.g., prednisone)	Rosuvastatin
Darunavir/ritonavir	Nevirapine	Sulfasalazine
Dronedarone	Pioglitazone	Topotecan
Erythromycin	Rufinamide	
Diltiazem	Vemurafenib	

INHIBITORS OR INDUCERS		SUBSTRATES
Fluconazole		
Fosamprenavir		
Imatinib		
Verapamil		
Weak CYP3A Inhibitors:	**Inhibitors of OATP1B1/B3 (venetoclax only):**	**Substrates of OATP1B1/B3 (venetoclax only):**
Alprazolam	Gemfibrozil	Atrasentan
Amiodarone	Eltrombopag	Atorvastin
Amlodipine	Cyclosporine	Ezetimibe
Atorvastatin	Tipranavir	Fluvastatin
Bicalutamide		Glyburide
Cilostazol		Olmesartan
Cimetidine	**Inhibitors of BCRP (venetoclax only):**	Rosuvastatin
Cyclosporine	Cyclosporine	Simvastatin acid
Fluvoxamine	Geftinib	Pitavastatin
Fluoxetine		Pravastatin
Ginkgo		Repaglinide
Goldenseal	**Inhibitors of P-gp (venetoclax only):**	Telmisartan
Isoniazid	Amiodarone	Valsartan
Nilotinib	Azithromycin	
Oral contraceptives	Captopril	
Pazopanib	Carvedilol	
Ranitidine	Cyclosporine	
Ranolazine	Dronedarone	
Suboxone	Felodipine	
Tipranavir/ritonavir	Quercetin	
Ticagrelor	Quinidine	
Zileutin	Ranolazine	
	Ticagrelor	

BCRP = breast cancer resistance protein; CYP3A = cytochrome P450 3A; OAT = organic ion transporter; P-gp = P-glycoprotein

a. Allowed to dose with 140 mg ibrutinib based on clinical data.

Note: This is not an exhaustive list. Further information can be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm.

APPENDIX G. HOWARD CRITERIA FOR LABORATORY AND CLINICAL TUMOR LYSIS SYNDROME

Metabolic Abnormality	Criteria for Classification of Laboratory Tumor Lysis Syndrome[a]	Criteria for Classification of Clinical Tumor Lysis Syndrome[a]
Hyperuricemia	Uric acid > 8.0 mg/dL (475.8 µmol/liter) in adults or above the upper limit of the normal range for age in children	
Hyperphosphatemia	Phosphorus > 4.5 mg/dL (1.5 mmol/liter) in adults or > 6.5 mg/dL (2.1 mmol/liter) in children	
Hyperkalemia	Potassium > 6.0 mmol/liter	Cardiac dysrhythmia or sudden death probably or definitely caused by hyperkalemia
Hypocalcemia	Corrected calcium < 7.0 mg/dL (1.75 mmol/liter) or ionized calcium < 4.5 mg/dL (1.12 mmol/liter)[b]	Cardia dysrhythmia, sudden death, seizure, neuromuscular irritability (tetany, paresthesia, muscle twitching, carpopedal spasm, Trousseau's sign, Chvostek's sign, laryngospasm, or bronchospasm), hypotension, or heart failure probably or definitely caused by hypocalcemia
Acute kidney injury[c]	Not applicable	Increase in the serum creatinine level of 0.3 mg/dL (26.5 µmol/liter) (or a single value > 1.5 times the upper limit of the age-appropriate normal range if no baseline creatinine measurement is available) or the presence of oliguria, defined as an average urine output of < 0.5 mL/kg/hr for 6 hours

a. In laboratory TLS, two or more metabolic abnormalities must be present during the same 24 hour period within 3 days before the start of therapy or up to 7 days afterward. Clinical TLS requires the presence of laboratory TLS plus an increased creatinine level, seizures, cardiac dysrhythmia, or death.

b. The corrected calcium level in milligrams per deciliter = measured calcium level in milligrams per deciliter + 0.8 × (4 - albumin in grams per deciliter).

c. Acute kidney injury is defined as an increase in the creatinine level of at least 0.3 mg per deciliter (26.5 µmol per liter) or a period of oliguria lasting 6 hours or more. By definition, if acute kidney injury is present, the patient has clinical TLS. Data about acute kidney injury are from Levin A, Warnock DG, Mehta RL, et al. Improving outcomes from acute kidney injury: report of an initiative. Am J Kidney Dis. 2007;50:1-4.

APPENDIX H. RECOMMENDATIONS FOR INITIAL MANAGEMENT OF ELECTROLYTE ABNORMALITIES AND PREVENTION OF TUMOR LYSIS SYNDROME

Section 1: First Dose of Venetoclax or Dose Escalation

- Within the first 24 hours after either the first dose or dose escalation, if any laboratory criteria below are met, the patient should be hospitalized for monitoring and the investigator notified. No additional venetoclax doses should be administered until resolution. A rapidly rising serum potassium is a medical emergency.
- Nephrology (or other acute dialysis service) should be contacted/consulted (per institutional standards to ensure emergency dialysis is available) on admission for any subject hospitalized prophylactically or in response to laboratory changes.
- IV fluids (e.g., D5 1/2 normal saline) should be initiated at a rate of at least 1 mL/kg/hr rounded to the nearest 10 mL (target 150 to 200 mL/hr; not < 50 mL/hr). Modification of fluid rate should also be considered for individuals with specific medical needs.
- Monitor for symptoms or signs of tumor lysis syndrome (TLS) (e.g., fever, chills, tachycardia, nausea, vomiting, diarrhea, diaphoresis, hypotension, muscle aches, weakness, paresthesias, mental status changes, confusion, seizures). If any clinical features are observed, recheck potassium, phosphorus, uric acid, calcium and creatinine within 1 hour STAT.
- Vital signs should be taken at time of all blood draws or any Intervention.
- The management recommendations below focus on the minimum initial responses required. If a diagnosis of TLS is established, ongoing intensive monitoring and multi-disciplinary management will be per institutional protocols.

In addition to the recommendations in the table below:

- For potassium increase ≥ 0.5 mmol/L from baseline, or any value > 5.0 mmol/L, recheck potassium, phosphorus, uric acid, calcium and creatinine within 1 hour STAT and follow first guideline.
- For phosphorus increase of > 0.5 mg/dL AND > 4.5 mg/dL, administer phosphate binder and recheck potassium, phosphorus, uric acid, calcium and creatinine within 1 hour STAT.

Abnormality	Management Recommendations[1,2]
Hyperkalemia (including rapidly rising potassium)	
Potassium ≥ 0.5 mmol/L increase from prior value (even if potassium within normal limits [WNL])	• Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. If further ≥ 0.2 mmol/L increase in potassium, but still < upper limit of normal (ULN), manage as per potassium ≥ ULN. Otherwise recheck in 1 hour. • Resume per-protocol testing if change in potassium is < 0.2 mmol/L, and potassium < ULN, and no other evidence of tumor lysis. • At discretion of Investigator, may recheck prior to hospitalization. If stable or decreased, and still WNL, hospitalization is at the discretion of the Investigator. Potassium, phosphorus, uric acid, calcium and • Creatinine must be rechecked within 24 hours.
Potassium > upper limit of normal	• Perform STAT ECG and commence telemetry. • Nephrology notification with consideration of initiating dialysis. • Administer Kayexalate 60 g (or Resonium A 60 g). • Administer furosemide 20 mg IV × 1. • Administer calcium gluconate 100 – 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. • If potassium < ULN 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 1, 2 and 4 hours, if no other evidence of tumor lysis.
Potassium ≥ 6.0 mmol/L (6.0 mEq/L) and/or symptomatic (e.g., muscle cramps, weakness, paresthesias, nausea, vomiting, diarrhea)	• Perform STAT ECG and commence telemetry. • Nephrology (or other acute dialysis service) assessment with consideration of initiating dialysis. • Administer Kayexalate 60 g (or Resonium A 60 g). • Administer furosemide 20 mg IV × 1. • Administer insulin 0.1 U/kg IV + D25 2 mL/kg IV. • Administer sodium bicarbonate 1 to 2 mEq/kg IV push. • If sodium bicarbonate is used, rasburicase should not be used as this may exacerbate calcium phosphate precipitation. • Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. Do not administer in same IV line as sodium bicarbonate. • Recheck potassium, phosphorus, uric acid, calcium and creatinine every hour STAT.

Abnormality	Management Recommendations[1,2]
Hyperuricemia	
Uric acid ≥ 8.0 mg/dL (476 µmol/L)	• Consider rasburicase (0.2 mg/kg as an intravenous infusion over 30 minutes). • If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT.
Uric acid ≥ 10 mg/dL (595 µmol/L) OR Uric acid ≥ 8.0 mg/dL (476 µmol/L) with 25% increase and creatinine increase ≥ 0.3 mg/dL (≥ 0.027 mmol/L) from pre-dose level	• Administer rasburicase (0.2 mg/kg as an intravenous infusion over 30 minutes). • When rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Consult nephrology (or other acute dialysis service). • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. • If uric acid < 8.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.
Hypocalcemia	
Calcium ≤ 7.0 mg/dL (1.75 mmol/L) AND Patient symptomatic (e.g., muscle cramps, hypotension, tetany, cardiac arrhythmias)	• Administer calcium gluconate 50 to 100 mg/kg IV slowly with ECG monitoring. • Telemetry. • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. • If calcium normalized 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours later, if no other evidence of tumor lysis. Calculate corrected calcium and check ionized calcium if albumin low.
Hyperphosphatemia	
Phosphorus ≥ 5.0 mg/dL (1.615 mmol/L) with ≥ 0.5 mg/dL (0.16 mmol/L) increase	• Administer a phosphate binder (e.g., aluminum hydroxide, calcium carbonate, sevelamer hydroxide, or lanthanum carbonate). • Nephrology (or other acute dialysis service) notification (dialysis required for phosphorus ≥ 10 mg/dL). • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. • If phosphorus < 5.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours later, if no other evidence of tumor lysis.

Abnormality	Management Recommendations[1,2]
Creatinine	
Increase ≥ 25% from baseline	• Start or increase rate of IV fluids. • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 to 2 hours STAT.

Section 2: Ongoing Dosing of Venetoclax

Management of electrolyte changes from last value at intervals >24 hours after either the first dose or dose escalation (e.g., 48 or 72 hours) are as below.

Note: If the patient is hospitalized, no additional venetoclax doses should be administered until resolution.

- For potassium, admit patient for any increase ≥ 1.0 mmol/L (1.0 mEq/L), or any level > upper limit of normal.
- Refer to the management guidelines for electrolyte changes observed within the first 24 hours after either the first dose or dose escalation (see table above).
- If a smaller potassium increase is observed that does not meet the criteria for admission above, recheck potassium, phosphorus, uric acid, calcium and creatinine in 24 hours and confirm no evidence of tumor lysis prior to further venetoclax dosing.
- For uric acid, calcium, phosphorus and creatinine, refer to the management guidelines for electrolyte changes observed within the first 24 hours after either the first dose or dose escalation (see table above).

References

1. Coiffier B, Altman A, Pui CH, et al. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. J Clin Oncol. 2008;26(16):2767-78.
2. Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. Br J Haematol. 2004;127(1):3-11.

APPENDIX I. COVID-19-RELATED INSTRUCTIONS

Instructions related to the COVID-19 pandemic are listed below.

Benefits and Risks to Subjects

Considering the coronavirus (COVID-19) pandemic, the benefit and risk to subjects participating in this study has been re-evaluated. Subjects receiving venetoclax and ibrutinib may be at an increased risk for COVID-19 infection or experience serious illness if infected. Management of these AEs will be made on a case-by-case basis with consideration of benefit/risk by the investigators. However, based on the population, the disease being studied, and the anticipation that COVID-19-related risks are unknown between study subjects and the broader population of subjects receiving treatment for mantle cell lymphoma, no known change to the benefit/risk balance for subjects in this study is expected.

Refer to Section 5.1 for COVID-19 specific eligibility criteria.

Study Subject Information and Informed Consent

Due to the COVID-19 pandemic, it is possible that additional protocol modifications not outlined in this protocol may become necessary. If this situation arises, in addition to the study informed consent, additional verbal consent may be obtained prior to these adaptations or substantial changes in study conduct in accordance with local regulations. An appropriately signed and dated informed consent form should be obtained from the subject afterwards, as soon as possible.

COVID-19 Pandemic-Related Acceptable Protocol Modifications for Study Procedures

During the COVID-19 pandemic, if it is not possible for all study procedures to be performed as specified due to travel restrictions or other reasons, the following modifications are allowed:

- Some study visits and/or activities (e.g., physical examination, vital signs, ECOG) may be performed by phone/virtually. Refer to the sections below for further details.
- Some study visits and/or activities (e.g., ECG) may be performed by a local clinic/hospital/laboratory. These study visits and/or activities are listed in the operations manual under 'Local Labs & Exam'. All procedures performed at local facilities must be performed by appropriately qualified personnel.
- Some study visits cannot be performed locally or virtually and can only be performed at the central lab (e.g., PK and MRD assessment). Refer to the sections below for further details.
- Study Visits and/or activities should be performed as scheduled whenever possible. If it is not possible to do so due to the pandemic, the following modifications are allowed:
    - If an activity is missed during a virtual visit, perform the activity at the earliest feasible opportunity. Laboratory draws must be obtained within 24 hours from the scheduled visit.

Study procedures to be Completed at the Site at Next Feasible Visit

In the event sample collections may not be performed at the primary research site due to study modifications related to the COVID-19 pandemic the following procedures can be completed at the next earliest feasible visit:

- PK assessments
- Biomarker sample collection
- ECG (If necessary, the 12-lead ECG may be completed at an alternative local facility)
- PET/CT (or MRI) scan (If necessary, the PET/CT [or MRI] scan may be completed at an alternative local facility
- Endoscopy (If necessary, the endoscopy may be completed at an alternative local facility)

  and/or
- Disease assessments

The study site will use CB Trial Laboratory provided supplies and collect PK and biomarker samples as detailed in the CB Trial Laboratory Manual. These samples must be collected only after proper dosing and other specific requirements per the protocol have been met. If a subject is unable to go on-site for these samples due to COVID-19, these samples may be delayed until the subject is able to return to the study site at a later date, following proper dosing and other requirements per-protocol.

Study Procedures that can be Completed virtually via Phone or Video Conference due to COVID-19

If permitted by local regulations, the IRB/IEC, and the subject, some study visits may be conducted via phone or video conference if disease assessment is not required, and no dose modifications are anticipated. In these situations, vital signs may be obtained by the subject or caregiver as needed.

The physical examination can be performed via video, if possible. If not possible, the examination can be completed at the next visit when the subject is able to go to the site or can be completed by the subject's local physician. If subject has a home blood pressure and pulse kit and weight scale, subject may report these readings over the phone or via video. In these situations, height and weight may be performed by the subject or caregiver as needed. Additionally, the procedures outlined below can be conducted over the phone or via video.

Adverse event and ECOG assessment can be done over the phone or via video.

Clinical Laboratory Tests

If travel restrictions or other changes in local regulations in light of the COVID-19 pandemic prevent the subject from having blood drawn for laboratory testing at the study site, if possible, arrange for subjects to have laboratory work done at a local lab, hospital, or other facility. Local laboratory results should be obtained along with reference ranges and kept within the subjects' source documentation. The investigator should review local laboratory results as soon as possible.

The investigator or designee should confirm with the subject when the lab samples were collected.

Once subject is on a stable dose of venetoclax and ibrutinib for at least 4 weeks, if safety laboratory samples cannot be obtained, study drug administration may be continued provided the investigator has reviewed all prior laboratory results within 4 weeks and confirms and discusses with the subject that there is no safety concern for the subject to continue use of the study drug in the absence of current

labs. The subject should be scheduled for laboratory draws as soon as feasible within 3 days from the scheduled visit.

Urine pregnancy tests can be done at a local lab or test kits can be shipped by site staff to the subject. Home pregnancy tests should be performed monthly, regardless of ability to obtain other laboratory testing.

Withdrawal of Subjects and Discontinuation of Study: COVID-19 Pandemic-Related Acceptable Protocol Modification

During the COVID-19 pandemic, it has been necessary to employ mitigation strategies to enable the investigator to ensure subject safety and continuity of care. Acceptable mitigation strategies are identified and included in the Operations Manual in Appendix K.

The investigator should contact the Sponsor medical contact before discontinuing a subject from the study for a reason other than described in the protocol to ensure all acceptable mitigation steps have been explored.

Interruption/Discontinuation of Study Drug Due to COVID-19 Infection

During the Study Drug Dosing Period, a subject with confirmed (viral test positive) or suspected COVID19 infection can only be dosed with study drug(s) if the following COVID-19 viral clearance criteria are met:

- At least 10 days since first positive test result have passed in asymptomatic patients or at least 10 days since recovery, defined as resolution of fever without use of antipyretics and improvement in symptoms.

Delays in study drug dosing due to the above COVID-19 testing guidance for subjects must be discussed with the AbbVie medical contact, along with the possibility of premature discontinuation from the study drug dosing period. Follow Section 5.6 for subjects who discontinued study drug. Frequency or timing of COVID-19 testing and intervals between testing for the above viral clearance criteria may be adjusted to account for epidemiologic trends, updated information regarding infectivity, and local/institutional guidelines.

Direct-to-patient Study Drug Shipment

If a subject is unable to come to the study site to pick up their study drug due to COVID-19, a direct-to-patient (DTP) study drug shipment can be made from the study site to the subject if allowed by local regulations. AbbVie will submit any required notifications to the regulatory authority as applicable.

The following DTP criteria must be met:

- Direct-to-patient (DTP) shipment of study drug is allowed by local regulations and the relevant ethics committee
- Study drug can be administered by the subject (or subject's caregiver) at home
- Subject agrees to have the study drug shipped directly to their home
    - Shipments may also include other study supplies (e.g., drug dosing diaries, paper copies of the patient-reported outcomes). Instructions will be provided by AbbVie as to how a study

site can initiate a DTP shipment using Marken, a global vendor selected by AbbVie to provide this service when necessary. Shipments of study drugs from the study site to a subject's home will be appropriately temperature controlled (qualified shipper or temperature monitoring) within the labeled storage conditions. Signature is required upon delivery; due to COVID-19-related social distancing, this may be provided by the courier after delivery. Documentation of the shipment is to be retained by the clinical site.

- AbbVie will not receive subject identifying information related to these shipments, as the site will work directly with the courier.

The study site is responsible for meeting IRB/IEC reporting requirements related to DTP shipments of study drug, and for obtaining consent to provide delivery information to the courier and documenting this consent in source documents.

Ethical Conduct of the Study

Investigators should notify AbbVie if any urgent safety measures are taken to protect the subjects against any immediate hazard.

Source Documents and Case Report Form Completion

During the COVID-19 pandemic, remote data review/verification may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

Supplemental study case report forms should be completed in the event of COVID-19-related missed/virtual visits, study drug interruptions or discontinuations, or adverse events (including capture of specific signs/symptoms of infection and testing results).

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections should be captured as adverse events. If the event meets the criteria for a SAE, then follow the SAE reporting directions per the protocol. The following COVID-19-related supplemental eCRFs should be completed (for both serious and nonserious events of SARS-CoV-2 infections):

- COVID-19 Supplemental Signs/Symptoms
- COVID-19 Status Form

If a subject has a confirmed or suspected SARS-CoV-2 infection and study drug was interrupted, the investigator should contact the Sponsor emergency medical contact listed above before reintroducing study drug.

Reactions known to be associated with the SARS-CoV-2 vaccine should be reported as adverse events. If the event meets the criteria for an SAE, then follow the SAE reporting directions. All adverse events associated with the SARS-CoV-2 vaccine will be linked to the vaccine on the COVID-19 Vaccine eCRF.

COVID-19 Pandemic-Related Vaccination Guidance

Given the ongoing COVID-19 pandemic, selected non-live vaccines (e.g., messenger Ribonucleic acid [mRNA], non-replicating viral vector, protein subunit, etc.) to prevent SARS-CoV-2 infection may be

administered during screening or the treatment period, as long as components of the vaccine are not contraindicated.

The decision to receive a locally available vaccine should be based on local guidance and an individual discussion between the treating physician and the subject.

The potential impact of venetoclax and ibrutinib on SARS-CoV-2 vaccination is unknown and there is no restriction related to the administration of study drugs in this study.

Note: The above guidance applies to all SARS-CoV-2 vaccine doses given as part of the complete vaccination course.

These recommendations may be subject to change based on the evolving knowledge around the use of SARS-CoV-2 vaccines in patients with mantle cell lymphoma and as more data are collected in real-world scenarios and clinical trials.

Any SARS-CoV-2 vaccine information must be documented on the COVID-19 vaccine eCRF. Refer to the 'Source Documents and Case Report Form Completion' section of Appendix I for instructions on reporting any adverse events associated with the COVID-19 vaccine.

COVID-19 Vaccine-related Lymphadenopathy and FDG PET/CT Timing

Transient flurodeoxyglucose (FDG) uptake in normal or enlarged axillary, supraclavicular, and cervical lymph nodes have been reported after an ipsilateral deltoid vaccination. This phenomenon may confound interpretation in oncology patients undergoing FDG PET/CT. It is recommended to consider influence of the COVID-19 vaccination to PET/CT, this includes leaving an interval of 4-6 weeks after inoculation by the Japan Cancer Treatment Society.

Given increased immunogenicity of mRNA vaccines and to allow resolution of lymphadenopathy, the optimal timing for disease assessment is 4-6 weeks after COVID-19 vaccination. Although, vaccine-related lymphadenopathy and FDG uptake on PET/CT can mimic cancer and lead to confounding imaging results in some cases, it is reported that PET/CT should **not** be delayed when clinically indicated to be performed sooner.[35-37]

As per the discussion with AbbVie's internal study team, we propose the following strategies to be followed for the Disease Assessments:

- Please schedule the study visits including the PET/CT imaging and the Disease Assessments as outlined in Appendix E and the Operations Manual.
- If a COVID-19 vaccination (1st or 2nd dose) is also scheduled around the same time as of the scheduled study visits, it is preferable that the vaccine to be injected after all the study procedures including the PET/CT scans have already been performed.
- If a Disease Response assessment shows Partial remission, Stable Disease, or Disease Progression after COVID-19 vaccination, the Sponsor may ask investigator to perform confirmatory PET/CT scans to determine the validity of this assessment.

These recommendations may be subject to change based on the evolving knowledge around the use of SARS-CoV-2 vaccines in patients with relapsed/refractory Mantle Cell Lymphoma and as more data are collected in real-world scenarios and clinical trials.

Any SARS-CoV-2 vaccine information must be documented on the COVID-19 vaccine eCRF. If you have any questions, please do not hesitate to contact your responsible CRA or the study Medical Monitor/Therapeutic Area Medical Director.

APPENDIX J. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	07 May 2020
Version 2.0	31 October 2020
Version 3.0	17 February 2022
Administrative Change 1	12 July 2022
Version 4.0	04 January 2023

The purpose of this version is to correct clerical errors for consistency throughout the protocol and incorporate necessary protocol modifications, including those outlined as follows:

- The list of signatories in Appendix C was updated.
- In Appendix E and Appendix K requirements for PET scans during response assessments and scheduled follow-up visits were removed reflect that primary analysis was completed and further IRC assessment will not be conducted.
- Appendix G replaced hypocalcemia classification for lab TLS from "Corrected calcium < .75 mg/dL (1.75 mmol/liter) or ionized calcium < 1.12 mg/dL (0.03 mmol/liter)") to "Corrected calcium < 7.0 mg/dL (1.75 mmol/liter) or ionized calcium < 4.5 mg/dL (1.12 mmol/liter)" to align with the review article from which the value was cited.[38]
- The SAE reporting fax numbers in Appendix K were updated.