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PROTOCOL

TITLE:	Phase 3 Study of Ibrutinib in Combination with Venetoclax in Subjects with Mantle Cell Lymphoma
PROTOCOL NUMBER:	PCYC-1143-CA
STUDY DRUG:	Ibrutinib
IND NUMBER:	102,688
EudraCT NUMBER:	2017-000129-12
SPONSOR MEDICAL MONITOR:	[redacted] MD, PhD Pharmacyclics LLC Phone: [redacted] Email:
SPONSOR:	Pharmacyclics LLC, an AbbVie company 1000 Gateway Boulevard South San Francisco, CA 94080 United States of America
DATE FINAL:	16 December 2016
Amendment 0.1	16 May 2017 (UK only)
Amendment 1	17 November 2017
Amendment 2	7 November 2019
Amendment 2.1	27 April 2020 (France only)
Amendment 3	25 March 2021
Amendment 4:	16 September 2022

PROTOCOL APPROVAL PAGE

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Amendment 3: 25 March 2021

Amendment 4: 16 September 2022

I have carefully read Protocol PCYC-1143-CA entitled "Phase 3 study of ibrutinib in combination with venetoclax in subjects with mantle cell lymphoma." I agree to conduct this study as outlined herein and in compliance with Good Clinical Practices (GCP) and all applicable regulatory requirements. Furthermore, I understand that the Sponsor, Pharmacyclics LLC, and the Institutional Review Board/Research Ethics Board/Independent Ethics Committee (IRB/REB/IEC) must approve any changes to the protocol in writing before implementation.

I agree not to divulge to anyone, either during or after the termination of the study, any confidential information acquired regarding the investigational product and processes or methods of Pharmacyclics LCC. All data pertaining to this study will be provided to Pharmacyclics LLC. The policy of Pharmacyclics LLC requires that any presentation or publication of study data by clinical Investigators be reviewed by Pharmacyclics LLC, before release, as specified in the protocol.

Principal Investigator's Signature Date

Print Name

[redacted]presentative is authorized to sign the protocol and any

03 Oct 2022
Date

Clinical Development, Pharmacyclics LLC

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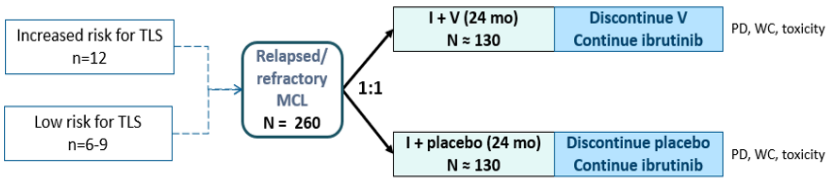
SYNOPSIS

Study Title:	Phase 3 study of ibrutinib in combination with venetoclax in subjects with mantle cell lymphoma (MCL)
Protocol Number:	PCYC-1143-CA
Study Phase:	3
Study Duration:	Estimated to be 5 years
Investigational Product and Reference Therapy:	Ibrutinib will be supplied as 140 mg hard gelatin capsules or 560 mg tablets for oral (PO) administration. Venetoclax will be supplied as 10 mg, 50 mg, and 100 mg tablets for oral (PO) administration.
Objectives: (Safety Run-in [SRI] Period and Randomization Phase)	**Safety Run-in Period** **Primary Objective:** To evaluate the occurrence of tumor lysis syndrome (TLS) and dose-limiting toxicities (DLTs) with the concurrent administration of ibrutinib and venetoclax. **Secondary Objectives:** To evaluate response (partial and complete response), progression-free survival (PFS), duration of response (DOR), and overall survival (OS). **Randomization Phase** **Primary Objective:** To evaluate whether the combination of ibrutinib and venetoclax will result in prolongation of PFS compared to ibrutinib and placebo in subjects with relapsed or refractory MCL. **Secondary Objectives:** • To evaluate whether the combination of ibrutinib and venetoclax will increase the complete response (CR) rate, the overall response rate (ORR), the minimal residual disease (MRD) negative remission rate in subjects who were MRD positive at screening and achieve CR, OS, DOR, and time-to-next treatment (TTNT) compared to ibrutinib and placebo. • To evaluate the frequency, severity, and relatedness of adverse events (AEs); frequency, severity and management of TLS; AEs requiring dose reductions and/or discontinuation of study drug, or leading to death. • To determine the pharmacokinetics (PK) of ibrutinib and venetoclax. • To evaluate whether the combination of ibrutinib and venetoclax will improve quality of life using a Health-related quality of life questionnaire (FACT-Lym, etc.), compared to ibrutinib and placebo.
Objectives: (Treatment-naive Open-label Arm)	**Primary Objective:** To evaluate the complete response (CR) rate with the combination of ibrutinib and venetoclax in subjects with treatment-naive MCL **Secondary Objectives:** • To evaluate the overall response rate (ORR), the duration of response (DOR) and duration of CR • To evaluate the minimal residual disease (MRD)-negative remission rate in subjects who achieve CR who were MRD positive at screening

	• To evaluate progression-free survival (PFS), overall survival (OS), and time-to-next treatment (TTNT) with the combination of ibrutinib and venetoclax • To evaluate the frequency, severity, and relatedness of adverse events (AEs); frequency, severity and management of TLS; AEs requiring dose reductions and/or discontinuation of study drug, or leading to death • To determine the pharmacokinetics (PK) of ibrutinib and venetoclax **Exploratory Objectives:** • To evaluate biomarkers in relationship to efficacy outcomes • To evaluate whether the combination of ibrutinib and venetoclax will improve quality of life using a health-related quality of life questionnaire (EQ-5D-5L, etc.)
Study Design: 1. Safety Run-in Period 2. Randomization Phase 3. Treatment-naive Open-label Arm	This Phase 3 multinational, randomized, double-blind study is designed to compare the efficacy and safety of the combination of ibrutinib and venetoclax vs. ibrutinib and placebo in subjects with MCL. Approximately 287 subjects will be enrolled. In the treatment-naive open-label arm, approximately 75 subjects will be enrolled. **1. Safety Run-in Period** The study will start with an open-label Safety Run-in Period to evaluate the occurrence of tumor lysis syndrome (TLS) and DLTs with the concurrent administration of ibrutinib and venetoclax. TLS and DLT occurrence will be assessed during the venetoclax Ramp-up Period for a minimum of 5 weeks. Up to 27 subjects may be enrolled during the Safety Run-in Period (Figure 1): **Figure 1. Study Schematic – Safety Run-in Period**  PD = progressive disease; WC = withdrawal of consent **Tumor Lysis Syndrome (TLS) Categories** Two TLS risk categories will be evaluated separately and in parallel: • Increased 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 creatinine clearance (CrCl) < 60 mL/min. During the Safety Run-in Period, subjects at increased risk for TLS will be hospitalized for a minimum of 24 hours (and up to 48 hours at the discretion of the investigator) at the start of the 20 mg ramp-up dose and again at the start of the 50 mg ramp-up dose of venetoclax for monitoring and prophylaxis of TLS. • Low risk for TLS – Subjects not meeting the criteria described above

TLS events are defined as follows:

- Clinical TLS – any event that meets Howard criteria (Appendix G) with the following exceptions:
  - For the purpose of TLS assessment during the Safety Run-in 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

Dose-Limiting Toxicities (DLT)

A DLT is defined as any Grade 3 or higher non-TLS AE 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:

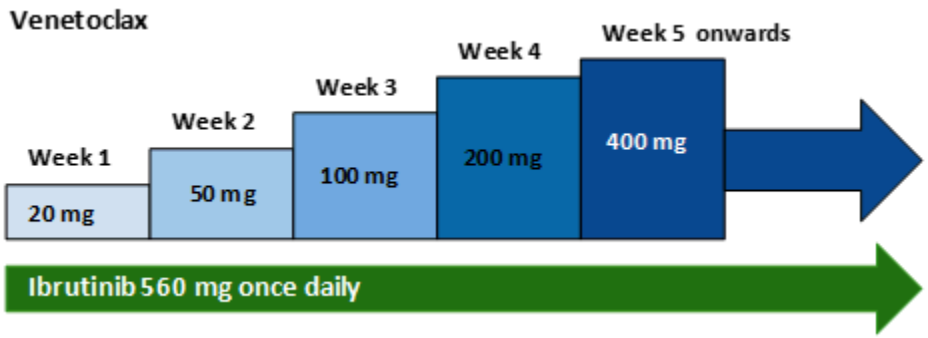
- Grade ≥ 3 nausea, vomiting or diarrhea uncontrolled despite maximum medical supportive care and persisting > 5 days
- Grade 3 fatigue persisting > 7 days
- Grade 3 infection is not a DLT, however an infection with life-threatening consequences or requiring urgent intervention (Grade 4) will be considered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

Initially, 6 subjects at low risk for TLS and 12 subjects at increased risk for TLS will receive ibrutinib at 560 mg once daily and venetoclax starting at 20 mg, and gradually ramped up to a target dose of 400 mg once daily over a 5-week period (see Figure 2 below). TLS events and DLTs will be assessed during the venetoclax Ramp-up Period for a minimum of 5 weeks.

Figure 2. Standard Ramp-up Schedule



Subjects at Low Risk for TLS

Evaluation of TLS

Three additional subjects will be dosed, if 1 out of 6 subjects at low risk for TLS experiences a laboratory TLS event and no subjects experience a clinical TLS event. If 0 out of 6 or ≤ 1 out of 9 subjects experience a laboratory TLS event and no subjects experience a clinical TLS event, the Randomization Phase will start using the standard ramp-up schedule for subjects at low risk for TLS.

If ≥ 2 out of 6-9 subjects at low risk for TLS experience a laboratory TLS event or any subject experiences a clinical TLS event, the Randomization Phase will start with a 4-week ibrutinib lead-in followed by the standard Ramp-up Schedule (Figure 2) for subjects in both TLS risk categories.

Evaluation of DLTs

With respect to DLTs, if < 2 out of 6 or < 3 out of 9 subjects experience DLT(s) during the DLT assessment period, the Randomization Phase will commence using the standard Ramp-up Schedule for subjects at low risk for TLS (Figure 2). However, if ≥ 3 out of 9 subjects experience DLT(s), the Randomization Phase will commence with a 4-week ibrutinib lead-in followed by the standard Ramp-up Schedule for subjects in both TLS risk categories (Figure 2).

The Safety Review Committee (SRC) will evaluate TLS and DLT data during the Safety Run-in Period prior to initiation of the Randomization Phase.

Subjects at Increased Risk for TLS

Evaluation of TLS

If < 3 out of the 12 subjects at increased risk for TLS experience a laboratory TLS event and no subjects experience a clinical TLS event, enrollment of increased-risk TLS subjects to the Randomization Phase will commence using the standard Ramp-up Schedule for subjects at increased risk for TLS (Figure 2).

However, if ≥ 3 out of the 12 increased risk subjects experience a laboratory TLS event or any of these subjects experience a clinical TLS event, at least 6 subjects at increased risk for TLS should be treated with the 4-week ibrutinib lead-in and assessed for safety either in an external study or within this study. If ≤ 2 out of these 6 subjects experience a laboratory TLS event and no subjects experience a clinical TLS event, the Randomization Phase will commence with a 4-week ibrutinib lead-in followed by the standard Ramp-up Schedule for subjects at increased risk of TLS (Figure 2).

Evaluation of DLTs

If < 4 out of the 12 subjects at increased risk for TLS experience DLT(s) during the DLT assessment period, the Randomization Phase will commence using the standard Ramp-up Schedule. However, if ≥ 4 out of the 12 subjects experience DLT(s), the Randomization Phase will commence with a 4-week ibrutinib lead-in followed by the standard Ramp-up Schedule for subjects at increased risk of TLS.

The SRC will evaluate TLS and DLT data during the Safety Run-in Period prior to the Randomization Phase.

Subjects in either TLS risk category who experience a laboratory or clinical TLS event will be managed according to standard institutional practice.

For subjects who experience laboratory TLS, dosing of venetoclax will be withheld per protocol and may be resumed when all laboratory abnormalities have returned to baseline. Dose reduction of venetoclax is not allowed for subjects enrolled in the Safety Run-in Period. Once venetoclax dosing is resumed, the applicable ramp-up week will re-start at the same dose level.

Those subjects incurring clinical TLS (regardless of TLS risk category) must be documented and discussed with the study medical monitor to determine whether the risk-benefit ratio justifies the subject remaining on study.

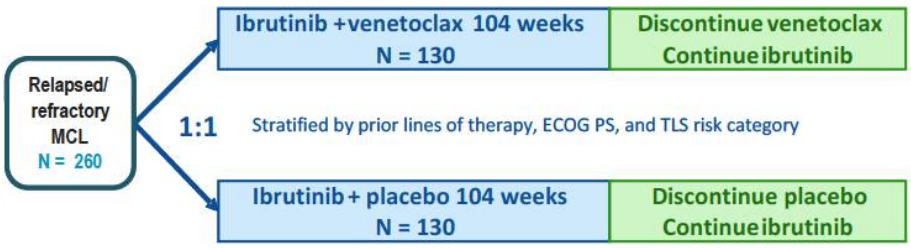
Subjects will be treated with ibrutinib and venetoclax for approximately 104 weeks followed by ibrutinib monotherapy until disease progression (PD), unacceptable toxicity or withdrawal of consent. Venetoclax will be discontinued after 104 weeks of treatment regardless of response assessment. Subjects who discontinue study treatment for any reason will be followed for progression (if not progressed before treatment discontinuation), subsequent anti-cancer therapy and survival status until study closure.

2. Randomization Phase

The Randomization Phase portion of the study will follow a randomized, double-blind design (Figure 3). Ibrutinib and venetoclax/placebo will be administered using the Standard Ramp-up Schedule.

Subject eligibility will be determined up to 28 days prior to randomization. Approximately 260 eligible subjects will be randomized at a 1:1 ratio to ibrutinib and venetoclax or ibrutinib and placebo. Randomization will be stratified by number of prior lines of therapy, ECOG performance status (PS), and by TLS risk category.

Figure 3. Randomization Phase Schematic



Initially, subjects at increased risk of TLS will be hospitalized for a minimum of 24 hours (and up to 48 hours at the discretion of the investigator) at the start of the 20 mg ramp-up dose and again at the start of the 50 mg ramp-up dose of venetoclax for monitoring and prophylaxis of TLS. The data monitoring committee (DMC) will review unblinded safety data during the course of the study to determine whether continued hospitalization of these subjects during ramp-up remains warranted.

Subjects will be treated with either ibrutinib and venetoclax or ibrutinib and placebo for approximately 104 weeks, followed by ibrutinib monotherapy until PD, unacceptable toxicity or withdrawal of consent. Venetoclax/placebo will be discontinued after 104 weeks of treatment, regardless of response assessment.

Subjects who discontinue study treatment for any reason will be followed for progression (if not progressed before treatment discontinuation), subsequent anticancer therapy, and survival status until study closure.

3. Treatment-naive Open-label Arm

A separate open-label arm is designed to explore the efficacy and safety of the combination of ibrutinib and venetoclax in subjects with treatment-naive MCL (Figure 5).

In the treatment-naive open-label arm, approximately 75 subjects will be enrolled and treated with ibrutinib 560 mg and venetoclax 400 mg. Among them, approximately 50 subjects ≥ 65 years and approximately 25 subjects with a TP53 mutation will be enrolled.

Ibrutinib and venetoclax will be administered using the 5-week ramp-up schedule shown in Figure 4. Treatment-naive MCL patients will use the same dose and schedule as established in the Safety Run-in for the Randomization Phase of the study. Therefore, there will be no Safety Run-in for the treatment-naive cohort.

Note: Sponsor may hold enrollment for patients in the treatment-naive open-label arm to ensure that at least 25 patients with a TP53 mutation are enrolled.

Figure 4. Venetoclax Ramp-up Schedule for Treatment-naive Open-label Arm

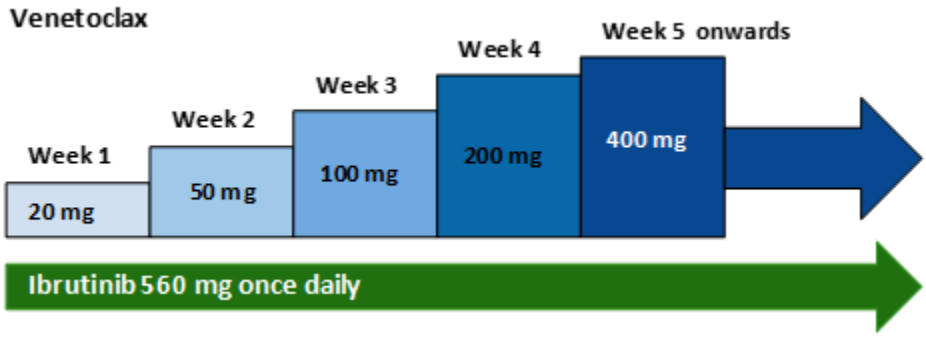


	Figure 5. Study Schema for Treatment-naive Open-label Arm  PD = progressive disease; WC = withdrawal of consent Subject eligibility will be determined up to 28 days prior to the first dose of study drug. Subjects in the protocol-defined increased risk for tumor lysis syndrome (TLS) group will be hospitalized for a minimum of 24 hours (and up to 48 hours at the discretion of the investigator) at the start of the 20 mg and 50 mg ramp-up dose of venetoclax for monitoring and prophylaxis of TLS; subjects in the low-risk for TLS group may be hospitalized at the discretion of the investigator. Subjects will be treated with ibrutinib and venetoclax for approximately 104 weeks (2 years), followed by ibrutinib monotherapy until PD, unacceptable toxicity or withdrawal of consent or study closure. Venetoclax will be discontinued after 104 weeks (2 years) of treatment, regardless of response assessment. CT and PET or PET/CT: A CT scan (with contrast unless contraindicated) of the neck, chest, abdomen, and pelvis and any other disease sites (eg, extremity) and a PET scan are required for the pretreatment tumor assessment within 28 days of the 1st dose. Thereafter, CT scans will be done for tumor assessments on Week 13 Day 1 (±7 days); every 12 weeks for the remainder of the 1st year; every 16 weeks during the 2nd and 3rd years; and every 24 weeks thereafter until PD. PET or PET/CT is mandatory for all subjects at the Week 13 visit (+/- 7 days), the Week 25 visit (+/- 7 days) for subjects in SD or PR who did not achieve CR at Week 13, and at the 1-year visit (Week 49 +/- 7 days) for all subjects, as well as at any other time point to confirm a CR. Other PET or PET/CT scans that are NOT mandatory can be performed within a 30-day window of the visit. Subjects who discontinue study treatment for any reason other than progressive disease will be followed for disease progression from the first dose of study drug every 12 weeks for the remaining of the 1st year; every 16 weeks during the 2nd and 3rd years; and every 24 weeks thereafter until subsequent anticancer therapy, and survival status until study closure.
Population:	**SRI and Randomization Phase:** Subjects with relapsed/refractory mantle cell lymphoma **Treatment-naive Open-label Arm:** Subjects with treatment-naive mantle cell lymphoma
Centers:	Multiple, US and ex-US

Inclusion Criteria: SRI and Randomization Phase) Refer to Section 4.1 for the complete and detailed list of inclusion/exclusion criteria.	*Disease-Related (see Section 4.1.1 for details)* • Pathologically confirmed MCL (in tumor tissue), with documentation of either overexpression of cyclin D1 in association with other relevant markers (eg, CD19, CD20, PAX5, CD5) or evidence of t(11;14) as assessed by cytogenetics, fluorescent in situ hybridization (FISH), or polymerase chain reaction (PCR) • At least 1 measurable site of disease 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 partial response (PR) with, or documented disease progression after, the most recent treatment regimen • Subjects must have adequate fresh or paraffin embedded tissue *Laboratory (see Section 4.1.1 for details)* • Adequate hematologic function • Adequate hepatic and renal function *Demographic* • Men and women ≥ 18 years of age • Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≤ 2
Exclusion Criteria: (SRI and Randomization Phase)	*Disease-Related (see Section 4.1.2 for details)* • History or current evidence of central nervous system lymphoma *Concurrent Conditions (see Section 4.1.2 for details)* • Concurrent enrollment in another therapeutic investigational study or prior therapy with ibrutinib or other BTK inhibitors • Prior treatment with venetoclax or other BCL2 inhibitors • Anticancer therapy including chemotherapy, radiotherapy, small molecule and investigational agents ≤ 21 days prior to receiving the first dose of study drug • Treatment with any of the following **within 7 days** prior to the first dose of study drug: o moderate or strong cytochrome P450 3A (CYP3A) inhibitors o moderate or strong CYP3A inducers
Inclusion Criteria: (Treatment-naive Open-label Arm)	1. Pathologically confirmed treatment-naive MCL (tumor tissue), with documentation of either overexpression of cyclin D1 in association with other relevant markers (eg, CD19, CD20, PAX5, CD5) or evidence of t(11;14), as assessed by cytogenetics, fluorescent in situ hybridization (FISH), or polymerase chain reaction (PCR). • A report from the local laboratory is acceptable if available; however, it must be reviewed and approved by the central pathology laboratory to verify the above criteria prior to enrollment. • If the report from the local laboratory is not available, a tumor block or slides must be sent to the central pathology laboratory for confirmation of the MCL diagnosis prior to enrollment

	2. Men and women ≥ 18 years of age with a TP53 mutation[1] 3. At least 1 measurable site of disease that is ≥ 2.0 cm in the longest diameter and measurable in 2 perpendicular dimensions per CT 4. Subjects must have adequate fresh or paraffin-embedded tissue 5. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≤ 2 6. Adequate hematologic function independent of transfusion and growth factor support for at least 7 days prior to first dose, with the exception of pegylated G-CSF (pegfilgrastim) and darbepoeitin which require at least 14 days prior to the first dose defined as: • Absolute neutrophil count (ANC) > 1000 cells/mm^3 (1.0 x 10^9/L) • Platelet count > 50,000 cells/mm^3 (50 x 10^9/L) • Hemoglobin > 8.0 g/dL 7. Adequate hepatic and renal function defined as: • Serum aspartate transaminase (AST) or alanine transaminase (ALT) ≤ 3.0 x upper limit of normal (ULN) • Estimated Creatinine Clearance (CrCl) ≥ 30 mL/min (Cockcroft-Gault) • Bilirubin ≤ 1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin) 8. Prothrombin time (PT) or International normal ratio (INR) < 1.5 x upper limit of normal (ULN) and PTT (activated partial thromboplastin time [aPTT]) < 1.5 x ULN (unless abnormalities are unrelated to coagulopathy or bleeding disorder). When treated with warfarin or other vitamin K antagonists, then INR ≤ 3.0 9. Male and female subjects of reproductive potential who agree to use both a highly effective method of birth control (eg, implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], complete abstinence[2], or sterilized partner) and a barrier method (eg, condoms, cervical ring, sponge, etc) during the period of therapy and for 90 days after the last dose of study drug
Exclusion Criteria: (Treatment-naive Open-label Arm)	1. Blastoid variant of MCL 2. History or current evidence of central nervous system lymphoma 3. Concurrent enrollment in another therapeutic investigational study or prior therapy, including ibrutinib or other BTK inhibitors 4. Prior treatment with venetoclax or other BCL2 inhibitors

[1] TP53 test by local or central lab

[2] Complete abstinence is a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.
http://www hma.eu/fileadmin/dateien/Human_Medicines/01
About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

	5. 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 6. Vaccinated with live, attenuated vaccines within 4 weeks of the first dose of study drug 7. Clinically significant infection requiring IV systemic treatment that was completed ≤ 14 days before the first dose of study drug 8. Any uncontrolled active systemic infection 9. Known bleeding disorders (eg, von Willebrand's disease or hemophilia) 10. History of stroke or intracranial hemorrhage within 6 months prior to enrollment 11. Known history of human immunodeficiency virus (HIV) or active with hepatitis C virus (HCV) or hepatitis B virus (HBV). Subjects who are positive for hepatitis B core antibody, or hepatitis C antibody must have a negative polymerase chain reaction (PCR) result before enrollment. Those who are hepatitis B surface antigen (HBsAg) or PCR positive will be excluded. 12. Major surgery within 4 weeks of the first dose of study drug. 13. Any 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 14. Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class 3 or 4 congestive heart failure as defined by the New York Heart Association Functional Classification; or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to randomization 15. Unable to swallow capsules or tablets, or 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 16. 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 (Appendix D) • Moderate or strong CYP3A inducers (Appendix D) 17. 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 18. Known allergy to xanthine oxidase inhibitors and/or rasburicase for subjects with known risk factors (as defined by high tumor burden and/or diminished renal function, as detailed in "Study Design" section above) for TLS

	19. Subjects with chronic liver disease with hepatic impairment Child-Pugh class B or C 20. Female subject who is pregnant, breastfeeding or is considering becoming pregnant during the study or for approximately 90 days after the last dose of study drug 21. Male subject who is considering fathering a child or donating sperm during the study or for approximately 90 days after the last dose of study drug 22. Unwilling or unable to participate in all required study evaluations and procedures 23. Unable to understand the purpose and risks of the study and to provide a signed and dated informed consent form (ICF) and authorization to use protected health information (in accordance with national and local subject privacy regulations) 24. Known hypersensitivity to the active ingredient or other components of one or more study drugs
Study Treatment: (Safety Run-in and Randomization Phase)	**Ibrutinib:** 560 mg of ibrutinib dosed orally once daily. Ibrutinib may be supplied either as 560 mg tablet (maximum of 1 tablet dosed once daily) or as 140 mg capsules (maximum of 4 capsules dosed once daily) **Venetoclax:** Orally once daily venetoclax started either concurrently with ibrutinib using the standard Ramp-up Schedule **Placebo:** Oral matching placebo for venetoclax started concurrently with ibrutinib using the standard Ramp-up Schedule
Study Treatment: (Treatment-naive Open-label Arm)	**Ibrutinib:** 560 mg of ibrutinib dosed orally once daily. Ibrutinib may be supplied either as a 560 mg tablet (maximum 1 tablet dosed once daily) or as 140 mg capsules (maximum of 4 capsules dosed once daily) ***Important: If using tablets, please ensure that patients do not take more than one 560 mg tablet per day.*** **Venetoclax:** Orally once daily venetoclax started concurrently with ibrutinib using the Venetoclax Standard Ramp-up Schedule (Figure 4).
Concomitant Therapy:	Caution is advised when administering moderate or strong CYP3A inhibitors or inducers or P-gp inhibitors. Refer to Section 6 for information on concomitant therapy.
Sample Size Determination: (SRI and Randomization Phase)	**Safety Run-in Period** Sample size determination for the Safety Run-in Period follows the standard dose escalation convention as described in the DLT and TLS assessment section. Up to 27 subjects may be enrolled in the Safety Run-in Period for evaluation.

	Randomization Phase The primary efficacy endpoint of PFS will be determined by investigator assessment. Approximately 260 subjects will be enrolled and randomized at a 1:1 ratio. With a targeted HR of 0.61 (corresponding to an improvement in median PFS from 14 months to 23 months), 134 PFS events will provide at least 80% power at a 1-sided overall significance level of 0.025. Overall survival will be analyzed at the time of the primary analysis of PFS when the superiority boundary for PFS is crossed. Details are presented in Section 10 of the protocol.
Sample Size Determination: (Treatment-naive Open-label Arm)	A sample size of 75 treatment-naive subjects is needed to exclude a 35% CR rate at a 1-sided significance level of 0.025 with approximately 80% power, assuming a target CR rate of 51%. For the subpopulation with a TP53 mutation, a sample size of 48 subjects is needed to exclude a 25% CR rate with approximately 80% power, assuming a target CR rate of 45%. The TP53 population could be a mix of treatment-naive MCL subjects and/or R/R MCL subjects with a TP53 mutation.
Statistical Methods/Data Analysis: **(SRI and Randomization Phase)**	Endpoints for the Safety Run-in Period will be summarized descriptively and separately from the Randomization Phase data. The primary endpoint in the Randomization Phase, PFS, will be compared between treatment arms using the stratified log-rank test. The hazard ratio will be estimated using a stratified Cox proportional hazard model. Details are presented in Section 10 of the protocol.
Statistical Methods/Data Analysis: (Treatment-naive Open-label Arm)	The CR rate is the primary endpoint for the open-label arm and will be estimated based on exact binomial distribution. The confidence interval will be provided. Details are presented in Section 10 of the protocol.

ABBREVIATIONS

AE	adverse event
AESI	Adverse Events of Special Interest (AESI)
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BCL-2	B-cell lymphoma 2
BCR	B-cell receptor
BCRP	Breast Cancer Resistance Protein
BTK	Bruton's tyrosine kinase
BUN	blood urea nitrogen
CI	confidence interval
CLL	chronic lymphocytic leukemia
C_{max}	maximum observed plasma concentration
CR	complete response rate
CrCl	creatinine clearance
CFR	Code of Federal Regulations
CRF	case report form (paper or electronic as appropriate for this study)
cGVHD	chronic graft vs. host disease
CMH	Cochran-Mantel-Haenszel
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLT	Dose-limiting toxicity
DMC	Data Monitoring Committee
DOR	duration of response
ECOG	Eastern Cooperative Oncology Group
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	electronic data capture
EMR	electronic medical records
EOT	End of treatment
EQ5-D	European Quality of Life- 5 Dimensions
EU	European Union
FDA	Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded tumor tissue
FL	follicular lymphoma
GCP	Good Clinical Practice
G-CSF	granulocyte colony-stimulating factor

HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDPE	high density polyethylene
HIV	human immunodeficiency virus
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
IV	Intravenous
IC_{50}	concentration that inhibits a process by 50%
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
ILD	Interstitial Lung Disease
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
LDH	lactate dehydrogenase
MCL	mantle cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MDS	myelodysplastic syndrome
MRD	minimal residual disease
MRI	Magnetic Resonance Imaging
MRU	Medical Resource Utilization
MTD	maximum tolerated dose
NCI-ODWG	National Cancer Institute Organ Dysfunction Working Group
NHL	Non-Hodgkin's Lymphoma
ORR	overall response rate
OS	overall survival
PCR	polymerase chain reaction
PD	progressive disease
PET	Positron Emission Tomography
PFS	Progression free survival
P-gp	P-glycoprotein
PK	Pharmacokinetics
PML	progressive multifocal leukoencephalopathy
PR	partial response
PRO	patient-reported outcome(s)
PS	performance status
aPTT	activated partial thromboplastin time
PT	prothrombin time
QTc	QT interval corrected for heart rate
REB	Research Ethics Board
RP3D	Recommended Phase 3 Dose

SAE	serious adverse event
SAP	Statistical Analysis Plan
SCARs	severe cutaneous adverse reactions
SJS	Stevens-Johnson syndrome
SLL	small lymphocytic lymphoma
SmPC	Summary of product characteristics
SRI	Safety Run-in
$t_{1/2}$	half-life
T_{max}	time to maximum plasma concentration
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
TN	treatment-naive
TTNT	time-to-next treatment
ULN	upper limit of normal
USPI	United States Prescribing Information
WC	withdrawal of consent

1 BACKGROUND

1.1 Mantle Cell Lymphoma

1.1.1 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 (Lennert 1981), MCL has subsequently been shown to harbor the translocation t(11,14)(q13;q32), which results in constitutive overexpression of cyclin D1 (Zucca 1994). These features are now considered requisite for the diagnosis of the disease.

Mantle cell lymphoma accounts for about 6-9% of all NHL cases in the Western world. The annual incidence of MCL has increased during recent decades to 1-2/100,000. MCL occurs more frequently in older adults (Zhou 2008). Most patients with MCL are men (median age: 65 years) who present with advanced stage disease (ie, Stage III or IV) and most cases follow an aggressive clinical course (Dreyling 2014). The typical presentation is with generalized lymphadenopathy, and extranodal involvement frequently occurs in the gastrointestinal 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) (Lenz 2004). There is no curative therapy for MCL. A few patients may achieve long-term, disease-free survival after allogeneic stem cell transplantation (Goy 2011), 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 (LDH) levels, performance status, and Ki-67 proliferative index (Hoster 2008).

1.1.2 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 PFS, while maintaining a favorable safety profile among patients with previously untreated MCL (Robinson 2008, Rummel 2005).

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. (Dreyling 2013, NCCN 2016). 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 FDA approved for previously treated patients with MCL in the US. In the European Union, approved treatment in the relapsed and refractory MCL setting was limited to temsirolimus until the approval of ibrutinib in 2014. Based on registration trials, the ORR for these drugs are 68% (21% CR) 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 (Campo 2015). These drugs are being combined with rituximab and incorporated into standard therapeutic and maintenance regimens showing some improved efficacy (Ghielmini 2009). Despite the fact that results from ibrutinib showed marked improvement over temsirolimus (Dreyling 2016), the median PFS of approximately 14 months underscores the need to improve further on the dismal outcome for relapsed MCL patients. However, new strategies are needed that may substantially improve outcomes for R/R MCL patients and may in long-term obviate intensive chemotherapy and/or transplantation in younger MCL patients and chemotherapy in older patients with MCL (Campo 2015). Based on the preliminary data showing a CR rate of 70% with an acceptable safety profile observed in an ongoing study of ibrutinib and venetoclax in patients with relapsed or refractory MCL (Tam 2016) 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 (Rule 2016, Gerecitano 2015), the combination of ibrutinib and venetoclax is expected to induce deep and durable responses in patients with relapsed/refractory MCL.

1.2 Ibrutinib Overview

Ibrutinib (IMBRUVICA®) is a first-in-class, potent, orally administered, covalently binding inhibitor of Bruton's tyrosine kinase (BTK) co-developed by Pharmacyclics LLC and Janssen Research & Development LLC for the treatment of B-cell malignancies.

Ibrutinib has been approved in many regions, including the United States (US) and European Union (EU), for indications including the treatment of patients with MCL who have received at least 1 prior therapy, patients with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) including CLL/SLL with a deletion of the short arm of chromosome 17 (del17p), patients with Waldenström's macroglobulinemia (WM), patients with marginal zone lymphoma (MZL) who require systemic therapy and have received at least one prior anti-CD20-based therapy, and cGVHD after failure of one or more lines of systemic therapy.

For the most up-to-date and comprehensive nonclinical and clinical information regarding ibrutinib background, safety, efficacy, in vitro and in vivo preclinical activity, and toxicology of ibrutinib, always refer to the latest version of the ibrutinib Investigator's Brochure (IB) and/or the applicable regional labeling information.

1.2.1 Summary of Nonclinical Data

1.2.1.1 Pharmacology

Ibrutinib was designed as a selective and covalent inhibitor of BTK (Pan 2007). In vitro, ibrutinib is a potent inhibitor of BTK activity (IC_{50} = 0.39 nM). The irreversible binding of ibrutinib to Cys-481 in the active site of BTK results in sustained inhibition of BTK catalytic activity and enhanced selectivity over other kinases that do not contain a cysteine at this position. When added directly to human whole blood, ibrutinib inhibits signal transduction from the BCR and blocks primary B-cell activation (IC_{50} = 80 nM) as assayed by anti-IgM stimulation followed by CD69 expression (Herman 2011).

Ibrutinib arrested cell growth and induced apoptosis in human B-cell lymphoma cell lines in vitro and inhibited tumor growth in vivo in xenograft models (Herman 2011). Ibrutinib also inhibited adhesion and migration of MCL cells in co-culture and reduced tumor burden in lymph node and bone marrow in a murine model of MCL dissemination and progression (Chang 2013a, Chang 2013b)

For more detailed and comprehensive information regarding nonclinical pharmacology, please refer to the current ibrutinib IB.

1.2.1.2 Safety Pharmacology and Toxicology

No treatment-related effects were observed in the central nervous system or respiratory system in rats at any dose tested. Further, no treatment-related corrected QT interval (QTc) prolongation effect was observed at any tested dose in a cardiovascular study using telemetry-monitored dogs. Based on data from rat and dog including general toxicity studies up to 13 weeks duration, the greatest potential for human toxicity with ibrutinib is predicted to be in lymphoid tissues (lymphoid depletion) and the gastrointestinal tract (soft feces/diarrhea with or without inflammation). Additional toxicity findings seen in only one species with no observed human correlate in clinical studies to date include pancreatic acinar cell atrophy (rat), minimally decreased trabecular and cortical bone (rat) and corneal dystrophy (dog). In studies in pregnant rats and rabbits, ibrutinib administration was associated with malformations (teratogenicity) at ibrutinib doses that result in approximately 14 and 2 times the exposure (area under the concentration-time curve [AUC]) in patients administered the dose of 560 mg daily, respectively. Fetal loss and reduced fetal body weights were also seen in treated pregnant animals. Carcinogenicity studies have not been conducted with ibrutinib. In vitro and in vivo genetic toxicity studies showed that ibrutinib is not genotoxic. No effects on fertility or reproductive capacities were observed in a study in male and female rats.

For the most up-to-date and comprehensive information regarding nonclinical safety pharmacology and toxicology, please refer to the current ibrutinib IB.

1.2.2 Summary of Clinical Data

1.2.2.1 Pharmacokinetics and Product Metabolism

Following oral administration of ibrutinib at doses ranging from 420 to 840 mg/day, exposure to ibrutinib increased proportionally with substantial inter-subject variability. The mean terminal plasma elimination half-life ($t_{1/2}$) of ibrutinib ranged from 4 to 13 hours, with a median time to maximum plasma concentration (T_{max}) of 2 hours. Despite the doubling in mean systemic exposure when dosed with food, the favorable safety profile of ibrutinib allows dosing with or without food. Ibrutinib is extensively metabolized primarily by cytochrome P450 (CYP) 3A4. The on-target effects of the main metabolite PCI-45227 are not considered clinically relevant. Steady-state exposure of ibrutinib and PCI-45227 was less than 2-fold of first dose exposure implying non-clinically relevant accumulation. Less than 1% of ibrutinib is excreted in the urine. Ibrutinib exposure is not altered in patients with creatinine clearance (CrCl) > 30 mL/min. Patients with severe renal impairment or patients on dialysis have not been studied. Following single-dose administration, the AUC of ibrutinib increased 2.7-, 8.2- and 9.8-fold in subjects with mild (Child-Pugh class A), moderate (Child-Pugh class B), and severe (Child-Pugh class C) hepatic impairment compared to subjects with normal liver function. A higher proportion of Grade 3 or higher adverse reactions were reported in patients with B-cell malignancies (CLL, MCL and WM) with mild hepatic impairment based on NCI organ dysfunction working group (NCI-ODWG) criteria for hepatic dysfunction compared to patients with normal hepatic function.

For the most recent and the most comprehensive information regarding pharmacokinetics (PK) and product metabolism, please refer to the current ibrutinib IB.

1.2.3 Summary of Clinical Safety

A brief summary of safety data from monotherapy and combination therapy studies is provided below. For the most up to date and most comprehensive safety information regarding ibrutinib, please refer to the current ibrutinib IB. Additional safety information may be available for approved indications in regional prescribing labels where the study is conducted (eg, USPI, SmPC).

1.2.3.1 Monotherapy Studies

Pooled safety data from a total of 1578 subjects treated with ibrutinib monotherapy in 20 studies in B-cell malignancies that have completed primary analysis or final analysis as of 12 November 2018 are summarized below.

The most frequently reported treatment-emergent adverse events (TEAEs) in subjects receiving ibrutinib as monotherapy (N=1578) included:

Most frequently reported TEAEs ≥15%	Most frequently reported Grade 3 or 4 TEAEs ≥3%	Most frequently reported Serious TEAEs ≥2%
Diarrhea	Neutropenia	Pneumonia
Fatigue	Pneumonia	Atrial fibrillation
Nausea	Thrombocytopenia	Pyrexia
Cough	Anemia	Febrile neutropenia
Anemia	Hypertension	
Pyrexia	Diarrhea	
Upper respiratory tract infection	Atrial fibrillation	
Neutropenia		
Oedema peripheral		
Thrombocytopenia		

1.2.3.2 Combination Studies

Pooled safety data from a total of 1449 subjects treated with various therapies in combination with ibrutinib from 13 studies conducted in subjects with B-cell malignancies are briefly summarized below. Therapies used in combination with ibrutinib in these studies included BR (bendamustine and rituximab), FCR (fludarabine, cyclophosphamide, and rituximab), ofatumumab, and R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone).

The most frequently reported TEAEs in subjects receiving ibrutinib in combination therapy (N=1449) included:

Most frequently reported TEAEs ≥20%	Most frequently reported Grade 3 or 4 TEAEs ≥3%	Most frequently reported Serious TEAEs ≥2%
Diarrhea	Neutropenia	Febrile neutropenia
Neutropenia	Anemia	Pneumonia
Nausea	Febrile neutropenia	Atrial fibrillation
Fatigue	Thrombocytopenia	Pyrexia
	Neutrophil count decreased	Anemia
		Neutropenia
Anemia	Pneumonia	
Thrombocytopenia	White cell count decreased	
	Leukopenia	
Pyrexia	Platelet count decreased	
	Diarrhea	
	Hypertension	
	Atrial fibrillation	
	Hyponatraemia	
	Diarrhea	

1.2.4 Risks

1.2.4.1 Bleeding-related Events

There have been reports of hemorrhagic events in subjects treated with ibrutinib, both with and without thrombocytopenia. These include minor hemorrhagic events such as contusion, epistaxis, and petechiae; and major hemorrhagic events, some fatal, including gastrointestinal bleeding, subdural intracranial hemorrhage, and hematuria. Subjects with congenital bleeding diathesis have not been studied.

In an in vitro platelet function study, inhibitory effects of ibrutinib on collagen-induced platelet aggregation were observed, refer to Section 6.2.4. Use of either anticoagulant or antiplatelet agents concomitantly with ibrutinib increases the risk of major bleeding. A higher risk for major bleeding was observed with anticoagulant than with antiplatelet agents. Consider the risks and benefits of anticoagulant or antiplatelet therapy when co-administered with ibrutinib. Monitor for signs or symptoms of bleeding. See Section 6.2.4 for guidance on concomitant use of anticoagulants, antiplatelet therapy and/or supplements.

Supplements such as fish oil and vitamin E preparations should be avoided. Ibrutinib should be held at least 3 to 7 days pre- and post-surgery, depending upon the type of surgery and the risk of bleeding. See Section 6.3 for guidance on ibrutinib management with surgeries or procedures. Subjects with congenital bleeding diathesis have not been studied.

1.2.4.2 Leukostasis

There were isolated cases of leukostasis reported in subjects treated with ibrutinib. A high number of circulating white blood cells (> 400,000/µL) may confer increased risk. For subject and ibrutinib management guidance, refer to Section 5.3.1.5.

1.2.4.3 Infections

Infections (including sepsis, bacterial, viral, or fungal infections) were observed in subjects treated with ibrutinib therapy. Some of these reported infections have been associated with hospitalization and death. Consider prophylaxis according to standard of care in patients who are at increased risk for opportunistic infections (see Section 6.1). Although causality has not been established, cases of progressive multifocal leukoencephalopathy (PML) have occurred in subjects treated with ibrutinib. Subjects should be monitored for symptoms (fever, chills, weakness, confusion), and appropriate therapy should be instituted as indicated.

1.2.4.4 Cytopenias

Treatment-emergent Grade 3 or 4 cytopenias (neutropenia, thrombocytopenia, and anemia) were reported in subjects treated with ibrutinib. Monitor complete blood counts monthly.

1.2.4.5 Interstitial Lung Disease (ILD)

Cases of interstitial lung disease (ILD) have been reported in subjects treated with ibrutinib. Monitor subjects for pulmonary symptoms indicative of ILD. If symptoms develop, interrupt ibrutinib and manage ILD appropriately. If symptoms persist, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines as needed (see Section 5.3.1.4).

1.2.4.6 Cardiac Arrhythmias and Cardiac Failure

Atrial fibrillation, atrial flutter, and cases of ventricular tachyarrhythmia and cardiac failure including some fatal events, have been reported in subjects treated with ibrutinib, particularly in subjects with cardiac risk factors, hypertension, acute infections, and a previous history of cardiac arrhythmia. At baseline and then periodically, monitor subjects clinically for cardiac arrhythmia and cardiac failure. Subjects who develop arrhythmic symptoms (eg, palpitations, lightheadedness, syncope, chest discomfort or new onset of dyspnea) should be evaluated clinically and, if indicated, have an ECG performed. For cardiac arrhythmias or cardiac failure which persist, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines (see Section 5.3.1.4).

1.2.4.7 Tumor Lysis Syndrome

Tumor lysis syndrome has been reported with ibrutinib therapy. Subjects at risk of tumor lysis syndrome are those with high tumor burden prior to treatment. Monitor subjects closely and take appropriate precautions.

1.2.4.8 Non-melanoma Skin Cancer

Non-melanoma skin cancers have occurred in subjects treated with ibrutinib. Monitor subjects for the appearance of non-melanoma skin cancer.

1.2.4.9 Lymphocytosis

Upon initiation of single agent treatment with ibrutinib, a reversible increase in lymphocyte counts (ie, ≥ 50% increase from baseline and an absolute count > 5,000/µL), often associated with reduction of lymphadenopathy, has been observed in most subjects (66%) with CLL/small lymphocytic lymphoma (SLL). This effect has also been observed in some subjects (35%) with MCL treated with ibrutinib. This observed lymphocytosis is a pharmacodynamic effect and should not be considered progressive disease in the absence of other clinical findings. In both disease types, lymphocytosis typically occurs during the first month of ibrutinib therapy and typically resolves within a median of 8 weeks in subjects with MCL and 14 weeks in subjects with CLL/SLL (range 0.1 to 104 weeks). When ibrutinib was administered in combination with BR or with obinutuzumab in subjects with CLL/SLL, lymphocytosis was infrequent (7% with ibrutinib + BR versus 6% with placebo + BR and 7% with ibrutinib + obinutuzumab versus 1%

with chlorambucil + obinutuzumab). Lymphocytosis was not observed with WM treated with ibrutinib.

For subject and ibrutinib management guidance, refer to Section 5.3.1.5.

1.2.4.10 Cerebrovascular Accidents

Although causality has not been established, cases of cerebrovascular accident, transient ischemic attack, and ischemic stroke including fatalities have been reported with the use of ibrutinib in the post-marketing setting, with and without concomitant atrial fibrillation and/or hypertension. Regular monitoring and appropriate treatment of conditions that can contribute to the occurrence of these events is recommended.

1.2.4.11 Diarrhea

Diarrhea is the most frequently reported non-hematologic AE with ibrutinib monotherapy and combination therapy. Other frequently reported gastrointestinal events include nausea, vomiting, and constipation. These events are rarely severe and are generally managed with supportive therapies including antidiarrheals and antiemetics. Subjects should be monitored carefully for gastrointestinal AEs and cautioned to maintain fluid intake to avoid dehydration. Medical evaluation should be made to rule out other etiologies such as *Clostridium difficile* or other infectious agents. Should symptoms be severe or prolonged follow the protocol dose modification guidelines (see Section 5.3.1.4).

1.2.4.12 Rash

Rash has been commonly reported in subjects treated with either single agent ibrutinib or in combination with chemotherapy. Rash occurred at a higher rate in the ibrutinib arm than in the ofatumumab arm in Study 1112. Most rashes were mild to moderate in severity. Isolated cases of severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) have been reported in subjects treated with ibrutinib. Subjects should be closely monitored for signs and symptoms suggestive of SCAR including SJS. Subjects receiving ibrutinib should be observed closely for rashes and treated symptomatically, including interruption of the suspected agent as appropriate. In addition, hypersensitivity-related events including erythema, urticaria, and angioedema have been reported.

1.2.4.13 Hypertension

Hypertension has been commonly reported in subjects treated with ibrutinib. Monitor subjects for new onset of hypertension or hypertension that is not adequately controlled after starting ibrutinib. Adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.

1.3 Venetoclax Overview

Venetoclax (VENCLEXTA®) is a potent, orally administered inhibitor of B-cell lymphoma 2 (BCL-2) co-developed by AbbVie Inc and Genentech Inc for the treatment of B-cell malignancies.

Venetoclax has been granted accelerated approval in the US based on overall response rate in the US for the treatment of patients with CLL with 17p deletion, as detected by an FDA approved test, who have received at least one prior therapy. In the EU, venetoclax in combination with rituximab is indicated for the treatment of adult patients with CLL who have received at least 1 prior therapy. Monotherapy is indicated for the treatment of CLL in the presence of 17p del or TP53 mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor, or in the absence of 17p del or TP53 mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor. Similarly, the Australian Therapeutic Goods Administration approved venetoclax for the treatment of patients with relapsed/refractory CLL with 17p deletion, and for patients without 17p deletion who have no other suitable treatment options.

The Bcl-2 family proteins are important regulators of the intrinsic apoptosis pathway. The Bcl-2 oncogene was first identified in follicular lymphoma (FL) where the t(14;18) chromosomal translocation results in significant over-expression of the protein in B-cells. The Bcl-2 family of genes encodes a family of closely related proteins that possess either pro-apoptotic or anti-apoptotic activity and share up to four Bcl-2 Homology (BH) domains (Willis 2003, Cory 2002, Borner 2003, Cory 2003). Bcl-2 overexpression is a major contributor to the pathogenesis of some types of lymphoid malignancies.

Venetoclax (also known as ABT-199) is a novel, orally available, small molecule Bcl-2 family protein inhibitor that binds with high affinity (Ki < 0.010 nM) to Bcl-2 and with lower affinity to other Bcl-2 family proteins Bcl- xL and Bcl-w (> 4,000-fold and > 2,000- to > 20,000-fold lower affinity than to Bcl-2, respectively) (Souers 2013). Selective inhibition by venetoclax disrupts Bcl-2 signaling and rapidly induces multiple hallmarks of apoptotic cell death in Bcl-2-dependent human tumor cell lines (venetoclax Investigator's Brochure [IB]). Importantly, venetoclax inhibition of Bcl-2 is independent of p53 activity.

1.3.1 Summary of Nonclinical Data

In vitro, venetoclax demonstrated broad cell killing activity against a panel of lymphoma and leukemia cells including B-cell follicular lymphomas (FLs), mantle cell lymphomas (MCLs), diffuse large B-cell lymphomas (DLBCLs), and acute myeloid leukemias (AMLs). Venetoclax was especially potent against cell lines expressing high levels of Bcl-2. Leukemia and lymphoma cell lines bearing the t(14;18) translocation were significantly more sensitive to venetoclax than nonmutated lines. A detailed discussion of the non-clinical toxicology, metabolism, and pharmacology can be found in the venetoclax IB.

1.3.2 Summary of Venetoclax Clinical Data

1.3.2.1 Clinical Pharmacokinetics

Following multiple oral administrations under fed conditions, maximum plasma concentration of venetoclax was reached 5-8 hours after dose. Venetoclax steady state AUC increased proportionally over the dose range of 150-800 mg. Food can increase venetoclax exposure (3.4-fold with a low-fat meal and 5.1- to 5.3-fold with a high-fat meal). Venetoclax should be administered with a meal. The population estimate for the terminal elimination half-life of venetoclax was approximately 26 hours. In vitro studies demonstrated that venetoclax is predominantly metabolized by CYP3A4/5. Less than 0.1% of venetoclax is excreted renally. Venetoclax exposures in subjects with mild or moderate renal impairment are similar to those with normal renal function. The PK of venetoclax has not been studied in subjects with severe renal impairment (CrCl < 30 mL/min) or subjects on dialysis. Venetoclax exposures are similar in subjects with mild and moderate hepatic impairment and normal hepatic function based on the NCI Organ Dysfunction Working Group criteria. Mild hepatic impairment was defined as normal total bilirubin and aspartate transaminase (AST) > upper limit of normal (ULN) or total bilirubin > 1.0 to 1.5 times ULN, moderate hepatic impairment as total bilirubin > 1.5 to 3.0 times ULN, and severe hepatic impairment as total bilirubin > 3.0 times ULN. The PK of venetoclax has not been studied in subjects with severe hepatic impairment.

For the most comprehensive information regarding PK and product metabolism, please refer to the current venetoclax IB.

1.3.2.2 Summary of Clinical Safety

Doses administered in venetoclax clinical studies have ranged from 20 mg to 1200 mg.

As of 28 November 2018, on the basis of open-label and unblinded data available in the clinical databases for company-sponsored studies in the venetoclax oncology development program, a total of 2543 adult subjects (1313 CLL/SLL, 361 AML, 218 MM, 570 NHL, and 59 MDS, 20 ALL, 1 rhabdomyosarcoma, and 1 Evans tumor in the pooled analysis dataset across all monotherapy and combination therapy oncology studies in the venetoclax development program have been exposed to at least 1 dose of venetoclax. An additional 20 pediatric subjects (< 18 years of age; 5 ALL, 10 AML, 3 neuroblastoma, other solid tumors) have been exposed to at least 1 dose of venetoclax.

As of 28 November 2018, a total of 576 NHL subjects treated with venetoclax in the oncology clinical program had open-label or unblinded safety data available, including 136 subjects who received venetoclax monotherapy, and 440 subjects who received venetoclax in combination with other agents including rituximab, BR, R-CHOP, or G-CHOP. Fifty additional subjects received BR in Study BO29337. Of the 576 NHL subjects treated with venetoclax, 570 subjects are included in the pooled analyses across all studies, and data from the remaining 6 subjects

who crossed over to venetoclax treatment in Study BO29337 are excluded from the pooled analyses.

Overall for NHL, when treated with venetoclax as a single agent or in combination with other therapies, the most common adverse events were nausea, neutropenia, and diarrhea. Approximately three-fourths of subjects experienced ≥ Grade 3 adverse events, and the most common events were neutropenia, thrombocytopenia, and anaemia. The most common SAEs were febrile neutropenia, neutropenia, and pneumonia. Of the fatal events in the NHL program, the majority were adverse events of malignant neoplasm progression. Findings from the analysis based on the exposure-adjusted incidence rates were consistent with the findings from the analysis based on the subject incidence rates. Many of the adverse events reported in the current NHL studies are consistent with underlying disease or concomitant medical conditions, as well as other combination agents used to treat NHL patients. Safety in combination agents appears to be consistent with that observed in monotherapy trials and combination backbone regimen.

The incidence of TLS in NHL studies is low with reports of 2 cases (1.9%) of laboratory TLS in monotherapy Study M12-175, 4 cases of laboratory TLS (2.5%) in combination Study BO29337 (1 subject venetoclax + R, 3 subjects venetoclax + BR), and 4 cases of laboratory TLS (1.5%) in combination Study GO27878 (venetoclax + R-CHOP or G-CHOP). All cases of TLS resolved, and none led to discontinuation of study drug. No cases of clinical TLS were reported. Neutropenia has a similar frequency in the NHL clinical program as in CLL with higher frequency in NHL combination studies. Serious adverse events of neutropenia and febrile neutropenia, albeit in small numbers, occurred in higher frequency in combination studies. Infections, including serious, were observed in the NHL clinical program, with similar incidence in monotherapy and combination studies.

For the most comprehensive venetoclax safety and efficacy data, please refer to the most current venetoclax IB.

1.3.3 Risks

1.3.3.1 Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is an important identified risk for venetoclax in oncology studies, especially in CLL and MCL. As a result of on-target effects, the potential for TLS was identified early in the program.

TLS in CLL and MCL

The risk is during the first 5 weeks of ramp-up period. A low starting dose followed by gradual dose ramp-up allows for the tumor size to be gradually reduced and has been effective in reducing the risk of TLS. Venetoclax should be initiated with the 20 mg dose and gradually ramp-up/titrate up to 400 mg target dose over 5 weeks. In general, before initiating venetoclax, a subject's risk for developing TLS should be assessed based on extent of disease, renal function, and known propensity and risk factors for TLS in that tumor type. Prophylaxis with hydration

and uric-acid reducing agents is recommended as appropriate. Clinical chemistries should be corrected. Choice of initial dose and ramp up to reach the final dose is based on the risk assessment in the indications. Monitor clinical chemistries and manage electrolyte abnormalities promptly, as clinically indicated.

1.3.3.2 Neutropenia

Neutropenia is an important identified risk for venetoclax. Clinical data from the oncology studies suggest that the neutropenia adverse events are observed among subjects who receive venetoclax as a single agent or in combination with other therapeutic agents, with slightly higher frequency observed in some combination studies. Serious adverse events of neutropenia or neutropenia events that lead to discontinuations are few across the entire venetoclax oncology program. For the oncology studies, neutropenia management guidelines are provided in the protocol. Granulocyte colony stimulating factors can be used for supportive measures, however the guidance for their use in non- CLL indications, especially in AML, is per routine local oncology practice, as well as protocol-specific.

1.3.3.3 Serious Infections

Serious infection is an important identified risk for venetoclax. Infections have been reported in the oncology clinical studies; however, these events are confounded by the underlying disease, comorbidities, and other immunosuppressive medications. To date, no clear relationship has been noted between serious infectious events and neutropenia. The types of infectious events observed generally have been consistent with those anticipated in the elderly population of heavily pretreated subjects with hematologic malignancies and are similar across all indications. Infections are closely monitored in venetoclax program across all indications. Patients should be advised to report fever and should be assessed for further management as per standard medical practice. In the oncology studies, recommendations are included in the protocol regarding the need for anti-infective prophylaxis per standard of care (eg, National Comprehensive Cancer Network guidelines [NCCN] for oncology subjects).

1.4 Study Rationale

1.4.1 Rationale for the Ibrutinib and Venetoclax Combination

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 (combo: 23%, ibrutinib: 3.8%, venetoclax: 3.0%) (Portell 2014). 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 BCL2 pathways (Zhao 2015) 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 (Zhao 2013).

With respect to venetoclax monotherapy activity, in clinical trial M12-175, venetoclax was tested in 28 subjects with relapsed/refractory MCL at target doses of 200 to 1200 mg. The ORR was found to be 75% with a CR rate of 21% (Gerecitano 2015). Based on these data and prior ibrutinib studies, the ongoing AIM Trial (ABT-199 and ibrutinib in MCL) is evaluating the combination of ibrutinib at 560 mg and venetoclax at a target dose of 400 mg in subjects with relapsed and refractory MCL. This study is using a 4-week venetoclax ramp-up after 4 weeks of ibrutinib monotherapy. Twenty-one subjects have completed response assessments at the primary endpoint landmark of 16 weeks; 10 subjects achieved confirmed CR (including MRD clearance), 4 subjects achieved unconfirmed CR, and 4 subjects achieved PR (Tam 2017). These results display a high initial response rate for the ibrutinib and venetoclax combination.

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 relapsed/refractory MCL have started enrollment, though no toxicity or safety data have yet been reported (Portell 2016, Le Gouill 2016).

1.4.2 Dose Rationale

As of 28 November 2015, safety data are available from 346 NHL subjects treated with venetoclax (128 from monotherapy studies and 218 from combination studies). The venetoclax Phase 1 dose escalation study M12-175 included 106 subjects with relapsed/refractory NHL treated in 8 dose cohorts with escalated doses from 100 mg to 1200 mg. The primary objectives of this study were to assess the safety profile, characterize the PK, and determine the maximum tolerated dose (MTD) of venetoclax monotherapy. Two dose-limiting toxicities (DLTs) (Grade 3 febrile neutropenia and Grade 4 neutropenia) were observed, both at the 600 mg dose level, and the MTD was not reached. The most frequent all-grade AEs were: nausea (46.1%), diarrhea (42.2%), fatigue (35.2%), and vomiting (20.3%), and the most frequent Grade ≥ 3 AEs were anemia (14.1%) and neutropenia (12.5%).

In the PCYC-1143-CA study, ibrutinib will be administered at 560 mg/day (approved dose for MCL) in combination with venetoclax at a target dose of 400 mg. This dose combination has previously been administered in an ongoing dose-escalation study in subjects with relapsed or refractory MCL (Portell 2016) with low/intermediate risk for TLS. In the AIM study using a 4-week venetoclax ramp-up (50, 100, 200 and 400 mg) after 4 weeks of ibrutinib monotherapy at 560 mg, 16 subjects with relapsed or refractory MCL (Tam 2017) were dosed and have completed the ramp-up with TLS events reported in two 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. Common AEs (≥ 25%) were diarrhea, fatigue, nausea and/or vomiting, upper respiratory tract infection, gastroesophageal reflux, neutropenia, cough, and dyspnea. The most frequent Grade 3-4 AE was neutropenia, and no Grade 5 AEs have been reported. The ORR was 71%, and the CR rate was 63%. All CR subjects were confirmed by PET, endoscopy (if baseline gut involvement was present) and bone marrow aspirate, including MRD clearance (assessed by flow cytometry with minimum sensitivity of 10^{-4}).

These preliminary data suggest that the combination had an acceptable safety profile without unexpected toxicities and resulted in high rates of deep remission.

1.4.3 Rationale for the Safety Run-in Period

Among the 106 subjects with relapsed/refractory NHL enrolled in the M12-175 study, 2 cases (1.9%) of laboratory TLS were observed during the Ramp-up Period at the 200 mg and 300 mg dose levels in subjects with bulky disease (tumor > 10 cm) with MCL (n=28) and DLBCL (n=41), respectively. To mitigate the risk of TLS observed in Cohort 1 in study M12-175, a Ramp-up Schedule of 3-4 weeks was used for subsequent cohorts.

The concurrent administration of ibrutinib and venetoclax in subjects at increased risk of TLS has not been investigated. In an ongoing dose-escalation study in subjects with relapsed/ refractory MCL (Portell 2016), the concurrent administration of 420 mg of ibrutinib and 400 mg of venetoclax to subjects with low/intermediate risk for TLS observed no cases of TLS, despite the fact that the ramp-up started at 100 mg of venetoclax and was only of 3 weeks duration (100, 200 and 400 mg). In the AIM MCL study, 560 mg of ibrutinib was administered 4 weeks prior to the administration of venetoclax. This was based on the rationale that the ibrutinib lead-in will reduce the risk of TLS. However, some subjects with high tumor burden did not respond to the ibrutinib lead-in and initiated venetoclax with increased, rather than reduced, tumor burden (Tam 2016). Therefore, given that the frequency of TLS in the setting of MCL has been reported to be low and to prevent early progression with single-agent ibrutinib, the concomitant administration of ibrutinib and venetoclax is warranted to initially evaluate the safety profile for the combination.

During the Safety Run-in Period, 12 subjects at increased risk for TLS (ie, subjects with high tumor burden and/or baseline creatinine clearance [CrCl] < 60 mL/min) and 6-9 subjects at low risk for TLS (not meeting these criteria) will receive ibrutinib at 560 mg plus venetoclax starting at 20 mg and ramped-up to a target dose of 400 mg over a 5-week period.

Depending on the number of TLS events and DLTs in each of the TLS risk categories, the Randomization Phase will start with either the concurrent administration of ibrutinib and venetoclax using the 5-week standard Ramp-up Schedule (see Section 3) or with a 4-week ibrutinib lead-in followed by the initiation of venetoclax using the 5-week standard Ramp-up Schedule.

During the Safety Run-in Period, subjects at increased risk for TLS will be hospitalized for a minimum of 24 hours (and up to 48 hours at the discretion of the investigator) at the start of the 20 mg ramp-up dose and again at the start of the 50 mg ramp-up dose of venetoclax for monitoring and prophylaxis of TLS. During the Randomization Phase, an independent Data Monitoring Committee (DMC) will review unblinded safety data to determine whether continued hospitalization of these subjects during ramp-up remains warranted.

1.4.4 Rationale for the Design of the Treatment Arms

The comparison between the ibrutinib and venetoclax combination with ibrutinib and placebo will evaluate the ability of the combined treatment to increase the complete response rate and progression-free survival (PFS) compared to ibrutinib monotherapy. Ibrutinib has shown a higher ORR and CR rate as monotherapy among treatments approved for relapsed or refractory MCL, (Campo 2015) and therefore serves as an appropriate control arm for this study.

1.4.5 Rationale for the PFS Assumption of 23 Months in the Ibrutinib and Venetoclax Relapsed/Refractory Treatment Arm

The primary endpoint in this study is PFS, with a null hypothesis of hazard ratio (HR) ≥ 1 for the ibrutinib and venetoclax group relative to ibrutinib and placebo group and an alternative hypothesis of HR of 0.61 corresponding to an improvement in median PFS from 14 months to 23 months. The PFS of 14 months for the ibrutinib + placebo group is based on results from previous studies with ibrutinib monotherapy in subjects with relapsed/refractory MCL (PCYC-1104-CA, MCL2001 and MCL3001), and the assumption of a PFS of 23 months for the ibrutinib and venetoclax group is based on the 24-month PFS rate estimated from subjects who achieved a CR in these studies.

In the pooled analysis of ibrutinib studies PCYC-1104-CA, MCL2001 and MCL3001, the ORR and CR rate were 65.7% and 20.0%, respectively. Importantly, the estimated 24-month PFS was 70% in the subjects who achieved a CR, compared to 19% in subjects who failed to achieve a CR (Rule 2016). In the venetoclax phase I trial, the CR rate in subjects with MCL was 21% (Gerecitano 2015), and no subjects with CR had experienced relapse. Therefore, based on these studies, subjects with a CR are likely to have better PFS. In addition, based on the preliminary efficacy results of the AIM study (Tam 2016, Tam 2017) for ibrutinib and venetoclax treatment, if the CR rate in the 1143 trial exceeds 55%, then under the exponential distribution assumption for PFS, the median PFS with the combination is predicted to be ≥ 23 months.

1.4.6 Rationale for MRD Testing

The prognostic impact of MRD was analyzed in 259 patients with MCL treated within 2 randomized trials of the European MCL Network (MCL Younger and MCL Elderly trial). After rituximab-based induction treatment, 106 of 190 evaluable patients (56%) achieved MRD negativity (by allele specific RT-PCR with sensitivity of at least 10^{-4}) based on blood and/or

bone marrow (BM) analysis. MRD negativity resulted in a significantly improved duration of response (DOR 87% vs 61% patients in remission at 2 years, P = 0.004) (Pott 2010).

Whether MRD-negative remissions with non-chemo regimens will also translate into improved clinical outcomes in MCL is not yet known. The prognostic significance of MRD negativity by flow cytometry and clonoSEQ will be assessed. The correlation between assays and the correlation between peripheral blood and bone marrow MRD findings will also be determined.

1.4.7 Rationale for Treatment-naive Open-label Arm, Inclusion of Patients with a TP53 Mutation and Exclusion of Blastoid Variant

In the AIM study that included 24 patients with relapsed/refractory MCL (23 patients) or treatment-naive MCL with a TP53 mutation (1 patient), patients were treated open-label with ibrutinib 560 mg and venetoclax 400 mg (Tam 2018). Patients had a median age of 68 years and had received 0 - 6 prior lines of therapy. Fifty percent of patients (n=12) had aberrations of TP53. The complete response rate according to PET was 62% at Week 16 (primary endpoint) and 71% overall. For patients with a TP53 mutation, the CR rate was 50% with and without PET, and the ORR was 58% without PET and 50% with PET. MRD clearance was confirmed by flow cytometry in 67% of patients. In a time-to-event analysis, 78% of the patients with a response were estimated to have an ongoing response at 15 months (Tam 2018). Tumor lysis syndrome occurred in 2 patients. Common side effects were generally low grade and included diarrhea (in 83% of patients), fatigue (in 75%), and nausea or vomiting (in 71%). In this study and compared to historical controls, treatment with ibrutinib and venetoclax was consistent with improved outcomes in patients with MCL who had been predicted to have poor outcomes with current therapy (Tam 2018). Based on these encouraging results including 1 treatment-naive MCL patient with a TP53 mutation who responded, it is of interest to explore the combination of ibrutinib and venetoclax in treatment-naive MCL in patients that are ≥ 65 years of age and transplant-ineligible and in patients with a TP53 mutation. In treatment-naive MCL, the standard of care for patients that are ≥ 65 years of age and transplant-ineligible is BR or a variety of other options based on fitness level. The reported overall response rates with different therapeutic approaches for treatment-naive MCL patients with varying fitness levels (BR, R-CHOP, VR-CHOP, VR-CAP, FCR, R-CHOP/R-DHAP, R-Hyper CVAD) vary from 75 – 94% (Flinn 2014, Lenz 2005, Robak 2015, Kluin-Nelemans 2012, Hermine 2016, Rummel 2014, Chen 2017, Merli 2012, Rummel 2013, Rummel 2017); the corresponding CR rates vary from 35 – 72%, and for BR, one of the most commonly used therapies used in the transplant-ineligible and less fit treatment-naive MCL population, are approximately around 50% (Flinn 2014, Rummel 2005, Rummel 2014, Chen 2017, Rummel 2017). Based on the encouraging results in patients with a TP53 mutation, it is of interest to explore the combination of ibrutinib and venetoclax in treatment-naive MCL in patients with a TP53 mutation, which is a population that is chemo-insensitive and therefore has limited treatment options (Eskelund 2017, Delfau-Larue 2015, Halldorsdottir 2011, Ferrero 2017, Obr 2018). For patients with a TP53 mutation, the available literature focuses on PFS and OS outcomes (Eskelund 2017, Delfau-Larue 2015, Halldorsdottir 2011, Ferrero 2017, Obr 2018), and CR rates are underreported; it is hypothesized

that CR rates for MCL with a TP53 mutation are below the CR rates around 50% reported for BR in treatment-naive MCL. In the AIM study (Tam 2018), the CR rate for subjects with TP53 aberrations (mutations and deletions, n=12) is 50%; in the PHILEMON study, where R/R MCL patients received a combination of ibrutinib, rituximab and lenalidomide, similar proportions of patients with and without a TP53 mutation had an overall response and CR; when correcting for other prognostic factors, no PFS difference was seen between patients with and without a TP53 mutation (Jerkeman 2018). These encouraging data support the use of ibrutinib and venetoclax in patients with a TP53 mutation.

The randomized portion for R/R MCL has a PFS endpoint. For treatment-naive MCL, the endpoint of CR rate was chosen, also considering the small sample size (n=75). Durable CRs may represent clinical benefit and can be assessed earlier (compared to PFS).

In summary, exploring the combination of ibrutinib and venetoclax in treatment-naive MCL patients with or without a TP53 mutation is of interest with the goal to explore CR rates and other efficacy and safety parameters that can be achieved with this combination in comparison with historical CR rates and efficacy and safety data.

The R/R MCL population in this study is inclusive of MCL patients with blastoid variant; blastoid variant and MCL with a TP53 mutation are considered high-risk MCL populations. Since favorable outcomes in younger/fit/transplant-eligible patients with blastoid variant were observed with high-dose chemotherapy, high-dose consolidation and stem cell transplant (Dreyling 2018), contrasting young/fit/transplant-eligible patients with TP53 mutations who do not benefit from intensive chemotherapy and often relapse early (Eskelund 2017, Delfau-Larue 2015), MCL patients with blastoid variant are excluded from the open-label treatment-naive arm, and the focus is on the population with a TP53 mutation as the high-risk group for treatment-naive subjects.

1.4.8 Sample Size Considerations for Treatment-naive Open-label Arm Including Patients with a TP53 Mutation

A sample size of 75 treatment-naive subjects is needed to exclude a 35% CR rate at a 1-sided significance level of 0.025 with approximately 80% power, assuming a target CR rate of 51%.

For the subpopulation with a TP53 mutation, a sample size of 48 subjects is needed to exclude a 25% CR rate with approximately 80% power, assuming a target CR rate of 45%. The TP53 population could be a mix of treatment-naive MCL subjects and/or R/R MCL subjects with a TP53 mutation.

Based on a historical CR rate of approximately 50% with BR (Flinn 2014, Rummel 2005, Rummel 2014, Chen 2017, Rummel 2017) in transplant-ineligible treatment-naive MCL subjects, the success criteria were set at excluding a CR rate of 40% for the transplant-ineligible treatment-naive MCL patients ≥ 65 years. Since the CR rates for MCL patients with TP53 mutations are estimated to be lower (Eskelund 2017), the success criteria were set at excluding a

25% CR rate for the MCL patients with a TP53 mutation. In combination, for the entire cohort of 75 treatment-naive MCL patients, which contain at least one third of patients (n=25) with a TP53 mutation, the success criteria were set at excluding a 35% CR rate.

2 STUDY OBJECTIVES

2.1 Safety Run-in Period

2.1.1 Primary Objective

To evaluate the occurrence of TLS and DLTs with the concurrent administration of ibrutinib and venetoclax.

2.1.2 Secondary Objectives

To evaluate response (partial and complete response), PFS, DOR, and OS.

2.2 Randomization Phase

2.2.1 Primary Objective

To evaluate whether the combination of ibrutinib and venetoclax will result in prolongation of PFS compared to ibrutinib and placebo in subjects with relapsed or refractory MCL.

2.2.2 Secondary Objectives

- To evaluate whether the combination of ibrutinib and venetoclax will increase the CR rate, the overall response rate (ORR), the minimal residual disease (MRD) negative remission rate in subjects who were MRD positive at screening and achieve CR, OS, DOR, and time-to-next treatment (TTNT) compared to ibrutinib and placebo.
- To evaluate the frequency, severity, and relatedness of AEs; frequency, severity and management of TLS; AEs requiring dose reductions and/or discontinuation of study drug, or leading to death.
- To determine the PK of ibrutinib and venetoclax.
- To evaluate whether the combination of ibrutinib and venetoclax will improve quality of life using a Health-related quality of life questionnaire (FACT-Lym) compared to ibrutinib and placebo.

2.2.3 Exploratory Objectives

- To determine the prognostic significance of MRD negative remission by comparing the correlation to the efficacy outcomes in the two treatment arms.
- To evaluate whether the combination of ibrutinib and venetoclax will decrease MRD positive relapse in subjects who achieve MRD negative remission compared to ibrutinib and placebo.
- To evaluate the correlation of MRD negative remission in blood vs. bone marrow.
- To evaluate the correlation of MRD negative remission determined by flow cytometry and clonoSEQ.
- To evaluate PFS2: time from randomization to death or next disease progression (defined as the earliest of disease progression after the first subsequent anti-cancer therapy or start of the second subsequent therapy).
- To identify alterations in genes or proteins associated with sensitivity or resistance to the ibrutinib and venetoclax combination.
- To evaluate patient-reported outcomes as measured by European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire EuroQoL Five-Dimension (EQ-5D-5L)
- To evaluate medical resource utilization (MRU) (eg, requirements of hospitalizations, emergency department visits, transfusions, and use of hematopoietic growth factors)

2.3 Treatment-naive Open-label Arm

2.3.1 Primary Objective

To evaluate the complete response (CR) rate with the combination of ibrutinib and venetoclax in subjects with treatment-naive MCL

2.3.2 Secondary Objectives

- To evaluate the overall response rate (ORR), the duration of response (DOR) and duration of CR
- To evaluate the minimal residual disease (MRD)-negative remission rate in subjects who were MRD positive at screening and achieve CR
- To evaluate progression-free survival (PFS), overall survival (OS), and time-to-next treatment (TTNT) with the combination of ibrutinib and venetoclax
- To evaluate the frequency, severity, and relatedness of adverse events (AEs); frequency, severity and management of TLS; AEs requiring dose reductions and/or discontinuation of study drug, or leading to death
- To determine the pharmacokinetics (PK) of ibrutinib and venetoclax

2.3.3 Exploratory Objectives

- To evaluate biomarkers in relationship to efficacy outcomes
- To evaluate whether the combination of ibrutinib and venetoclax will improve quality of life using a health-related quality of life questionnaire (EQ-5D-5L)

3 STUDY DESIGN

3.1 Overview of Study Design

This Phase 3 multinational, randomized, double-blind study is designed to compare the efficacy and safety of the combination of ibrutinib and venetoclax vs. ibrutinib and placebo in subjects with MCL.

Approximately up to 287 subjects with R/R MCL will be enrolled.

A separate open-label arm is designed to explore the efficacy and safety of the combination of ibrutinib and venetoclax in subjects with treatment-naive MCL.

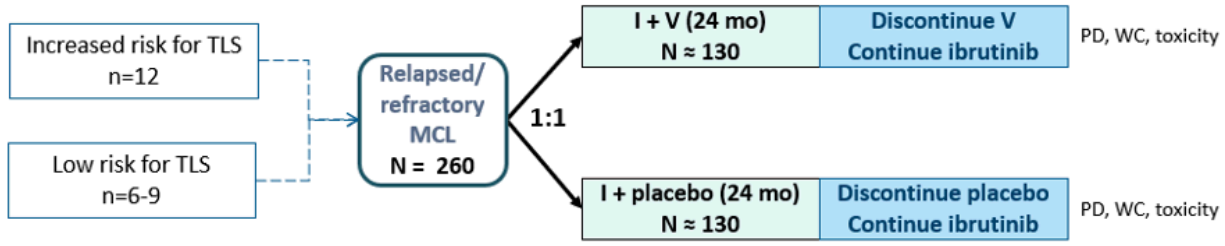
In the treatment-naive open-label arm, approximately 75 subjects will be enrolled and treated with ibrutinib 560 mg and venetoclax 400 mg. Among them, approximately 50 subjects ≥ 65 years and approximately 25 subjects with a TP53 mutation will be enrolled. Treatment-naive MCL patients will use the same dose and schedule as established in the Safety Run-in for the Randomization Phase of the study. Therefore, there will be no Safety Run-in for the treatment-naive cohort.

3.1.1 Safety Run-in Period

The study will start with an open-label Safety Run-in Period to evaluate the occurrence of TLS and DLTs with the concurrent administration of ibrutinib and venetoclax. TLS and DLT occurrence will be assessed during the venetoclax Ramp-up Period for a minimum of 5 weeks.

Up to 27 subjects may be enrolled during the Safety Run-in Period (Figure 6).

Figure 6. Study Schematic – Safety Run-in Period



PD = progressive disease; WC = withdrawal of consent

Tumor Lysis Syndrome (TLS) Categories

Two TLS risk categories will be evaluated separately and in parallel:

- Increased 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 creatinine clearance (CrCl) < 60 mL/min. During the Safety Run-in Period, subjects at increased risk for TLS will be hospitalized for a minimum of 24 hours (and up to 48 hours at the discretion of the investigator) at the start of the 20 mg ramp-up dose and again at the start of the 50 mg ramp-up dose of venetoclax for monitoring and prophylaxis of TLS.
- Low risk for TLS – Subjects not meeting the criteria described above.

TLS events are defined as follows:

- Clinical TLS – any event that meets Howard criteria (Appendix G) with the following exceptions:
  - For the purpose of TLS assessment during the Safety Run-in 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.

Dose-Limiting Toxicity (DLT)

A DLT is defined as any Grade 3 or higher non-TLS AE 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:

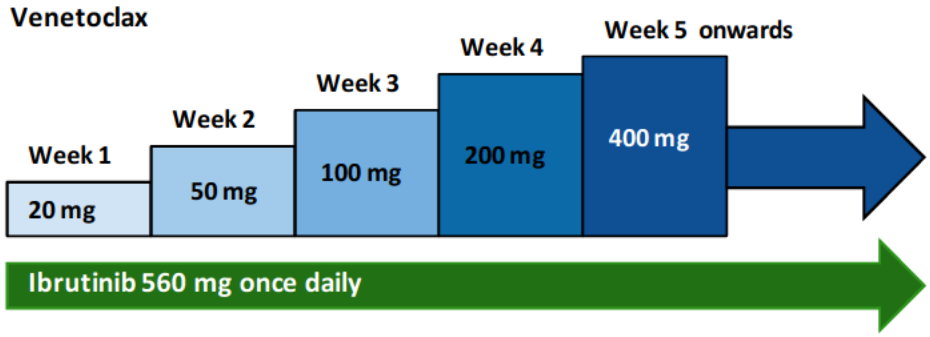
- Grade ≥ 3 nausea, vomiting or diarrhea uncontrolled despite maximum medical supportive care and persisting > 5 days
- Grade 3 fatigue persisting > 7 days
- Grade 3 infection is not a DLT, however an infection with life-threatening consequences or requiring urgent intervention (Grade 4) will be considered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

Initially, 6 subjects at low risk for TLS and 12 subjects at increased risk for TLS will receive ibrutinib at 560 mg once daily and venetoclax starting at 20 mg and gradually ramped up to a target dose of 400 mg once daily over a 5-week period (see Figure 7 below). TLS events and DLTs will be assessed during the venetoclax Ramp-up Period for a minimum of 5 weeks.

Figure 7. Standard Ramp-up Schedule



Subjects at Low Risk for TLS

Evaluation of TLS

Three additional subjects will be dosed if 1 out of 6 subjects at low risk for TLS experiences a laboratory TLS event and no subjects experience a clinical TLS event. If 0 out of 6 or ≤ 1 out of 9 subjects experience a laboratory TLS event and no subjects experience a clinical TLS event, the Randomization Phase will start using the standard Ramp-up Schedule for subjects at low risk for TLS.

If ≥ 2 out of 6-9 subjects at low risk for TLS experience a laboratory TLS event, or any subject experiences a clinical TLS event, the Randomization Phase will start with a 4-week ibrutinib lead-in followed by the standard Ramp-up Schedule (Figure 7) for subjects in both TLS risk categories.

Evaluation of DLTs

With respect to DLTs, if < 2 out of 6 or < 3 out of 9 subjects experience DLT(s) during the DLT assessment period, the Randomization Phase will commence using the standard Ramp-up Schedule for subjects at low risk for TLS (Figure 7). However, if ≥ 3 out of 9 subjects experience DLT(s), the Randomization Phase will commence with a 4-week ibrutinib lead-in followed by the standard Ramp-up Schedule for subjects in both TLS risk categories (Figure 7).

The Safety Review Committee (SRC) will evaluate TLS and DLT data after 6-9 subjects in the low TLS risk category have completed the TLS/DLT assessment period (the Ramp-up Period with a minimum of 5 weeks). Members of SRC will include the Sponsor (Medical Monitor or designee, Drug Safety Representative and Biostatistician) as well as participating investigators.

Subjects at Increased Risk for TLS

Evaluation of TLS

With respect to TLS only, if < 3 out of the 12 subjects at increased risk for TLS experience a laboratory TLS event and no subjects experience a clinical TLS event, enrollment of increased-risk TLS subjects to the Randomization Phase will commence using the standard Ramp-up Schedule for subjects at increased risk for TLS (Figure 7).

However, if ≥ 3 out of the 12 increased risk subjects experience a laboratory TLS event or any of these subjects experience a clinical TLS event, at least 6 subjects at increased risk for TLS should be treated with the 4-week ibrutinib lead-in and assessed for safety in either in an external study or within this study. If ≤ 2 out of these 6 subjects experience a laboratory TLS event and no subjects experience a clinical TLS event, the Randomization Phase will commence with a 4-week ibrutinib lead-in followed by the standard Ramp-up Schedule for subjects at increased risk of TLS (Figure 7).

Evaluation of DLTs

With respect to DLTs, if < 4 out of the 12 subjects at increased risk for TLS experience DLT(s) during the DLT assessment period, the Randomization Phase will commence using the standard Ramp-up Schedule. However, if ≥ 4 out of the 12 subjects experience DLT(s), the Randomization Phase will commence with a 4-week ibrutinib lead-in followed by the standard Ramp-up Schedule for subjects at increased risk of TLS.

The SRC will evaluate TLS and DLT data after all 12 subjects in the increased TLS risk category have completed the TLS and DLT assessment period prior to the Randomization Phase, and if required, after an additional 6 subjects have completed the TLS and DLT assessment period (the Ramp-up Period with a minimum of 5 weeks) after the 4-week ibrutinib lead-in.

Subjects in either TLS risk category who experience a laboratory or clinical TLS event will be managed according to standard institutional practice.

For subjects who experience laboratory TLS, dosing of venetoclax will be withheld per protocol and may be resumed when all laboratory abnormalities have returned to baseline. Dose reduction of venetoclax is not allowed for subjects enrolled in the Safety Run-in Period. Once venetoclax dosing is resumed, the applicable ramp-up week will re-start at the same dose level.

Those subjects incurring clinical TLS (regardless of TLS risk category) must be documented and discussed with the study medical monitor to determine whether the risk-benefit ratio justifies the subject remaining on study.

Subjects will be treated with ibrutinib and venetoclax for approximately 104 weeks followed by ibrutinib monotherapy until PD, unacceptable toxicity or withdrawal of consent. Venetoclax will be discontinued after 104 weeks of treatment regardless of response assessment.

Subjects who discontinue study treatment for any reason will be followed for progression (if not progressed before treatment discontinuation), subsequent anti-cancer therapy and survival status until study closure.

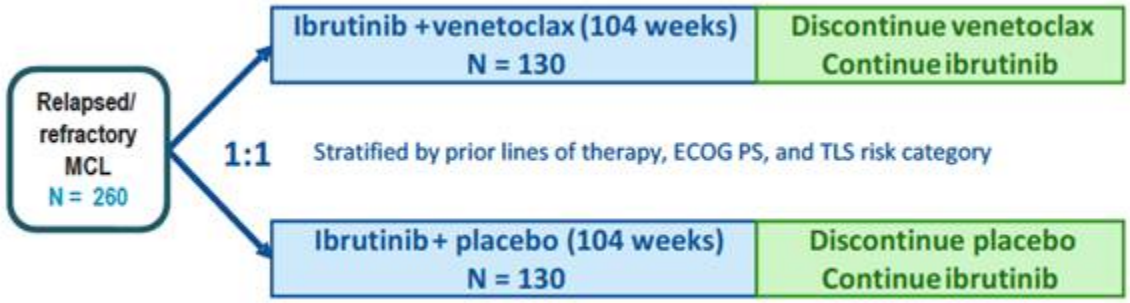
3.1.2 Randomization Phase

The Randomization Phase portion of the study will follow a randomized, double-blind design. Ibrutinib and venetoclax/placebo will be administered using the Ramp-up Schedule that was determined to be appropriate for each TLS risk category. The Data Monitoring Committee (DMC) will review the safety recommendations made by the SRC and will be responsible for giving recommendations on continuing, modifying, or stopping the Randomization Phase of the trial (Figure 8).

Subject eligibility will be determined up to 28 days prior to randomization. Approximately 260 eligible subjects will be randomized at a 1:1 ratio to ibrutinib and venetoclax or ibrutinib and

placebo. Randomization will be stratified by number of prior lines of therapy, ECOG PS, and by TLS risk category.

Figure 8. Randomization Phase Schematic



Initially, subjects at increased risk of TLS will be hospitalized for a minimum of 24 hours (and up to 48 hours at the discretion of the investigator) at the start of the 20 mg ramp-up dose and again at the start of the 50 mg ramp-up dose of venetoclax for monitoring and prophylaxis of TLS. The DMC will review unblinded safety data during the course of the study to determine whether continued hospitalization of these subjects during ramp-up remains warranted.

Subjects will be treated with either ibrutinib and venetoclax or ibrutinib and placebo for approximately 104 weeks, followed by ibrutinib monotherapy until PD, unacceptable toxicity or withdrawal of consent. Venetoclax/placebo will be discontinued after 104 weeks of treatment regardless of response assessment.

Subjects who discontinue study treatment for any reason will be followed for progression (if not progressed before treatment discontinuation), subsequent anti-cancer therapy, and survival status until study closure.

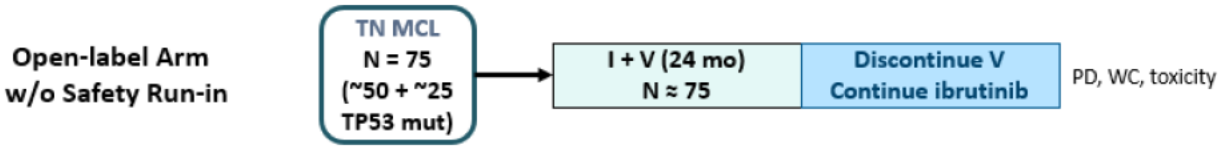
The independent Data Monitoring Committee (DMC) will review unblinded safety data including all deaths and any progression associated with safety 6-9 months after initiation of the Randomization Phase to evaluate the safety of the combination of ibrutinib and venetoclax and to confirm continued dosing with the combination is warranted. In addition, the DMC will review TLS data in the course of the study to ascertain whether the continued hospitalization of subjects with high tumor burden and/or creatinine clearance < 60 mL/min during ramp-up is needed. The make-up of the DMC, responsibilities, authorities, and procedure will be detailed in a separate DMC charter.

The rationale for the study concept is provided in Section 1.4.

3.1.3 Treatment-naive Open-label Arm

In the treatment-naive open-label arm, approximately 75 subjects will be enrolled and treated with ibrutinib 560 mg and venetoclax 400 mg. Among them, approximately 50 subjects ≥ 65 years and approximately 25 subjects with a TP53 mutation will be enrolled (Figure 9).

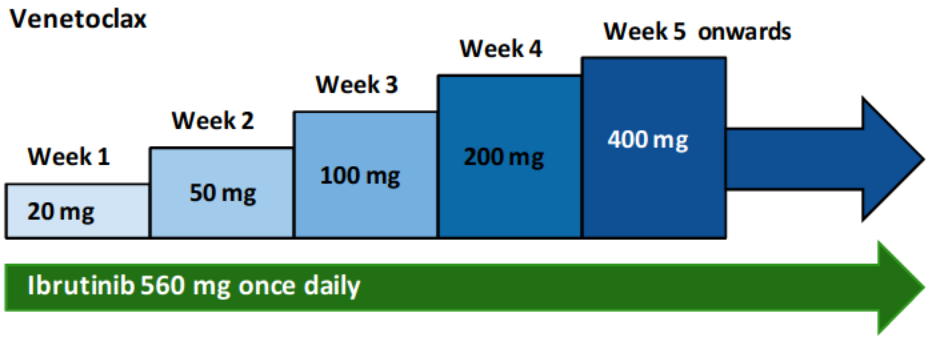
Figure 9. Study Design: Treatment-naive Open-label Arm



w/o = without; PD = progressive disease; WC = withdrawal of consent

Ibrutinib and venetoclax will be administered using the 5-week ramp-up schedule shown in Figure 10. Treatment-naive MCL patients will use the same dose and schedule as established in the Safety Run-in for the Randomization Phase of the study. Therefore, there will be no Safety Run-in for the treatment-naive cohort. *Note: Sponsor may hold enrollment for patients in the treatment-naive open-label arm to ensure that at least 25 patients with a TP53 mutation are enrolled.*

Figure 10. Venetoclax Standard Ramp-up Schedule



Subject eligibility will be determined up to 28 days prior to first dose of study treatment.

Subjects in the protocol-defined increased-risk for tumor lysis syndrome (TLS) group will be hospitalized for a minimum of 24 hours (and up to 48 hours at the discretion of the investigator) at the start of the 20 mg and 50 mg ramp-up dose of venetoclax for monitoring and prophylaxis of TLS; subjects in the low-risk for TLS group may be hospitalized at the discretion of the investigator.

Subjects will be treated with ibrutinib and venetoclax for approximately 104 weeks (2 years), followed by ibrutinib monotherapy until PD, unacceptable toxicity or withdrawal of consent or study closure. Venetoclax will be discontinued after 104 weeks (2 years) of treatment, regardless of response assessment.

CT and PET or PET/CT: A CT scan (with contrast unless contraindicated) of the neck, chest, abdomen, and pelvis and any other disease sites (eg, extremity) and a PET scan are required for the pretreatment tumor assessment within 28 days of the 1st dose. Thereafter, CT scans will be done for tumor assessments on Week 13 Day 1 (±7 days); every 12 weeks for the remainder of the 1st year; every 16 weeks during the 2nd and 3rd years; and every 24 weeks thereafter until PD. PET or PET/CT is mandatory for all subjects at the Week 13 visit (+/- 7 days), the Week 25 visit (+/- 7 days) for subjects in SD or PR who did not achieve CR at Week 13, and at the 1-year visit (Week 49 +/- 7 days) for all subjects, as well as at any other time point to confirm a CR. Other PET or PET/CT scans that are NOT mandatory can be performed within a 30-day window of the visit. For MRI refer to Section 7.1.3.2.

Subjects who discontinue study treatment for any reason will be followed for disease progression, subsequent anticancer therapy, and survival status until study closure.

4 SUBJECT SELECTION

4.1 Eligibility Criteria for SRI and Randomization Phase

4.1.1 Inclusion Criteria

Prior to enrollment, each potential subject must satisfy all of the following inclusion criteria. These criteria must continue to be met by the subject prior to first dose of study treatment.

Disease-Related

1. Pathologically confirmed MCL (tumor tissue), with documentation of either overexpression of cyclin D1 in association with other relevant markers (eg, CD19, CD20, PAX5, CD5) or evidence of t(11;14), as assessed by cytogenetics, fluorescent in situ hybridization (FISH), or polymerase chain reaction (PCR)
    - A report from the local laboratory is acceptable if available; however, it must be reviewed and approved by the central pathology laboratory to verify the above criteria prior to randomization (for Randomization Phase subjects only).
    - If the report from the local laboratory is not available prior to randomization (for Randomization Phase subjects only), the tumor block or slides must be sent to the central pathology laboratory for confirmation of the MCL diagnosis.
2. At least 1 measurable site of disease that is ≥ 2.0 cm in the longest diameter and measurable in 2 perpendicular dimensions per CT
3. At least 1, but no more than 5, prior treatment regimens for MCL including at least 1 prior rituximab/anti-CD20 containing regimen
4. Failure to achieve at least partial response (PR) with, or documented disease progression after, the most recent treatment regimen
5. Subjects must have adequate fresh or paraffin embedded tissue (Section 7.1.3.4).

Laboratory

6. Adequate hematologic function independent of transfusion and growth factor support for at least 7 days prior to first dose (Safety Run-in Period) or to randomization (for the Randomization Phase), with the exception of pegylated G-CSF (pegfilgrastim) and darbepoeitin which require at least 14 days prior to the first dose (Safety Run-in Period) or to randomization (for the Randomization Phase), defined as:
    - Absolute neutrophil count (ANC) > 1000 cells/mm^3 (1.0 x 10^9/L)
    - Platelet count > 50,000 cells/mm^3 (50 x 10^9/L)
    - Hemoglobin > 8.0 g/dL

Note: Subjects in the Randomization Phase with bone marrow involvement may be enrolled without meeting the above hematologic function criteria after documented discussion with the medical monitor.

7. Adequate hepatic and renal function defined as:
    - Serum aspartate transaminase (AST) or alanine transaminase (ALT) ≤ 3.0 x upper limit of normal (ULN)
    - Estimated Creatinine Clearance (CrCl) ≥ 30 mL/min (Cockcroft-Gault)
    - Bilirubin ≤ 1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin)
8. Prothrombin time (PT)/International normal ratio (INR) < 1.5 x upper limit of normal (ULN) and PTT (activated partial thromboplastin time [aPTT]) < 1.5 x ULN (unless abnormalities are unrelated to coagulopathy or bleeding disorder). When treated with warfarin or other vitamin K antagonists, then INR ≤ 3.0.

Demographic

9. Men and women ≥ 18 years of age
10. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≤ 2

Ethical/Other

11. Male and female subjects of reproductive potential who agree to use both a highly effective method of birth control (eg, implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], complete abstinence[3], or sterilized partner) and a barrier method (eg, condoms, cervical ring, sponge, etc) during the period of therapy and for 90 days after the last dose of study drug.

4.1.2 Exclusion Criteria

To be enrolled in the study, potential subjects must meet NONE of the following exclusion criteria (These criteria must continue to be not met by the subject until first dose of study treatment):

Disease-Related

1. History or current evidence of central nervous system lymphoma

Concurrent Conditions

2. Concurrent enrollment in another therapeutic investigational study or prior therapy with ibrutinib or other BTK inhibitors
3. Prior treatment with venetoclax or other BCL2 inhibitors
4. Anticancer therapy including chemotherapy, radiotherapy, small molecule and investigational agents ≤ 21 days (or at least 5 drug half-lives, whichever is shorter) prior to first administration of study treatment and/or monoclonal antibody ≤ 3weeks (or at least 5 drug half-lives, whichever is shorter) prior to receiving the first dose of study drug
5. 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
6. Vaccinated with live, attenuated vaccines within 4 weeks of the first dose of study drug

[3] Complete abstinence is a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. http://www hma.eu/fileadmin/dateien/Human_Medicines/01 About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

7. Clinically significant infection requiring IV systemic treatment that was completed ≤ 14 days before the first dose of study drug
8. Any uncontrolled active systemic infection
9. Unresolved toxicities from prior anticancer therapy, defined as having not resolved to Common Terminology Criteria for Adverse Event (CTCAE, v4.03), Grade 0 or 1, or to the levels dictated in the inclusion/exclusion criteria with the exception of alopecia
10. Known bleeding disorders (eg, von Willebrand's disease or hemophilia)
11. History of stroke or intracranial hemorrhage within 6 months prior to enrollment
12. Prior stem cell transplant that requires ongoing immunosuppressive therapy or clinical graft vs host disease (GVHD)
13. Known history of human immunodeficiency virus (HIV) or active with hepatitis C virus (HCV) or hepatitis B virus (HBV). Subjects who are positive for hepatitis B core antibody, hepatitis B surface antigen (HBsAg), or hepatitis C antibody must have a negative polymerase chain reaction (PCR) result before enrollment. Those who are PCR positive will be excluded.
14. Major surgery within 4 weeks of the first dose of study drug.
15. Any 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
16. Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class 3 or 4 congestive heart failure as defined by the New York Heart Association Functional Classification; or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to randomization
17. Unable to swallow capsules or tablets, or 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
18. 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 (see Appendix D for examples)
    - moderate or strong CYP3A inducers (see Appendix D for examples)
19. 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
20. Known allergy to xanthine oxidase inhibitors and/or rasburicase for subjects with known risk factors (as defined by high tumor burden and/or diminished renal function, as detailed in "Study Design" section above) for TLS

21. Subjects with chronic liver disease with hepatic impairment Child-Pugh class B or C (Appendix F)
22. Female subject who is pregnant, breastfeeding or is considering becoming pregnant during the study or for approximately 90 days after the last dose of study drug
23. Male subject who is considering fathering a child or donating sperm during the study or for approximately 90 days after the last dose of study drug
24. Unwilling or unable to participate in all required study evaluations and procedures
25. Unable to understand the purpose and risks of the study and to provide a signed and dated informed consent form (ICF) and authorization to use protected health information (in accordance with national and local subject privacy regulations)
26. Known hypersensitivity to the active ingredient or other components of one or more study drugs

4.2 Eligibility Criteria for the Treatment-naive Open-label Arm

4.2.1 Inclusion Criteria for the Treatment-naive Open-label Arm

1. Pathologically confirmed treatment-naive MCL (tumor tissue), with documentation of either overexpression of cyclin D1 in association with other relevant markers (eg, CD19, CD20, PAX5, CD5) or evidence of t(11;14), as assessed by cytogenetics, fluorescent in situ hybridization (FISH), or polymerase chain reaction (PCR)
    - A report from the local laboratory is acceptable if available; however, it must be reviewed and approved by the central pathology laboratory to verify the above criteria prior to enrollment
    - If the report from the local laboratory is not available, a tumor block or slides must be sent to the central pathology laboratory for confirmation of the MCL diagnosis prior to enrollment
2. Men and women ≥ 18 years of age with a TP53 mutation[4]
3. At least 1 measurable site of disease that is ≥ 2.0 cm in the longest diameter and measurable in 2 perpendicular dimensions per CT
4. Subjects must have adequate fresh or paraffin-embedded tissue
5. Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≤ 2
6. Adequate hematologic function independent of transfusion and growth factor support for at least 7 days prior to first dose, with the exception of pegylated G-CSF (pegfilgrastim) and darbepoeitin which require at least 14 days prior to the first dose defined as:
    - Absolute neutrophil count (ANC) > 1000 cells/mm^3 (1.0 x 10^9/L)

[4] TP53 test by local or central lab

- Platelet count > 50,000 cells/mm^3 (50 x 10^9/L)
- Hemoglobin > 8.0 g/dL

7. Adequate hepatic and renal function defined as:
    - Serum aspartate transaminase (AST) or alanine transaminase (ALT) ≤ 3.0 x upper limit of normal (ULN)
    - Estimated Creatinine Clearance (CrCl) ≥ 30 mL/min (Cockcroft-Gault)
    - Bilirubin ≤ 1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin)
8. Prothrombin time (PT) or International normal ratio (INR) < 1.5 x upper limit of normal (ULN) and PTT (activated partial thromboplastin time [aPTT]) < 1.5 x ULN (unless abnormalities are unrelated to coagulopathy or bleeding disorder). When treated with warfarin or other vitamin K antagonists, then INR ≤ 3.0
9. Male and female subjects of reproductive potential who agree to use both a highly effective method of birth control (eg, implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], complete abstinence[5], or sterilized partner) and a barrier method (eg, condoms, cervical ring, sponge, etc) during the period of therapy and for 90 days after the last dose of study drug

4.2.2 Exclusion Criteria for the Treatment-naive Open-label Arm

1. Blastoid variant of MCL
2. History or current evidence of central nervous system lymphoma
3. Concurrent enrollment in another therapeutic investigational study or prior therapy, including ibrutinib or other BTK inhibitors
4. Prior treatment with venetoclax or other BCL2 inhibitors
5. 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

[5] Complete abstinence is a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject. http://www hma.eu/fileadmin/dateien/Human_Medicines/01 About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

6. Vaccinated with live, attenuated vaccines within 4 weeks of the first dose of study drug
7. Clinically significant infection requiring IV systemic treatment that was completed ≤ 14 days before the first dose of study drug
8. Any uncontrolled active systemic infection
9. Known bleeding disorders (eg, von Willebrand's disease or hemophilia)
10. History of stroke or intracranial hemorrhage within 6 months prior to enrollment
11. Known history of human immunodeficiency virus (HIV) or active with hepatitis C virus (HCV) or hepatitis B virus (HBV). Subjects who are positive for hepatitis B core antibody, or hepatitis C antibody must have a negative polymerase chain reaction (PCR) result before enrollment. Those who are hepatitis B surface antigen (HBsAg) or PCR positive will be excluded.
12. Major surgery within 4 weeks of the first dose of study drug.
13. Any 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
14. Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class 3 or 4 congestive heart failure as defined by the New York Heart Association Functional Classification; or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to randomization
15. Unable to swallow capsules or tablets, or 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
16. 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 (Appendix D)
    - Moderate or strong CYP3A inducers (Appendix D)
17. 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
18. Known allergy to xanthine oxidase inhibitors and/or rasburicase for subjects with known risk factors (as defined by high tumor burden and/or diminished renal function, as detailed in "Study Design" section above) for TLS
19. Subjects with chronic liver disease with hepatic impairment Child-Pugh class B or C
20. Female subject who is pregnant, breastfeeding or is considering becoming pregnant during the study or for approximately 90 days after the last dose of study drug

21. Male subject who is considering fathering a child or donating sperm during the study or for approximately 90 days after the last dose of study drug
22. Unwilling or unable to participate in all required study evaluations and procedures
23. Unable to understand the purpose and risks of the study and to provide a signed and dated informed consent form (ICF) and authorization to use protected health information (in accordance with national and local subject privacy regulations)
24. Known hypersensitivity to the active ingredient or other components of one or more study drugs

5 TREATMENT OF SUBJECTS

5.1 Treatment Allocation and Blinding

5.1.1 Safety Run-in Period

Up to 27 subjects may be enrolled during the Safety Run-in Period. Initially, 6-9 subjects at low risk for TLS and 12 subjects at increased risk for TLS will receive ibrutinib at 560 mg once daily and open-label venetoclax at a starting dose of 20 mg once daily and gradually ramped up to a target dose of 400 mg once daily over a 5-week period. TLS events and DLT occurrence will be assessed during the venetoclax Ramp-up Period for a minimum of 5 weeks. Depending on the occurrence of TLS events and DLTs, a minimum of 6 additional subjects at increased risk for TLS may be treated with the 4-week ibrutinib lead-in during the Safety Run-in Period.

Subjects dosed in the Safety Run-in Period will continue on open-label ibrutinib at 560 mg once daily and open-label venetoclax at a target dose of 400 mg for up to approximately 104 weeks, followed by ibrutinib monotherapy until disease progression, unacceptable toxicity or withdrawal of consent.

5.1.2 Randomization Phase

The Randomization Phase portion of the study will follow a randomized, double-blind design. After written informed consent has been obtained and eligibility has been established, the study site will obtain the subject's identification number and treatment assignment from the Interactive Response Technology (IRT) System.

5.1.2.1 Randomization

Approximately 260 eligible subjects will be randomized at a 1:1 ratio to ibrutinib and venetoclax or ibrutinib and placebo treatment arms. Randomization will be stratified by number of prior lines of therapy (1-2, ≥ 3), ECOG PS (0-1, 2), and by TLS category (low risk, increased risk for TLS). Subjects will be dosed within 3 days of randomization.

Subjects will continue treatment with either ibrutinib and venetoclax or ibrutinib and placebo for at least 104 weeks, followed by ibrutinib monotherapy until PD, unacceptable toxicity or

withdrawal of consent. Venetoclax/placebo will be discontinued after 104 weeks of treatment, regardless of response assessment.

A stratified, permuted-block randomization will be implemented in order to obtain a balanced assignment to each treatment within levels of the stratification factors.

5.1.2.2 Blinding

Subjects, investigators, and the Sponsor's study team members will remain blinded to treatment assignment. The investigator will not be provided with randomization codes nor the treatment received. The codes will be maintained within the IRT System, which has the functionality to allow the investigator to break the blind for an individual subject if necessary to appropriately manage or treat the subject. Data that may potentially unblind the treatment assignment (ie, study drug plasma concentrations) will be handled with special care to ensure that the integrity of the blind is maintained and the potential for bias is minimized.

Telephone contact with the Sponsor or its designee will be available 24 hours per day, 7 days per week. In the event the blind is broken, the Sponsor must be informed as soon as possible. The date and time of the unblinding must be documented within the IRT System, in the appropriate section of the eCRF and in the source document. The confirmation received from the IRT System indicating the code break must be retained with the subject's source documents in a secure manner. A subject whose treatment assignment has been unblinded may continue the study treatment if the subject is expected to continue to receive clinical benefit. The subject should continue to return for scheduled study visits. The single-blind (ie, subject remains blinded to treatment assignment) should be maintained, provided the subject's safety is not compromised.

5.1.3 Replacement of Subjects

Subjects who miss ≥ 20% of the planned doses of ibrutinib or venetoclax for reasons other than toxicity (eg, non-compliance, withdrawal of consent, disease progression) during the TLS and DLT assessment period (venetoclax ramp-up during the Safety Run-in Period), or subjects who do not complete the TLS and DLT assessment period for any reason other than TLS or a DLT will be replaced.

Randomized subjects will not be replaced in the Randomization Phase.

5.1.4 Treatment-naive Open-label Arm

In the treatment-naive open-label arm, approximately 75 subjects will be enrolled and treated with ibrutinib 560 mg and venetoclax 400 mg. Among them, approximately 50 subjects ≥ 65 years and approximately 25 subjects with a TP53 mutation will be enrolled. Ibrutinib and venetoclax will be administered using the 5-week ramp-up schedule.

Subject eligibility will be determined up to 28 days prior to the first dose of study drug.

After written informed consent has been obtained and eligibility has been established, the study site will obtain the subject's identification number from the Interactive Response Technology (IRT) System.

Subjects in the protocol-defined increased-risk for tumor lysis syndrome (TLS) group will be hospitalized for a minimum of 24 hours (and up to 48 hours at the discretion of the investigator) at the start of the 20 mg and 50 mg ramp-up dose of venetoclax for monitoring and prophylaxis of TLS; subjects in the low-risk for TLS group may be hospitalized at the discretion of the investigator.

Subjects will be treated with ibrutinib and venetoclax for approximately 104 weeks (2 years), followed by ibrutinib monotherapy until PD, unacceptable toxicity or withdrawal of consent. Venetoclax will be discontinued after 104 weeks (2 years) of treatment, regardless of response assessment.

Subjects who discontinue study treatment for any reason will be followed for disease progression, subsequent anticancer therapy, and survival status until study closure.

5.2 Study Treatment

5.2.1 SRI and Randomized Phase

Ibrutinib

- Orally once daily ibrutinib 560 mg (4 x 140 mg capsules OR 1 x 560 mg tablet) continuously

Note: Dose modification of ibrutinib for AEs is specified in Section 5.3.1.4, Section 5.3.1.6, and Section 6.2.1.1.

Important: If using tablets, please ensure that patients do not take more than one 560 mg tablet per day.

Venetoclax

- Orally once daily venetoclax at a target dose of 400 mg (4 X 100 mg)

Note: Dose modification of venetoclax/placebo for AEs is specified in Section 5.3.2.5 and Section 6.2.1.2.

Placebo

- Oral once daily matching placebo for venetoclax at a target dose of 400 mg (4 X 100 mg)

Note: Dose modification of venetoclax/placebo for AEs is specified in Sections 5.3.2.5 and Section 6.2.1.2.

5.2.2 Treatment-naive Open-label Cohort

Ibrutinib

- Orally once daily ibrutinib 560 mg (4 x 140 mg capsules OR 1 x 560 mg tablet) continuously

Note: Dose modification of ibrutinib for AEs is specified in Section 5.3.1.4, Section 5.3.1.6, and Section 6.2.1.1.

Important: If using tablets, please ensure that patients do not take more than one 560 mg tablet per day.

Venetoclax

- Orally once daily venetoclax at a target dose of 400 mg (4 X 100 mg) dosed concurrently with ibrutinib

Note: Dose modification of venetoclax/placebo for AEs is specified in Section 5.3.2.5 and Section 6.2.1.2.

5.3 Study Medication

5.3.1 Ibrutinib

5.3.1.1 Formulation/Packaging/Storage

Ibrutinib is provided either as hard gelatin capsules each containing 140 mg of ibrutinib, or as film coated tablets each containing 560 mg of ibrutinib. All formulation excipients are compendial and are commonly used in oral formulations. Refer to the ibrutinib IB for a list of excipients.

The ibrutinib capsules will be packaged in opaque high-density polyethylene plastic bottles with labels bearing the appropriate label text as required by governing regulatory agencies and child-resistant packaging. The ibrutinib tablets 560 mg will be packaged in blisters.

Refer to the Pharmacy Manual/site investigational product manual for additional guidance on dose modifications for subjects on ibrutinib tablets, study drug storage, preparation and handling.

Study drug labels will contain information to meet the applicable regulatory requirements.

5.3.1.2 Dose and Administration

Ibrutinib 560 mg (4 x 140 mg capsules or 1 x 560 mg tablet) is administered orally once daily. The ibrutinib capsules or tablet are/is to be taken with venetoclax/placebo tablets at approximately the same time each day with a meal and water. The capsules or tablet should be swallowed intact and subjects should not attempt to open capsules, break the tablet or dissolve

them in water. The use of strong CYP3A inhibitors/inducers, and grapefruit and Seville oranges should be avoided for the duration of the study (Appendix D).

If a dose is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The subject should not take extra capsules to make up the missed dose.

For subjects starting with the concurrent administration of ibrutinib and venetoclax using the standard Ramp-up Schedule, ibrutinib will be delivered in the clinic on Days 1, 2 (all subjects) and 3 (hospitalized subjects) of Weeks 1 and 2; on Days 1 of the remaining weeks during the venetoclax Ramp-up Period (see Section 8.2); and on the PK sample collection day (see Section 7.1.4.1 and Section 7.1.4.2). Otherwise, ibrutinib dosing is typically done on an outpatient basis.

Ibrutinib will be dispensed to subjects at each dispensing visit. Study drug may not be shipped to the subject without approval from the Sponsor and may not be dispensed to anyone other than the subject. Unused ibrutinib dispensed during previous visits must be returned to the site and drug accountability records (Section 12.8) updated at each visit. Returned drug must not be redispensed to anyone and must not be destroyed without prior written approval of Clinical Monitor/CRA and /or the Sponsor. Study drugs can only be destroyed after full accountability and reconciliation by the Clinical Monitor/CRA unless required by local institutional policy.

5.3.1.3 Overdose

There is no specific experience in the management of ibrutinib overdose in patients. No MTD was reached in the Phase 1 study in which subjects received up to 12.5 mg/kg/day (1400 mg/day). Healthy subjects were exposed up to a single dose of 1680 mg. One healthy subject experienced reversible Grade 4 hepatic enzyme increases (AST and ALT) after a dose of 1680 mg. Subjects who ingested more than the recommended dosage should be closely monitored and given appropriate supportive treatment.

Refer to Section 11.3 for further information regarding special reporting situations as a result of overdose.

5.3.1.4 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 1 and Table 2 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. See Section 6.1 for instructions regarding the use of growth factor support.

- 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 2 recommendations for Grade 3 or greater cardiac failure and cardiac arrhythmias)
- Grade 2 cardiac failure (Table 2)
- Any other Grade 4 or unmanageable Grade 3 toxicity

If clinically indicated, the use of anticoagulants or antiplatelet agents may be considered for the thromboprophylaxis of atrial fibrillation (Section 6.2.4 and Section 1.2.4.6).

For other AEs including grade 2 AEs that are deemed per the investigator potentially manageable by dose reduction, these can be managed with a one dose level dose reduction.

In the event that the investigator feels deviation from the recommendations above is required, please consult the medical monitor to discuss for approval.

Dose changes must be recorded in the Dose Administration eCRF.

Table 1. Ibrutinib Dose Modifications

Hematologic AEs	
Occurrence	Action to be Taken
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 original 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 3)
Other Hematologic and Non-Hematologic AEs (for Events not Specified in Table 2)	
Occurrence	Action to be Taken
First	Withhold ibrutinib until recovery to Grade ≤ 1 or baseline; may restart at original dose level[a]
Second	Withhold ibrutinib until recovery to Grade ≤ 1 or baseline; restart at 1 dose level lower* (3 capsules [ie 420 mg daily]) (refer to Table 3)
Third	Withhold ibrutinib until recovery to Grade ≤ 1 or baseline; restart at 1 dose level lower (2 capsules [ie 280 mg daily]) (refer to Table 3)
Fourth	Discontinue ibrutinib

[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.

* Dose reduction due to a TLS event or a DLT is not applicable for Safety Run-in subjects.

Note: 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 Section 5.3.1.6 and Section 6.2.1.

Table 2. Ibrutinib Dose Modifications for Cardiac Failure or Cardiac Arrhythmias

Events	Occurrence	Action
Grade 2 cardiac failure	**First**	**Hold study drug until recovery to Grade ≤ 1 or baseline; restart at 1 dose level lower (3 capsules [ie, 420 mg daily])**
	Second	**Hold study drug until recovery to Grade ≤ 1 or baseline; restart at 1 dose level lower (2 capsules [ie, 280 mg daily])**
	Third	**Discontinue study drug**
Grade 3 cardiac arrhythmias	**First**	**Hold study drug until recovery to Grade ≤ 1 or baseline; restart at 1 dose level lower (3 capsules [ie, 420 mg daily])[a]**
	Second	**Discontinue study drug**
Grade 3 or 4 cardiac failure **Grade 4 cardiac arrhythmias**	**First**	**Discontinue study drug**

a Evaluate the benefit-risk before resuming treatment.

Table 3. 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

For required dose modification for hepatic impairment refer to Section 5.3.1.6 and for concomitant treatment with CYP3A inhibitors refer to Section 6.2.1.

5.3.1.5 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, and the medical monitor should be contacted.

5.3.1.6 Dose Modification for Hepatic Impaired Subjects

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

- For subjects with existing chronic mild hepatic impairment (Child-Pugh class A) at enrollment, the starting dose has to 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.
- For subjects who develop moderate hepatic impairment while on study (Child-Pugh class B), the recommended dose reduction is to a level of 140 mg daily (one capsule).
- Subjects who develop severe hepatic impairment (Child-Pugh class C) must hold study drug until resolved to moderate impairment (Child-Pugh class B) 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 in Section 5.3.1.4.

5.3.2 Venetoclax

5.3.2.1 Formulation/Packaging/Storage

The individual study drug information is presented in Table 4.

Table 4. Identity of Venetoclax/Placebo Drug Product

Study Drug	Trademark	Formulation	Route of Administration	Manufacturer
Venetoclax/placebo	N/A	10 mg tablet Film coated	Oral	AbbVie
Venetoclax/placebo	N/A	50 mg tablet Film coated	Oral	AbbVie
Venetoclax/placebo	N/A	100 mg tablet Film coated	Oral	AbbVie

Packaging and Labeling

The venetoclax/placebo tablets will be packaged in blister packs during the initial dose ramp-up period and in high density polyethylene (HDPE) plastic bottles thereafter to accommodate the study design. Each container will be labeled as required per country requirements. Labels must remain affixed to the container.

Storage and Disposition of Study Drug

The venetoclax/placebo supplied in this study is for investigational use only, and must only be used within this study. All study drug must be maintained under adequate security and stored under conditions specified on the label until dispensed for subject use or returned to the Sponsor or representative.

The tablets must be stored at a controlled room temperature of 15° to 25°C (59° to 77°F).

5.3.2.2 Venetoclax Toxicity Management

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 6-8 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 a greater risk of TLS when initiating venetoclax. Reduced renal function further increases the risk. The risk may decrease as tumor burden decreases with venetoclax treatment.

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

The prophylaxis measures listed below should be followed and more intensive measures (including hospitalization) should be employed as overall risk increases:

Hydration: Ensure adequate hydration (1.5-2 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 intravenous (IV) fluids as indicated based on overall risk of TLS or for those who cannot maintain adequate oral hydration.

Anti-hyperuricemic agents: Administer 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, 8, 12, 24 and, as needed, 48 hours after the venetoclax dose. For outpatient subjects, monitor blood chemistries at 6-8 hours and at 24 hours after the venetoclax dose. Electrolyte abnormalities should be corrected promptly (see Appendix H for Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis). The next dose of venetoclax should not be administered until the 24-hour blood chemistry results have been evaluated. The same monitoring schedule should be followed when starting each subsequent ramp-up dose.

Hospitalization: Based on investigator assessment, 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 CrCl < 60 mL/min, are at greater risk of TLS and require hospitalization the first 24-48 hours of treatment at the 20 mg and the 50 mg ramp-up doses of venetoclax for more intensive prophylaxis and monitoring. Consider hospitalization for subsequent ramp-up doses based on reassessment of risk. During the course of the study, the DMC will review unblinded TLS data to determine whether continued hospitalization of these subjects is warranted.

5.3.2.3 Dose and Administration

Venetoclax/placebo tablets should be taken orally once daily with a meal and water at approximately the same time each day with ibrutinib capsules. Venetoclax/placebo tablets should be swallowed whole and not chewed, crushed, or broken prior to swallowing. If the subject misses a dose of venetoclax/placebo within 8 hours of the time it is usually taken, the subject should take the missed dose as soon as possible on the same day and resume the normal daily dosing schedule. If a subject misses a venetoclax/placebo dose by more than 8 hours, the subject should not take the missed dose and resume the usual dosing schedule the following day. The use of strong CYP3A inhibitors/inducers, and grapefruit and Seville oranges should be avoided for the duration of the study (Appendix D).

For subjects starting with the concurrent administration of ibrutinib and venetoclax using the standard Ramp-up Schedule, venetoclax/placebo will be delivered in the clinic on Days 1, 2 (all subjects) and 3 (hospitalized subjects) of Weeks 1 and 2; on Days 1 of the remaining weeks during the Ramp-up Period (see Section 8.2); and on the PK sample collection day (see Section 7.1.4.1 and Section 7.1.4.2). Otherwise, venetoclax dosing will be done on an outpatient basis. Subjects should strictly adhere to the Ramp-up Schedule. In the event of TLS, dosing of venetoclax will be withheld and/or modified per the protocol and may be resumed at the investigator's discretion, when all laboratory abnormalities have returned to baseline. If venetoclax is resumed at the same dose level, the 7-day count should be re-started. In cases of vomiting after taking venetoclax/placebo, no additional dose (tablets) should be taken that day. The next dose should be taken at the usual time the following day.

5.3.2.4 Overdose

There is no specific antidote for venetoclax/placebo. For subjects who experience overdose, closely monitor and provide appropriate supportive treatment; during the Ramp-up Period, interrupt venetoclax/placebo and monitor carefully for signs and symptoms of TLS along with other toxicities. Based on the venetoclax (assume for placebo) large volume of distribution and extensive protein binding, dialysis is unlikely to result in significant removal of venetoclax (assume for placebo).

Refer to Section 11.3 for further information regarding special reporting situations as a result of overdose.

5.3.2.5 Dose Modification for Adverse Reactions

Venetoclax/placebo dosing interruption and/or dose reduction may be required. See Table 5 for dose modifications for hematologic and other toxicities related to venetoclax/placebo. 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 reinitiation with a reduced dose is necessary (eg, all or some levels of the dose Ramp-up Schedule).

Dose reduction of venetoclax is not allowed for subjects enrolled in the Safety Run-in Period (see Section 3.1.1).

Table 5. Recommended Dose Modifications for Venetoclax/placebo-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 24-48 hours of last dose, resume at the same dose.
		For any blood chemistry changes requiring more than 48 hours to resolve, resume at a reduced dose* (see Table 6)
		For any events of clinical TLS, resume at a reduced dose following resolution (see Table 6)*
Non-Hematologic Toxicities		
Grade 3 or 4 non-hematologic toxicities	1st occurrence	Interrupt venetoclax/placebo Once the toxicity has resolved to Grade 1 or baseline level, venetoclax/placebo therapy may be resumed at the same dose. No dose modification is required.
	2nd and subsequent occurrences	Interrupt venetoclax/placebo. Follow dose reduction guidelines in Table 6 when resuming treatment with venetoclax/placebo after resolution. 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)	1st occurrence	Interrupt venetoclax/placebo. To reduce the infection risks associated with neutropenia, granulocyte-colony stimulating factor (G-CSF) may be administered with venetoclax/placebo if clinically indicated. Once the toxicity has resolved to Grade 1 or baseline level, venetoclax/placebo may be resumed at the same dose.
	2nd and subsequent occurrence	Interrupt venetoclax/placebo. Consider using G-CSF as clinically indicated. Follow dose reduction guidelines* in Table 6 when resuming venetoclax/placebo after resolution. Additional dose reductions may occur at the discretion of the investigator

* Dose reduction due to a TLS event or a DLT is not applicable for Safety Run-in Period subjects.

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

If the dose of venetoclax/placebo is reduced, at the investigator's discretion, the dose of venetoclax/placebo 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. Dose changes must be recorded in the Dose Administration eCRF.

Table 6. Dose Modification for Toxicity During Venetoclax/placebo 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.

5.3.2.6 Dose Modification for Hepatic Impaired Subjects

No dose adjustment is recommended in subjects with mild or moderate hepatic impairment based on results of the population pharmacokinetic analysis. A recommended dose has not been determined for subjects who develop severe hepatic impairment.

5.4 Criteria for Permanent Discontinuation of Study Drug

Investigators are encouraged to keep a subject who is experiencing clinical benefit in the study unless significant toxicity puts the subject at risk or routine noncompliance puts the study outcomes at risk. Subjects who discontinue either ibrutinib or venetoclax/placebo (but not both) for tolerability issues may continue in the study as long as they are receiving at least one study drug. For a complete list of criteria for permanent discontinuation of study treatment, refer to Section 9.2.

An End-of-Treatment Visit (Section 8.2.3) is required for all subjects except for those subjects who have withdrawn full consent.

6 CONCOMITANT MEDICATIONS/PROCEDURES

6.1 Permitted Concomitant Medications

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

Usage of antimicrobial prophylaxis in accordance with standard practice (eg, ASCO guidelines [Flowers 2013]) is permitted and should be considered in patients who are at increased risk for opportunistic infections.

Use of neutrophil growth factors (filgrastim and pegfilgrastim) red blood cell growth factors (erythropoietin) and transfusion is permitted in accordance with institutional policy (eg, ASCO Guidelines [Smith 2006]).

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

6.2 Medications to be Used with Caution

6.2.1 CYP3A Inhibitors/Inducers

6.2.1.1 Concomitant Use with Ibrutinib

Ibrutinib is metabolized primarily by CYP3A4. Avoid concomitant use of systemic strong or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition.

- If a strong CYP3A inhibitor must be used, reduce ibrutinib dose to 140 mg or withhold treatment for the duration of inhibitor use. Subjects should be monitored for signs of ibrutinib toxicity.
- If a moderate CYP3A inhibitor must be used, reduce ibrutinib to 140 mg for the duration of the inhibitor use. Avoid grapefruit and Seville oranges during ibrutinib/placebo treatment, as these contain moderate inhibitors of CYP3A (see Section 6.2.1.1).
- No dose adjustment is required in combination with mild inhibitors.

Table 7 summarizes the recommended dose modifications with moderate and strong CYP3A inhibitors. Avoid concomitant use of systemic strong CYP3A inducers (eg, carbamazepine, rifampin, phenytoin, and St. John's Wort). Consider alternative agents with less CYP3A induction.

A list of common CYP3A inhibitors and inducers is provided in Appendix D. For further information, please refer to the current ibrutinib IB and examples of inhibitors, inducers, and substrates can be found at http://medicine.iupui.edu/clinpharm/ddis/main-table/. This website is continually revised and should be checked frequently for updates.

6.2.1.2 Concomitant Use with Venetoclax/placebo

Concomitant use of venetoclax/placebo with strong CYP3A inhibitors at initiation and during the Ramp-up Period increases the risk for TLS. Concomitant use of venetoclax/placebo with strong CYP3A inhibitors at initiation (7 days prior to first dose) and during the Ramp-up Period is

contraindicated. For subjects who have completed the Ramp-up Period and are on a steady daily dose of venetoclax/placebo, reduce the venetoclax/placebo dose by at least 75% when strong CYP3A inhibitors must be used concomitantly.

Avoid concomitant use of moderate CYP3A inhibitors with venetoclax. Consider alternative treatments. If a moderate CYP3A inhibitor must be used, reduce the doses of venetoclax/placebo by at least 50%. Monitor subjects more closely for signs of toxicities. Table 7 summarizes the recommended dose modifications with moderate and strong CYP3A inhibitors.

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

Avoid concomitant use of venetoclax/placebo with strong CYP3A inducers (eg, carbamazepine, phenytoin, rifampin, St. John's Wort) or moderate CYP3A inducers (eg, bosentan, efavirenz, etravirine, modafinil, nafcillin). Consider alternative treatments with less CYP3A induction.

A list of common CYP3A inhibitors and inducers is provided in Appendix D. For further information, please refer to the current venetoclax IB.

A sample list of cautionary medications that fall into these categories is provided in Appendix D.

Table 7. Management of Potential Ibrutinib and Venetoclax/placebo Interactions with CYP3A Inhibitors

	Venetoclax/placebo		Ibrutinib
Inhibitors	Initiation and Ramp-up Period	Target Daily Dose (After Ramp-up)	At any time
Strong CYP3A inhibitor	Contraindicated	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

6.2.2 Drugs that May have Their Plasma Concentration Altered by Ibrutinib

In vitro studies indicated that ibrutinib is a mild P-gp inhibitor. Ibrutinib is not expected to have systemic drug-drug interactions with P-gp substrates. However, it cannot be excluded that ibrutinib could inhibit intestinal P-gp after a therapeutic dose. There is no clinical data available. Therefore, 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.

6.2.3 Drugs That May Have Their Plasma Concentrations Altered by Venetoclax

Venetoclax is a P-gp and BCRP substrate as well as a P-gp and BCRP inhibitor and weak OATP1B1 inhibitor *in vitro*. To avoid a potential interaction in the gastrointestinal tract, coadministration of narrow therapeutic index 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.

A list of medications that are P-gp substrates is provided in Appendix D. For further information, please refer to the current venetoclax IB.

6.2.4 Antiplatelet Agents and Anticoagulants

6.2.4.1 Concomitant Use with Ibrutinib

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. Bleeding events of any grade, including bruising and petechiae, occurred in patients treated with ibrutinib and the mechanism for the bleeding events is not well understood. Subjects with congenital bleeding diathesis have not been studied. Ibrutinib should be held at least 3 to 7 days pre- and post-surgery, depending upon the type of surgery and the risk of bleeding (see Section 6.3).

Subjects requiring the initiation of therapeutic anticoagulation therapy (eg, atrial fibrillation), consider the risks and benefits of continuing ibrutinib treatment. If therapeutic anticoagulation is clinically indicated, treatment with ibrutinib/placebo should be held and not be restarted until the subject is clinically stable and has no signs of bleeding. No dose reduction is required when study drug is restarted. Subjects should be observed closely for signs and symptoms of bleeding.

6.2.4.2 Concomitant Use with Venetoclax

In a drug-drug interaction study in three healthy subjects, administration of a single 400 mg dose of venetoclax with 5 mg warfarin resulted in 18% to 28% increase in C_{max} and AUC_{∞} of R-warfarin and S-warfarin. Because venetoclax was not dosed to steady state, it is recommended that the international normalized ratio (INR) be monitored closely in subjects receiving warfarin.

6.2.5 Prohibited Concomitant Medications and Products for Ibrutinib and/or Venetoclax/placebo

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

Corticosteroids for the treatment of the underlying malignancy are prohibited (refer to Section 6.1 for further guidance).

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 ibrutinib and venetoclax 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 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.

6.3 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:

6.3.1 Minor Surgical Procedures

For minor procedures (such as 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.

6.3.2 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.

7 STUDY EVALUATIONS

7.1 Description of Procedures

7.1.1 Assessments

7.1.1.1 ICF

The subject must read, understand, and sign the Institutional Review Board/Research Ethics Board/Independent Ethics Committee (IRB/REB/IEC) approved ICF confirming his or her willingness to participate in this study before any study-specific screening procedures are performed. Subjects in the US must also grant permission to use protected health information per the Health Insurance Portability and Accountability Act (HIPAA). In addition, subjects must sign all approved ICF amendments per the site IRB/REB/IEC guidelines during the course of the study.

7.1.1.2 Confirm Eligibility

All necessary procedures and evaluations must be performed to document that the subject meets all of the inclusion criteria and none of the exclusion criteria until first dose of study drug (Section 4).

7.1.1.3 Medical History and Demographics

The subject's relevant medical history through review of medical records and by interview will be collected and recorded. Concurrent medical signs and symptoms must be documented to establish baseline severities. A disease history, including the date of initial diagnosis and list of all prior anticancer regimens, dates administered, and responses and DOR to these treatments, will also be recorded.

7.1.1.4 Prior and Concomitant Medications

All medications at least 14 days prior to the first dose through 30 days after the last dose of study drug will be documented.

7.1.1.5 Adverse Events

The accepted regulatory definition for an AE is provided in Section 11.1. The occurrence of an AE at the time the ICF is signed until first dose should be recorded under medical history in the eCRF form. All medical occurrences after the first dose with study drug/treatment until 30 days after the last dose of study drug that meet the AE definition must be recorded as AEs in the eCRF. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in dose reduction or treatment discontinuations, necessitate therapeutic medical intervention, meet protocol specific criteria or if the investigator considers them to be AEs. Additional important requirements for AE and SAE reporting are explained in Section 11.4.

7.1.1.6 Physical Examination

The Screening and End-of-Treatment physical examination will include, at a minimum, the general appearance of the subject, height (Screening only) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, nervous system, and lymphatic system.

A limited symptom-directed physical examination may be required at selected timepoints as outlined in Section 8.

7.1.1.7 Eye-related Symptom Assessment

The subjects will be asked about eye-related symptoms.

If there are any eye-related symptoms of severity Grade ≥ 2 at Screening or if the subject develops any eye-related symptoms of severity Grade ≥ 2 while on study treatment, an ophthalmologic evaluation/consult must be performed, and the outcome must be reported on the ophthalmologic eCRF.

7.1.1.8 ECOG

The ECOG performance index is provided in Appendix C.

7.1.1.9 Vital Signs

Vital signs will include blood pressure, heart rate, and body temperature. Vital signs will be assessed after the subject has rested in the sitting position for ≥ 3 minutes.

7.1.1.10 Tumor Lysis Syndrome (TLS) Risk Assessment

At Screening, all study subjects will be assessed for risk of developing TLS. The risk of TLS is a continuum based on multiple factors, including comorbidities. Subjects at increased risk are defined as having at least one lesion > 10 cm; or at least one lesion > 5 cm and circulating lymphocytes > 25,000 cells/mm^3 and/or have reduced renal function CrCl < 60 mL/min. The risk may decrease as tumor burden decreases with venetoclax treatment.

Blood chemistry (creatinine, uric acid, potassium, phosphorus, calcium, and albumin if available) assessments will be performed in all subjects within 72 hours prior to initiating venetoclax treatment.

Subjects with high tumor burden at baseline and/or CrCl < 60 mL/min will be hospitalized during the first 24-48 hours of treatment at the 20 mg (Week 1) and the 50 mg (Week 2) venetoclax dose. Blood chemistry (creatinine, uric acid, potassium, phosphorus, calcium, and albumin if available) should be monitored pre-dose and 4±1, 8±1, 12±1, 24±2 and, as needed, 48±2 hours after the venetoclax dose. (Hospitalization for subjects lacking immediate access to a

facility capable of correcting TLS promptly or for subjects who are otherwise considered at risk for TLS should be discussed with the medical monitor). For all other subjects, blood chemistry will be monitored pre-dose, 6-8 and 24±2 hours after the venetoclax dose at the 20 mg and the 50 mg dose levels.

During the remaining ramp-up weeks (weeks 3-5), for subjects at increased risk for TLS at baseline, blood chemistries will be monitored at pre-dose and 6-8 hours after each dose increase.

Appropriate venetoclax dosing and management of subjects throughout their study treatment is guided by their individual risk for developing TLS. Risk-based TLS prophylaxis and management measures are described in Section 5.3.2.2.

7.1.1.11 B-Symptoms

B-symptoms include fever > 38°C for at least 3 consecutive days, drenching night sweats or weight loss > 10% since the last disease assessment.

7.1.2 Laboratory

All laboratory tests will be collected by local lab.

7.1.2.1 Hematology

Hematology parameters will include a complete blood count: white blood cells, red blood cells, hemoglobin, hematocrit, platelets, neutrophils, lymphocytes, monocytes, eosinophils, basophils.

7.1.2.2 Chemistry (Serum)

Blood chemistry parameters will include sodium, potassium, chloride, blood urea nitrogen (BUN)/Urea, creatinine, glucose, calcium, and albumin, if available, total protein, AST, ALT, alkaline phosphatase, total bilirubin, LDH, phosphorus, uric acid, magnesium and bicarbonate.

7.1.2.3 Coagulation Studies

Measurement of PT, INR and aPTT will be performed at Screening using a local laboratory. INR should be followed more closely in subjects on warfarin therapy.

7.1.2.4 Hepatitis Serologies

Hepatitis serologies include hepatitis C antibody, hepatitis B surface antigen, and hepatitis B core antibody. If hepatitis B core antibody, hepatitis B surface antigen, or hepatitis C antibody is positive, then PCR to quantitate hepatitis B DNA or hepatitis C RNA must be performed and must be negative prior to randomization/enrollment. This applies to the SRI and Randomization Phase only. Treatment-naive open-label arm subjects with a positive hepatitis B surface antigen test are excluded from the trial.

7.1.2.5 Serum β2-microglobulin

One blood sample(s) for β2-microglobulin will be taken during the screening period.

7.1.2.6 Urinalysis

Urinalysis includes pH, ketones, specific gravity, bilirubin, protein, blood, and glucose.

7.1.2.7 Pregnancy Test

Serum or urine pregnancy test will be required at Screening by local laboratory only for women of childbearing potential. A serum or urine pregnancy test will also be performed on Day 1 prior to first dose. If positive, pregnancy must be ruled out by ultrasound, at least 3 weeks after a positive urine pregnancy test, to be eligible. This test may be performed more frequently if required by local regulatory authorities.

7.1.3 Diagnostics/Procedures

7.1.3.1 ECG

A single 12-lead ECG will be done at Screening and at the EOT visit. Subjects should be in a supine position and resting for at least 10 minutes before obtaining the ECG. During the treatment period, ECGs may be performed at the investigator's discretion, particularly in subjects with arrhythmic symptoms (eg, palpitations, lightheadedness) or new onset dyspnea.

During visits in which both ECGs and blood draws are performed, ECGs should be performed first.

Abnormalities noted at the Screening ECG should be included in the medical history.

7.1.3.2 CT/MRI and PET

SRI and Randomized Phase

Pretreatment tumor assessment will be performed within 28 days before the first dose of study drug.

A CT scan (with contrast unless contraindicated) of the neck, chest, abdomen, and pelvis and any other disease sites and a PET scan are required for the pretreatment tumor assessment. CT scans with contrast will be done for tumor assessments on Week 13 Day 1 (±7 days); every 12 weeks for the remainder of the first year; every 16 weeks during the second and third years; and every 24 weeks thereafter until PD. In subjects with positive PET at baseline, PET or PET/CT is mandatory to confirm a CR. Disease assessments may be repeated as clinically indicated to confirm response or progression.

Lesions that have been irradiated cannot be included in the tumor assessment unless unequivocal tumor progression has been documented in these lesions after radiation therapy. There must be radiographically measurable disease at Screening (at least one lymph node ≥ 2.0 cm in the longest diameter). Up to 6 measurable lymph nodes (target lesions > 1.5 cm in the longest diameter), clearly measurable in 2 perpendicular dimensions, will be followed as target lesions for each subject. Measurable sites of disease should be chosen such that they are representative of the subject's disease. In addition, selection of target lesions should be from as disparate regions of the body as possible when these areas are significantly involved. If additional lesions are present but are not included in the target lesion assessment, they can be added as non-target lesions and followed throughout the study.

Information on extranodal involvement (eg, gastric or ocular disease) will also be recorded. Lesions in anatomical locations that are not well visualized by CT may be measured by MRI instead and should continue to be measured by MRI until disease progression.

In the case where CT contrast is contraindicated, an alternative would be MRI of the abdomen and pelvis with MRI contrast and CT of the chest and neck without CT contrast. In this case, neck nodes cannot be used as target lesions.

NOTE: PET/CT hybrid scanners may be used to acquire the required CT images only if the CT produced by the scanner is of diagnostic quality, adheres to the specified slice thickness/scan parameters, and includes the use of intravenous (IV) contrast. Additionally, the CT images must be separated from the PET data prior to submitting the data and cannot be transmitted as fused CT/PET images.

If using a hybrid machine to acquire both PET and CT, the PET must be performed prior to the CT with IV contrast as to not compromise PET results.

If a CT with contrast scan indicates suspected CR, a confirmatory PET scan may be performed within 30 days.

For subjects who remain stable with PR for > 6 months with residual lymph node lesions > 1.5 cm that remain relatively unchanged, a PET scan may be performed to determine if CR has been achieved and MRD testing should be implemented.

De-identified copies of all scans and radiology reports (including those from screening) must be provided to the Sponsor or designee (eg, central imaging vendor). At the Sponsor's discretion, the Sponsor or its designee may conduct an independent review of the investigator responses.

Treatment-naive Open-label Arm

CT and PET or PET/CT scans (with contrast unless contraindicated) of the neck, chest, abdomen, and pelvis and any other disease sites (eg, extremity) and a PET scan are required for the pretreatment tumor assessment within 28 days of the 1st dose. Thereafter, CT scans will be

done for tumor assessments on Week 13 Day 1 (±7 days); every 12 weeks for the remainder of the 1st year; every 16 weeks during the 2nd and 3rd years; and every 24 weeks thereafter until PD. PET or PET/CT is mandatory for all subjects at the Week 13 visit (+/- 7 days), the Week 25 visit (+/- 7 days) for subjects in SD or PR who did not achieve CR at Week 13, and at the 1-year visit (Week 49 +/- 7 days) for all subjects, as well as at any other time point to confirm a CR. Other PET or PET/CT scans that are NOT mandatory can be performed within a 30-day window of the visit. For MRI refer to Section 7.1.3.2.

7.1.3.3 Endoscopy

Endoscopy is optional at baseline but is required and must be negative to confirm CR (preferably within 30 days of the initial documentation of CR) in subjects with known endoscopy-positive GI involvement at baseline.

7.1.3.4 Tumor Tissue

Approximately 20 slides of fresh or most recent dated FFPE archival tumor biopsy tissue will be collected at study entry and evaluated for biomarker assessment. An optional fresh tumor biopsy may be collected at the time of disease progression.

Confirmation of MCL diagnosis is required prior to enrollment; a report from the local laboratory is acceptable. The diagnosis of MCL from the local laboratory must include morphology and expression of either cyclin D1 in association with other relevant markers (eg, CD20 and CD5) or evidence of t(11;14)(q13;q32) as assessed by cytogenetics or fluorescent in situ hybridization (FISH). The report containing this information must be sent to the central laboratory and the sponsor for confirmation of the diagnosis prior to enrollment.

For subjects who do not have this report available, the formalin-fixed paraffin embedded (FFPE) tumor tissue block or slides must be sent to the central laboratory and confirmation of MCL diagnosis must be obtained from the central laboratory prior to enrollment.

7.1.3.5 Bone Marrow Biopsies for Evaluation of Bone Marrow Involvement

A unilateral bone marrow biopsy must be collected at Screening up to 28 days prior to the first administration of study drug to be evaluated for bone marrow involvement, unless prior bone marrow biopsy is obtained within 90 days prior to study treatment. Additional bone marrow biopsy will be collected in subjects with documented CR.

Bone marrow involvement must be assessed locally prior to enrollment. A local pathology report must be available for review. If a local pathology report is not available, bone marrow involvement will be assessed at the central lab. For subjects that meet CR criteria, if a local pathology report is not available, a bone marrow biopsy will need to be tested to ensure there is no lymphoma involvement in the bone marrow to confirm CR.

If the subject's physical examination findings, laboratory evaluations, radiographic evaluations and endoscopy (if applicable) suggest that CR has been achieved in all other response parameters, a bone marrow biopsy must be obtained for subjects with bone marrow involvement at baseline (by standard pathology) to confirm the CR. If the response parameters indicate a suspected CR, a bone marrow biopsy may be collected within 30 days to confirm CR.

7.1.3.6 Bone Marrow Aspirate and Peripheral Blood for Minimal Residual Disease (MRD) Assessment

Minimal residual disease assessment will be performed by flow cytometry at Screening for every subject to detect a dominant clone in peripheral blood or bone marrow aspirate. MRD negativity will be assessed by flow cytometry both in the peripheral blood and the bone marrow aspirate collected at documented CR. Thereafter subjects should be followed with peripheral blood MRD analyses by flow cytometry every 12 weeks (±7 days) for the remaining first year; every 16 weeks during the second and third years; and every 24 weeks thereafter until PD. MRD-negative remission is defined as undetectable MRD at documented CR in subjects who were MRD positive at screening as assessed by flow cytometry in bone marrow (BM) aspirate and/or peripheral blood and a consecutive peripheral blood sample 12 weeks later.

If the MRD assessment is positive in bone marrow at CR, a repeat bone marrow aspirate is required 24 weeks later if the subject remains in CR to evaluate MRD status in the bone marrow.

If peripheral blood becomes positive for MRD, a bone marrow sample will not be necessary; however, equivocal cases should be discussed with the medical monitor to determine the need for repeat bone marrow testing.

MRD-positive relapse is defined as a detectable increase in disease after a MRD-negative remission, as assessed by flow cytometry of a peripheral blood or BM aspirate sample.

7.1.3.7 Bone Marrow Aspirate and Peripheral Blood for Biomarker Assessment

Bone marrow aspirates and peripheral blood samples will be stored for exploratory biomarker analysis. ClonoSEQ (Adaptive Biotechnologies), a highly sensitive and exploratory MRD detection assay, will also be used for retrospective assessment of MRD in a subset of collected samples of bone marrow and peripheral blood to compare MRD negativity as determined by flow cytometry. If the ClonoSeq technology assay is not available for use or a technically superior assay for MCL MRD has emerged at the time of testing, an alternative molecular MRD assay with equivalent or better analytical performance may be used for analysis.

7.1.4 Pharmacokinetics/Biomarkers

7.1.4.1 Pharmacokinetics for Safety Run-in and Randomization Phase

Ibrutinib and venetoclax should be dosed together at the same time with 8 ounces of water and a meal. It is anticipated that steady state will be reached after 1 week of administration of the highest venetoclax dose. Ibrutinib and venetoclax PK samples will be collected at steady state on the PK days as shown in Table 8 at the time points listed in Table 9.

Table 8. Ibrutinib and Venetoclax PK Samples Schedule at the Target Dose

Dosing Schedule	PK Day
Standard ramp-up	Week 6 Day 1

Pharmacokinetics of ibrutinib and venetoclax when dosed in combination will be determined at time-points specified in Table 9 below.

Table 9. Pharmacokinetic Sample Schedule for Ibrutinib and Venetoclax or placebo on the PK Days

Study Drugs	Pre-dose PK[a]	Dose[b]	Time after ibrutinib and venetoclax dose				
			1 hour (± 15 min)	2 hour (± 15 min)	4 hour (± 30 min)	6 hour (± 30 min)	8 hour (± 1 h)
Ibrutinib and Venetoclax or Placebo*	X	X	X	X	X	X	X

a Predose samples should be collected 30 minutes prior to the administration of ibrutinib and venetoclax or placebo
b Ibrutinib/venetoclax or placebo should be dosed the same time within 30 minutes after completion of the meal.
Example:

Predose PK	7:00 am
Breakfast	7:00 to 7:30 am
Dose	7:30 am
1 hr PK	8:30 am
2 hr PK	9:30 am
4 hr PK	11:30 am
6 hr PK	1:30 pm
8 hr PK	3:30 pm

* Unscheduled PK sampling schedule based on Medical Monitor request, e.g. dose modification (at least 7 days after dose modification)

Refer to the laboratory binder for instructions on collecting and processing these samples. On the day of the sampling visit, the clinical staff will instruct the subject to not take a dose before arrival at the clinic. Study drug intake will be observed by clinic staff. The actual time (versus requested time) that each sample is drawn must be recorded using a 24-hour format. The same clock should be used for recording the time of dosing. In the event that medical management is needed, use of concomitant medications should be recorded. In the case of ibrutinib or

venetoclax/placebo dose holds or modifications prior to the above time points, please consult with medical monitor to determine the most appropriate time at which to obtain PK blood samples.

For subjects who must start a moderate or strong CYP3A inhibitor while on treatment with ibrutinib or venetoclax, additional PK blood samples for the evaluation of ibrutinib and venetoclax exposure is requested at least one week after the initiation of the concomitant CYP3A inhibitor. PK samples will be collected at the time points described above.

7.1.4.2 Pharmacokinetics Treatment-naive Open-label Arm

Ibrutinib and venetoclax should be dosed together at the same time with 8 ounces of water and a meal. It is anticipated that steady state will be reached after 1 week of administration of the highest venetoclax dose. Ibrutinib and venetoclax PK samples will be collected at steady state on the PK days as shown at the time points listed in Table 10.

Table 10. Pharmacokinetic Sample Schedule for Treatment-naive Open-label Arm

Study Arm	Week	Study Day	Predose[a]		Time Point Postdose				
				Dose[b]	1h (± 15 min)	2h (±15min)	4h (± 30 min)	6h (±30 min)	8h (±1 h)
Treatment-naive Open-label*	4	7	X	X	X	X	X	X	X
	6	1	X	X	X	X	X	X	X
	13 & beyond	(+/- 7 days)	X	X	X	X			

a Predose samples should be collected 30 minutes prior to the administration of ibrutinib and venetoclax
b Ibrutinib and venetoclax should be dosed the same time within 30 minutes after completion of the meal.
* Unscheduled PK sampling schedule based on Medical Monitor request, e.g. dose modification (at least 7 days after dose modification)

Refer to the laboratory binder for instructions on collecting and processing these samples. On the day of the sampling visit, the clinical staff will instruct the subject to not take a dose before arrival at the clinic. Study drug intake will be observed by clinic staff. The actual time (versus requested time) that each sample is drawn must be recorded using a 24-hour format. The same clock should be used for recording the time of dosing. In the event that medical management is needed, use of concomitant medications should be recorded. In the case of ibrutinib or venetoclax dose holds or modifications prior to the above time points, please consult with medical monitor to determine the most appropriate time at which to obtain PK blood samples.

For subjects who must start a moderate or strong CYP3A inhibitor while on treatment with ibrutinib or venetoclax, additional PK blood samples for evaluation of ibrutinib and venetoclax exposure is requested at least one week after the initiation of the concomitant CYP3A inhibitor. PK samples will be collected at the time points described above.

7.1.4.3 Exploratory Biomarkers

Blood samples and a buccal swab will be collected and sent to the central laboratory at selected time points specified in the Schedule of Assessments (Appendix A and Appendix B).

Approximately 20 slides of fresh or most recent dated FFPE archival tumor biopsy tissue will be collected at study entry. An optional fresh tumor biopsy may be collected at the time of disease progression. A bone marrow aspirate and a bone marrow biopsy will be collected based on Section 7.1.3.5 and Section 7.1.3.6. Tumor cells from peripheral blood, bone marrow and/or tumor tissue may be studied for genomic alterations, as well as gene and/or protein expression profiling. Non-cancer cell genes derived from the buccal swab will only be used as a control for the cancer gene mutation analysis. In addition to the markers known to be involved in MCL prognosis, inhibition of BCR signaling and BCL-2 pathways may also be explored. These efforts may identify biomarkers that could support the understanding of the disease or assist with future development of treatment options.

Bone marrow aspirate and peripheral blood samples will be stored for exploratory biomarker analysis by clonoSEQ. Samples collected in this study may be stored at a biorepository for up to 10 years (or according to local regulations) for additional research as new assays are developed for ibrutinib, venetoclax and MCL. Samples will only be used to better understand the effects ibrutinib and venetoclax in MCL; sensitivity and/or resistance to the investigational treatment regimen in this study.

The research may begin at any time during the study or the post-study storage period. Stored samples will be coded throughout the sample storage and analysis process, and will not be labeled with personal identifiers.

7.1.5 Patient-Reported Outcomes

7.1.5.1 FACT-Lym for Safety Run-in and Randomization Phase

The FACT-Lym questionnaires (Appendix I) will be administered in this study. The FACT-Lym was originally developed to assess functional status and well-being of patients with NHL (Eremenco 2004). Reliability and validity have been assessed in NHL (Webster 2005) and more recently construct validity has been supported in subjects with relapsed/refractory MCL (Carter 2008).

The FACT-Lym consists of the Functional Assessment of Chronic Illness Therapy - General (FACT-G) and a lymphoma-specific additional concerns subscale (Lym).

Responses to all items are rated on a 5-point scale ranging from 0 “not at all” to 4 “very much”. The recall period is the past 7 days. The lymphoma subscale includes 15 items and scores range from 0 to 60. Two summary scores may also be calculated: the FACT-Lym total score (FACT-G plus Lym) and the FACT-Lym trial outcome index (TOI) score (physical well-being+functional

well-being+lymphoma). Higher scores represent better functional status and well-being for all subscales and summary scales.

The subscale of most interest in this study will be the Lym subscale. Carter (Carter 2008) and Cella et al. (Cella 2005) reported a minimal important change score for the Lym subscale in a relapsed/refractory MCL population range from approximately 2.9 to 5.4. Therefore, a 5-point change in the Lym subscale was selected as a conservative estimate of clinically meaningful deterioration in lymphoma symptoms. Time to complete the FACT-Lym is approximately 7 to 12 minutes. All translations not currently available will be completed according to best practice guidelines for translating PRO instruments to the local language(s) (Wild 2005).

The FACT-Lym questionnaire (Appendix I) will be administered at the beginning of the clinic visits prior to any procedures or physician interactions to prevent influencing subject perceptions. The questionnaires will be administered on Week 1 Day 1, Week 13 Day 1 (±7 days); every 4 weeks for the remainder of the first year; every 8 weeks during the second and third years; and every 12 weeks thereafter until disease progression.

7.1.5.2 EQ-5D-5L for SRI, Randomization Phase and Treatment-naive Open-label Arm

The EQ-5D-5L (Appendix J) is a standardized instrument used to measure health outcome (EuroQol Group 1990) and consists of a 5-item questionnaire and a "thermometer" visual analog scale ranging from 0 (worst imaginable health state) to 100 (best imaginable health state). The scores for the 5 dimensions are used to compute a single utility score ranging from 0 to 1, representing the general health status of the individual. The 5 dimensions evaluated are mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The questionnaire will be administered on the same visit schedule as the FACT-Lym.

7.1.6 Medical Resource Utilization (MRU)

Medical resource utilization including hospitalizations, emergency department visits, and hematopoietic growth factor use will be collected for each treatment arm throughout the study treatment period.

7.2 Efficacy Evaluations

7.2.1 Overall Response Assessments

Overall response assessments will include physical examinations, recording of symptoms, hematological test results, bone marrow aspirate or bone marrow biopsy, CT/PET radiological evaluations and endoscopy per the schedule of assessments (Appendix A and Appendix B). Response assessments will be performed according to the Revised Criteria for Response Assessment of Malignant Lymphoma (Cheson 2014), as assessed by investigators (Appendix E) until disease progression or withdrawal of consent from the study.

7.2.2 Survival

After progression, survival status will be assessed approximately every 12 weeks until death, withdrawal by subject, or study terminated by Sponsor, whichever comes first. Data on the subsequent lines of anticancer therapy will be captured. Survival sweeps will be conducted at the time of the final analysis. All subjects who are on study and not known to have died prior to the survival sweep will be contacted at that time.

7.3 Sample Collection and Handling

The actual dates and times of sample collection must be recorded in source documents for transcription to the eCRF or laboratory requisition form. Refer to the Schedule of Assessments (Appendix A and Appendix B) for the timing and frequency of all sample collections.

Instructions for the collection, handling, and shipment of samples are found in the Laboratory Manual.

8 STUDY PROCEDURES

8.1 Screening Phase

Screening procedures will be performed up to 28 days before the first dose of ibrutinib and venetoclax/placebo, unless otherwise specified, and may be performed over more than 1 visit. All subjects must first read, understand, and sign the IRB/REB/IEC-approved ICF before any study-specific screening procedures are performed. After signing the ICF, Screening, and being deemed eligible for entry, subjects will be enrolled in the study.

8.1.1 Screening/Consenting Visit

The following procedures will be performed at the Screening Visit within 28 days prior to enrollment unless otherwise noted:

- Review of eligibility criteria
- Medical history including demographic information and prior treatments for MCL (if applicable)
- Collection of pathology report for cytogenetics/FISH documenting MCL diagnosis (if available)
- Collection of approximately 20 slides of fresh or most recent dated FFPE archival tumor biopsy tissue, OR tumor biopsy obtained by core needle biopsy prior to randomization
- Document bone marrow disease involvement (bone marrow biopsy must be obtained at Screening or up to 90 days before the first dose of study drug for disease confirmation)

- Record concomitant medications (including chemotherapy, radiation, over-the-counter drugs, vitamins, and herbs)
- Perform a complete physical examination, including height (may use prior height measurement if available in source documents), weight and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system
- B-symptom assessment
- Obtain vital signs (including blood pressure, heart rate, and body temperature) after the subject has rested in the sitting position for ≥ 3 minutes.
- Evaluation of ECOG PS
- Determination of Medical Resource Utilization (MRU)
- Obtain a single 12-lead ECG after the subject has been in a supine position and resting for at least 10 minutes.
- AEs (record as Medical History on eCRF)
- Obtain bone marrow biopsy and aspirate (within 28 days prior to first dose) as described in Section 7.1.3.5
- Obtain blood specimens for the following laboratory tests

  - Hematology
  - Blood chemistry (including creatinine clearance)
  - Coagulation panel (PT/INR, aPTT)
  - Hepatitis Serologies
  - Serum β2-microglobulin
  - Urinalysis
  - Obtain serum or urine pregnancy test for women of childbearing potential only
    - Imaging by CT and/or other modality as described in Section 7.1.3.2.
    - TLS risk assessment and prophylaxis within 72 hours of first dose of venetoclax
  - Serum creatinine, uric acid, potassium, phosphorus, calcium, and albumin, if available
  - Determination of level of risk and need for hospitalization
  - Hydration: subject education
  - Prescription of allopurinol (and rasburicase for high risk subjects)

8.2 Treatment Phase

Following completion of the Screening Visit and once eligibility has been confirmed (per inclusion/exclusion criteria), subjects will initiate study treatment (see Section 5.2 for ibrutinib and venetoclax dosing).

Refer to the Schedule of Assessments (Appendix A and Appendix B) for a complete list of procedures to be performed at each scheduled study visit.

8.2.1 Treatment Visits for Standard Ramp-up Schedule for SRI, Randomization Phase, and Treatment-naive (TN) Open-label Arm

8.2.1.1 Week 1 Day 1 and Week 2 Day 1

Pre-dose (within 72 hours prior to the first venetoclax dose and before each dose increase)

- Confirmation of eligibility (per inclusion/exclusion criteria) at week 1 only.
- Update medical history at week 1 only
- AEs
- Concomitant medications (including chemotherapy, radiation, over-the-counter drugs, vitamins, and herbs)
- Physical examination
- Vital signs
- ECOG PS (Week 1 Day 1 only)
- PRO at week 1 only
- Determination of Medical Resource Utilization (MRU)
- TLS risk assessment and prophylaxis
- Hospitalization of subjects with high tumor burden
- Laboratory Tests
  - Hematology
  - Blood chemistry
  - Serum or urine pregnancy test (for women of childbearing potential only) (Week 1 Day 1 only)
  - MRD peripheral blood (Week 1 Day 1 only)
  - Biomarker blood sample (Week 1 Day 1 only)
  - Buccal Swab (Week 1 Day 1 only)

Dosing – Week 1 Day 1 and Week 2 Day 1

The dose of venetoclax or placebo should not be administered until the blood chemistry results have been evaluated.

- In-clinic administration of venetoclax or placebo with a meal
- In-clinic administration of ibrutinib

Post-dose

- For hospitalized subjects, serum creatinine, uric acid, potassium, phosphorus, calcium, and albumin, if available should be monitored at 4±1, 8±1, 12±1 hours, after the venetoclax/placebo dose.
- For all outpatient subjects, serum creatinine, uric acid, potassium, phosphorus, calcium, and albumin, if available should be monitored at 6-8 hours after the venetoclax/placebo dose.
- Any changes in these parameters should be managed promptly and treatment modified before any further venetoclax/placebo is administered.

8.2.1.2 Week 1 Day 2 and Week 2 Day 2

Pre-dose

- AEs
- Concomitant medications (including chemotherapy, radiation, over-the-counter drugs, vitamins, and herbs)
- Vital signs
- Laboratory Tests
  - Blood chemistry (creatinine, uric acid, potassium, phosphorus, calcium, and albumin, if available)
- TLS risk assessment and prophylaxis
- Determination of Medical Resource Utilization (MRU)

Dosing – Week 1 Day 2 and Week 2 Day 2

The dose of venetoclax/placebo should not be administered until the 24-hour blood chemistry monitoring results have been evaluated.

- In-clinic administration of venetoclax/placebo with a meal
- In-clinic administration of ibrutinib

8.2.1.3 Week 1 Day 3 and Week 2 Day 3 (Hospitalized Subjects Only)

Pre-dose

- AEs
- Concomitant medications (including chemotherapy, radiation, over-the-counter drugs, vitamins, and herbs)
- Laboratory Tests
  - Blood chemistry monitoring (creatinine, uric acid, potassium, phosphorus, calcium, and albumin, if available)

- TLS risk assessment and prophylaxis
- Determination of Medical Resource Utilization (MRU)

Dosing – Week 1 Day 3 and Week 2 Day 3

The dose of venetoclax/placebo should not be administered until the blood chemistry monitoring results have been evaluated.

- In-clinic administration of venetoclax/placebo with a meal
- In-clinic administration of ibrutinib

Dosing – Week 1 Day 3 and Week 2 Day 3

The dose of venetoclax or placebo should not be administered until the blood chemistry monitoring results have been evaluated.

- In-clinic administration of venetoclax or placebo with a meal
- In-clinic administration of ibrutinib

8.2.1.4 Weeks 3, 4, and 5 Day 1 for Standard Ramp-up Schedule

Pre-dose

- AEs
- Concomitant medications (including chemotherapy, radiation, over-the-counter drugs, vitamins, and herbs)
- Physical examination
- Vital signs
- ECOG PS (Week 3 Day 1 only)
- Determination of Medical Resource Utilization (MRU)
- TLS risk assessment and prophylaxis
- Laboratory Tests
  - Hematology
  - Blood chemistry

- Pharmacokinetics (**only for TN open-label arm**, on Week 4 Day 7). Pre-dose (± 30 min);

Dosing

The dose of venetoclax or placebo should not be administered until the blood chemistry results have been evaluated.

- In-clinic administration of venetoclax or placebo with a meal
- In-clinic administration of ibrutinib

Post-dose

- Blood chemistry monitoring (creatinine, uric acid, potassium, phosphorus, calcium, and albumin, if available)
- Post-dose 1 hour (±15 min), 2 hours (±15 min), 4 hours (±30 min), 6 hours (±30 min) and 8 hours (±1 hour) after the administration of ibrutinib and venetoclax
    - For subjects with high tumor burden, serum creatinine, uric acid, potassium, phosphorus, calcium, and albumin, if available should be monitored at 6-8 hours after the start of the venetoclax or placebo dose at each ramp-up dose level. Any changes in these parameters should be managed promptly and treatment modified before any further venetoclax or placebo is administered.

8.2.1.5 Week 6 Day 1

Pre-dose

- AEs
- Concomitant medications (including chemotherapy, radiation, over-the-counter drugs, vitamins, and herbs)
- Physical examination
- Vital signs
- ECOG PS
- Determination of Medical Resource Utilization (MRU)
- TLS risk assessment and prophylaxis
- Laboratory Tests
    - Hematology
    - Blood chemistry
    - PK samples for ibrutinib and venetoclax or placebo

Dosing

- In-clinic administration of venetoclax or placebo with a meal
- In-clinic administration of ibrutinib

Post-dose

- PK samples for ibrutinib and venetoclax or placebo 1 hour (±15 min), 2 hours (±15 min), 4 hours (±30 min), 6 hours (±30 min) and 8 hours (±1 hour) after the administration of ibrutinib and venetoclax or placebo (see Section 7.1.4)

8.2.1.6 Week 8 Day 1 (± 1 Day) and Week 10 Day 1 (± 1 Day)

- AEs
- Concomitant medications (including chemotherapy, radiation, over-the-counter drugs, vitamins, and herbs)
- Physical examination
- Vital signs
- Determination of Medical Resource Utilization (MRU)
- TLS risk assessment and prophylaxis
- Laboratory Tests
  - Hematology
  - Blood chemistry

Dosing

- In-clinic administration of venetoclax or placebo with a meal
- In-clinic administration of ibrutinib

8.2.1.7 Week 13 and beyond (±7 Days)

- AEs
- Concomitant medications (including chemotherapy, radiation, over-the-counter drugs, vitamins, and herbs)
- PRO at response assessment visits (see Section 7.1.5 for all timepoints [Appendix I])
- Physical examination
- Vital signs
- ECOG PS
- Determination of Medical Resource Utilization (MRU)
- TLS risk assessment and prophylaxis
- Response Assessments

- **For TN open-label arm only**
  - Week 13 mandatory PET scan for all subjects.
  - Week 25 mandatory PET scan for subjects in SD and PR at Week 13.
  - Week 49, mandatory PET scan for all subjects
- Laboratory Tests
  - Hematology
  - Blood chemistry
- For TN open-label arm only
  - Week 13 Day 1: Pharmacokinetics. Pre-dose (±30 min); Post-dose 1 hour (±15 min), 2 hours (±15 min) after the administration of ibrutinib and venetoclax

After Week 13, clinic visits are scheduled every 4 weeks for one year; every 8 weeks during the second and third years; and every 12 weeks thereafter until treatment discontinuation. At each clinic visit subject should be supplied with enough study drug to last until the next clinic visit.

8.2.2 Response Evaluation

Response assessment visits should occur on Week 13 Day 1, then every 12 weeks for the first year; every 16 weeks during the second and third years; and every 24 weeks thereafter until PD. In addition, response assessments can be performed as clinically indicated to confirm response or progression.

- CT/PET/MRI/endoscopy
- Overall response assessment
- B-symptoms
- Laboratory Tests
  - Hematology
  - MRD BMA (at CR only)
  - Biomarker BMA (at CR only)
  - MRD peripheral blood
  - Biomarker peripheral blood
  - Bone marrow biopsy (at CR only, if baseline is positive for lymphoma or missing)
- Determination of Medical Resource Utilization (MRU)

8.2.3 End-of-Treatment Visit

- AEs
- Concomitant medications (including chemotherapy, radiation, over-the-counter drugs, vitamins, and herbs)
- ECG
- Determination of Medical Resource Utilization (MRU)
- Laboratory Tests
  - Hematology
  - Blood chemistry
  - Urinalysis
  - Serum or urine pregnancy test for women of childbearing potential only
  - MRD peripheral blood
  - Biomarker blood
- Physical Exam
- Vital signs

8.3 Follow-up Phase

Once a subject has completed the End-of-Treatment Visit, they will enter the Follow-up Phase.

8.3.1 Response Follow-up

Subjects who discontinue treatment for reasons other than PD will participate in the response follow-up. From the time of first dose (Safety Run-in Period and TN open-label arm) or randomization (for Randomization Phase), these subjects will be followed every 12 weeks for the first year; every 16 weeks during the second and third years; and every 24 weeks thereafter until PD. Once subjects progress (for subjects who have not withdrawn consent), they will start the Long-term Follow-up.

8.3.2 Long-term Follow-up

Subjects in Long-term Follow-up will be contacted approximately every 12 weeks (±14 days) by clinic visit or telephone to assess survival and the use of alternative anticancer therapy. Subjects will be contacted until death, subject withdrawal, or study termination by the Sponsor, whichever occurs first.

9 SUBJECT COMPLETION AND WITHDRAWAL

9.1 Completion

A subject will be considered to have completed the study, if he or she has died before the end of the study, has not been lost to follow up, or has not withdrawn consent before the end of the study.

9.2 Withdrawal from Study Treatment

Study treatment 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
- Withdrawal of consent for treatment by subject
- Investigator decision (such as chronic noncompliance, significant protocol deviation, clinical deterioration, or best interest of the subject)
- Study termination by Sponsor
- Subject becomes pregnant

All subjects, regardless of reason for discontinuation of study treatment will undergo an End-of-Treatment Visit and, if applicable, be followed for progression and survival.

The investigator should notify the Sponsor within 24 hours if a subject discontinues study treatment (ibrutinib and/or venetoclax/placebo) due to disease progression and should provide documentation of disease progression for review by the medical monitor. If a subject shows signs of disease progression on physical examination or laboratory assessment, the subject may continue study treatment until disease progression is confirmed. These subjects should stay in the study to be followed for survival.

9.3 Withdrawal from Study

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
- Study termination by Sponsor
- Death

If a subject is lost to follow-up, every reasonable effort should be made by the study site personnel to contact the subject. The measures taken to follow up should be documented.

When a subject withdraws before completing the study, the following information should be documented in the source documents:

- Reason for withdrawal;
- Whether the subject withdraws full consent (ie, withdraws consent to treatment and all further contact) or partial consent (ie, withdraws consent to treatment but agrees to participate in follow-up visits).

10 STATISTICAL METHODS AND ANALYSIS

Statistical analysis will be done by the Sponsor or under the authority of the Sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details including alpha allocation, study power consideration, secondary endpoint ranking, analysis populations, and detailed analysis plan will be provided in a separate Statistical Analysis Plan (SAP). The SAP may supersede the protocol specifics, provided modifications to the protocol are justified and clearly documented.

The study consists of an open-label Safety Run-in portion and a double-blind Randomization Phase portion for subjects with relapsed/refractory MCL. The Safety Run-in portion is to evaluate the occurrence of TLS and DLTs with the concurrent administration of ibrutinib and venetoclax. The double-blind portion is to evaluate the efficacy and safety of the combination of ibrutinib and venetoclax in comparison to the combination of ibrutinib and placebo. Endpoints from the Safety Run-in Period will be summarized descriptively and separately from the Randomization Phase data. Endpoints from the Randomization Phase portion will be summarized and analyzed as described in the later sections.

The study includes a separate open-label arm for treatment-naive subjects: A total of approximately 75 subjects, with approximately 50 subjects ≥ 65 years of age and approximately 25 subjects with a TP53 mutation. Endpoints for the Treatment-naive Open-label arm will be summarized and analyzed as described in Section 10.5.2.

10.1 Analysis Population

10.1.1 Safety Run-in Period Evaluable Population

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

10.1.2 Safety Population

The Safety Population consists of all subjects treated with at least one dose of any study drug (ibrutinib or venetoclax) in the double-blind portion. The safety population will be used for the analysis of safety data.

Subjects receiving at least one dose of study drug in the Treatment-naive Open-label arm will be included in the All-Treated population described in Section 10.2.5.

10.1.3 Intent-to-Treat Population in Randomization Phase

The Intent-to-Treat (ITT) Population consists of all subjects randomized into the Randomization Phase portion of the study, with subjects grouped according to the treatment assigned at randomization. It will be used for the analysis of Randomization Phase efficacy data.

10.1.4 All-Treated Population for Treatment-naive Open-label Arm

The All-Treated Population for the open-label arm consists of treatment-naive subjects who received at least one dose of study drug (ibrutinib or venetoclax) and will be used as the primary population for the efficacy and safety analyses.

10.1.5 Additional Analysis Population

Additional analysis populations will be defined in the SAP.

10.2 Endpoints

10.2.1 Safety Run-in Period

- Frequency of TLS and DLTs
- Frequency, severity, and relatedness of AEs
- Frequency of AEs causing study drug discontinuation, or dose reductions or leading to death
- Response (CR, PR), DOR, and PFS
- OS

Unless indicated otherwise, the safety and efficacy data from the Safety Run-in portion will be summarized descriptively including all treated subjects and separately from the double-blind portion of the study. Details will be specified in the SAP.

10.2.2 Randomization Phase Primary Endpoint

The primary efficacy endpoint of the Randomization Phase portion of this study is PFS, defined as the duration from the date of randomization to the date of investigator-assessed disease

progression using the Revised Response Criteria for Malignant Lymphoma (Cheson 2014), or death from any cause, whichever occurs first.

10.2.3 Randomization Phase Secondary Endpoints

Efficacy:

- Complete response rate (CR) based on the best overall response per investigator assessment according to the Revised Response Criteria for Malignant Lymphoma (Cheson 2014).
- Overall response rate (ORR), defined as CR or PR per investigator assessment according to the Revised Response Criteria for Malignant Lymphoma (Cheson 2014).
- MRD-negative remission rate in subjects who achieve CR per investigator assessment. A MRD-negative remission is defined as undetectable MRD at documented CR in subjects who were MRD positive at screening as assessed by flow cytometry in bone marrow and/or peripheral blood, with requirement of confirmation of MRD negativity in the subsequent peripheral blood 12 weeks later. OS, defined as the time from randomization to death from any cause.
- DOR, defined for subjects who achieve an overall response as the time from the first occurrence of response (CR or PR) to disease progression or death, whichever occurs first.
- TTNT, defined as the duration from the date of randomization to the start date of any anti-lymphoma treatment subsequent to study treatment.

Safety:

- Frequency, severity, and relatedness of AEs
- Frequency, severity and management of TLS
- Frequency of AEs requiring discontinuation of study drug or dose reductions, or leading to death

Pharmacokinetics:

- Pharmacokinetics of ibrutinib at steady state
- Pharmacokinetics of venetoclax at steady state

Patient Reported Outcomes (PRO):

- Time to worsening in FACT-Lym subscale of the health-related quality of life questionnaire (FACT-Lym)

10.2.4 Randomization Phase Exploratory Endpoints

- Patient-reported outcomes by EQ-5D-5L
- Medical resource utilization (MRU)

10.2.5 Treatment-naive Open-label Arm Primary Endpoint

The primary efficacy endpoint of the treatment-naive open-label arm is the complete response (CR) rate based on the best overall response according to the Revised Response Criteria for Malignant Lymphoma (Cheson 2014).

10.2.6 Treatment-Naive Open-Label Arm Secondary Endpoints

- Overall response rate (ORR), defined as CR or PR according to the Revised Response Criteria for Malignant Lymphoma (Cheson 2014)
- Duration of Response (DOR), defined for subjects who achieve an overall response as the time from the first occurrence of response (CR or PR) to disease progression or death, whichever occurs first
- Duration of CR, defined for subjects who achieve CR as the time from the first occurrence of CR to disease progression or death, whichever occurs first
- MRD-negative remission rate in subjects who were MRD positive at screening and achieve CR. MRD-negative remission is defined the same as described in Section 10.2.3.
- PFS, defined as the time from the date of the first dose of study treatment to the date of disease progression using the Revised Response Criteria for Malignant Lymphoma (Cheson 2014), or death from any cause, whichever occurs first
- OS, defined as the time from the date of the first dose of study treatment to death from any cause
- TTNT, defined as the duration from the date of the first dose of study treatment to the start date of any anti-lymphoma treatment subsequent to study treatment

10.2.7 Treatment-naive Open-label Arm Exploratory Endpoints

- Identification of biomarkers that are predictive of response (or resistance) to study treatment
- Patient-reported outcome by EQ-5D-5L

10.3 Sample Size Determination (Randomization Phase)

The Randomization Phase sample size will be powered based on the primary endpoint of PFS. Approximately 260 subjects will be randomized at a 1:1 ratio.

The null hypothesis is hazard ratio (HR) ≥ 1 for the ibrutinib and venetoclax group relative to ibrutinib and placebo group. The alternative hypothesis is HR < 1.

With a targeted HR of 0.61 (corresponding to an improvement in median PFS from 14 months to 23 months), 134 PFS events will provide at least 80% power at a 1-sided overall significance level of 0.025. Assuming an enrollment rate of approximately 10-11 subjects per month (a rough estimate based on 3 pieces of enrollment rates), the accrual is projected to complete approximately 21 months from the first subject in. Detailed projection of the enrollment schedule will be provided in a separate document. The actual length of the study and the time to the final analysis will depend on the actual enrollment rate and the number of events that occur.

The sample size and power calculations for the study are based on a 1-sided log-rank test for PFS and were calculated using the software package, East 6.4.1 (Cytel Software Corp, Cambridge, MA).

OS will be analyzed at the time of the primary analysis of PFS when the superiority boundary for PFS is crossed. It is anticipated that 112 and 155 OS events in total will be observed at the interim analysis (at ~40 months) and at the final analysis (at ~57 months), respectively. This is based on the assumption that the median OS for the ibrutinib and placebo group is approximately 30 months (estimated based on data from subjects treated with ibrutinib monotherapy in MCL3001), and the hazard ratio is 0.65 (corresponding to a median OS of 46.2 months for the ibrutinib and venetoclax group). With 155 OS events, the study has ~76% power at a 1-sided overall significance level of 0.025. At the interim analysis, if 112 OS events are observed, the information fraction will be 72.3%. The 1-sided alpha spending is 0.008 at the interim analysis based on a group sequential design with Lan-Demets spending function with O'Brien-Fleming boundary. This will ensure control of the overall type I error for the study. The exact alpha boundary will be calculated using the actual number of events observed at the interim analysis.

The calculations for OS are based on the software package, East 6.5 (Cytel Software Corp, Cambridge, MA).

10.4 Sample Size Determination (Treatment-naive Open-label Arm)

A sample size of 75 treatment-naive subjects is needed to exclude a 35% CR rate at a 1-sided significance level of 0.025 with approximately 80% power, assuming a target CR rate of 51%.

For the subpopulation with a TP53 mutation, a sample size of 48 subjects is needed to exclude a 25% CR rate with approximately 80% power, assuming a target CR rate of 45%. The TP53 population could be a mix of treatment-naive MCL subjects and/or R/R MCL subjects with a TP53 mutation.

10.5 Efficacy Analysis

10.5.1 Randomization Phase

10.5.1.1 Analysis for Primary Efficacy Endpoint

The primary efficacy endpoint of the Randomization Phase portion of this study is PFS, defined as the duration from the date of randomization to the date of investigator-assessed disease progression using the Revised Response Criteria for Malignant Lymphoma (Cheson 2014), or death from any cause, whichever occurs first. PFS will be compared between treatment arms using the stratified log rank test. The HR for PFS will be estimated using a stratified Cox proportional hazards model. The 95% CI for the HR will be provided. The stratification factors will be the same as the randomization stratification factors: prior lines of therapy, ECOG PS, and the TLS categories. The stratification factors will be obtained at the time of randomization. Kaplan Meier estimates and associated plot will be generated. The median PFS for each treatment arm and the associated 95% CI will be constructed using the Brookmeyer-Crowley methodology (Brookmeyer 1982).

10.5.1.2 Analysis for Secondary Efficacy Endpoints

Details of the analysis methods, models, and multiplicity adjustments to control the overall Type 1 error rate will be specified in the SAP.

10.5.1.2.1 Complete Response Rate

CR rate is the proportion of subjects with CR as the best overall response by the time of analysis.

The CR rate will be compared between treatment arms using stratified Cochran-Mantel-Haenszel (CMH) test. The difference in CR rate between treatment arms and its 95% CI will be calculated using the normal approximation to the binomial distribution.

10.5.1.2.2 Overall Response Rate

Overall response rate (ORR) is the proportion of subjects with CR or PR. The analysis methods for ORR will be the same as those described in Section 10.5.1.2.1.

10.5.1.2.3 Minimal Residual Disease-Negative Remission Rate

The MRD-negative remission rate in subjects who were MRD positive at screening and achieve a CR will be calculated. The analysis methods of MRD-negative remission rate will be the same as those described in Section 10.5.1.2.1.

10.5.1.2.4 Overall Survival

The interim analysis for OS will be conducted at the primary analysis of PFS. Details for the interim and final analyses for OS will be specified in the SAP.

In the Randomization Phase, OS will be compared between treatment arms using the stratified log rank test. All deaths will be considered as an event. Data for subjects who have not died by the time of analysis will be censored at the date of last contact. Methods for comparison of OS between treatment arms will be the same as the methods for the primary efficacy endpoint of PFS.

10.5.1.2.5 Duration of Response

In the Randomization Phase, DOR will be summarized using Kaplan-Meier estimates for subjects who achieve an overall response. The censoring rule for DOR is the same as PFS.

10.5.1.2.6 Time-to-next Treatment

In the Randomization Phase, Time-to-next Treatment will be compared between treatment arms. Methods for comparison of TTNT between treatment arms will be the same as the methods for the primary efficacy endpoint of PFS.

10.5.1.2.7 Time to Worsening in FACT-Lym Subscale

In the Randomization Phase, time to worsening in FACT-Lym subscale of the health-related quality of life questionnaire (FACT-Lym) will be compared between treatment arms. Methods for comparison will be the same as the methods for the primary efficacy endpoint of PFS as appropriate.

10.5.2 Treatment-naive Open-label Arm

Analyses in the following sections will be conducted for treatment-naive subjects enrolled in the open-label arm. In addition, analyses on the subjects with a TP53 mutation will be conducted; R/R MCL subjects with a TP53 mutation may be included in the analyses. Analysis details will be specified in the SAP.

10.5.2.1 Analysis for the Primary Efficacy Endpoint

The primary efficacy endpoint of the treatment-naive open-label arm is the CR rate, defined as the proportion of subjects with a CR as the best overall response using the Revised Response Criteria for Malignant Lymphoma (Cheson 2014).

The CR rate will be estimated, and the 95% CI will be calculated based on exact binomial distribution.

10.5.2.2 Analysis for Secondary Efficacy Endpoints

10.5.2.2.1 Analyses of ORR, DOR, Duration of CR, and MRD-Negative Remission Rate

The analysis method for the ORR and the MRD-negative remission rate will be the same as those described for the CR rate.

DOR and the duration of CR will be summarized using Kaplan-Meier estimates for subjects who achieve a response.

10.5.2.2.2 Analyses of PFS, OS, and TTNT

Kaplan-Meier estimates will be provided for PFS, OS, and TTNT. Censoring conventions will be provided in the SAP.

10.6 Safety Analysis

The safety variables to be analyzed include exposure of study drugs, AEs, and clinical laboratory test results (hematology and chemistry). In general, continuous variables will be summarized using descriptive statistics (n, mean, median, standard deviation, standard error and range). Categorical variables will be summarized using frequencies and percentages. No formal statistical testing is planned.

Adverse Events

Adverse event parameters to be evaluated are SOC, preferred terms, incidence, and intensity of AEs; the relationship of AEs to study treatment; and the action taken with respect to study treatment due to AEs.

The verbatim terms used in the eCRF by investigators to identify AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).

Treatment-emergent period is defined as the period of time from the first dose of study treatment, until the earlier of:

- Thirty days following the last dose of ibrutinib or venetoclax, whichever occurs later

OR

- The start date of a new anticancer therapy.

The TEAEs are those events that:

- Are not present prior to the treatment-emergent period and occur during the treatment-emergent period,
- The onset dates are missing and end dates are during the treatment-emergent period,

- Are considered related to study drug by the investigator regardless of the start dates of the events, or
- Are present prior to the treatment-emergent period but worsen in severity during the treatment-emergent period or are subsequently considered related to study drug by the investigator.

All treatment-emergent AEs will be included in the analysis. For each AE, the number and percentage of subjects who experience at least one occurrence of the given event will be summarized. The number and percent of subjects with TEAEs will be summarized according to intensity (CTCAE, v4.03) and drug relationship, as well as categorized by system organ class and preferred term. For analysis, only AEs with a causal relationship of "possibly related" and "related" will be considered as related to study drug. Summaries, listings, datasets, or subject narratives may be provided, as appropriate, for those subjects who die, who discontinue treatment due to an AE, or who experience a severe adverse reaction or a SAE.

Clinical Laboratory Tests

Laboratory tests will be summarized separately for hematology and serum chemistry. All laboratory values will be graded using the CTCAE v4.03. The worst toxicity grade for selected laboratory tests will be tabulated.

10.7 Pharmacokinetic Analysis

10.7.1 Ibrutinib

Ibrutinib and PCI-45227 bioanalytical data will be used in a noncompartmental PK analysis. Plasma concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics. All subjects and samples excluded from the analysis will be clearly documented in the PK report.

Descriptive statistics will be used to summarize ibrutinib and PCI-45227 concentrations at each sampling time point (including, but not limited to: C_{max}, T_{max}, AUC_{last}, and $t_{1/2}$) at each dosing interval.

10.7.2 Venetoclax

Venetoclax bioanalytical data will be used in a noncompartmental PK analysis. Plasma concentrations below the lowest quantifiable concentration will be treated as zero in the summary statistics. All subjects and samples excluded from the analysis will be clearly documented in the PK report.

Descriptive statistics will be used to summarize venetoclax concentrations at each sampling time point and PK parameters (including, but not limited to: C_{max}, T_{max}, and AUC) at each dosing interval.

10.8 Biomarker Analyses

Biomarker exploratory analyses are planned to identify biomarkers that are predictive of response (or resistance) to ibrutinib and venetoclax treatment. Descriptive statistics will be used to summarize these exploratory endpoints.

11 ADVERSE EVENT REPORTING

Timely, accurate, and complete reporting and analysis of safety information from clinical studies are crucial for the protection of subjects, investigators, and the Sponsor, and are mandated by regulatory agencies worldwide. The Sponsor has established Standard Operating Procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of safety information; all clinical studies conducted by the Sponsor or its affiliates will be conducted in accordance with those procedures.

11.1 Definitions

11.1.1 Adverse Events

An AE is any untoward medical occurrence in a 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 a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational study drug, whether or not considered related to the study drug (ICH-E2A 1995).

For the purposes of this clinical study, AEs include events which are either new or represent detectable exacerbations of pre-existing conditions.

The term “disease progression” should not be reported as an AE term. As an example, "worsening of underlying disease" or the clinical diagnosis that is associated with disease progression should be reported.

Adverse events may include, but are not limited to:

- Subjective or objective symptoms provided by the subject and/or observed by the investigator or study staff including laboratory abnormalities of clinical significance
- Any AEs experienced by the subject through the completion of final study procedures
- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with the underlying disease that were not present before the AE reporting period
- Complications that occur as a result of protocol-mandated interventions (eg, invasive procedures such as biopsies).

The following are NOT considered AEs:

- **Pre-existing condition:** A pre-existing condition (documented on the medical history CRF) is not considered an AE unless the severity, frequency, or character of the event worsens during the study period.
- **Per protocol, pre-planned, or elective hospitalization:** Per-protocol hospitalizations for TLS prophylaxis and management are not considered SAEs, unless a hospitalization is prolonged beyond 3 days due to an AE. A hospitalization planned before signing the ICF is not considered an SAE, but rather a therapeutic intervention. However, if during the pre-planned hospitalization an event occurs, which prolongs the hospitalization or meets any other SAE criteria, the event will be considered an SAE. Surgeries or interventions that were under consideration, but not performed before enrollment in the study, will not be considered serious if they are performed after enrollment in the study for a condition that has not changed from its baseline level. Elective hospitalizations for social reasons, solely for the administration of chemotherapy, or due to long travel distances, are also not SAEs.
- **Diagnostic Testing and Procedures:** Testing and procedures should not be reported as AEs or SAEs, but rather the cause for the test or procedure should be reported.
- **Asymptomatic Treatment-related Lymphocytosis:** This event should also not be considered an AE. Subjects with treatment-related lymphocytosis should remain on study treatment and continue with all study-related procedures.

11.1.2 Serious Adverse Events

A SAE based on International Conference on Harmonisation (ICH) and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use is any untoward medical occurrence that at any dose:

- Results in death (ie, the AE actually causes or leads to death)
- Is life-threatening. Life-threatening is defined as an AE in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe. If either the investigator or the Sponsor believes that an AE meets the definition of life-threatening, it will be considered life-threatening.
- Requires in-patient hospitalization > 24 hours or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity (ie, the AE results in substantial disruption of the subject's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect
- Is an important medical event that may not result in death, be immediately life-threatening or require hospitalization, but may be considered an SAE when, based upon appropriate medical judgment, the event may jeopardize the subject or

subject may require intervention to prevent one of the other outcomes listed in this definition. Examples of such events are intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias, or convulsion that does not result in hospitalization; or development of drug dependency or drug abuse

Given that the investigator's perspective may be informed by having actually observed the event, and the Sponsor is likely to have broader knowledge of the drug and its effects to inform its evaluation of the significance of the event, if either the Sponsor or the investigator believes that the event is serious, the event will be considered serious.

11.1.3 Severity Criteria (Grade 1-5)

Definitions found in the Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v4.03) will be used for grading the severity (intensity). The CTCAE v4.03 displays Grades 1 through 5 with unique clinical descriptions of severity for each referenced AE. Should a subject experience any AE not listed in the CTCAE v4.03, the following grading system should be used to assess severity:

- Grade 1 (Mild AE) – experiences which are usually transient, requiring no special treatment, and not interfering with the subject's daily activities
- Grade 2 (Moderate AE) – experiences which introduce some level of inconvenience or concern to the subject, and which may interfere with daily activities, but are usually ameliorated by simple therapeutic measures
- Grade 3 (Severe AE) – experiences which are unacceptable or intolerable, significantly interrupt the subject's usual daily activity, and require systemic drug therapy or other treatment
- Grade 4 (Life-threatening or disabling AE) – experiences which cause the subject to be in imminent danger of death
- Grade 5 (Death related to AE) – experiences which result in subject death

11.1.4 Causality (Attribution)

The investigator is to assess the causal relation (ie, whether there is a reasonable possibility that the study medication caused the event) using the following definitions:

Not Related:	Another cause of the AE is more plausible; a temporal sequence cannot be established with the onset of the AE and administration of the investigational product; or, a causal relationship is considered biologically implausible.
Unlikely:	The current knowledge or information about the AE indicates that a relationship to the investigational product is unlikely.
Possibly Related:	There is a clinically plausible time sequence between onset of the AE and administration of the investigational product, but the AE could also be attributed to concurrent or underlying disease, or the use of other drugs or procedures. Possibly related should be used when the investigational product is one of several biologically plausible AE causes.
Related:	The AE is clearly related to use of the investigational product.

11.2 Unexpected Adverse Events

An “unexpected” AE is an AE that is not listed in the ibrutinib IB/package insert or is not listed at the specificity or severity that has been observed. For example, hepatic necrosis would be “unexpected” (by virtue of greater severity) if the ibrutinib IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be “unexpected” (by virtue of greater specificity) if the ibrutinib IB/package insert listed only cerebral vascular accidents. "Unexpected" also refers to AEs that are mentioned in the ibrutinib IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the study drug under investigation.

11.3 Special Reporting Situations

Special reporting situation on a Sponsor study may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of any study drug
- Suspected abuse/misuse of a study drug
- Inadvertent or accidental exposure to a study drug
- Medication error involving a product (with or without subject exposure to the study drug, eg, name confusion)

If any special reporting situation meets the criteria of an AE, it should be reported on the Serious Adverse Event Report Form. Please report all overdoses on a SAE form regardless of the

outcome. The Serious Adverse Event Report Form should be sent via email or fax to Pharmacyclics LLC Drug Safety or designee within 24 hours of awareness.

11.4 Documenting and Reporting of Adverse Events and Serious Adverse Events by Investigators

11.4.1 Assessment of Adverse Events

Investigators will assess the occurrence of AEs and SAEs at all subject evaluation timepoints during the study. All AEs and SAEs, whether volunteered by the subject, discovered by study personnel during questioning, detected through physical examination, clinically significant laboratory test, or other means, will be recorded in the subject's medical record and on the AEs CRF and, when applicable, on the Serious Adverse Event Report Form.

Each recorded AE or SAE will be described by its duration (ie, start and end dates), severity, regulatory seriousness criteria (if applicable), suspected relationship to the investigational product, and any actions taken.

11.4.2 Adverse Event Reporting Period

All AEs whether serious or non-serious, will be documented from the time the signed and dated ICF is obtained until 30 days following the last dose of study drug. SAEs will be reported to the Sponsor Drug Safety via an SAE reporting form and will be recorded in the eCRF from the time of ICF signing. Non-serious AEs will be recorded in the source documents from the time of ICF signing and will be recorded in the eCRF from the first dose of study drug.

Serious adverse events reported after 30 days following the last dose of study drug should also be reported if considered related to study drug. Resolution information after 30 days should be provided.

Progressive disease should NOT be reported as an event term, but instead symptoms/clinical signs of disease progression may be reported (see Section 11.1.1).

All AEs, regardless of seriousness, severity, or presumed relationship to study drug, must be recorded using medical terminology in the source document. All records will need to capture the details of the duration and the severity of each episode, the action taken with respect to the study drug, investigator's evaluation of its relationship to the study drug, and the event outcome. Whenever possible, diagnoses should be given when signs and symptoms are due to a common etiology (eg, cough, runny nose, sneezing, sore throat, and head congestion should be reported as "upper respiratory infection"). Investigators must record in the CRF their opinion concerning the relationship of the AE to study therapy. All measures required for AE management must be recorded in the source document and reported according to Sponsor instructions.

All deaths should be reported with the primary cause of death as the AE term, as death is typically the outcome of the event, not the event itself. Autopsy and postmortem reports must be

forwarded to the Sponsor, or designee, as outlined above, if allowed per local regulatory guidelines.

If a death occurs within 30 days after the last dose of study drug, the death must be reported to the Sponsor as a SAE.

11.4.3 Expediting Reporting Requirements for Serious Adverse Events

All SAEs (initial and follow-up information) will be reported on the Serious Adverse Event Report Form and sent via email or fax to Pharmacyclics LLC Drug Safety, or designee, within 24 hours of the discovery of the event or information. Pharmacyclics LLC may request follow-up and other additional information from the investigator (eg, hospital admission/discharge notes and laboratory results). The contact information (phone, email and fax) for Pharmacyclics LLC Drug Safety can be found on the Serious Adverse Event Report Form and instructions.

All SAEs that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline, if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct.
- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow up after demonstration of due diligence with follow-up efforts)

The Sponsor assumes responsibility for appropriate reporting of AEs to the regulatory authorities and governing bodies according to the local regulations.

The investigator (or Sponsor where required) must report these events to the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB) that approved the protocol unless otherwise required and documented by the IEC/IRB.

11.4.4 Pregnancy

Before study enrollment, subjects must agree to take appropriate measures to avoid pregnancy. However, should a pregnancy occur in a female study subject, consent to provide follow-up information regarding the outcome of the pregnancy and the health of the infant until 30 days old will be requested.

A female subject or female partner of a male subject must immediately inform the investigator if she becomes pregnant from the time of consent to 90 days after the last dose of study drug(s).

Any female subjects receiving study drug(s) who become pregnant must immediately discontinue study drug. The investigator should counsel the subject, discussing any risks of continuing the pregnancy and any possible effects on the fetus.

Although pregnancy itself is not regarded as an AE, the outcome will need to be documented. Any pregnancy occurring in a female subject or female partner of a male subject must be reported from the time of first dose up until 90 days after the last dose of study drug(s). Any occurrence of pregnancy must be recorded on the Pregnancy Report Form Part I and sent via email or fax to Pharmacyclics LLC Drug Safety, or designee, within 24 hours of learning of the event. All pregnancies will be followed for outcome, which is defined as elective termination of the pregnancy, miscarriage, or delivery of the fetus. For pregnancies with an outcome of live birth, the newborn infant will be followed until 30 days old by completing the Pregnancy Report Form Part II. Any congenital anomaly/birth defect noted in the infant must be reported as a SAE.

11.4.5 Other Malignancies

All new malignant tumors including solid tumors, skin malignancies and hematologic malignancies will be reported for the duration of study treatment and during any protocol-specified follow-up periods including post-progression follow-up for OS. If observed, enter data in the corresponding eCRF.

11.4.6 Eye-Related Adverse Events

New or worsening eye-related symptoms that are Grade 2 or higher, or a symptom that was Grade 2 or higher at baseline and worsens should be evaluated by an ophthalmologist, whose findings should be reported on the ophthalmologic eCRF.

11.4.7 Adverse Events of Special Interest (AESI)

Specific AEs, or groups of AEs, will be followed as part of standard safety monitoring activities by the Sponsor. These events (regardless of seriousness) should be reported on the Serious Adverse Event Report Form and sent via email or fax to Pharmacyclics LLC Drug Safety, or designee, within 24 hours of awareness.

11.4.7.1 Major Hemorrhage

Major hemorrhage is defined as any of the following:

- Any treatment-emergent hemorrhagic AEs of Grade 3 or higher*
- Any treatment-emergent serious adverse events of bleeding of any grade
- Any treatment-emergent central nervous system hemorrhage/hematoma of any grade

*All hemorrhagic events requiring transfusion of red blood cells should be reported as Grade 3 or higher AE per CTCAE v4.03.

Events meeting the definition of major hemorrhage will be captured as an event of special interest according to Section 11.4.7 above.

12 STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS

12.1 Regulatory and Ethical Compliance

This clinical study was designed and will be implemented in accordance with the protocol, the ICH Harmonized Tripartite Guidelines for Good Clinical Practices, with applicable local regulations (including US Code of Federal Regulations [CFR] Title 21 and European Directive 2001/20/EC), and with the ethical principles laid down in the Declaration of Helsinki.

12.2 Institutional Review Board (IRB), Research Ethics Board (REB) and Independent Ethics Committee (IEC) Approval

The investigator will submit this protocol, the ICF, IB, and any other relevant supporting information (eg, all advertising materials or materials given to the subject during the study) to the appropriate IRB/REB/IEC for review and approval before study initiation. Amendments to the protocol and ICF must also be approved by the IRB/REB/IEC before the implementation of changes in this study.

The investigator is responsible for providing the IRB/REB/IEC with any required information before or during the study, such as SAE expedited reports or study progress reports.

The IRB/REB/IEC must comply with current United States (US) regulations (§21 CFR 56) as well as country-specific national regulations and/or local laws.

The following documents must be provided to Pharmacyclics LLC or its authorized representative before entering subjects in this study: (1) a copy of the IRB/REB/IEC letter that grants formal approval; and (2) a copy of the IRB/REB/IEC-approved ICF.

12.3 Informed Consent

The ICF and process must comply with the US regulations (§ 21 CFR Part 50) as well as country-specific national regulations and/or local laws. The ICF will document the study-specific information the investigator or his/her designee provides to the subject and the subject's agreement to participate.

The investigator or designee (designee must be listed on the Delegation of Authority log) **must** explain in terms understandable to the subject the purpose and nature of the study, study procedures, anticipated benefits, potential risks, possible AEs, and any discomfort participation in the study may entail. This process must be documented in the subject's source record. Each subject must provide a signed and dated ICF before any study-related (nonstandard of care) activities are performed. The original and any amended signed and dated consent forms must remain in each subject's study file at the study site and be available for verification by

study monitors at any time. A copy of each signed consent form must be given to the subject at the time that it is signed by the subject.

12.4 Quality Control and Quality Assurance

Sponsor shall implement and maintain quality control and quality assurance procedures to ensure that the study is conducted and data are generated, documented and reported in compliance with the protocol, GCP, and applicable regulatory requirements. This study shall be conducted in accordance with the provisions of the Declaration of Helsinki (October 2008) and all revisions thereof, and in accordance with the Food and Drug Administration (FDA) regulations (21 CFR Parts 11, 50, 54, 56, and 312, Subpart D – Responsibilities of Sponsors and investigators) and with the ICH guidelines on GCP (ICH-E6 1996).

12.5 Protected Subject Health Information Authorization

Information on maintaining subject confidentiality in accordance to individual local and national subject privacy regulations must be provided to each subject as part of the informed consent process (refer to Section 7.1.1.1), either as part of the ICF or as a separate signed document (for example, in the US, a site-specific HIPAA consent may be used). The investigator or designee **must** explain to each subject that for the evaluation of study results, the subject's protected health information obtained during the study may be shared with Pharmacyclics LLC and its designees, regulatory agencies, and IRBs/REBs/IECs. As the study Sponsor, Pharmacyclics LLC will not use the subject's protected health information or disclose it to a third party without applicable subject authorization. It is the investigator's or designee's responsibility to obtain written permission to use protected health information from each subject. If a subject withdraws permission to use protected health information, it is the investigator's responsibility to obtain the withdrawal request in writing from the subject **and** to ensure that no further data will be collected from the subject. Any data collected on the subject before withdrawal will be used in the analysis of study results.

During the review of source documents by the monitors or auditors, the confidentiality of the subject will be respected with strict adherence to professional standards and regulations.

12.6 Study Files and Record Retention

The investigator **must** keep a record of **all** subjects who have consented to enroll in the study. For those subjects subsequently excluded from enrollment, the reason(s) for exclusion is to be recorded.

The investigator/study staff must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. Essential documentation includes, but is not limited to, the IB, signed protocols and amendments, IRB/REB/IEC approval letters (dated), regulatory approval letters (dated, where applicable), signed investigator agreements (eg, Form FDA 1572s or equivalent) and Financial Disclosures,

signed ICFs (including subject confidentiality information), drug dispensing and accountability records, shipping records of investigational product and study-related materials, signed (electronically), dated and completed case report forms (CRFs), and documentation of CRF corrections, SAE forms transmitted to Pharmacyclics LLC and notification of SAEs and related reports, source documentation, normal laboratory values, decoding procedures for blinded studies, curricula vitae for study staff, and all relevant correspondence and other documents pertaining to the conduct of the study.

All essential documentation will be retained by the investigator for at least 2 years after the date the last marketing application is approved for the drug for the indication for which it is being investigated and until there are no pending or contemplated marketing applications; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after formal discontinuation of clinical development of the drug.

The investigator must notify Pharmacyclics LLC and obtain written approval from Pharmacyclics LLC before destroying any clinical study documents or images (eg, scan, radiograph, ECG tracing) at any time. Should an investigator wish to assign the study records to another party or move them to another location, advance written notice will be given to Pharmacyclics LLC. Pharmacyclics LLC will inform the investigator of the date that study records may be destroyed or returned to Pharmacyclics LLC.

Pharmacyclics LLC must be notified in advance of, and Pharmacyclics LLC must provide express written approval of, any change in the maintenance of the foregoing documents if the investigator wishes to move study records to another location or assign responsibility for record retention to another party. If the investigator cannot guarantee the archiving requirements set forth herein at his or her study site for all such documents, special arrangements must be made between the investigator and Pharmacyclics LLC to store such documents in sealed containers away from the study site, so that they can be returned sealed to the investigator for audit purposes.

12.7 Case Report Forms and Record Maintenance

The CRFs will be used to collect the clinical study data and must be completed for each enrolled subject with all required study data accurately recorded such that the information matches the data contained in medical records (eg, physicians' notes, nurses' notes, clinic charts and other study-specific source documents). Authorized study site personnel (ie, listed on the Delegation of Authority log) will complete CRFs designed for this study according to the completion guidelines that will be provided. The investigator will ensure that the CRFs are accurate, complete, legible, and completed within a reasonable period of time. At all times, the investigator has final responsibility for the accuracy and authenticity of all clinical data.

The CRFs exist within an electronic data capture (EDC) system with controlled access managed by Pharmacyclics LLC or its authorized representative for this study. Study staff will be appropriately trained in the use of CRFs and application of electronic signatures before the start

of the study and before being given access to the EDC system. Original data and any changes of data will be recorded using the EDC system, with all changes tracked by the system and recorded in an electronic audit trail. The investigator attests that the information contained in the CRFs is true by providing electronic signature within the EDC system. After database lock, the investigator will receive a copy of the subject data (eg, paper, CD, or other appropriate media) for archiving at the study site.

12.8 Investigational Study Drug Accountability

Ibrutinib, venetoclax/placebo and any Pharmacyclics LLC supplied comparator used must be kept in a locked limited access room. The study drug must not be used outside the context of the protocol. Under no circumstances should the investigator or other site personnel supply ibrutinib, venetoclax/placebo or comparator to other investigators, subjects, or clinics or allow supplies to be used other than as directed by this protocol without prior authorization from Pharmacyclics LLC.

Accountability records for ibrutinib, venetoclax/placebo, and any Pharmacyclics LLC supplied comparator must be maintained and readily available for regular inspection by representatives of Pharmacyclics and are open to inspections by regulatory authorities at any time.

An Investigational Drug Accountability Log must be used for drug accountability. For additional details on investigational study drug management, please refer to the Pharmacy Manual.

12.9 Study Monitoring/Audit Requirements

Representatives of Pharmacyclics LLC or its designee will monitor this study until completion. Monitoring will be conducted through personal visits with the investigator and site staff, remote monitoring, as well as any appropriate communications by mail, fax, email, or telephone. The purpose of monitoring is to ensure that the study is conducted in compliance with the protocol, standard operating procedures (SOPs), and other written instructions and regulatory guidelines, and to ensure the quality and integrity of the data. This study is also subject to reviews or audits.

To assure the accuracy of data collected in the CRFs, it is mandatory that the monitor/auditor have access to all original source documents, including all electronic medical records (EMR) at reasonable times and upon reasonable notice. If access to the EMR cannot be granted to the monitor, the site must ensure that all certified copies of documents are available during monitoring visits for all screened and enrolled subjects. During the review of source documents, every effort will be made to maintain the anonymity and confidentiality of all subjects during this clinical study. However, because of the experimental nature of this treatment, the investigator agrees to allow the IRB/REB/IEC, representatives of Pharmacyclics LLC, its designated agents and authorized employees of the appropriate Regulatory Authority to inspect the facilities used in this study and, for purposes of verification, allow direct access to the hospital or clinic records of all subjects enrolled into this study. A statement to this effect will be

included in the informed consent and permission form authorizing the use of protected health information.

Pharmacyclics LLC or its authorized representative may perform an audit at any time during or after completion of this study. All study-related documentation must be made available to the designated auditor. In addition, a representative of the FDA or other Regulatory Agencies may choose to inspect a study site at any time before, during, or after completion of the clinical study. In the event of such an inspection, Pharmacyclics LLC will be available to assist in the preparation. All pertinent study data should be made available as requested to the Regulatory Authority for verification, audit, or inspection purposes.

12.10 Investigator Responsibilities

A complete list of investigator responsibilities are outlined in the clinical trial research agreement and the investigator agreements (eg, Statement of Investigator Form FDA 1572s or equivalent), both of which are signed by the investigator before commencement of the study. In summary, the investigator will conduct the study according to the current protocol; will read and understand the IB; will obtain IRB/REB/IEC approval to conduct the study; will obtain informed consent from each study participant; will maintain and supply to the Sponsor or designee, auditors and regulatory agencies adequate and accurate records of study activity and drug accountability for study-related monitoring, audits, IRB/REB/IEC reviews and regulatory inspections; will report SAEs to the Sponsor or designee and IRB/ REB/IEC according to the specifics outlined in this protocol; will personally conduct or supervise the study; and will ensure that colleagues participating in the study are informed about their obligations in meeting the above commitments.

12.11 Sponsor Responsibilities

A complete list of the Sponsor responsibilities is outlined in the clinical trial research agreement and in the laws and regulation of the country in which the research is conducted. In summary, the Sponsor will select qualified investigators, provide them with the information they need to properly conduct the study, ensure adequate monitoring of the study, conduct the study in accordance with the general investigational plan and protocols and promptly inform investigators, health and regulatory agencies/authorities as appropriate of significant new adverse effects or risks with respect to the drug.

12.12 Financial Disclosure

A separate financial agreement will be made between each principal investigator and Pharmacyclics LLC or its authorized representative before the study drug is delivered.

For this study, each investigator and sub-investigator (as designated on the investigator agreements [eg, Form FDA1572 or equivalent]) will provide a personally signed Financial Disclosure Form in accordance with § 21 CFR 54. Each investigator will notify

Pharmacyclics LLC or its authorized representative of any relevant changes in financial disclosure information during the conduct of the study and for 1 year after the study has been completed.

12.13 Liability and Clinical Trial Insurance

In the event of a side effect or injury, appropriate medical care as determined by the investigator/designee will be provided.

The ICF will include a description of treatment in the event of a study-related injury and handling of the costs associated therewith, incorporating country-specific national regulations and/or local laws. Financial compensation for lost wages, disability or discomfort due to the study is not available.

Clinical trial insurance has been undertaken according to the laws of the countries where the study will be conducted. An insurance certificate will be made available to the participating sites at the time of study initiation.

12.14 Protocol Amendments

Pharmacyclics LLC will initiate any change to the protocol in a protocol amendment document. The amendment will be submitted to the IRB/REB/IEC together with, if applicable, a revised model ICF. Written documentation of IRB/REB/IEC and required site approval must be received by Pharmacyclics LLC before the amendment may take effect at each site. Additionally under this circumstance, information on any change in risk and/or change in scope must be provided to subjects already actively participating in the study, and they must read, understand and sign each revised ICF confirming willingness to remain in the trial.

No other significant or consistent change in the study procedures, except to eliminate an immediate hazard, shall be effected without the mutual agreement of the investigator and Pharmacyclics LLC.

12.15 Publication of Study Results

Pharmacyclics LLC may use the results of this clinical study in registration documents for Regulatory Authorities in the US or abroad. The results may also be used for papers, abstracts, posters, or other material presented at scientific meetings or published in professional journals or as part of an academic thesis by an investigator. In all cases, to avoid disclosures that could jeopardize proprietary rights and to ensure accuracy of the data, Pharmacyclics LLC reserves the right to preview all manuscripts and abstracts related to this study, allowing Pharmacyclics LLC sufficient time to make appropriate comments before submission for publication.

In most cases, the investigators at the sites with the highest accruals of eligible subjects shall be listed as lead authors on manuscripts and reports of study results. The medical monitor, study director and/or lead statistician may also be included in the list of authors. This custom can be

adjusted upon mutual agreement of the authors and Pharmacyclics LLC and in accordance with current standards for authorship as recorded in professional conference and journal submission instructions.

12.16 Study Discontinuation

The Sponsor reserves the right to terminate the study at any time. Should this be necessary, both the Sponsor and the investigator will arrange discontinuation procedures. In terminating the study, the Sponsor and the investigator will assure that adequate consideration is given to the protection of the subjects' interests.

12.17 Study Completion

The study is expected to be completed approximately 5 years from the first subject enrolled, the time all subjects have exited the study for any reason, or study termination at the Sponsor's discretion, whichever occurs first.

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14 APPENDICES

Appendix A. Schedule of Assessments – Standard Ramp-up Schedule

	Week	1			2			3	4	5	6	8	10	Week 13 & beyond[a] (±7 days)	Response Assessment[b] (±7 days)	EOT[c] (±7 days)	RFU[d]	LTFU[w]
	Day	1	2	3	1	2	3	1	1	1	1	1 (±1 day)	1 (±1 day)				(±14 days)	
Study Drug Administration																		
Ibrutinib 560 mg daily		Continuous															----	
Venetoclax daily dose / placebo		20mg			50mg			100mg	200mg	400mg continuous target daily dose							----	
Procedure	**Screening Day -28 to -1**																	
Informed consent	X																	
Medical history/demographic/prior treatment	X	X																
Confirm eligibility	X	X																
Concomitant medications[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		
AEs[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		
Physical exam[g]	X	X			X			X	X	X	X	X	X	X		X		
Vital signs [h]	X	X	X		X	X		X	X	X	X	X	X	X		X		
ECOG	X	X						X			X			X				
ECG[i]	X															X		
Disease Assessment																		
CT/PET/MRI/endoscopy[j]	X														X		X	
Tumor tissue[k]	X														(X)			
Bone marrow biopsy[x]	X														(X)			
B-symptoms	X														X		X	
Overall response assessment[m]															X		X	
MRD Bone marrow aspirate[l]	X														(X)			
MRD assessment in blood[n]		X													X	X		
TLS Risk Assessment[o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
PRO[p]		X												X				
Medical resource utilization (MRU)		Hospitalizations, emergency department visits, hematopoietic growth factor use to be documented throughout study treatment period																
Biomarker Bone marrow Aspirate[l]	X														(X)			
Biomarker Peripheral Blood[u]		X													X	X	X	

Week		**1**			**2**			**3**	**4**	**5**	**6**	**8**	**10**	**Week 13 & beyond[a] (±7 days)**	**Response Assessment[b] (±7 days)**	**EOT[c] (±7 days)**	**RFU[d]**	**LTFU[w]**
Day		**1**	**2**	**3**	**1**	**2**	**3**	**1**	**1**	**1**	**1**	**1 (±1 day)**	**1 (±1 day)**				**(±14 days)**	
Study Drug Administration																		
Ibrutinib 560 mg daily		**Continuous**															**----**	
Venetoclax daily dose / placebo		**20mg**			**50mg**			**100mg**	**200mg**	**400mg continuous target daily dose**							**----**	
Procedure	**Screening Day -28 to -1**																	
Hematology[q]	X	X			X			X	X	X	X	X	X	X	X	X		
Blood chemistry[r]	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		
Urinalysis[s]	X															X		
Serum or Urine Pregnancy	X	X														X		
Hepatitis serologies[t]	X																	
Coagulation panel	X																	
Buccal Swab		X																
Serum β_2-microglobulin	X																	
PK blood sampling[v]											X							
Survival status, incl. other malignancies[w]																		X
Subsequent Anticancer Therapy																	X	X

Abbreviations:
EOT = End-of-Treatment Visit; RFU = Response Follow-up Visit; LTFU = Long-term Follow up; PRO = patient-reported outcome;

Footnotes:

[a] After week 13, study drug dispensing visits are scheduled every 4 weeks for one year; every 8 weeks during the 2nd and 3rd years; and every 12 weeks thereafter until treatment discontinuation.

[b] Response assessment visits are scheduled on Week 13 Day 1 (±7 days); every 12 weeks for the remainder of the 1st year; every 16 weeks during the 2nd and 3rd years, and every 24 weeks thereafter until PD. In addition, response assessments can be performed as clinically indicated to confirm response or progression.

[c] An EOT visit will occur 30 days (±7) from the last dose of study drug or prior to the start of a new anticancer treatment.

[d] Subjects who discontinue for reasons other than PD will have follow-up response assessments (based on Week 1 Day 1 for a subject) every 12 weeks (± 14 days) from the 1st dose for the 1st year; every 16 weeks (± 14 days) during the 2nd and 3rd years; and every 24 weeks (± 14 days) thereafter until PD.

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

[f] See Section 11 for details regarding the reporting of AEs.

[g] A complete physical examination (at Screening and EOT) will include, at a minimum, the general appearance of the subject, height (may use prior height measurement if available in source documents) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. At other timepoints, a limited symptom-directed physical exam will be performed. The physical exam should include an eye-related symptom assessment.

[h] Vital signs (blood pressure, heart rate, and body temperature) will be assessed after the subject has rested in the sitting position for ≥ 3 minutes.

[i] A single 12-lead ECG will be done at Screening and at the EOT visit. Subjects should be in a supine position and resting for at least 10 minutes before obtaining the ECG. During the treatment period, ECG's may be performed at the investigator's discretion, particularly in subjects with arrhythmic symptoms (eg, palpitations, lightheadedness) or new onset dyspnea.

[j] CT and PET or PET/CT: A CT scan (with contrast unless contraindicated) of the neck, chest, abdomen, and pelvis and any other disease sites (eg, extremity) and a PET or PET/CT scan (CT should be of diagnostic quality) are required for the pretreatment tumor assessment within 28 days of the first dose. Thereafter, CT scans will be done for tumor assessments on Week 13 Day 1 (±7 days); every 12 weeks for the remainder of the 1st year; every 16 weeks during the 2nd and 3rd years; and every 24 weeks thereafter until PD. PET or PET/CT is mandatory to confirm a CR. For MRI refer to Section 7.1.3.2.

[k] A total of up to 20 slides of fresh or the most recent dated FFPE archival tumor biopsy tissue will be required at study entry. An optional tumor biopsy should be collected at the time of disease progression if feasible.

[l] A unilateral bone marrow aspirate will be done at Screening or up to 28 days before the 1st administration of study drug for MRD testing. A 2nd bone marrow aspirate will be performed in all subjects who achieve a CR. Subsequent bone marrow aspirates will be obtained as needed (ie, if MRD in BM at CR was positive, and subject remains CR) to confirm MRD-negative CR.

[m] Response assessments will be completed by the investigator using the Revised Response Criteria for Malignant Lymphoma (Cheson 2014).

[n] Blood will be drawn for MRD assessments at baseline, at documented complete response and onwards every 12 weeks (±7 days) for the remainder of the 1st year; every 16 weeks during the 2nd and 3rd years; and every 24 weeks thereafter until PD.

[o] Risk of TLS is to be re-assessed prior to each venetoclax dose ramp-up. Administration of prophylaxes as needed is to occur within 72 hours of dosing. Subjects with high tumor burden at baseline may be hospitalized for a minimum of the first 24 hours of treatment (and up to 48 hours at the discretion of the investigator) at the start of the 20 mg (ramp-up dose) and the 50 mg dose levels and blood chemistry (creatinine, uric acid, potassium, phosphorus, calcium, and albumin, if available) should be monitored pre-dose and 4±1, 8±1, 12±1, 24±2 and as needed 48±2 hours after the venetoclax dose. Additionally, for high-risk TLS subjects, post-dose blood chemistries will be monitored at pre-dose and 6-8 hours after the venetoclax dose during ramp up of the 100 mg, 200 mg and 400 mg dose levels. For all other subjects, blood chemistry will be monitored pre-dose, 6-8 and 24±2 hours after the venetoclax dose at the 20 mg and the 50 mg dose levels.

[p] PRO questionnaires (FACT-Lym, EQ-5D-5L) should be completed prior to any assessments, and before being clinically evaluated by the study nurse or physician. The questionnaires will be administered on Week 1 Day 1, Week 13 Day 1 (±7 days); every 4 weeks for the remainder of the 1st year; every 8 weeks during the 2nd and 3rd years; and every 12 weeks thereafter until disease progression.

[q] Hematology includes complete blood count with differential and platelet counts.

[r] Blood chemistry: Sodium, potassium, chloride, BUN, creatinine, glucose, calcium, total protein, albumin, AST, ALT, alkaline phosphatase, total bilirubin, LDH, phosphate, uric acid, urea, magnesium and bicarbonate. Serum creatinine, uric acid, potassium, phosphorus and calcium should be assessed within 72 hours prior to the 1st venetoclax dose and before each dose increase.

[s] Urinalysis: pH, ketones, specific gravity, bilirubin, protein, blood, and glucose.

[t] Hepatitis C antibody, hepatitis B surface antigen and hepatitis B core antibody will be evaluated. If hepatitis B core antibody or hepatitis B surface antigen or Hepatitis C antibody is positive, then PCR to quantitate hepatitis B DNA or hepatitis C RNA must be performed. DNA PCR needs to be confirmed negative (< 29 U) prior to enrollment in subjects who are hepatitis B core antibody or hepatitis B surface antigen positive. For subjects who are hepatitis C antibody positive, hepatitis C PCR needs to be confirmed negative prior to enrollment.

[u] Blood biomarker samples will be drawn at baseline, at documented complete response and onwards every 12 weeks (±7 days) for the remainder of the 1st year; every 16 weeks during the 2nd and 3rd years; and every 24 weeks thereafter until PD.

[v] PK samples will be drawn at protocol-specified timepoints: pre-dose (30min), 1hr (±15min), 2hrs (±15min), 4hrs (±30min), 6hrs (±30min), and 8hrs (±1hr) post dose.

[w] After progression, survival status, other malignancies and subsequent anticancer therapy will be collected approximately every 12 weeks (based on Week 1 Day 1 for a subject) until death, withdrawal by subject, loss to follow-up, or study terminated by Sponsor, whichever comes first.

[x] A unilateral bone marrow biopsy will be done at Screening or up to 28 days before the 1st administration of study drug for standard pathology. A 2nd bone marrow biopsy will be performed in subjects with positive bone marrow involvement at baseline by standard pathology who achieve a CR.

Appendix B. Schedule of Assessments – Treatment-naive Open-label Arm

	Week	**1**			**2**			**3**	**4**		**5**	**6**	**8**	**10**	**Week 13 & beyond[a] (±7 days)**	**Response Assessment[b] (±7 days)**	**EOT[c] (±7 days)**	**RFU[d]**	**LTFU[w]**
	Day	**1**	**2**	**3**	**1**	**2**	**3**	**1**	**1**	**7**	**1**	**1**	**1 (±1 day)**	**1 (±1 day)**				**(±14 days)**	
Study Drug Administration																			
Ibrutinib 560 mg daily		**Continuous**																**----**	
Venetoclax daily dose		**20mg**			**50mg**			**100mg**	**200mg**		**400mg continuous target daily dose**							**----**	
Procedure	**Screening Day -28 to -1**																		
Informed consent	X																		
Medical history/ demographic/ central lab pathology report confirmation or tissue test	X	X																	
Confirm eligibility*	X	X																	
Concomitant medications[e]	X	X	X	X	X	X	X	X	X		X	X	X	X	X		X		
AEs[f]	X	X	X	X	X	X	X	X	X		X	X	X	X	X		X		
Physical exam[g]	X	X			X			X	X		X	X	X	X	X		X		
Vital signs [h]	X	X	X		X	X		X	X		X	X	X	X	X		X		
ECOG	X	X						X				X			X				
ECG[i]	X																X		
Disease Assessment																			
CT/PET/MRI/endoscopy[j]	X														X	X		X	
Tumor tissue[k]	X															(X)			
Bone marrow biopsy[x]	X															(X)			
B-symptoms	X															X		X	
Overall response assessment[m]															X	X		X	
MRD Bone marrow aspirate[l]	X															(X)			
MRD assessment in blood[n]		X														X	X		
TLS Risk Assessment[o]	X	X	X	X	X	X	X	X	X		X	X	X	X	X				
PRO[p]		X													X				
Medical resource utilization (MRU)	Hospitalizations, emergency department visits, hematopoietic growth factor use to be documented throughout study treatment period																		
Biomarker Bone marrow Aspirate[l]	X															(X)			
Biomarker Peripheral Blood[u]		X														X	X	X	
Hematology[q]	X	X			X			X	X		X	X	X	X	X	X	X		
Blood chemistry[r]	X	X	X	X	X	X	X	X	X		X	X	X	X	X		X		

Week		**1**			**2**			**3**	**4**		**5**	**6**	**8**	**10**	**Week 13 & beyond[a] (±7 days)**	**Response Assessment[b] (±7 days)**	**EOT[c] (±7 days)**	**RFU[d]**	**LTFU[w]**
Day		**1**	**2**	**3**	**1**	**2**	**3**	**1**	**1**	**7**	**1**	**1**	**1 (±1 day)**	**1 (±1 day)**				**(±14 days)**	
Study Drug Administration																			
Ibrutinib 560 mg daily		**Continuous**																**----**	
Venetoclax daily dose		**20mg**			**50mg**			**100mg**	**200mg**		**400mg continuous target daily dose**							**----**	
Procedure	**Screening Day -28 to -1**																		
Urinalysis[s]	X																X		
Serum or Urine Pregnancy	X	X															X		
Hepatitis serologies[t]	X																		
Coagulation panel	X																		
Buccal Swab		X																	
Serum β_2-microglobulin	X																		
PK blood sampling[v]										X		X			X				
Survival status, incl. other malignancies[w]																			X
Subsequent Anticancer Therapy																		X	X

Abbreviations:
EOT = End-of-Treatment Visit; RFU = Response Follow-up Visit; LTFU = Long-term Follow up; PRO = patient-reported outcome; *TP53 mutation test by local or central lab

Footnotes:

[a] After week 13, study drug dispensing visits are scheduled every 4 weeks for 1 year; every 8 weeks during the 2nd and 3rd years; and every 12 weeks thereafter until treatment discontinuation.

[b] Response assessment visits are scheduled on Week 13 Day 1 (±7 days); every 12 weeks for the remainder of the 1st year; every 16 weeks during the 2nd and 3rd years, and every 24 weeks thereafter until PD. In addition, response assessments can be performed as clinically indicated to confirm response or progression. PET scans will be performed at screening, at Week 13, Week 25, Week 49 and at suspected CR.

[c] An EOT visit will occur 30 days (±7) from the last dose of study drug or prior to the start of a new anticancer treatment.

[d] Subjects who discontinue for reasons other than PD will have follow-up response assessments (based on Week 1 Day 1 for a subject) every 12 weeks (± 14 days) from the 1st dose for the 1st year; every 16 weeks (± 14 days) during the 2nd and 3rd years; and every 24 weeks (± 14 days) thereafter until PD.

[e] Concomitant medications are collected from 30 days before 1st dose through the 30 days after the last dose of study drug.

[f] See Section 11 for details regarding the reporting of AEs.

[g] A complete physical examination (at Screening and EOT) will include, at a minimum, the general appearance of the subject, height (may use prior height measurement if available in source documents) and weight, and examination of the skin, eyes, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. At other timepoints, a limited symptom-directed physical exam will be performed. The physical exam should include an eye-related symptom assessment.

[h] Vital signs (blood pressure, heart rate, and body temperature) will be assessed after the subject has rested in the sitting position for ≥ 3 minutes.

[I] A single 12-lead ECG will be done at Screening and at the EOT visit. Subjects should be in a supine position and resting for at least 10 minutes before obtaining the ECG. During the treatment period, ECG's may be performed at the investigator's discretion, particularly in subjects with arrhythmic symptoms (eg, palpitations, lightheadedness) or new onset dyspnea.

[j] CT and PET or PET/CT: A CT scan (with contrast unless contraindicated) of the neck, chest, abdomen, and pelvis and any other disease sites (eg, extremity) and a PET or PET/CT scan (CT should be of diagnostic quality) are required for the pretreatment tumor assessment within 28 days of the 1st dose. Thereafter, CT scans will be done for tumor assessments on Week 13 Day 1 (±7 days); every 12 weeks for the remainder of the 1st year; every 16 weeks during the 2nd and 3rd years; and every 24 weeks thereafter until PD. PET or PET/CT is mandatory for all subjects at the Week 13 visit (+/- 7 days), the Week 25 visit (+/- 7 days) for subjects in SD or PR who did not achieve CR at Week 13, and at the 1-year visit (Week 49 +/- 7 days) for all subjects, as well as at any other time point to confirm a CR. Other PET or PET/CT scans that are NOT mandatory can be performed within a 30-day window of the visit. For MRI refer to Section 7.1.3.2.

[k] A total of up to 20 slides of fresh or the most recent dated FFPE archival tumor biopsy tissue will be required at study entry. An optional tumor biopsy should be collected at the time of disease progression if feasible.

[l] A unilateral bone marrow aspirate will be done at Screening or up to 28 days before the 1st administration of study drug for MRD testing. A 2nd bone marrow aspirate will be performed in all subjects who achieve a CR. Subsequent bone marrow aspirates will be obtained as needed (ie, if MRD in BM at CR was positive, and subject remains CR) to confirm MRD-negative CR.

[m] Response assessments will be completed by the investigator using the Revised Response Criteria for Malignant Lymphoma (Cheson 2014).

[n] Blood will be drawn for MRD assessments at baseline, at documented complete response and onwards every 12 weeks (±7 days) for the remainder of the 1st year; every 16 weeks during the 2nd and 3rd years; and every 24 weeks thereafter until PD.

[o] Risk of TLS is to be re-assessed prior to each venetoclax dose ramp-up. Administration of prophylaxes as needed is to occur within 72 hours of dosing. Subjects with high tumor burden at baseline may be hospitalized for a minimum of the first 24 hours of treatment (and up to 48 hours at the discretion of the investigator) at the start of the 20 mg (ramp-up dose) and the 50 mg dose levels and blood chemistry (creatinine, uric acid, potassium, phosphorus, calcium, and albumin, if available) should be monitored pre-dose and 4±1, 8±1, 12±1, 24±2 and as needed 48±2 hours after the venetoclax dose. Additionally, for high risk TLS subjects, post-dose blood chemistries will be monitored at pre-dose and 6-8 hours after the venetoclax dose during ramp up of the 100 mg, 200 mg and 400 mg dose levels. For all other subjects, blood chemistry will be monitored pre-dose, 6-8 and 24±2 hours after the venetoclax dose at the 20 mg and the 50 mg dose levels.

[p] PRO questionnaires (EQ-5D-5L) should be completed prior to any assessments, and before being clinically evaluated by the study nurse or physician. The questionnaires will be administered on Week 1 Day 1, Week 13 Day 1 (±7 days); every 4 weeks for the remainder of the 1st year; every 8 weeks during the 2nd and 3rd years; and every 12 weeks thereafter until disease progression.

[q] Hematology includes complete blood count with differential and platelet counts.

[r] Blood chemistry: Sodium, potassium, chloride, BUN, creatinine, glucose, calcium, total protein, albumin, AST, ALT, alkaline phosphatase, total bilirubin, LDH, phosphate, uric acid, urea, magnesium and bicarbonate. Serum creatinine, uric acid, potassium, phosphorus and calcium should be assessed within 72 hours prior to the first venetoclax dose and before each dose increase.

[s] Urinalysis: pH, ketones, specific gravity, bilirubin, protein, blood, and glucose.

[t] Hepatitis C antibody, hepatitis B surface antigen and hepatitis B core antibody will be evaluated. If hepatitis B core antibody or hepatitis B surface antigen or Hepatitis C antibody is positive, then PCR to quantitate hepatitis B DNA or hepatitis C RNA must be performed. DNA PCR needs to be confirmed negative (< 29 U) prior to enrollment in subjects who are hepatitis B core antibody or hepatitis B surface antigen positive. For subjects who are hepatitis C antibody positive, hepatitis C PCR needs to be confirmed negative prior to enrollment. Subjects who are Hepatitis B surface antigen positive are excluded from the trial.

[u] Blood biomarker samples will be drawn at baseline, at documented complete response and onwards every 12 weeks (±7 days) for the remainder of the 1st year; every 16 weeks during the 2nd and 3rd years; and every 24 weeks thereafter until PD.

[v] PK samples will be drawn at Week 4 Day 7 and Week 6 Day 1: pre-dose (±30min), 1hr (±15min), 2hrs (±15min), 4hrs (±30min), 6hrs (±30min), and 8hrs (±1hr) post dose. In addition, at Week 13: pre-dose (±30min), 1hr (±15min), 2hrs (±15min). Unscheduled PK sampling is allowed based on Medical Monitor request, e.g. dose modification (at least 7 days after dose modification)

[w] After progression, survival status, other malignancies and subsequent anticancer therapy will be collected approximately every 12 weeks (based on Week 1 Day 1 for a subject) until death, withdrawal by subject, loss to follow-up, or study terminated by Sponsor, whichever comes first.

[x] A unilateral bone marrow biopsy will be done at Screening or up to 28 days before the first administration of study drug for standard pathology. A second bone marrow biopsy will be performed in subjects with positive bone marrow involvement at baseline by standard pathology who achieve a CR.

Appendix C. ECOG Status Scores

Status	Eastern Cooperative Oncology Group (ECOG) Performance Status**
0	Fully active, able to carry on all predisease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light housework, office work.
2	Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

**Oken MM, Creech RH, Tormey DC, et al: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol. 5:649-655, 1982.
Available at: http://www.ecog.org/general/perf_stat html. Accessed January 4, 2008.

Appendix D. Sample List of Cautionary Medications

Cautionary medications are defined as follows. Refer to Section 6.2.1.1 and Section 6.2.1.2 on instructions for concomitant use of CYP3A inhibitors and inducers with ibrutinib and venetoclax, respectively.

The below medications apply to both ibrutinib and venetoclax unless otherwise specified.

INHIBITORS OR INDUCERS		SUBSTRATES
Strong CYP3A inhibitors:	**Strong CYP3A inducers:**	**Substrates of P-gp**
Boceprevir	Avasimibe	aliskiren
Clarithromycin	Carbamazepine	Ambrisentan
Cobicistat	phenobarbitalPhenobarbital	Colchicines
Conivaptan	Phenytoin	dabigatran etexilate
Indinavir	Rifabutin	Digoxin
Itraconazole	Rifampin	Everolimus
Ketoconazole	St. John's Wort	Fexofenadine
Lopinavir		Lapatinib
Mibefradil		Loperamide
Nefazodone	**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*		Topotecan
Moderate CYP3A inhibitors:	**Weak CYP3A inducers:**	**Substrates of BCRP (Venetoclax only)**
Aprepitant	Amprenavir	Methotrexate
Amprenavir	aprepitant,	mitoxantrone
Atazanavir	Armodafinil	irrinotecan
Ciprofloxacin	Clobazamechinacea	lapatinib
Crizotinib	glucocorticoids (eg, prednisone)	rosuvastatin
Darunavir/Ritonavir	Nevirapine	sulfasalazine
Dronedarone	Pioglitazone	topotecan
Erythromycin	Rufinamide	
Diltiazem	Vemurafenib	
Fluconazole		
Fosamprenavir		
Imatinib		
Verapamil		

INHIBITORS OR INDUCERS		SUBSTRATES
Weak CYP3A inhibitors:	**Inhibitors of OATP1B1/B3 (Venetoclax)**	**Substrates of OATP1B1/B3 (Venetoclax only)**
Alprazolam	Gemfibrozil	atrasentan
Amiodarone	Eltrombopag	atorvastatin
amlodipine	Cyclosporine	ezetimibe
atorvastatin	Tipranavir	fluvastatin
bicalutamide		glyburide
cilostazol		olmesartan
Cimetidine	**Inhibitors of BCRP (Venetoclax)**	rosuvastatin
Cyclosporine	Cyclosporine	simvastatin acid
Fluvoxamine	Geftinib	pitavastatin
fluoxetine		pravastatin
ginkgo		repaglinide
goldenseal	**Inhibitors of P-gp (Venetoclax)**	telmisartan
Isoniazid	Amiodarone	valsartan
Nilotinib	Azithromycin	
oral contraceptives	Captopril	
Pazopanib	Carvedilol	
Ranitidine	Cyclosporine	
Ranolazine	Dronedarone	
Suboxone	Felodipine	
tipranavir/ritonavir	Quercetin	
Ticagrelor	Quinidine	
Zileuton	Ranolazine	
	Ticagrelor	

*Allowed to dose with 140 mg ibrutinib based on clinical data
Note that this is not an exhaustive list. Further information can be found at the following websites:
http://medicine.iupui.edu/clinpharm/ddis/main-table/ and
http://www fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499 htm.

In addition to the medications listed in this table, subjects receiving venetoclax should not consume grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or starfruits.

Appendix E. 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, eg, 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 $\leq$ 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 disease in marrow	Normal by morphology; if indeterminate, IHC negative
	Partial Metabolic Response (PMR)	**Partial Remission (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	$\geq$ 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 5mm x 5mm as the default value. When no longer visible, 0x0 mm For a node > 5mm x 5mm, 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
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 (eg, 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
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology, eg, 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

* 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).

SPD – sum of the product of the perpendicular diameters for multiple lesions

LDi – Longest transverse diameter of a lesion

SDi – Shortest axis perpendicular to the LDi

PPD – Cross product of the LDi and perpendicular diameter

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, eg, liver, spleen, kidneys, lungs, etc, gastrointestinal 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, eg, gastrointestinal tract, liver, and bone marrow, FDG uptake may be greater than mediastinum with CMR, but should be no higher than surrounding normal physiologic uptake, eg, with marrow activation due to chemotherapy or myeloid growth factors.

**PET Five Point Scale (5-PS)

1. No uptake 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 F. Child-Pugh Score for Subjects with Liver Impairment

Measure	1 point	2 points	3 points
Total bilirubin, μmol/L (mg/dL)	< 34 (< 2)	34-50 (2-3)	> 50 (> 3)
Serum albumin, g/L (g/dL)	> 35 (> 3.5)	28-35 (2.8-3.5)	< 28 (< 2.8)
PT/INR	< 1.7	1.71-2.30	> 2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)

Points	Class
5-6	A
7-9	B
10-15	C

Sources:

Child CG, Turcotte JG. “Surgery and portal hypertension”. In Child CG. The liver and portal hypertension. Philadelphia:Saunders. 1964. pp. 50-64.

Pugh RN, Murray-Lyon IM, Dawson L, et al. “Transection of the oesophagus for bleeding oesophageal varices”. The British journal of surgery, 1973;60: 646-9.

Appendix G. Howard Criteria for Laboratory and Clinical TLS* (Howard et al, NEJM 2011)

Metabolic Abnormality	Criteria for Classification of Laboratory Tumor Lysis Syndrome	Criteria for Classification of Clinical Tumor Lysis Syndrome
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 < 1.12 (0.3 mmol/liter)†	Cardiac dysrhythmia, sudden death, seizure, neuromuscular irritability (tetany, paresthesias, 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‡	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 hr

* 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.

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

‡ 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 2007).

Note: Only post-dose laboratory assessments will be considered when applying Howard Criteria for laboratory and clinical TLS.

Appendix H. Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome (TLS)

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 (eg, 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 TLS (eg, 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. o 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 (eg, 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. o 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.
Hyperuricemia	
Uric acid ≥ 8.0 mg/dL (476 µmol/L)	• Consider rasburicase (0.2 mg/kg as an intravenous infusion over 30 minutes). o 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.

Abnormality	Management Recommendations[1,2]
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 (≥ 0.027mmol/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 (eg, 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.
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 (eg, 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. FACT-Lym questionnaire (version 4)

(http://www.facit.org/FACITOrg/Questionnaires)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4

GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box ☐ and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4

GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
LEU1	I am bothered by lumps or swelling in certain parts of my body (e.g., neck, armpits, or groin)	0	1	2	3	4
BRM3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
ES3	I have night sweats	0	1	2	3	4
LYM1	I am bothered by itching	0	1	2	3	4
LYM2	I have trouble sleeping at night	0	1	2	3	4
BMT6	I get tired easily	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
Ga1	I have a loss of appetite	0	1	2	3	4
HI8	I have trouble concentrating	0	1	2	3	4
N3	I worry about getting infections	0	1	2	3	4
LEU6	I worry that I might get new symptoms of my illness	0	1	2	3	4
LEU7	I feel isolated from others because of my illness or treatment	0	1	2	3	4
BRM9	I have emotional ups and downs	0	1	2	3	4
LEU4	Because of my illness, I have difficulty planning for the future	0	1	2	3	4

Appendix J. EQ-5D-5L

(English version for the UK)

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐