TITLE: *An Open-Label Trial of Venetoclax with Ibrutinib in Relapsed or Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Leukemia*

NCT03045328

Coordinating Center of a Multi-Center Study

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Regulatory Information

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Protocol Synopsis

Study Title	An Open-Label Trial of Venetoclax with Ibrutinib in Relapsed or Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Leukemia
Study Design	This is an open-label non-randomized two-center phase 2 study evaluating the safety and efficacy of concurrent therapy with ibrutinib and venetoclax in subjects with relapsed or refractory CLL/SLL. Screening, including CT scans and bone marrow aspirate and biopsy, must be performed within 28 days of study drug initiation. Ibrutinib 420 mg PO daily will be initiated on Week 1. Intra-patient dose ramp-up of venetoclax will be initiated at Week 9 at 20 mg PO daily with the dose increasing weekly to 50 mg; 100 mg; 200 mg; and 400 mg as per FDA-approved dosing guidelines. Upon completion of ibrutinib + venetoclax combination treatment at Week 117, participants will have completed the trial and may transition off-study to receive commercial ibrutinib at the discretion of the investigator. Restaging CT/MRI imaging must be performed at Week 9, Week 38, Week 62, and within 1 month of completion of therapy at Week 117. Study visits will be conducted on Day 1 of each of the following weeks: Week 1; Week 5; Week 9 through Week 14; Week 18; Week 22; Week 26; Week 30; Week 38; and every 12 weeks thereafter, until study completion. If an investigator has determined that a subject should discontinue the study, or a subject voluntarily withdraws, a Final Visit will be conducted as well as a 30-Day Safety Follow-Up. If the subject is discontinued from the study due to toxicities attributable to either study drug, additional Follow-Up Visits will be conducted as clinically appropriate until satisfactory clinical resolution of the adverse event.
Study Phase	Phase 2
Study Duration	117 weeks of treatment and up to 1 month of follow up to complete final assessment.
Primary Objective(s)	The primary objective of this study is to evaluate the efficacy of concurrent therapy with ibrutinib and venetoclax in patients with relapsed and refractory chronic lymphocytic leukemia (CLL) and small lymphocytic leukemia (SLL).
Primary Endpoint(s)	Complete response rate (CR)
Secondary Objectives	To define the safety and tolerability of combination therapy with ibrutinib and venetoclax.

Secondary Endpoint(s)	For the combination of venetoclax and ibrutinib:
	• Overall response rate (ORR)
	• Duration of response (DOR)
	• Time-to-progression (TTP)
	• Progression-free survival (PFS)
	• Overall survival (OS)
	• Rate of minimal residual disease (MRD) negativity in the bone marrow
	• 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

Exploratory Objectives	• Time to next CLL treatment (TNT) • Change in mutation landscape at time of progression • Pharmacokinetics of ibrutinib and venetoclax when administered in combination
Indication	Relapsed or refractory CLL/SLL patients
Investigational Drug	Venetoclax in combination with ibrutinib
Dose	Venetoclax will be administered PO with single daily doses QD starting at Week 9. Venetoclax dose increments will proceed weekly from 20 mg → 50 mg → 100 mg → 200 mg → 400 mg. Ibrutinib will be supplied as 140 mg hard gelatin capsules for oral (PO) administration. Subjects will receive 420 mg ibrutinib PO daily.
Sample Size	22 subjects
Summary of Eligibility Criteria	**Inclusion Criteria** • Voluntarily sign and date an informed consent form (ICF) with authorization to use protected health information (in accordance with national and local subject privacy regulations) and approved by the Institutional Review Board (IRB) prior to initiation of any study specific procedures • Diagnosis of chronic lymphocytic leukemia CLL) or small lymphocytic leukemia (SLL) meeting IWCLL criteria, and relapsed after or refractory to at least 1 prior treatment • Measurable nodal disease by computed tomography (CT) *Laboratory* • Adequate hematologic function independent of transfusion and

growth factor support for at least 7 days prior to screening, (except for pegylated G-CSF (pegfilgrastim) and darbepoetin which require at least 14 days prior to screening) defined as the following.

- Absolute neutrophil count > 750 cells/mm^3 (0.75 x 10^9/L)
- Platelet count > 30,000 cells/mm^3 (30 x 10^9/L) without transfusion support; evidence of mucosal bleeding; a known bleeding episode within 3 months of screening; or a history of a bleeding disorder
- Hemoglobin > 8.0 g/dL

If the bone marrow evaluation shows heavy infiltration with underlying disease, growth factor support may be administered to achieve the eligibility criteria.

- Adequate hepatic and renal function defined as:
  - Serum aspartate transaminase (AST) or alanine transaminase (ALT) ≤ 2.5 x upper limit of normal (ULN)
  - Estimated Creatinine Clearance ≥ 30 mL/min (24-hour measured GFR or modified Cockcroft-Gault)
  - Bilirubin ≤ 1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin)
- PT/INR < 1.5 x ULN and PTT (aPTT) < 1.5 x ULN

Demographic

- Men and women ≥ 18 years of age
- Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2

Ethical/Other

- Female subjects who are of non-reproductive potential (ie, post-menopausal by history - no menses for ≥ 1 year; OR history of hysterectomy; OR history of bilateral tubal ligation; OR history of bilateral oophorectomy).

  OR
- Female subjects of childbearing potential must have a negative serum pregnancy test upon study entry
- Male and female subjects must agree to use highly effective methods of birth control (eg, condoms, implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], sexual abstinence, or sterilized partner) during the period of therapy and for 90 days after the last dose of study drug

Exclusion Criteria

- Prior treatment with either ibrutinib or venetoclax
- Vaccinated with live, attenuated vaccine(s) within 28 days prior to first dose of study drug
- Received an allogeneic stem cell transplant within the past 1 year (if over 1 year post-allogeneic transplant, must not have active cGVHD)

	• Richter's transformation confirmed by biopsy • Active uncontrolled autoimmune cytopenias *Concurrent Conditions* • Chemotherapy ≤ 21 days prior to first administration of study treatment and/or monoclonal antibody ≤ 4 weeks prior to first administration of study treatment. • History of other malignancies, except: o 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 o Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease o Adequately treated carcinoma *in situ* without evidence of disease • Concurrent systemic immunosuppressant therapy [eg, cyclosporine A, tacrolimus, etc, or chronic administration (> 14 days) of > 20 mg/day of prednisone] within 28 days of the first dose of study drug • Recent infection requiring systemic treatment that was completed ≤ 14 days before the first dose of study drug • Unresolved toxicities from prior anti-cancer therapy, defined as having not resolved to Common Terminology Criteria for Adverse Event (CTCAE, v4.03), Grade ≤ 1, or to the levels dictated in the inclusion/exclusion criteria except for alopecia • Known bleeding disorders (eg, von Willebrand's disease) or hemophilia • History of stroke or intracranial hemorrhage within 6 months prior to first dose of study drug • 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 B surface antigen must have a negative polymerase chain reaction (PCR) result before enrollment in order to meet eligibility for this criterion. Those who are PCR-positive will be excluded*. • Any uncontrolled active systemic infection • Major surgery within 4 weeks of first dose of study drug • 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 • 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 screening • Unable to swallow capsules; malabsorption syndrome; disease

<table>
<tr><td></td><td>significantly affecting gastrointestinal function; resection of the stomach or entire small bowel; symptomatic inflammatory bowel disease or ulcerative colitis; or partial or complete bowel obstruction
• Concomitant use of warfarin or other Vitamin K antagonists
• Subjects who received a strong cytochrome P450 (CYP) 3A inhibitor or inducer within 7 days prior to the first dose of ibrutinib or subjects who require continuous treatment with a strong cytochrome P450 CYP3A inhibitor or inducer (see Appendix C)
• Lactating or pregnant
• Unwilling or unable to participate in all required study evaluations and procedures
• Unable to understand the purpose and risks of the study
• Subjects with chronic liver disease with hepatic impairment Child-Pugh class B or C</td></tr>
<tr><td>Treatment and Procedural Summary</td><td>Ibrutinib 420 mg PO daily will be initiated on Week 1 Day 1. Venetoclax will be initiated at 20 mg PO daily on Week 9 Day 1 and increased every 7 days to 50 mg; 100 mg; 200 mg; and 400 mg. Upon completion of ibrutinib + venetoclax combination treatment at Week 117, participants will have completed the trial and may transition off-study to receive commercial ibrutinib at the discretion of the investigator.
<table>
<tr><th colspan="3">Ibrutinib and Venetoclax Dose and Schedule</th></tr>
<tr><td>Week</td><td>Ibrutinib</td><td>Venetoclax</td></tr>
<tr><td>1</td><td>420</td><td>0</td></tr>
<tr><td>9</td><td>420</td><td>20</td></tr>
<tr><td>10</td><td>420</td><td>50</td></tr>
<tr><td>11</td><td>420</td><td>100</td></tr>
<tr><td>12</td><td>420</td><td>200</td></tr>
<tr><td>13 to 117</td><td>420</td><td>400</td></tr>
</table></td></tr>
<tr><td>Safety Plan</td><td>Adverse event (AE) monitoring; vital signs; physical examination; ECG; and laboratory values will be assessed. Guidelines for tumor lysis syndrome (TLS) management are provided. Chemistry labs (including potassium; calcium; uric acid; phosphorus; and creatinine) will be performed pre-dose; 8 hours; and 24 hours post-dose for the first and each escalated venetoclax dose and additionally as deemed necessary to monitor TLS.</td></tr>
<tr><td>Statistical Considerations</td><td>All efficacy analyses will be performed using the intent-to-treat (ITT) population.
<u>Primary Efficacy Analysis:</u>
<u>Complete Response Rate</u>
The proportion of subjects with a complete response (per investigator assessment) will be calculated for all subjects based on IWCLL criteria. A 95% confidence interval based on binomial distribution will be constructed for the calculated CR rate.</td></tr>
</table>

Secondary Efficacy Analysis:

Overall Response Rate

The proportion of subjects with an overall response (per investigator assessment) will be calculated for all subjects based on IWCLL criteria. A 95% confidence interval based on binomial distribution will be constructed for the calculated ORR.

Duration of Response

Duration of response will be defined as the number of days from the date of first response per investigator assessment to the earliest recurrence or PD per investigator assessment. If a subject is still responding, then the subject's data will be censored at the date of the subject's last available clinical disease assessment. For subjects who never experienced response, the subject's data will be censored on the date of enrollment. Duration of response will be analyzed by Kaplan-Meier methodology using data for all enrolled subjects who receive study treatment. Median duration of response will be calculated and the corresponding 95% confidence interval will be presented.

Time-to-progression

Time-to-progression will be defined as the number of days from the date of first dose to the date of earliest disease progression (per the investigator assessment). All disease progression will be included regardless whether the event occurred while the subject was taking study drug or had previously discontinued study drug. If the subject does not experience disease progression, then the data will be censored at the date of the last available disease assessment. TTP will be analyzed by Kaplan-Meier methodology using data for all enrolled subjects. Median time TTP will be calculated and 95% confidence interval for median time TTP will be presented.

Progression-Free Survival

Progression-Free Survival will be defined as the number of days from the date of first dose to the date of earliest disease progression (per the investigator assessment) or death. All disease progression will be included regardless whether the event occurred while the subject was taking study drug or had previously discontinued study drug. If the subject does not experience disease progression or death, then the data will be censored at the date of the last disease assessment. PFS will be analyzed by Kaplan Meier methodology using data for all dosed subjects. Median PFS time will be calculated and 95% confidence interval for median PFS time will be presented.

Overall Survival

Overall survival will be defined as the number of days from the date of first dose to the date of death for all dosed subjects. The data for subjects who did not die will be censored at the date of last study visit or the last known date to be alive, whichever is later. OS will be analyzed

by Kaplan-Meier methodology using data from all dosed subjects. Median time survival will be calculated and 95% confidence interval for the median time survival will be presented.

Rate of Minimal Residual Disease (MRD) Negativity in the Bone Marrow

MRD negativity will be defined as less than one CLL cell per 10,000 leukocytes (or below 10^{-4}) on bone marrow-based flow cytometry. Rate of MRD negativity will be defined as the proportion of subjects who have MRD negativity on bone marrow assessment. Ninety-five percent (95%) confidence intervals based on the binomial distribution will be provided.

Safety Endpoints and Analysis

A safety analysis will be performed for all dosed subjects unless otherwise indicated. For the entire study, AEs will be evaluated and summarized. Laboratory test results and vital signs will be explored for trends and summarized as appropriate.

Endpoints:

- 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

Exploratory Efficacy Analysis:

Pharmacokinetics

Pharmacokinetic samples for ibrutinib will be collected on the first day of ibrutinib dose administration (Week 1 Day1) and each day when dosed in combination with a newly escalated dose of venetoclax in all subjects enrolled in the study at Stanford University.

Pharmacokinetic samples for venetoclax will be collected at 8 hours post-dose on the day of the first venetoclax dose administration and for each new escalated dose in all subjects enrolled in the study at Stanford University. Pharmacokinetic samples will be collected for the dose ramp-up stage.

Values for the pharmacokinetic parameters for ibrutinib and venetoclax including the maximum observed plasma concentration (C_{max}), the time to C_{max} (peak time, T_{max}), the area under the plasma concentration-time curve (AUC) from 0 to the time of the last measurable concentration (AUC_t) and AUC over a 24-hour dose interval (AUC_{0-24}) will be determined. Additional analyses may be performed if useful in the interpretation of the data.

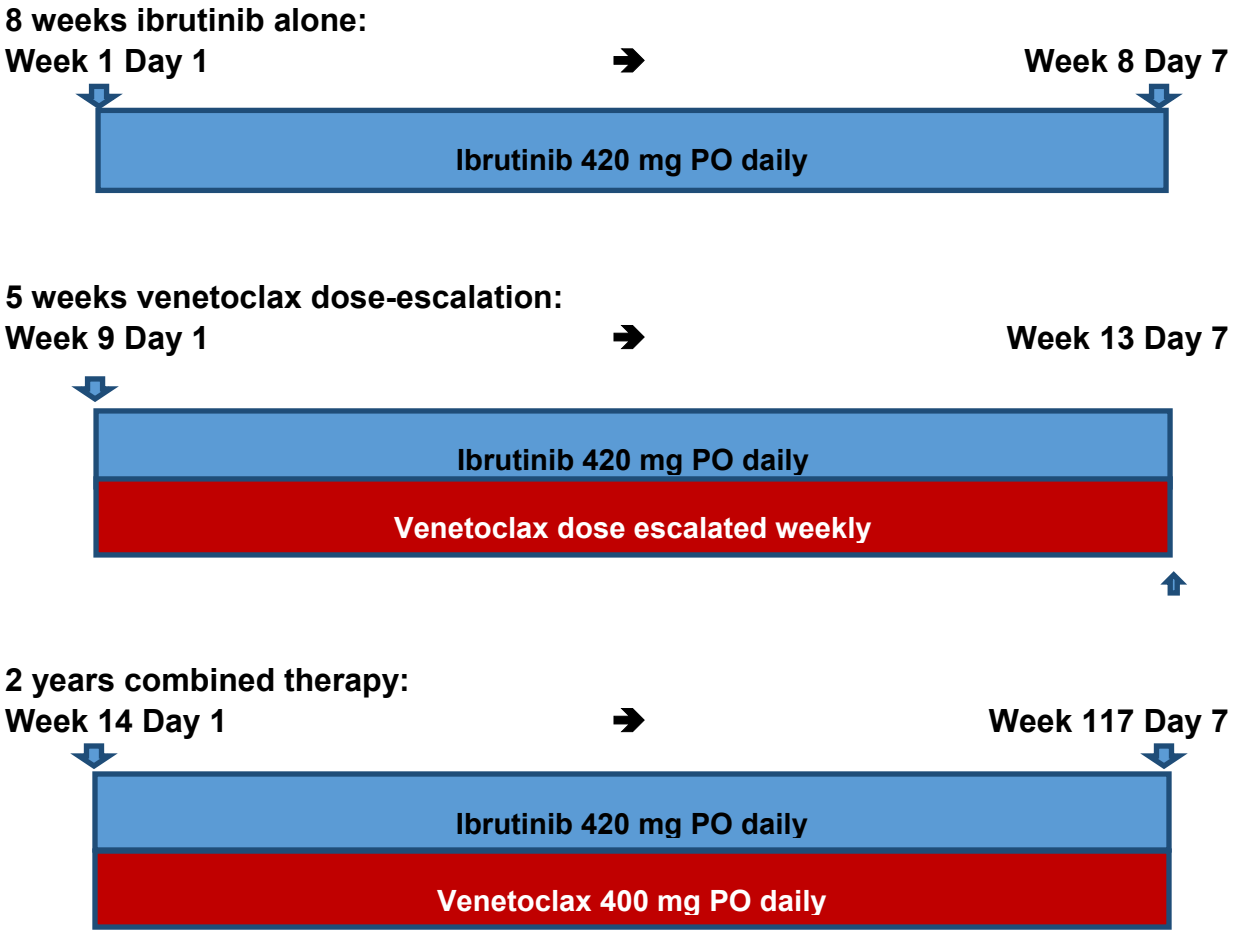
Time to Next Anti-CLL Treatment

Time to next anti-CLL treatment will be defined as the number of days from the date of the first dose of ibrutinib to the date of first dose of new non-protocol anti-leukemia therapy (NPT) or death from any cause. For

	subjects who did not take NPT, the data will be censored at the last known date to be free of NPT. TTNT will be analyzed by Kaplan-Meier methodology using data for all dosed subjects. Median TTNT time will be calculated. Change in mutation landscape at time of progression BTK mutation analysis (NeoGenomics) will be performed at baseline and at time of progression.
Interim Analysis	No interim analysis for efficacy is planned.

Protocol Schema

Figure 1. Administration of Ibrutinib and Venetoclax



List of Abbreviations and Definitions of Terms

AE	Adverse event	IgH	Immunoglobulin heavy chain
AESI	Adverse events of special interest	IRB	Institutional review board
ALC	Absolute lymphocyte count	IV	Intravenous
AML	Acute myeloid leukemia	IVRS	Interactive-voice response system
ANC	Absolute neutrophil count	IWRS	Interactive web response system
AUC	Area under curve (exposure)	IWCLL NCI-WG	International Workshop on Chronic Lymphocytic Leukemia National Cancer Institute-Working Group
BCR	B-cell receptor	LTLS	Laboratory Tumor Lysis Syndrome
BTK	Bruton's tyrosine kinase	MCL	mantle cell lymphomas
CBC	Complete blood count	MRD	Minimal residual disease
CLL	Chronic lymphocytic leukemia	NCI	National Cancer Institute
C_{max}	Maximum concentration of drug	NHL	non-Hodgkin's Lymphoma
CRF	Case report form (paper or electronic)	ORR	Overall response rate
CR	Complete response	OS	Overall survival
CT	Computed tomography	PD	Pharmacodynamics
CTCAE	Common Terminology Criteria for Adverse Events	PFS	Progression-free survival
CTEP	Cancer Therapy Evaluation Program	pK	Pharmacokinetics
CTLS	Clinical tumor lysis syndrome	PO	Oral
DCF	Data Clarification Form	PR	Partial Response
DLBCL	Diffuse large B-cell lymphoma	SAE	Serious adverse event
DLT	Dose-limiting Toxicity	SCI	Stanford Cancer Institute
DMC	Data monitoring committee	SLL	Small lymphocytic lymphoma
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders (4^{th} edition)	SRC	Scientific Review Committee
ECG	Electrocardiogram	TLS	Tumor lysis syndrome
eDC	Electronic data capture	T_{max}	Median time to maximum plasma concentration
FL	Follicular lymphomas	TPN	Total parenteral nutrition
GCP	Good Clinical Practice	T_{max}	Median time to maximum plasma concentration
HBsAg	Hepatitis B surface antigen	TTNT	Time to Next anti-cancer Treatment
HIV	Human immunodeficiency virus	TTP	Time-to-progression
ICF	Informed Consent Form	ULN	Upper limit of normal
ICH	International Conference on Harmonization	USP	United States Pharmacopeia

1 OBJECTIVES, ENDPOINTS, AND OUTCOMES

1.1 Objectives

1.1.1 Primary Objectives

The primary objective of this trial is to evaluate the efficacy of orally-administered venetoclax combined with ibrutinib in patients with CLL/SLL who have been previously treated with at least one agent but who are naïve to ibrutinib and venetoclax.

1.1.2 Secondary Objectives

The secondary objectives of this trial are to define the safety and tolerability of combination therapy with venetoclax and ibrutinib in relapsed and refractory CLL/SLL patients who have not been previously treated with either venetoclax or ibrutinib.

1.1.3 Exploratory Objectives

- To determine the time to next treatment.
- To perform BTK mutation analysis (NeoGenomnics) to identify potential mechanisms of resistance.
- To evaluate the pharmacokinetics of ibrutinib and venetoclax when administered in combination.

1.2 Endpoints (summary)

Endpoints for this study are presented in greater detail in Section 11.2 Endpoints.

1.2.1 Primary Endpoint(s)

Complete response rate (CR)

1.2.2 Secondary Endpoint(s)

Secondary Endpoints include:

- Overall response rate (ORR)
- Duration of response (DOR)
- Time-to-progression (TTP)
- Progression-free survival (PFS)
- Overall survival (OS)
- Rate of minimal residual disease (MRD) negativity in the bone marrow
- 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

1.3 Study Design

1.3.1 Overview

This is a Phase 2, open-label, non-randomized 2-center study that will evaluate the safety and efficacy of orally administered venetoclax combined with ibrutinib in patients with relapsed or refractory CLL/SLL and no prior treatment with either ibrutinib or venetoclax.

Table 1. Planned intra-patient dose ramp-up of venetoclax

Week	Venetoclax (mg/day)	Ibrutinib (mg/day)
1	0	420
9	20	420
10	50	420
11	100	420
12	200	420
13-117	400	420

1.3.2 Randomization

This is an open-label study. Participants will not be blinded or randomized to study treatment.

1.3.3 Number of Participants

A total of twenty-two (22) participants will be enrolled in this study.

1.4 ClinicalTrials.gov Registration, Outcomes, and Results

1.4.1 Interventional model

The intervention model of this study is a single group study.

1.4.2 Masking

This is an open-label, non-randomized study.

1.4.3 Type of Primary Objective / Outcome

The primary outcome of this study is to evaluate the efficacy of concurrent therapy with ibrutinib and venetoclax in patients with relapsed and refractory chronic lymphocytic leukemia (CLL) and small lymphocytic leukemia (SLL).

1.4.4 Outcomes Measures for ClinicalTrials.gov Results Reporting

1.4.4.1 Primary Outcome(s)

- **Primary Outcome Measure**: The primary outcome for this study, for the purposes of Clinical Trials.gov registration and results reporting, is the complete response rate.
- **Primary Outcome Measure Title**: Complete response rate when venetoclax is used in combination with 420 mg/day ibrutinib to treat chronic lymphocytic leukemia (CLL) and small lymphocytic leukemia (SLL).

- **Time Frame**: The time frame for assessment of the primary outcome / primary endpoint is 62 weeks.
- **Safety Issue**: Does not assess a safety issue.

1.4.4.2 Secondary Outcome(s)

- Overall response rate (ORR) based on IWCLL NCI-WG criteria
- Duration of response (DOR) defined as the number of days from the date of first response per investigator assessment to the earliest recurrence or progressive disease per investigator assessment
- Time-to-progression (TTP) defined as the number of days from the date of first dose (date of enrollment if not dosed) to the date of earliest disease progression (per the investigator assessment)
- Progression-free survival (PFS)
- Overall survival (OS)
- Rate of minimal residual disease (MRD) negativity in the bone marrow
- 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

1.5 Regulatory Status of Study Agents

The indication described in this study is considered investigational relative to the approved indications. Regulatory authorization to conduct this study is pursuant to IND 131,600 submitted by Steven E Coutre, MD.

1.5.1 Venetoclax

Venetoclax is approved for marketing in the United States, as Venclexta for the indication of treatment of chronic lymphocytic leukemia (CLL) with 17p deletion, after at least one prior therapy.

Venetoclax manufacturer AbbVie Inc has submitted to FDA a Letter of Authorization of Cross-reference to their IND 110,159 on behalf of this study.

1.5.2 Ibrutinib

Ibrutinib is approved for marketing in the United States, as Imbruvica for the indication of treatment of FDA for the treatment of CLL regardless of the presence or absence of the 17p deletion, and also to treat mantle cell lymphoma (MCL) after one prior therapy; relapsed or refractory marginal zone lymphoma (MZL); chronic graft-vs-host disease (GvHD) after failure of 1 or more systemic lines of therapy; or Waldenström's macroglobulinemia (WM). .

Ibrutinib manufacturer Pharmacyclics LLC has submitted to FDA a Letter of Authorization of Cross-reference to their ibrutinib IND 102,688 on behalf of this study. Ibrutinib continues to be studied in other disease settings.

2 BACKGROUND

2.1 Study Disease

2.1.1 Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Chronic lymphocytic leukemia (CLL), and its analogous disease small lymphocytic leukemia (SLL), is a lymphoproliferative disorder characterized by progressive accumulation of monoclonal, small, mature-appearing CD5+ B-cells in peripheral blood, bone marrow, and secondary lymphoid organs. It is the most common form of leukemia in adults in the Western World, accounting for approximately 30% of all leukemias.[1] Chronic lymphocytic leukemia primarily affects elderly individuals; however, approximately one third of patients are less than 60 years of age at diagnosis.[2] It is currently estimated that annually approximately 15,000 people will be diagnosed with CLL in the United States, and that almost 4,500 individuals will die of the disease.[3] In Europe, CLL accounts for approximately 30% of all leukemias in adults with a reported age-standardized incidence rate of 3.79 per 100,000 individuals (for CLL/SLL) in the years 2000 to 2002.[4] The approximate 5-year survival rate for patients with CLL is 73%.[5] CLL presents with a variable clinical course. Approximately one-third of patients have indolent disease with prolonged median survival that does not require treatment, and die of causes unrelated to disease. Another third have an initial indolent phase that is followed by rapid progression of the disease requiring therapy. The remaining third have aggressive disease and require treatment at the time of diagnosis. Chronic lymphocytic leukemia patients will often have compromised bone marrow reserve due to their underlying disease. The principal complication of CLL is immunodeficiency related to myelosuppression and as a result, infection is the major cause of death in patients with CLL.

2.1.2 Treatment Options

The current practice for early stage CLL patients is to take an expectant approach, while those with advanced stage disease who require treatment receive combination regimens. Chlorambucil, in use for several decades, can induce partial remissions in advanced CLL, but does not improve survival when used in asymptomatic early-stage CLL.[6] Fludarabine, approved as a second-line agent, improves response rates, progression-free survival (PFS), and in combination with cyclophosphamide and rituximab (FCR), overall survival (OS) compared to fludarabine and cyclophosphamide alone.[7-10] As such, FCR has emerged as the first line therapy in young patients with CLL. In 2008, bendamustine, an alkylator and antimetabolite, was approved as first line therapy for CLL, based on improvement in PFS versus chlorambucil. For patients over the age of 65-70, FCR is not tolerated; other therapies, such as chlorambucil ± rituximab, or bendamustine ± rituximab are commonly used in the up-front setting. For patients with del(17p13.1) none of these traditional approaches work effectively.

Standard chemotherapeutic options for CLL cause significant immune suppression and myelosuppression are not well tolerated by the elderly population and have not consistently offered survival advantage. Treatment decisions for patients with CLL are made based on considerations such as age, clinical stage, expected survival, and anticipated toxicities. With the notable exception of allogeneic stem cell transplantation, CLL is currently an incurable disease, despite good initial responses to chemoimmunotherapy. Nonetheless, globally access to allogeneic stem cell transplant and/or clinical trials is limited, and treatment options for relapsed disease tend to have increased toxicity and reduced antitumor activity.

2.1.3 Role of BTK and Bcl-2 Family Proteins in CLL/SLL

B-cells are lymphocytes with multiple functions in the immune response, including antigen presentation, antibody production, and cytokine release. B-cells express cell surface immunoglobulins comprising the B-cell receptor (BCR), which is activated by binding to antigen. Antigen binding induces receptor aggregation and the clustering and activation of multiple tyrosine kinases, which in turn activate further downstream signaling pathways.[11]

The process of B-cell maturation, including immunoglobulin chain rearrangement and somatic mutation, is tightly regulated. It is thought that B-cell lymphomas and CLL result from mutations and translocations acquired during normal B-cell development.[12] Several lines of evidence suggest that signaling through the BCR is necessary to sustain the viability of B-cell malignancies.

The protein Bruton's tyrosine kinase (BTK) is a Tec-family kinase that is exclusively expressed in B-cells and participates in the BCR signaling pathway. The upstream Src-family kinases Blk, Lyn and Fyn[13,14] activate BTK which in turn phosphorylates and activates phospholipase-Cγ (PLCγ); this leads to Ca^{2+} mobilization and activation of NFκB, MAP kinase and Akt pathways.[15] There is strong evidence that lymphomas require BCR signaling. A functional B-cell receptor is maintained, even as the non-expressed immunoglobulin heavy chain (IgH) is involved in oncogenic translocations.[16] Patients whose tumor cells developed resistance to anti-idiotype therapy did not produce BCR-negative tumor populations as a resistance strategy, indicating that the BCR provides important survival signals for lymphoma cells.[17] Selective knockdown of BCR components by siRNA causes apoptosis in B-cell lymphoma cell lines.[18] During recent years, evidence has accumulated consistent with signaling via the BCR being important in CLL with two small molecule inhibitors of BTK and PI3K approved in 2014 in the US for relapsed CLL patients.

The role of BTK in BCR signal transduction is demonstrated by the human genetic immunodeficiency disease X-linked agammaglobulinemia and the mouse genetic disease X-linked immunodeficiency, both caused by a mutation in the BTK gene. These genetic diseases are characterized by reduced BCR signaling and a failure to generate mature B-cells. The BTK protein is expressed in most hematopoietic cells except T-cells and natural killer cells, but the selective effect of BTK mutations suggests that its primary functional role is in antigen receptor signaling in B-cells.[19]

The Bcl-2 family proteins are important regulators of the intrinsic apoptosis pathway. The Bcl-2 oncogene was first identified in follicular lymphoma 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 domains.[20-23] Bcl-2 overexpression is a major contributor to the pathogenesis of some types of lymphoid malignancies. Bcl-2 is also overexpressed in acute and chronic leukemias. Chronic lymphocytic leukemia (CLL) is a genetic disease where the microRNAs miR15a and miR16-1 that negatively regulate the transcription of Bcl-2 are deleted or down regulated, resulting in uncontrolled expression of Bcl-2.[24,25]

2.2 Study Drugs

2.2.1 Venetoclax

Venetoclax is a novel, orally available small molecule Bcl-2 family protein inhibitor that binds with > 500-fold higher affinity (Ki < 0.010 nM) to Bcl-2 and with lower affinity to other Bcl-2 family proteins Bcl-XL (Ki – 48 nM) and Bcl-w (Ki – 245 nM).[26] Overexpression of anti-apoptotic Bcl-2 family proteins is associated with increased resistance to chemotherapy, and antagonism of the action of these proteins might enhance response to such therapy and overcome resistance. Anti-apoptotic Bcl-2 family members are associated with tumor initiation, disease progression, and drug resistance, making them compelling targets for antitumor therapy.

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 non-mutated cell lines.

Venetoclax inhibited subcutaneous murine xenograft growth of human tumor cell lines derived from acute lymphoblastic leukemia (ALL) and non-Hodgkin's Lymphoma (NHL). The drug was also active in a model of disseminated ALL.

Venetoclax is approved by the US Food and Drug Administration (FDA) for the treatment of

1) Chronic lymphocytic leukemia (CLL) in patients with 17p deletion who have received at least one prior therapy, and
2) CLL in patients with 17p deletion

More information on the nonclinical, pharmacology, and clinical data for venetoclax can be found in Section 5 of this protocol and in the current version of the venetoclax package insert and Investigator’s Brochure.

2.2.2 Ibrutinib

Ibrutinib is a potent, first-in-class, orally-administered covalently-binding inhibitor of Bruton’s tyrosine kinase (BTK). Inhibition of BTK blocks downstream BCR signaling pathways and thus prevents B-cell proliferation. *In vitro*, ibrutinib inhibits purified BTK and selected members of the kinase family with 10-fold specificity compared with non-BTK kinases.

Ibrutinib (Imbruvica) is approved by the US Food and Drug Administration (FDA) for the treatment of

1) Mantle cell lymphoma (MCL) in patients who have received at least one prior therapy based on overall response rate,
2) Chronic lymphocytic leukemia (CLL),
3) CLL in patients with 17p deletion,
4) Waldenström’s macroglobulinemia,
5) Marginal zone lymphoma (MZL) in patients who have received at least one prior anti-CD20-based therapy, and

6) Chronic graft-vs-host disease (GVHD) after failure of one or more lines of systemic therapy.

Ibrutinib is currently under investigation in various indications.

This study uses the FDA—approved dose of ibrutinib for patients with CLL/SLL (420 mg/day oral). More information on the nonclinical, pharmacology, and clinical data for ibrutinib can be found in Section 5 of this protocol and in the current version of the ibrutinib package insert and Investigator's Brochure.

2.3 Rationale

The optimal approach to CLL/SLL treatment with the multiple agents that are available and in development remains an open question. While the default approach continues to be serial treatment with different agents at the time of disease progression, concurrent treatment offers the possibility of deeper and more durable responses. Targeting multiple mediators of malignancy simultaneously with highly-active; well-tolerated therapies has the potential to eliminate CLL clones that may be resistant to a particular therapy and prevent the emergence of resistance through single escape mutations.

The combination of ibrutinib and venetoclax is compelling for multiple reasons. Both are well tolerated with high response rates as single agents. Multiple lines of evidence show activation of apoptosis in CLL cells in response to ibrutinib and the effect of venetoclax have the potential to dramatically enhance this response. Combination therapy with traditional chemoimmunotherapy has achieved higher rates of complete response than monotherapy with either antibodies or alkylators alone and a combination of targeted agents has the potential to achieve this goal, particularly in bone marrow response and in prolonging the duration of response.

The regimen is designed to start therapy with ibrutinib, and then ramp-up the dose of venetoclax as per FDA-approved dosing guidelines, followed by continue treatment along with the standard CLL/SLL dose of ibrutinib.

2.3.1 Primary Purpose of the Study

Treatment: The clinical trial described in this protocol is designed to determine whether CR rates can be improved in patients with relapsed or refractory CLL/SLL when venetoclax is used concurrently with ibrutinib.

3 PARTICIPANT SELECTION AND ENROLLMENT PROCEDURES

Subjects with relapsed or refractory CLL per IWCLL criteria without prior treatment with venetoclax or ibrutinib will be selected for this study. Subjects must undergo screening including CT and bone marrow aspirate and biopsy within 28 days prior to initial study drug administration.

3.1 Inclusion Criteria

To be enrolled in the study, each potential subject must satisfy all the following inclusion criteria.

1. Voluntarily sign and date an informed consent form (ICF) with authorization to use protected health information (in accordance with national and local subject privacy regulations) and approved by the Institutional Review Board (IRB) prior to initiation of any study specific procedures.
2. Diagnosis of chronic lymphocytic leukemia CLL) or small lymphocytic leukemia (SLL) meeting IWCLL/NCI-WG criteria, and relapsed after or refractory to at least 1 prior treatment.
3. Measurable nodal disease by computed tomography (CT).

Laboratory

4. Adequate hematologic function independent of transfusion and growth factor support for at least 7 days prior to screening [except for pegylated G-CSF (pegfilgrastim) and darbepoetin which require at least 14 days prior to screening defined as the following.
    - Absolute neutrophil count > 750 cells/mm^3 (0.75 x 10^9/L).
    - Platelet count > 30,000 cells/mm^3 (30 x 10^9/L) without transfusion support; evidence of mucosal bleeding; a known bleeding episode within 3 months of screening; or a history of a bleeding disorder.
    - Hemoglobin > 8.0 g/dL.

    If the bone marrow evaluation shows heavy infiltration with underlying disease, growth factor support may be administered after screening and prior to the first dose of therapy.
5. Adequate hepatic and renal function defined as:
    - Serum aspartate transaminase (AST) or alanine transaminase (ALT) ≤ 2.5 x upper limit of normal (ULN).
    - Estimated Creatinine Clearance ≥ 30 mL/min (24-hour measured GFR or modified Cockcroft-Gault)
    - Bilirubin ≤ 1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin)
6. PT/INR < 1.5 x ULN and PTT (aPTT) < 1.5 x ULN.

Demographic

7. Men and women ≥ 18 years of age.
8. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2.

Ethical/Other

9. Females:
    - Female subjects who are of non-reproductive potential (ie, post-menopausal by history - no menses for ≥ 1 year; OR history of hysterectomy; OR history of bilateral tubal ligation; OR history of bilateral oophorectomy).

      OR
    - Female subjects of childbearing potential must have a negative serum pregnancy test upon study entry.
10. Male and female subjects must agree to use highly effective methods of birth control (eg, condoms, implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], sexual abstinence, or sterilized partner) during the period of therapy and for 90 days after the last dose of study drug

3.2 Exclusion Criteria

To be enrolled in the study, potential subjects must meet NONE of the following exclusion criteria:

1. Prior treatment with either venetoclax or ibrutinib.
2. Vaccinated with live, attenuated vaccine(s) within 28 days prior to first dose of study drug
3. Received an allogeneic stem cell transplant in the past 1 year (if over 1 year post allogeneic transplant, must not have active cGVHD).
4. Richter's transformation confirmed by biopsy.
5. Active uncontrolled autoimmune cytopenias

Concurrent Conditions

6. Chemotherapy ≤ 21 days prior to first administration of study treatment and/or monoclonal antibody ≤ 4 weeks prior to first administration of study treatment.
7. 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.
8. Concurrent systemic immunosuppressant therapy [eg, cyclosporine A, tacrolimus, etc, or chronic administration (> 14 days) of > 20 mg/day of prednisone] within 28 days of the first dose of study drug.

9. Recent infection requiring systemic treatment that was completed ≤ 14 days before the first dose of study drug.

10. Unresolved toxicities from prior anti-cancer therapy, defined as having not resolved to Common Terminology Criteria for Adverse Event (CTCAE, v4.03), Grade ≤ 1, or to the levels dictated in the inclusion/exclusion criteria except for alopecia.

11. Known bleeding disorders (eg, von Willebrand's disease) or hemophilia.

12. History of stroke or intracranial hemorrhage within 6 months prior to first dose of study drug.

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 or hepatitis B surface antigen must have a negative polymerase chain reaction (PCR) result before enrollment in order to meet eligibility for this criterion. Those who are PCR-positive will be excluded.

14. Any uncontrolled active systemic infection.

15. Major surgery within 4 weeks of first dose of study drug.

16. 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.

17. 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 screening.

18. Unable to swallow capsules; malabsorption syndrome; disease significantly affecting gastrointestinal function; resection of the stomach or small bowel; symptomatic inflammatory bowel disease or ulcerative colitis; or partial or complete bowel obstruction.

19. Concomitant use of warfarin or other Vitamin K antagonists.

20. Received a strong cytochrome P450 (CYP) 3A inhibitor or inducer within 7 days prior to the first dose of ibrutinib, OR subjects who require continuous treatment with a strong cytochrome P450 CYP3A inhibitor or inducer (see Appendix C)

21. Lactating or pregnant.

22. Unwilling or unable to participate in all required study evaluations and procedures.

23. Unable to understand the purpose and risks of the study.

24. Subjects with chronic liver disease with hepatic impairment Child-Pugh class B or C

3.3 Informed Consent Process

Prior to participation in any study-specific procedure, including any invasive screening procedures, all candidates for participation will be provided a consent form describing the study. This consent form will provide sufficient information to make an informed decision regarding participation.

- If the person providing consent is fluent in English, the prospective subject must sign the IRB-approved informed consent.
- If the subject is considered “non-English speaking,” and the “Short Form” consent process will be used, the IRB-approved English consent form (aka, the “Summary Form”) will be signed by the person obtaining consent (POC) and the witness; and a Short Form in the language of the person providing consent will be signed by the subject and the witness.

The participant will be provided with a copy of the signed and dated consent document prior to any study procedure. 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.

The informed consent form (ICF) and consent process must comply with the US regulations (§ 21 CFR Part 50) as well as country specific national regulations and/or local laws. 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.

3.4 Eligibility Verification Procedures

To verify patient eligibility, the following documents should be completed by the study team and faxed or e-mailed (secure) to the Stanford Cancer Institute (SCI) Study Coordinator:

- Copy of required laboratory tests/procedures
- Signed patient consent form
- HIPAA authorization form
- Eligibility screening worksheet

The SCI Study Coordinator will have the Principal Investigator review the eligibility packet and if eligible, will:

- Assign a patient study number
- Fax or e-mail the patient study number to the participating site

3.5 Study Timeline

3.5.1 Completion of Study

Participants will complete this study if he or she has not been lost to follow up and has not withdrawn consent prior to the end of study or has died before the end of the study.

The study will be complete when the last subject being treated has completed the last dose of study medications and up to 1 month of follow up to complete the final assessment.

3.5.2 Study Follow-up Post-completion

This study will not follow patients after completion of therapy. Upon completion of ibrutinib + venetoclax combination treatment at Week 117, participants will have completed the trial and may transition off-study to receive commercial ibrutinib at the discretion of the investigator.

4 TREATMENT PLAN

4.1 Study Drug Administration

Study participants will start treatment in the outpatient setting with ibrutinib 420 mg PO daily on Week 1 Day 1 of treatment. After completion of 8 weeks of treatment with ibrutinib, they will subsequently begin co-administration of venetoclax once daily with the daily dose increased every 7 days through 5 dose levels (20 mg; 50 mg; 100 mg; 200 mg; 400 mg). The dosing schedule is depicted in Table 1 in Section 1.3.1.

Venetoclax will be administered orally once daily continuously from the time of treatment initiation with venetoclax. Each dose should be taken with approximately 240 mL of water (8 ounces) within 30 minutes after the completion of breakfast or the subject's first meal of the day with an effort to take venetoclax at the same time of day daily. Venetoclax should be taken at the same time as ibrutinib.

Ibrutinib 420 mg (3 x 140-mg capsules) will be administered orally once daily. The capsules are to be taken around the same time each day with 8 ounces (approximately 240 mL) of water. The capsules should be swallowed intact and subjects should not attempt to open capsules 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 (see Appendix C).

If a dose of either study drug 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.

4.2 Toxicity Management

Adverse event management and dose modifications are outlined in Section 6 Dose Modifications.

4.3 General Concomitant Medication and Supportive Care Guidelines

4.3.1 Prophylaxis and Management of Tumor Lysis Syndrome

There is a potential for tumor lysis syndrome (TLS) in subjects affected by hematologic malignancies, especially in those with bulky disease; elevated pretreatment lactate dehydrogenase (LDH) levels; elevated leukocyte count; renal dysfunction; and dehydration.

In response to the events of TLS reported in the Phase 1 studies in subjects with diagnosis of relapsed or refractory CLL treated with venetoclax monotherapy or in combination with an anti-CD20 antibody, an extensive review of the safety data was performed across all CLL trials in January of 2013. These clinical data suggest that size of baseline lymph nodes is a risk factor for TLS, with larger lymph nodes resulting in increased risk. In addition, creatinine clearance of ≤ 80 mL/min at Screening was identified as a risk factor for TLS. Data analyses have resulted in development of three risk categories, listed below.

- Risk category for an individual patient is determined upon study entry.

- A detailed description of risk factors for developing tumor lysis following treatment with venetoclax is available in the current Investigator's Brochure. Refer to Appendix F for laboratory and clinical definitions of TLS.

- TLS Prophylaxis and Monitoring Checklist will be completed throughout the lead-in period to ensure proper TLS prophylaxis measures.
    - The section below describes the management of patients throughout dosing based on their risk factors for developing TLS identified upon study entry.

For tumor lysis syndrome prophylaxis, all subjects enrolling into the study will be classified into 3 risk categories based on the tumor burden prior to venetoclax administration. The tumor burden assessed by the nodal disease and absolute lymphocyte count at Screening will be used to define each category as described below.

Table 2. TLS Risk Categories

Risk Categories for Developing TLS	TLS Risk Category Criteria
Low	All measurable lymph nodes with the largest diameter < 5 cm **AND** ALC < 25 × 10^9/L
Medium	Any measurable lymph node with the largest diameter ≥ 5 cm and < 10 cm, **OR** ALC ≥ 25 × 10^9/L
High	Any measurable lymph node with the largest diameter ≥ 10 cm, **OR** ALC ≥ 25 × 10^9/L **AND** any measurable lymph node with the largest diameter ≥ 5 cm but < 10 cm

4.3.1.1 First Dose of Venetoclax at 20 mg and at 50 mg

Tumor lysis syndrome prophylaxis must be initiated in **all** subjects irrespective of their TLS risk category prior to the first dose of venetoclax at 20 mg and at 50 mg. Tumor lysis syndrome prophylaxis includes:

- An oral agent to reduce the uric acid level (eg, allopurinol) to be initiated at least 72 hours prior to dosing. Treatment may need to be continued for up to 5 weeks based on the ongoing risk of TLS development. Subjects allergic to allopurinol must use another uric acid reducer.
- Oral hydration consisting of fluid intake of 1.5 to 2 L per day starting at least 48 hours prior to the start of treatment for all subjects prior to first dose and at all subsequent dose increment steps and continued for at least 24 hours after dosing and all the chemistries laboratory values remain within ULN.
- Serum chemistry and hematology laboratory samples must be drawn anytime within 72 hours prior to first dose and electrolyte values should be reviewed and not demonstrate any clinically significant abnormalities prior to the first dose of venetoclax to keep the treatment on schedule. If clinically significant laboratory abnormalities are observed in this baseline laboratory assessment, first dose of venetoclax must be delayed until resolution and initiate management per Appendix E, (Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis

Syndrome [TLS]), and if needed, patient should receive additional prophylactic treatment prior to the initiation dosing.

Additional TLS prophylaxis and monitoring procedures are tailored to the individual TLS risk category as follows:

I. Low Risk Category

Subjects in Low Risk category can begin venetoclax lead-in period in the outpatient setting if there is no indication to hospitalize.

- For subjects who are unable to maintain adequate oral hydration, IV hydration of 1.5 to 2 L is recommended in the outpatient setting on D1 of 20 mg and 50 mg dose to assure this full amount of hydration is achieved. For subjects in patients for whom volume overload is considered a significant risk, hospitalization should be considered.
- Chemistry and hematology laboratory tests are to be performed within 72 hours before the first dose of venetoclax. The investigator must review these laboratory values. The investigator's decision to proceed with venetoclax treatment initiation may be based on these laboratory values.
- Chemistry laboratory tests must be performed STAT at 0 hour (pre-dose), 8, and 24* hours post-dose after the first dose of venetoclax at 20 mg and at 50 mg. Pre-dose laboratory values will be collected and used as baseline to assess potential electrolyte abnormalities occurring post venetoclax administration. Results from pre-dose laboratory values are not required to be available prior to initiating venetoclax treatment. Subjects must remain at the hospital, or clinic, until the investigator has reviewed the 8-hour laboratory values.
- Day 2 dose should not be administered until the investigator reviews the 24 hours post-dose chemistry laboratory values.
- If no significant findings suggestive of clinical or lab TLS occur within 24 hours, the same dose will be continued until Day 7 in the outpatient setting.
- If any significant laboratory changes are observed within the first 24 hours after initiation of dosing, see Appendix E (Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome [TLS]) for procedures to follow. These laboratory values must be reviewed in real time by the investigator.
- Additional laboratory assessments may be performed per investigator discretion.
- Hematology laboratory tests must be performed 24* hours post-dose after the first dose of venetoclax at 20 mg and at 50 mg.

* All 24 hour post-dose laboratory assessments may be taken within a 2-hour window if necessary.

II. Medium Risk Category

Subjects in Medium Risk category who have creatinine clearance ≥ 80 mL/min will receive their initial doses of venetoclax at 20 and 50 mg as outpatients.

Subjects in the Medium Risk category who have creatinine clearance of < 80 mL/min and/or higher tumor burden may be handled as high-risk subjects per investigator discretion for the first dose of venetoclax at 20 mg and 50 mg (Refer to section for high-risk subjects below).

- Subjects will receive IV hydration of 1.5 to 2 L in the outpatient setting on D1 of 20 mg and 50 mg dose in addition to oral hydration as stated above. For subjects in whom volume overload is considered a significant risk, hospitalization should be considered.
- Chemistry and hematology laboratory tests are to be performed within 72 hours before the first dose of venetoclax. The investigator must review these laboratory values. The investigator's decision to proceed with venetoclax treatment initiation may be based on these laboratory values.
- Chemistry laboratory tests must be performed STAT at 0 hour (pre-dose), 8, and 24* hours after the first dose of venetoclax at 20 mg and at 50 mg. Pre-dose laboratory values will be collected and used as baseline to assess potential electrolyte abnormalities occurring post venetoclax administration.
- Results from pre-dose laboratory values are not required to be available prior to initiating venetoclax treatment. Subjects must remain at the hospital, or clinic, until the investigator has reviewed the 8-hour laboratory values.
- Day 2 dose should not be administered until the investigator reviews the 24 hours post-dose chemistry laboratory values.
- If no significant findings suggestive of clinical or lab TLS occur within 24 hours, the same dose will be continued until Day 7 in the outpatient setting.
- If any significant laboratory changes are observed within the first 24 hours after initiation of dosing, see Appendix E, (Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome [TLS]) for procedures to follow.
- Additional laboratory assessments may be performed per investigator discretion.
- Hematology laboratory tests must be performed 24* hours post-dose after the first dose of venetoclax at 20 mg and at 50 mg.

* All 24 hour post-dose laboratory assessments may be taken within a 2-hour window if necessary.

III. High-risk Category

Hospitalization and monitoring starting the night before administration of the first dose of 20 mg and 50 mg of venetoclax and continued till at least 24 hours post-dose chemistry laboratory values are reviewed by the investigator.

- Chemistry and hematology laboratory tests to be performed upon admission the night before first dose of venetoclax. The investigator's decision to proceed with venetoclax treatment initiation will be based on these laboratory values.
- Nephrology (or other acute dialysis service) consultation should be considered upon admission per institutional standards at investigators' discretion to ensure emergency dialysis is available and the appropriate staff is aware and prepared to handle any necessary intervention for TLS. Telemetry should also be considered. IV hydration must be started the night before dosing and continued for 24 hours after dose.
- Rasburicase must be administered per regional standards or institutional guidelines for subjects with elevated uric acid level at baseline (> ULN) or rapidly rising uric acid level as prophylaxis prior to the initial dose of venetoclax.). For patients with a

contraindication to rasburicase (ie, glucose-6-phosphate dehydrogenase [G6PD] deficiency), the TLS risk-mitigation plan must be reviewed with the Principal Investigator.

- Chemistry laboratory tests must be performed STAT at 0 (pre-dose, within 4 hours before venetoclax administration), 4, 8, 12 and 24* hours after the first dose of venetoclax at 20 mg and 50 mg. These laboratory values must be reviewed in real time by the investigator. Pre-dose laboratory values will be collected and used as baseline to assess potential electrolyte abnormalities occurring post venetoclax administration.
- Prophylactic reductions for potassium, inorganic phosphorus and/or uric acid above of normal range prior to dosing are recommended.
- If any significant laboratory changes are observed within the first 24 hours after initiation of dosing, see Appendix E, (Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome [TLS]), for additional laboratory assessments and management guidelines.
- Hematology laboratory tests performed pre-dose (within 4 hours before venetoclax administration) and 24* hours post-dose after the first dose of venetoclax at 20 mg and 50 mg.
- Day 2 dose should not be administered until the investigator reviews the 24 hours post-dose laboratory values.
- If no significant findings suggestive of clinical or lab TLS occur within 24 hours, the same dose will be continued until Day 7 in the outpatient setting.

* All 24 hour laboratory assessments may be taken within 2-hour window if necessary.

For all dose escalations, laboratory values for subject management must be reviewed prior to the subject's next dose. Based upon the laboratory values, the subject may continue dosing, may need to hold dose until resolution of laboratory abnormalities, may require additional post-dose laboratory checks or may require hospitalization for further monitoring. Please see Appendix E, (Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome [TLS]) for appropriate procedures to follow.

4.3.1.2 Dose Escalation of Venetoclax to 100 mg, 200 mg, and 400 mg

All subjects, irrespective of their risk category, must receive the following TLS prophylaxis measures prior to subsequent dose increases of venetoclax:

- Continue administration of an oral uric acid reducer as indicated above.
- Oral hydration consisting of fluid intake of approximately 1.5 to 2 L/day starting at least 48 hours days prior to each dose increment. IV hydration is encouraged at subsequent dose increases for subjects who are unable to maintain such oral hydration. IV hydration will be in the outpatient setting on the day of dose increment. For patients in whom volume overload is considered a significant risk, hospitalization should be considered.
- Chemistry and Hematology laboratory tests must be performed within 72 hours and the investigator must review results prior to each dose escalation. For subjects demonstrating any clinically significant laboratory abnormalities, additional prophylactic treatment should be administered prior to dosing (see Appendix E, Recommendations

for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome [TLS]).

Additional TLS prophylaxis and monitoring procedures are tailored to the individual TLS risk category as follows:

I. Low Risk Category

Subjects in Low Risk category will receive the subsequent dose escalations (100, 200 and 400 mg) as outpatients.

- Chemistry and Hematology laboratory tests will be performed at STAT at 0 hour (pre-dose), 8 and 24 hours after dose administration. These laboratory values must be reviewed in real time by the investigator. Pre-dose laboratory values will be collected and used as baseline to assess potential electrolyte abnormalities occurring post venetoclax administration.
- Subjects must remain at the hospital, or clinic, until the investigator has reviewed the 8-hour laboratory values.
- Day 2 dose should not be administered until the investigator reviews the 24 hours post-dose chemistry laboratory values.
- If no significant findings suggestive of clinical or lab TLS occur within 24 hours, the same dose will be continued until Day 7 in the outpatient setting.
- Additional laboratory assessments may be performed per investigator discretion.

II. Medium Risk Category

Subjects in Medium Risk category may receive their subsequent dose escalations in the outpatient setting. Subjects with creatinine clearance < 80 mL/min and/or higher tumor burden may be hospitalized per investigator's discretion.

For subjects who receive their subsequent dose escalations in the outpatient setting,

- Chemistry and Hematology laboratory tests will be performed 0 (pre-dose), 8 and 24 hours post dose administration. These laboratory values must be reviewed in real time by the investigator. Pre-dose laboratory values will be collected and used as baseline to assess potential electrolyte abnormalities occurring post venetoclax administration.
- Subjects must remain at the hospital, or clinic, until the investigator has reviewed the 8-hour laboratory values.
- Day 2 dose should not be administered until the investigator reviews the 24 hours post-dose chemistry laboratory values.
- If no significant findings suggestive of clinical or lab TLS occur within 24 hours, the same dose will be continued until Day 7 in the outpatient setting.
- Additional laboratory assessments may be performed per investigator discretion.

For subjects who are hospitalized during subsequent dose escalations,

- Chemistry and Hematology laboratory tests will be performed upon admission. Chemistry tests will be performed STAT at 0 hour (pre-dose), 4, 8, 12 and 24 hours post

dose. These laboratory values must be reviewed in real time by the investigator. Pre-dose laboratory values will be collected and used as baseline to assess potential electrolyte abnormalities occurring post venetoclax administration.

- IV hydration should be started with a target of approximately 2 L per day or as clinically appropriate for patients who are hospitalized.
- Hematology laboratory tests will be performed 24 hours post-dose.
- The 24-hour post-dose laboratory results must be reviewed by the investigator prior to the subject leaving the hospital or receiving any additional doses of the study drug.

III. High-risk Category

High-risk subjects may receive the subsequent dose increases as outpatients. Subjects with creatinine clearance < 80 mL/min may be hospitalized per investigator discretion. Hospitalization will begin the evening prior to the dose of venetoclax and continue for 24 hours after dose administration.

For subjects who are hospitalized during subsequent dose escalations,

- Chemistry and Hematology laboratory tests will be performed upon admission. Chemistry tests will be performed STAT at 0 hour (pre-dose); 4; 8; 12; and 24 hours post-dose. These laboratory values must be reviewed in real time by the investigator. Pre-dose laboratory values will be collected and used as baseline to assess potential electrolyte abnormalities occurring post venetoclax administration.
- IV hydration should be started with a target of approximately 2 L per day or as clinically appropriate for patients who are hospitalized.
- Hematology laboratory tests will be performed 24 hours post-dose.
- The 24-hour post-dose laboratory results must be reviewed by the investigator prior to the subject leaving the hospital or receiving any additional doses of the study drug.

For subjects who are not hospitalized,

- Chemistry and Hematology laboratory tests will be performed pre-dose (within 72 hours), and at 8 and 24 hours post dose administration. These laboratory values must be reviewed in real time by the investigator. Pre-dose laboratory values will be collected and used as baseline to assess potential electrolyte abnormalities occurring post venetoclax administration.
- Intravenous hydration (1.5 to 2 L) will be given in the outpatient setting with a target of approximately 2 L per day or as clinically appropriate.
- Subjects must remain at the hospital, or clinic, until the investigator has reviewed the 8-hour laboratory values.
- Day 2 dose should not be administered until the investigator reviews the 24 hours post-dose chemistry laboratory values.
- If no significant findings suggestive of clinical or lab TLS occur within 24 hours, the same dose will be continued until Day 7 in the outpatient setting.
- Additional laboratory assessments may be performed per investigator discretion.

Any subject, who at any dose level develops clinically significant electrolyte abnormalities must have their subsequent venetoclax dose held until the electrolyte abnormalities resolve. Electrolyte changes should undergo aggressive management and further monitoring as per Appendix E, (Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome [TLS]). The subject may resume dosing based on a risk assessment (including tumor burden status), as determined by the investigator. All subjects must receive the intended dose for at least 7 days before increasing to the next higher dose.

4.3.2 Permitted Concomitant Medications

Supportive medications in accordance with standard practice (such as for emesis, diarrhea, etc) are permitted. Use of neutrophil growth factors (filgrastim and pegfilgrastim) or red blood cell growth factors (erythropoietin) is permitted per institutional policy and in accordance with the ASCO guidelines.[27] Transfusions may be given in accordance with institutional policy.

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 do not exceed 100 mg per day of prednisone or equivalent are permitted.

The following may be considered: localized hormonal or bone sparing treatment for non-B-cell malignancies, and localized radiotherapy for medical conditions other than the underlying B-cell malignancies.

Treatment for autoimmune cytopenias are permitted for < 14 days at doses that do not exceed 100 mg per day of prednisone or equivalent.

4.3.3 Concomitant Medications to be Used with Caution

4.3.3.1 CYP3A Inhibitors / Inducers

Ibrutinib is metabolized primarily by CYP3A4. Concomitant use of ibrutinib and drugs that strongly or moderately inhibit CYP3A can increase ibrutinib exposure, and therefore strong CYP3A inhibitors should be avoided.

Table . Ibrutinib Dose Modification Guidance for Co-Administration with CYP3A Inhibitors

Patient Population	**Co-administered Drug**	**Recommended Ibrutinib Dose for the Duration of the Inhibitor Use[a]**
B-Cell Malignancies	Mild CYP3A inhibitors	420 mg or 560 mg once daily per indication. No dose adjustment required.
	Moderate CYP3A inhibitors	280 mg once daily.
	Voriconazole 200 mg twice daily Posaconazole suspension 100mg once daily, 100 mg twice daily, or 200 mg twice daily	140 mg once daily.
	Other strong CYP3A inhibitors Posaconazole at higher doses[b]	Avoid concomitant use and consider alternative with less CYP3A inhibitory potential. If these inhibitors will be used short-term (such as anti-infectives for seven days or less), interrupt ibrutinib. If the benefit outweighs the risk, and long-term dosing with a CYP3A inhibitor is required (more than seven days), reduce ibrutinib dose to 140 mg once daily for the duration of the inhibitor use.

a. Monitor for adverse reactions to IMBRUVICA and interrupt or modify dose as recommended (see Dosage and Administration).

b. Posaconazole at higher doses (posaconazole suspension 200 mg three times daily or 400 mg twice daily, posaconazole IV injection 300 mg once daily, posaconazole delayed-release tablets 300 mg once daily).

- No dose adjustment is required in combination with mild inhibitors.
- Avoid grapefruit and Seville oranges during ibrutinib treatment as these contain moderate inhibitors of CYP3A.

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 C. For further information, please refer to the current version of the ibrutinib Investigator Brochure and the examples of inhibitors, inducers, and substrates found at http://medicine.iupui.edu/clinpharm/ddis/main-table/. This website is continually revised and should be checked frequently for updates.

4.3.3.2 Drugs That May Have Their Plasma Concentrations Altered by Ibrutinib or Venetoclax

In vitro studies indicated that ibrutinib is not a substrate of P-glycoprotein (P-gp), but is a mild inhibitor (with an IC_{50} of 2.15 µg/mL). 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.

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, co-administration 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.

4.3.3.3 QT-Prolonging Agents

Any medications known to cause QT prolongation should be used with caution; periodic ECG and electrolyte monitoring should be considered.

4.3.3.4 Antiplatelet Agents and Anticoagulants

Use ibrutinib with caution in subjects requiring anticoagulants or medications that inhibit platelet function. Supplements such as fish oil and vitamin E preparations should be avoided during treatment with ibrutinib. In an *in vitro* platelet function study, inhibitory effects of ibrutinib on collagen-induced platelet aggregation were observed. Bleeding events of any grade, including bruising and petechiae, occurred in subjects treated with ibrutinib. 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. For guidance on ibrutinib and the use of anticoagulants during procedures/surgeries, see Section 4.3.5.

Subjects requiring the initiation of therapeutic anticoagulation therapy (eg, atrial fibrillation), should be monitored closely for signs and symptoms of bleeding and the risks and benefits of continuing ibrutinib treatment should be considered.

4.3.4 Prohibited Concomitant Medications

Any chemotherapy, anticancer immunotherapy, experimental therapy, or radiotherapy is prohibited while the subject is receiving ibrutinib treatment.

Corticosteroids for the treatment of the underlying disease are prohibited. Corticosteroids for the treatment of non-cancer related reasons for longer than 14 days and/or at doses > 100 mg of prednisone or its equivalent are prohibited.

Use of strong CYP3A inhibitors is contraindicated during venetoclax initiation and dose ramp-up. Subjects may not consume grapefruit or grapefruit products, Seville oranges (including marmalade containing Seville oranges) or star fruit within the 3-day period prior to the first venetoclax administration and until the last day of treatment is completed due to possible CYP3A mediated metabolic interaction.

Erythropoietic growth factors (eg, erythropoietin) and neutrophil growth factors (eg, filgrastim and peg-filgrastim) may be administered per standard practice.

4.3.5 Guidelines for Ibrutinib Management with Surgeries or Procedures

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

4.3.5.1 Minor Surgical Procedures

For minor procedures (such as a central line placement, needle biopsy, 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 for these procedures.

4.3.5.2 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 serosanguinous drainage or the need for drainage tubes.

4.4 Duration of Therapy

Upon completion of ibrutinib + venetoclax combination treatment at Week 117, participants will have completed the trial and may transition off-study to receive commercial ibrutinib at the discretion of the investigator. In the absence of treatment delays due to adverse event(s), combination treatment may continue through Week 117, or until one of the following criteria applies:

- Disease progression or relapse
- Unacceptable drug-related adverse event(s)
- Patient decides to withdraw from the study
- Investigator decision that discontinuation is in the best interests of the patient
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Pregnancy

4.5 Duration of Follow-up

Patients will be followed until end of treatment; withdrawal of consent; or death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

4.6 Criteria for Removal from Study

4.6.1 Removal from Study Treatment

Patients will be removed from study treatment when any of the criteria listed in Section 4.4 applies. The reason for treatment termination and the date the patient was removed must be documented in the Case Report Form (CRF).

4.6.2 Removal from Study

Withdrawal from the study including termination of all follow-up will occur if:

- The subject is lost to follow-up following reasonable effort from study staff to contact the subject
- The subject withdraws consent for follow-up observation
- The subject dies
- The study is terminated

Documentation of the reason for withdrawal and withdrawal of full (treatment and all further contact) or partial (withdrawal of consent to treatment but not to follow-up visits) consent will be must be documented in the Case Report Form (CRF).

4.7 Study Risk Information

Risks of the study drugs are described within the venetoclax and ibrutinib Investigator's Brochures and FDA-approved labeling for each.

4.8 Risk Mitigation

Risk mitigation will include safety assessments during clinic visits at weeks 1; 5; and 9 (ibrutinib treatment only); then weekly for 4 weeks during the venetoclax dose ramp-up; then, during the venetoclax + ibrutinib stage, every 4 weeks through Week 30; then at Week 38, Week 62, and every 12 weeks thereafter. Safety assessments will include hematology; serum chemistry; physical exam with vital signs, weight, and ECOG performance status; and subject interviews for adverse events and concomitant medications.

5 STUDY DRUG INFORMATION

5.1 Study Drug Venetoclax

5.1.1 Name

Study drug venetoclax is approved by the US Food and Drug Administration (FDA) as Venclexta. The approved uses of venetoclax are described at Section 2.2.1 Venetoclax.

5.1.2 Formulation

The venetoclax tablets will be packaged in high-density polyethylene (HDPE) plastic bottles or blister packs to accommodate the study design. Each container will be labeled per local regulatory requirements. Tablets are formulated with 10 mg, 50 mg and 100 mg doses.

Blister Packs will contain study drug for one week plus one extra day. Subjects will be instructed to take the extra day's dose (noted with an "X" on the Blister Pack) only if directed by the investigator.

5.1.3 Study Cohorts / Arms / Groups

This is a single-arm, open label study. All participants will receive ibrutinib for 8 weeks, then begin dose-escalation with venetoclax as described elsewhere in the protocol.

5.1.4 Mechanism of Action

Venetoclax is a novel, orally available small molecule Bcl-2 family protein inhibitor that binds with > 500-fold higher affinity (Ki < 0.010 nM) to Bcl-2 and with lower affinity to other Bcl-2 family proteins Bcl-XL (Ki – 48 nM) and Bcl-w (Ki – 245 nM). Overexpression of anti-apoptotic Bcl-2 family proteins is associated with increased resistance to chemotherapy, and antagonism of the action of these proteins might enhance response to such therapy and overcome resistance. Anti-apoptotic Bcl-2 family members are associated with tumor initiation, disease progression, and drug resistance, making them compelling targets for antitumor therapy.

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 non-mutated cell lines.

5.1.5 Non-clinical and Clinical Pharmacokinetics

In vitro studies have shown that venetoclax is metabolized primarily by CYP3A4; thus, co-administration of venetoclax with drugs that inhibit CYP3A4 (such as ketoconazole) is predicted to cause a significant increase in the exposure of venetoclax and will be undertaken with caution. In a phase-I dose-escalation trial in patients with relapsed/refractory NHL, after a single dose administration with a high-fat meal, venetoclax reached C_{max} at approximately 7 hours with a terminal half-life of about 15 hours. Food increased venetoclax exposure by approximately 3-fold.

5.1.6 Summaries of Non-Clinical Pharmacology and Toxicology Studies

Venetoclax inhibited subcutaneous murine xenograft growth of human tumor cell lines derived from acute lymphoblastic leukemia (ALL) and Non-Hodgkin's Lymphoma (NHL). The drug was also active in a model of disseminated ALL.

5.1.6.1 Non-Clinical Toxicology Studies

The nonclinical toxicology of venetoclax has been evaluated in repeated-dose studies in mice and dogs with up to 4 weeks of once daily oral dosing (and with 4-week recovery periods) and in dogs with 2 weeks of dosing (18-week recovery period); safety pharmacology studies (cardiovascular, neurofunctional, and pulmonary); and in genetic toxicity tests (Ames and in vitro chromosome aberrations assays).

The primary toxicities associated with venetoclax administration included effects on the hematologic system (lymphocytes and red blood cell parameters) in mice and dogs and on the male dog reproductive system. There was no evidence of genotoxicity of venetoclax. A severely toxic dose (STD10) was not identified in mice up to and including the top dose of 600 mg/kg/day (overall mean $AUC_{0\text{-}24}$ = 91.5 µg•hr/mL and C_{max} = 7.2 µg/mL). In dogs, the highest non-severely toxic dose (HNSTD) was 150 mg/kg/day, but due to overlapping exposures between the mid and high doses, the HNSTD was defined as the mid dose of 50 mg/kg/day (overall mean $AUC_{0\text{-}24}$ = 472 µg•hr/mL and C_{max} = 27.4 µg/mL).

Venetoclax causes decreases in circulating lymphocytes and lymphocytes in lymphoid tissue. After 4 weeks of dosing, the lymphocyte effects were reversible or partially reversible in the mouse but generally were less reversible in the dog at the end of a 4-week recovery period. However, in a 2-week dog study focused on lymphocyte recovery over an extended (18-week) period, reversibility of lymphocyte effects was demonstrated. Immunophenotyping was used to assess changes in peripheral blood lymphocyte subsets (ie, mature T-cells, helper T-cells, cytotoxic T-cells, and mature B-cells). At the end of the 18-week recovery period, both total and lymphocyte subset counts returned to within range of baseline and control values, and all effects on lymphoid tissue reversed. The venetoclax–related decreases in lymphocytes in blood and lymphoid tissues are considered pharmacologically mediated and non-adverse.

Additional hematological effects of venetoclax treatment included reversible decreases in red blood cell parameters (primarily, hematocrit and hemoglobin concentration) in mice and dogs. The decreases in red cell parameters were adverse only at the high dose levels in the 4-week studies (ie, at 600 mg/kg/day in mice and at 150 mg/kg/day in dogs, but all red cell parameters were reversible at the end of a 4-week recovery period. Effects on both lymphocytes and red cell mass are readily monitored in subjects.

Dogs at the high dose of 150 mg/kg/day in the 4-week study had clinical signs of itching and swelling of the skin on the ears, head (cranial area), and forepaws and/or hindpaws. Most of the animals (8 of 10 dogs) were affected. The clinical signs were mild to moderate in severity, transient and sporadic in occurrence, and were absent during the recovery period. The swelling reactions were observed after the first dose in 3 dogs, and therefore not consistent with drug-induced immediate (IgE-mediated, Type I) hypersensitivity; however, other immune-mediated mechanisms could be involved. Although the basis for the swelling reactions was not established, there were no signs of anaphylaxis. Any occurrences of swelling reactions in patients can be monitored and treated.

In an ongoing 9-month chronic toxicity study of dogs with venetoclax, hypopigmented (white) facial hair was observed after approximately 3 months of dosing (ongoing study Abbvie R&D/12/384). The finding was limited to the mid and high doses (6 and 20 mg/kg/day), and was observed in both males and females. Evidence from Bcl-2 knockout mouse (bcl-2-/-) studies indicates that hair hypopigmentation is consistent with the pharmacological effect of Bcl-2 functional loss, and occurs due to loss of hair follicle melanocytes dependent on Bcl-2 for survival.[28] A dedicated physical examination of the skin and extensive ophthalmic examinations determined that pigmentation of the skin and in the eye (particularly in the iris and fundus) appears unaffected. The potential for development of white (hypopigmented) hair in humans is unknown.

Venetoclax was tested in a battery of safety pharmacology assays and produced no effects in central nervous system/neurobehavioral, or respiratory studies in mice at oral doses up to 600 mg/kg. In an anesthetized dog cardiovascular model given intravenous doses of venetoclax, mild reductions in myocardial contractility (maximum rate of rise of left ventricular pressure [dP/dtmax]: –6% to –13%) and cardiac output (–11% to –19%) were observed at plasma concentrations of ≥ 16 µg/mL and ≥ 32 µg/mL, respectively. However, no effect on blood pressure, heart rate, or electrocardiogram (ECG) parameters were observed relative to baseline or controls in either the anesthetized dog study or in the conscious dog cardiovascular study using telemeterized animals at maximum drug concentrations of 46 µg/mL and 16 µg/mL, respectively.

Nonclinical safety pharmacology and toxicology evaluations of venetoclax, as well as nonclinical and human studies of related anti-apoptotic Bcl-2 family protein inhibitors, suggest potential mechanism-based toxicities may include lymphopenia and neutropenia,[29] signs of tumor lysis, reduction in red cell mass, decreased spermatogenesis, skin swelling, and hair hypopigmentation. Thrombocytopenia has not been observed in toxicology studies in mice and dogs. These findings are consistent with venetoclax as a Bcl-2 specific (Bcl-XL sparing) inhibitor. Consequently, thrombocytopenia is not expected to be a dose-limiting toxicity (DLT) clinically.

A detailed discussion of the preclinical toxicology, metabolism, and pharmacology can be found in the current version of the Investigator's Brochure.

5.1.6.2 Carcinogenesis, Mutagenesis, Impairment of Fertility

Male dog reproductive effects consisted of markedly reduced numbers of spermatogonia in the testes at all venetoclax dose levels after 4 weeks of dosing, with progression to severe decreases in the numbers of all germ cells in testes during the 4-week recovery period. Male mice did not have testicular changes associated with venetoclax administration. The translatability of the testicular findings in dogs to humans is unknown, but this change may be related to venetoclax pharmacology, as one or more members of the Bcl-2 family of proteins play a role in spermatogenesis.[30-32] In view of the potential treatment benefits of venetoclax, this finding is anticipated not to impact the treatment of subjects with advanced hematologic malignancies.

5.1.7 Summaries of Clinical Studies

As of 28 November 2015, data available in the AbbVie and Genentech/Roche clinical databases include a total of 1662 subjects who have been exposed to at least 1 dose of venetoclax in the oncology and immunology development programs. A total of 1498 oncology subjects have data

available in AbbVie and Genentech/Roche studies as of 28 November 2015. Of these 1498, 935 subjects had CLL/small lymphocytic leukemia (SLL), 346 subjects had NHL, 115 subjects had MM, 102 had AML. An additional 66 subjects were healthy volunteers. A total of 564 oncology subjects received the drug as monotherapy, 933 received the drug in combination with other therapies, and 1 subject received venetoclax as a single dose in a DDI study and did not re-enroll into a subsequent monotherapy study. Additionally, 98 subjects were exposed to at least 1 dose of venetoclax in the AbbVie immunology study, Study M13-093, as of 28 November 2015.

Preliminary efficacy results are available for subjects with CLL/SLL, NHL, MM, and AML as listed below. Preliminary data indicate that venetoclax continues to show promising efficacy in oncology subject populations.

- In venetoclax monotherapy Study M12-175 (as of 25 August 2015), the overall remission rate (ORR; investigator-assessed) in Arm A (R/R CLL/SLL) in the Dose-Escalation and Safety Expansion Cohorts was 79%.[33] The ORR (investigator-assessed) in Arm B (R/R NHL) was 38% for FL subjects and 18% for DLBCL subjects (Dose-Escalation and Safety Expansion Cohorts).
- In venetoclax monotherapy Study M13-982 (as of 30 April 2015), the ORR (IRC-assessed) for R/R CLL subjects was 74%.
- In venetoclax monotherapy Study M14-032 (as of 25 August 2015), the ORR for R/R CLL subjects in Arm A (ibrutinib-resistant) was 42% and in Arm B (idelalisib-resistant) was 29%.
- In Study M13-365 (as of 28 October 2015) the ORR for R/R CLL/SLL subjects treated with venetoclax + rituximab was 86%.
- In Study M12-630 (as of 17 September 2015), the ORR for R/R NHL subjects treated with venetoclax + BR was 67%.
- In Study M13-367 (as of 17 September 2015), the ORR for R/R MM subjects treated with venetoclax was 24% in t(11;14)-positive subjects and 4% in t(11;14)-negative subjects.
- In Study M12-901 (as of 17 September 2015), the ORR for R/R MM subjects treated with venetoclax and bortezomib/dexamethasone was 100% in bortezomib-naïve subjects, 71% in bortezomib-sensitive subjects, and 17% in bortezomib-refractory subjects.
- In Study M14-212 (as of 07 October 2014), the ORR for AML subjects treated with venetoclax monotherapy was 19%.
- In Study M14-358 (as of 19 September 2015), the ORR for AML subjects was 77%.
- In Study M14-387 (as of 28 November 2015), the ORR for AML subjects was 44%.

For the most comprehensive clinical information regarding venetoclax, refer to the current version of the Investigator's Brochure.

5.1.8 Major Route of Elimination

Following oral administration in mouse, rat, dog, and human, venetoclax and its metabolites were cleared primarily via biliary excretion and fecal elimination, with minimal renal clearance.

5.1.9 Safety Profile

The preliminary clinical data of venetoclax monotherapy in subjects with CLL/SLL, MCL and NHL have shown a favorable benefit to risk ratio in Study M12-175. As of 3 February 2014, a total of 153 subjects have been enrolled in Study M12-175, and had data available for the study (95 in Arm A and 58 in Arm B). The most common adverse events in Arm A (CLL/SLL subjects) were diarrhea (38.9%), neutropenia (37.9%), nausea (34.7%), upper respiratory tract infection (30.5%), fatigue (27.4%), and cough (20.0%). The most common adverse events in Arm B (NHL subjects) were nausea (32.8%), diarrhea (24.1%), and fatigue and upper respiratory tract infection (20.7% each).

The most common adverse events reported for all subjects in the study were nausea (34.0%), diarrhea (33.3%), neutropenia (29.4%), upper respiratory tract infection (26.8%), and fatigue (24.8%). The most common events Grade 3 or above reported in Arm A (CLL/SLL subjects) were neutropenia (34.7%) and anemia (10.5%), and in Arm B (NHL subjects) were anemia (15.5%) and neutropenia (10.3%). Overall, Grade 3 or 4 adverse events reported in > 5% of patients were anemia, neutropenia, febrile neutropenia, thrombocytopenia, hyperglycemia, and tumor lysis syndrome (TLS). These adverse events were mostly consistent with complications commonly observed in heavily pretreated patients with R/R CLL/SLL. Febrile neutropenia was the most common serious adverse event observed with venetoclax monotherapy treatment (7.0%); all events resolved on supportive treatment, and none resulted in discontinuation from the study. The only other serious adverse event reported in more than 2 subjects was TLS (11.0%) for venetoclax as a single agent. A comprehensive safety review identified risk factors for developing TLS from Study M12-175 as well as Study M13-365 (venetoclax in combination with rituximab), resulting in implementation of a modified dose-escalation regimen and revised TLS risk management procedures in ongoing studies in various hematologic malignancies.

5.1.9.1 Tumor Lysis Syndrome (TLS)

TLS is considered an important identified risk and is predominantly seen in the CLL population with high tumor burden. Primary CLL cells are essentially dependent on Bcl-2 for survival and are exquisitely sensitive to the Bcl-2 specific inhibitor venetoclax, and the on-target pharmacological effect can cause rapid reduction in size of tumor (debulk) and may pose a risk of TLS.

The management of the risk of TLS with venetoclax has evolved over time. In Study M12-175 (June 2011), substantial anti-tumor activity was observed in the first 3 subjects with CLL following a single dose of venetoclax of 100 to 200 mg. Within 24 hours, reductions in palpable lymphadenopathy were observed in all 3 subjects and dramatic reductions in lymphocyte count (> 95%) were observed in the 2 subjects with pretreatment lymphocytosis. This rapid response resulted in TLS in all 3 subjects, mainly characterized by increases in potassium, phosphate, and LDH levels which resolved without clinical complications in all 3 subjects.

Subsequently, the initial venetoclax dose for CLL subjects was reduced to 50 mg, and 2 to 3 weekly ramp-up steps were introduced to reach the final cohort dose. In addition, in all subjects, intensified monitoring and standard TLS prophylaxis measures were mandated, including protocol-specified laboratory tests, hydration, and treatment to prevent hyperuricemia. In the subsequent cohorts, a CLL subject developed TLS and acute renal failure requiring dialysis. This subject presented with elevated potassium and ECG changes indicating possible myocardial infarction. Subsequently, a cardiac catheterization was performed. The acute renal

failure may have also been due to the radiographic dye in the setting of TLS. Hospitalization of CLL/SLL subjects with the first dose of venetoclax became mandatory following the report of this serious adverse event.

In December 2012, 2 fatal adverse events in the setting of TLS were reported in subjects with CLL/SLL. The first death (in Study M13-365) occurred within 24 hours after the subject received his first dose of 50 mg venetoclax. The second death (in Study M12-175) occurred within 48 hours after the subject had escalated to the final dose of 1200 mg/daily of venetoclax, the highest dose administered in the venetoclax program to date. Following the report of 2 fatal adverse events in the setting of TLS in December 2012, the clinical program was halted and a comprehensive review of all safety data available from studies with venetoclax revealed:

- The highest risk period for developing TLS is at initiation of venetoclax. The risk is reduced as the tumor burden decreases.
- Subjects with TLS appeared to have had a higher venetoclax exposure than subjects without TLS. To reduce the initial exposure for all subjects to that of subjects not experiencing TLS (Cmax ≤ 0.23 µg/mL), trial simulation data indicated that subjects should receive 20 mg as a starting dose.
- Bulky lymph nodes ≥ 5 cm and elevated screening ALC ≥ 38.9×10^9/L were identified as risk factors for TLS following administration of venetoclax. Screening CrCl < 80 mL/min was also identified as a contributing factor. These TLS risk factors are not unique to venetoclax and have been previously identified in the literature.
- The 2 subjects who had fatal CTLS (Subject 167 in Study M12-175, and Subject 5503 in Study M13-365) had nodes greater than or approximately equal to 10 cm in size.

Based on the analyses and discussion with regulatory authorities, the clinical program was reinitiated in May 2013 with a modified venetoclax dosing regimen and enhanced TLS prophylaxis and monitoring measures: frequent blood draws, uric acid reducing agents ≥ 72 hours prior to first dose, and site education plan. Repeat analysis in January 2014 performed to evaluate the effectiveness of revised measures indicated a marked reduction in severity and frequency of TLS when compared to the previous analysis. None of the subjects experienced any serious (including fatal) or non-serious event of CTLS or laboratory TLS (LTLS) or had study treatment discontinued because of TLS. The revised dosing regimen, which includes a more gradual increase in dose, likely led to gradual debulking of the tumor and played a key role in mitigating the risk. Based on the results of this interim analysis, following revisions were made in May 2014:

- All subjects starting venetoclax treatment at 20 mg QD for 1 week followed by gradual weekly titration up to the 400 mg QD dose.
- More personalized approach for prophylaxis and monitoring measures, where subjects with low and medium risk for TLS could receive venetoclax on an out-patient basis with post-dose laboratory monitoring at 8 and 24 hours. Subjects at high risk for TLS were hospitalized for their initial dose at 20 mg and 50 mg and then managed on an out-patient basis.
- Oral uricosurics starting 72 hours prior and oral hydration starting 48 hours prior to starting venetoclax; additional IV fluids for high and medium risk subjects. Rasburicase is recommended for subjects at high risk, especially those with high baseline values.

- Reassessment of tumor burden based on current ALC followed by less intensive prophylaxis and monitoring was allowed, based on the investigator's discretion.

From May 2014 to 25 August 2015, a total of 105 subjects have received venetoclax following the above measures in monotherapy CLL Study M13-982 (safety expansion cohort) and Study M14-032. Adverse events of TLS are reported in 4/105 (3.8%) subjects, with no events of CTLS. Hyperkalemia (or blood potassium increased) was the most common laboratory adverse event relevant to TLS, and was reported in 17/105 (16.2%; one Grade 3 event) of subjects. Hyperphosphatemia was reported in 15/105 (14.3%, 22 Grade 3 events) subjects; hypocalcaemia in 10/105 (9.5%) subjects, and hyperuricemia in 9/105 (8.6%) subjects. All adverse events related to clinical chemistries resolved with standard electrolyte management without any clinical consequences.

Current recommendations for TLS prophylaxis and monitoring in CLL are summarized in Section 4.3.1.

5.1.10 Rationale for the Starting Dose and Regimen Selected

Daily oral dosing of venetoclax at 400 mg has been well tolerated in CLL patients previously as mono-agent therapy; higher doses have also been tested in other malignancies though without significantly increased efficacy in CLL/SLL. Implementation of intra-patient dose-escalation with venetoclax, pre-treatment TLS risk categorization, and enhanced prophylactic guidance and monitoring for TLS has eliminated the significant tumor lysis that was previously seen with initiation of venetoclax therapy at higher doses. A similar use of intra-patient dose-escalation for venetoclax in this study will allow rapid identification of the maximal tolerable dose while maintaining high sensitivity for adverse events and dose-limiting toxicities.

5.1.11 Maximum Allowable Dose/ Overdose

The maximum allowed dose of venetoclax in this study is 400 mg.

Any dose of study drug more than that specified in this protocol is considered an overdose. Signs and symptoms of an overdose that meet any Serious Adverse Event criterion must be reported as a Serious Adverse Event in the appropriate time frame and documented as clinical sequelae to an overdose.

There is no specific antidote for venetoclax. In the event of an overdose, subjects should be closely monitored and given appropriate supportive treatment.

Refer to Section 7 for further information regarding AE reporting.

5.1.12 Treatment Duration

Treatment duration of venetoclax for this study is 2 years in combination with ibrutinib.

5.2 Study Drug Ibrutinib

5.2.1 Names

Study drug ibrutinib is approved by the US Food and Drug Administration (FDA) as Imbruvica. The approved uses of ibrutinib are described at Section 2.2.2 Ibrutinib.

5.2.2 Formulation

Ibrutinib capsules are provided as a hard gelatin capsule containing 140 mg of ibrutinib. All formulation excipients are compendial and are commonly used in oral formulations. Refer to the ibrutinib Investigator's Brochure 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. All study drug will be dispensed in child-resistant packaging. Study drug labels will contain information to meet the applicable regulatory requirements.

The first dose of ibrutinib will be delivered in the clinic on Day 1, after which subsequent dosing is typically on an outpatient basis. Unused ibrutinib dispensed during previous visits must be returned to the site and drug accountability records updated at each visit.

Refer to the pharmacy manual/site investigational product manual for additional guidance on study drug storage, preparation and handling.

5.2.3 Study Cohorts

All study participants will receive ibrutinib daily starting at Week 1 Day 1 at the FDA-approved dose for CLL/SLL.

5.2.4 Mechanism of Action

Ibrutinib was designed as a selective and covalent inhibitor of Bruton's tyrosine kinase (BTK).[34] In vitro, ibrutinib is a potent inhibitor of BTK activity (IC_{50} = 0.39 nM). The irreversible binding of ibrutinib to cysteine-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 B-cell receptor and blocks primary B-cell activation (IC_{50} = 80 nM) as assayed by anti-IgM stimulation followed by CD69 expression.[35]

For more detailed and comprehensive information regarding pharmacology, refer to the current Investigator's Brochure.

5.2.5 Non-Clinical and Clinical Pharmacokinetics

Following oral administration of ibrutinib at doses ranging from 1.25 to 12.5 mg/kg/day as well as fixed dose levels of 420, 560, and 840 mg/day, exposure to ibrutinib increased as doses increased, with substantial inter-subject variability. The mean half-life ($t_{1/2}$) of ibrutinib across 3 clinical studies ranged from 4 to 9 hours, with a median time to maximum plasma concentration (T_{max}) of 2 hours. Administration of 420 mg ibrutinib with a high-fat breakfast in subjects with CLL approximately doubled the mean systemic exposure compared to intake after overnight fasting with median time to T_{max} delayed from 2 to 4 hours. Ibrutinib was extensively metabolized to the dihydrodiol metabolite PCI-45227, a reversible inhibitor of BTK, with approximately 15 times lower inhibitory potency compared to ibrutinib. The metabolite-to-parent

AUC ratio ranged from 0.7 to 3.4. Steady-state exposure of ibrutinib and PCI-45227 was less than 2-fold of first dose exposure.

Data from clinical Study PCYC-04753 demonstrate that although ibrutinib is rapidly eliminated from the plasma after oral administration, once daily dosing with ibrutinib is adequate to sustain maximal pharmacodynamic activity for 24 hours post dose at dose levels ≥ 2.5 mg/kg. In Study PCYC-04753, the BTK occupancies for the 2.5 mg/kg/day to 12.5 mg/kg/day cohorts and for the 560 mg continuous dosing cohort were all above 90% at either 4 or 24 hours after drug administration.

5.2.6 Summaries of Non-Clinical Pharmacology and Toxicology Studies

For the most comprehensive nonclinical information regarding ibrutinib, refer to the current version of the Investigator's Brochure.

5.2.6.1 Non-Clinical Toxicology Studies

In safety pharmacology assessments, 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 vitro and in vivo genetic toxicity studies showed that ibrutinib is not genotoxic. In a rat embryo-fetal toxicity study ibrutinib administration was associated with fetal loss and malformations (teratogenicity) at ibrutinib doses that result in approximately 6 times and 14 times the exposure (AUC) in patients administered the dose of 560 mg daily, respectively.

5.2.6.2 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with ibrutinib.

Ibrutinib was not mutagenic in a bacterial mutagenicity (Ames) assay, was not clastogenic in a chromosome aberration assay in mammalian (CHO) cells, nor was it clastogenic in an in vivo bone marrow micronucleus assay in mice at doses up to 2000 mg/kg.

Fertility studies with ibrutinib have not been conducted in animals. In the general toxicology studies conducted in rats and dogs, orally administered ibrutinib did not result in adverse effects on reproductive organs.

5.2.7 Summaries of Clinical Studies

The initial study of ibrutinib in relapsed/refractory CLL patients demonstrated an ORR of 90% but only a 7% CR rate with a median treatment duration of 23 months.[36] For the most comprehensive clinical information regarding ibrutinib, refer to the current version of the Investigator's Brochure.

5.2.8 Major Route of Elimination

The results of human mass balance study of [^{14}C]-ibrutinib conducted in 6 healthy male subjects demonstrated that less than 10% of the total dose of [^{14}C]-ibrutinib is renally-excreted, whereas approximately 80% is recovered in feces. Subjects with mild and moderate renal insufficiency (creatinine clearance > 30 mL/min) were eligible to enroll in Study PCYC-1102-CA in which pharmacokinetic (PK) assessments were included. No dose adjustment is needed for mild or moderate renal impairment (greater than 30 mL/min creatinine clearance). There is no data in patients with severe renal impairment or patients on dialysis. In a hepatic impairment study, data showed an increase in ibrutinib exposure. 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. The safety of ibrutinib in patients with hepatic impairment is currently in progress.

5.2.9 Safety Profile

Pooled safety data for a total of 1,971 subjects treated with various therapies in combination with ibrutinib from 17 studies that have completed primary or final analysis included in the CSR as of 12 November 2019 are summarized below. Therapies used in combination with ibrutinib in these studies, included BR (bendamustine and rituximab), FCR (fludarabine, cyclophosphamide, and rituximab), cytarabine, azacytidine, dexamethasone, durvalumab, ofatumumab, lenalidomide with EPOCH-R (cyclophosphamide, doxorubicin, etoposide, vincristine, prednisone +/- rituximab), nivolumab, Obinutuzumab, rituximab, carfilzomib +/- dexamethasone, pomalidomide and dexamethasone and R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone).

Table 3. Most frequently reported TEAEs in subjects receiving ibrutinib in combination therapy (N = 1,971)

Most frequently reported TEAEs > 20%	Most frequently reported Grade 3 or 4 TEAEs > 3%	Most frequently reported Serious TEAEs > 2%
Neutropenia	Neutropenia	Febrile neutropenia
Diarrhea	Thrombocytopenia	Pneumonia
Nausea	Febrile neutropenia	Atrial fibrillation
Thrombocytopenia	Pneumonia	Pyrexia
Fatigue	Hypertension	Anemia
Anemia	Neutrophil count decreased	
Pyrexia	Anemia	
Cough	Fatigue	
Upper respiratory tract infection	Diarrhea	
Constipation	Platelet count decreased	
	Hypokalemia	
	Lymphocyte count decreased	
	White blood cell count decreased	
	Atrial fibrillation	
	Hyponatremia	
	Leukocytosis	
	Leukopenia	
	Lymphocyte count increased	

For more detailed information, refer to the current version of the IB.

5.2.9.1 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 some major hemorrhagic events, some fatal, including gastrointestinal bleeding, intracranial hemorrhage and hematuria. Use of ibrutinib in subjects requiring other anticoagulants or medications that inhibit platelet function 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 and symptoms of bleeding. Subjects with congenital bleeding diathesis have not been studied. See Section 4.3.3.4 for guidance on concomitant use of anticoagulants, antiplatelet therapy and/or supplements. See Section 4.3.5 for guidance on ibrutinib management with surgeries or procedures. In an *in vitro* platelet function study, inhibitory effects of ibrutinib on collagen induced platelet aggregation were observed, refer to Section 4.3.3.4. 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.

5.2.9.2 Cardiac Arrhythmias

Atrial fibrillation, atrial flutter and cases of ventricular tachyarrhythmia 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 atrial fibrillation. Periodically monitor subjects clinically for cardiac arrhythmia. 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 that persists, consider the risks and benefits of ibrutinib treatment and follow the protocol dose modification guidelines.

5.2.9.3 Cytopenias

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

5.2.9.4 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.

5.2.9.5 Infections

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

5.2.9.6 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.

5.2.9.7 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.

5.2.9.8 Lymphocytosis and Leukostasis

5.2.9.1.1 Lymphocytosis

Upon initiation of treatment, a reversible increase in lymphocyte counts (ie, ≥ 50% increase from baseline and an absolute count > 5000/μL), often associated with reduction of lymphadenopathy, has been observed in most subjects (66%) with CLL/ small lymphocytic lymphoma (SLL) treated with ibrutinib. This effect has also been observed in some subjects with MCL treated with ibrutinib. This observed lymphocytosis (increase in the number of circulating lymphocytes eg, > 400,000/μL) 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 few weeks of ibrutinib therapy (median time 1.1 weeks) and typically resolves within a median of 8.0 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.

5.2.9.1.2 Leukostasis

There were isolated cases of leukostasis reported in subjects treated with ibrutinib. A high number of circulating lymphocytes (> 400,000/μL) may confer increased risk. Consider temporarily withholding ibrutinib. Subjects should be closely monitored. Administer supportive care including hydration and/or cytoreduction as indicated. For subject and ibrutinib management guidance, refer to Section 6.2.1.2.

5.2.9.9 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.

5.2.9.10 Interstitial Lung Disease

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 (see Section 6).

5.2.9.11 Hypertension

Hypertension has occurred in subjects treated with ibrutinib. Regularly monitor blood pressure in subjects treated with ibrutinib and initiate or adjust antihypertensive medication throughout treatment with ibrutinib as appropriate.

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.

Long-term safety

The long-term safety data over 5 years from 1,178 subjects (treatment-naïve CLL/SLL n = 162, relapsed/refractory CLL/SLL n=646, and relapsed/refractory MCL n=370) treated with ibrutinib were analyzed. The median duration of treatment for CLL/SLL was 51 months (range, 0.2 to 98 months) with 70% and 52% of subjects receiving treatment for more than 2 years and 4 years, respectively. The median duration of treatment for MCL was 11 months (range, 0 to 87 months) with 31% and 17% of subjects receiving treatment for more than 2 years and 4 years, respectively. The overall known safety profile of ibrutinib-exposed subjects remained consistent, other than an increasing prevalence of hypertension, with no new safety concerns identified. The prevalence for Grade 3 or greater hypertension was 4% (year 0-1), 6% (year 1-2), 8% (year 2 – 3), 9% (year 3- 4), and 9% (year 4-5). The incidence for the 5-year period was 11%.

5.2.9.12 Rationale for the Starting Dose and Regimen Selected

This study uses the FDA approved dose of ibrutinib 420 mg PO daily for CLL/SLL. Dose reduction of ibrutinib is allowed for attributable toxicity as specified in Section 6.2.

5.2.9.13 Maximum Allowable Dose / Overdose

There are limited data on the effects of ibrutinib overdose. No maximum tolerated dose (MTD) was reached in the Phase 1 study in which subjects received up to 12.5 mg/kg/day (1400 mg/day). In a separate study, 1 healthy subject who received a dose of 1680 mg experienced reversible Grade 4 hepatic enzyme increases (AST and ALT). There is no specific antidote to ibrutinib. Subjects who ingest more than the recommended dosage should be closely monitored and given appropriate supportive treatment.

Refer to Section 7 for further information regarding AE reporting.

5.2.9.14 Treatment Duration

All study participants will receive ibrutinib daily starting at Week 1 Day 1 and be dosed continuously throughout the study until completion of 2 years combined therapy with venetoclax, disease progression, development of intolerable side effects, need to initiate prohibited therapies, or participant withdrawal. Upon completion of ibrutinib + venetoclax combination treatment at Week 117, participants will have completed the trial and may transition off-study to receive commercial ibrutinib at the discretion of the investigator.

5.3 Study Drug Supply

5.3.1 Venetoclax Drug Supply

Venetoclax will be supplied by Abbvie.

5.3.1.1 Venetoclax Ordering

The investigational pharmacist will request drug supply using the form in Appendix H.

The form should be sent to supplies.team@abbvie.com.

5.3.2 Ibrutinib Drug Supply

Ibrutinib will be supplied by Pharmacyclics.

5.3.2.1 Ibrutinib Ordering

The investigational pharmacist will request drug supply using the form in Appendix I.

The form should be sent to ist.ctep@pcyc.com.

5.4 Venetoclax and Ibrutinib Accountability

All clinical supplies must be maintained under adequate security and stored under conditions specified on the label. The venetoclax tablets must be stored at 15° to 25°C (59° to 77°F).

Ibrutinib 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 or venetoclax to other Investigators, subjects, or clinics or allow supplies to be used other than as directed by this protocol. An Investigational Drug Accountability Log must be used for drug accountability. For accurate accountability, the following information must be noted when drug supplies are used during the study:

1. Study identification number
2. Subject identification number
3. Lot number(s) of ibrutinib or venetoclax dispensed for that subject
4. Date and quantity of drug dispensed
5. Any unused drug returned by the subject

6 DOSE MODIFICATIONS AND DISCONTINUATION

6.1 Venetoclax Dose Modification

If one or more electrolyte changes (from the pre-dose value) suggestive of tumor lysis syndrome (TLS) occurs within 24 hours of venetoclax initiation (20 mg dose) or dose escalation (50, 100, 200, 400 mg doses) and is confirmed by a repeat laboratory test within 1 to 2 hours, no additional venetoclax doses will be administered until resolution (within normal range) of those laboratory abnormalities. Upon resolution of laboratory abnormalities, the subject will remain at the current dose level of venetoclax (eg, if receiving 20 mg, will remain at 20 mg) through 7 doses.

The additional Warnings in the Package Insert are administration of live attenuated vaccines prior to, during, or after venetoclax treatment (prohibited in this protocol) and embryo-fetal toxicity.

See also Section 6.3 Dose Modification for Both Venetoclax and Ibrutinib.

6.2 Ibrutinib Dose Modification

The dose of ibrutinib should be modified according to the dose modification guidelines in Table 4 if any of the following toxicities attributable to ibrutinib occur:

- Grade 3 or greater non-hematological toxicities.
- Grade 3 or greater neutropenia with infection or fever
- Grade 3 thrombocytopenia (< 50,000/μL) in the presence of clinically-significant bleeding events.
- Grade 4 hematological toxicities, including thrombocytopenia < 20,000/μL.

If clinically indicated, the use of anticoagulants or antiplatelet agents may be considered for the thromboprophylaxis of atrial fibrillation (Section 4.3.3.4).

Recommended dose modifications are described in Table 4 below.

Table 4. Ibrutinib Dose Modifications

Occurrence	Action to be Taken
First	Withhold ibrutinib until recovery to Grade ≤ 1 or baseline; may restart at original dose level (420 mg/day)
Second	Withhold ibrutinib until recovery to Grade ≤ 1 or baseline; restart at ≤ 280 mg/day
Third	Withhold ibrutinib until recovery to Grade ≤ 1 or baseline; restart at ≤ 140 mg/day
Fourth	Discontinue ibrutinib

A high number of circulating malignant cells (> 400,000/uL) 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.

6.2.1.1 Dose Modification for Hepatic-Impaired Subjects

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 **Error! Reference source not found.**. Ibrutinib is metabolized in the liver. In the population PK analysis (1,202 subjects), 179 subjects (14.9%) had mild hepatic impairment according to National Cancer Institute criteria and 12 subjects (1.0%) had moderate hepatic impairment. These subjects did not show a significantly higher ibrutinib exposure compared with subjects with normal hepatic function. In a hepatic impairment study, data showed an increase in ibrutinib exposure. For subjects with mild liver impairment (Child-Pugh class A), the recommended dose is 280mg

daily. For subjects with moderate liver impairment (Child-Pugh class B), the recommended dose is 140mg daily. Monitor subjects for signs of ibrutinib toxicity and follow dose modification guidance as needed. It is not recommended to administer ibrutinib to subjects with severe hepatic impairment Subjects with clinically significant chronic hepatic impairment at the time of Screening (Child- Pugh class C) are excluded from study participation. Concomitant use of strong CYP inhibitors is not permitted in subjects with chronic hepatic impairment. Refer to Appendix D for Child-Pugh classification. Please refer to table below for dose modifications due to hepatic impairment.

Table . Dose Modification Guidance for Hepatic Impaired Subjects

	Child Pugh class A (Mild hepatic impairment)*		**Child Pugh Class B (Moderate hepatic impairment)****		**Child Pugh class C (Severe hepatic impairment)**
	Ongoing at time of enrollment	Develops during study	Ongoing at time of enrollment	Develops during study	Develops during study
Ibrutinib Dose (daily)	280 mg	280mg	140 mg	140 mg	Hold until improves to moderate [Class B] or better)

* If further reduction is needed due to non-hepatic toxicity, dose may be reduced to 140 mg. In the event that additional reduction is needed, ibrutinib should be held for non-hepatic toxicity until resolution.

** If further reduction is needed due to non-hepatic toxicity, ibrutinib should be held until resolution.

6.2.1.2 Leukocytosis / 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 of leukostasis; these subjects should be closely monitored. Administer supportive care such as hydration and/or leukapheresis as indicated. Consider temporarily withholding ibrutinib, and medical monitor should be contacted.

6.3 Dose Modification for Both Venetoclax and Ibrutinib

If the events below occur, no additional venetoclax doses will be administered until resolution of those laboratory abnormalities (≤ Grade 1), and ibrutinib dosing should continue or be discontinued per Table 4.

- Grade 4 ANC (< 500/μL) for more than 7 days. See Section 4.3.2 for instructions regarding the use of growth factor support.
- Any other Grade 4 toxicity, or unmanageable Grade 3 toxicity.

6.4 Treatment Discontinuation

Study treatment with venetoclax and ibrutinib will be permanently discontinued for any subject if any of the following occur.

- Grade 4 treatment-related (ie, possibly-, probably-, or definitely-related) non-hematologic toxicity.
- Grade 4 neutropenia lasting > 21 days
- Grade 4 thrombocytopenia lasting > 21 days or associated with clinically-significant bleeding (requiring > 3 units of packed red blood cells within 24 hours to replace loss OR bleeding from a site which in the Investigator's opinion is a potential life-threatening source irrespective of blood loss)

7 ADVERSE EVENTS AND REPORTING PROCEDURES

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.

Investigators will assess the occurrence of adverse events and serious adverse events at all subject evaluation time points during the study. All adverse events (AE) and serious adverse events (SAE) 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. Each recorded adverse event or serious adverse event 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.

The Protocol Director or designee will assess each AE to determine whether it is unexpected according to the Investigator's Brochure; Protocol; and Informed Consent, and whether it is related to the investigation (eg, study procedures) and/or the investigational agent. All SAEs will be tracked until resolution, or until at least 30 days after the last dose of the study treatment.

7.1 Adverse Events Definition

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 adverse event 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 due to 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.

- **Diagnostic Testing and Procedures:** Testing and procedures should not to 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.

An “unexpected” AE is an AE that is not listed in the Investigator's Brochure/package insert or is not listed at the specificity or severity that has been observed. "Unexpected" also refers to AEs that are mentioned in the Investigator's Brochure 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.

7.1.1 Serious Adverse Events Definition

For this investigational drug study, AEs will be determined to be Serious Adverse Events (SAEs) per 21CFR§312.32(a) and ICH GCP E6r1 (revision 1). An adverse event is considered "serious" if, in the opinion of the Protocol Director; investigator; or sponsor, it results in any of the following.

- Death
- Life-threatening, ie, immediate risk of death
  (***NOTE: Life-threatening does NOT include laboratory values that are “Grade 4 Life-threatening” per CTCAE v4.03, unless there is an immediate risk of death***)
- Requires, results in, or prolongs inpatient hospitalization
- Is a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly/birth defect in the offspring of a study participant
- Jeopardizes the subject, in the opinion of the Protocol Director; investigator; or sponsor
- Requires medical or surgical intervention to prevent one of the outcomes listed in this definition, in the opinion of the Protocol Director; investigator; or sponsor

The following are <u>NOT</u> considered SAEs:

- **Pre-planned or elective hospitalization:** A hospitalization planned before signing the informed consent form 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.

7.2 Adverse Event Reporting

Adverse events (AEs) will be graded according to CTCAE v4.03, except as noted below. 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

All treatment-emergent AEs will be captured from the first dose of study drug. SAEs will be reported to the Sponsor from the time of ICF signing. Both serious and non-serious AEs will be recorded in the eCRF from the first dose of study drug until 30 days after the last 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.

All adverse events, 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 eCRF their opinion concerning the relationship of the adverse event to study therapy

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. If a death occurs within 30 days after the last dose of study drug, the death must be reported as a serious adverse event.

All serious adverse events (SAEs) and AESIs (initial and follow-up information) will be reported to the FDA Medwatch (Form 3500A) or Suspect Adverse Event Report (CIOMS Form 1) IRB Reporting Form and sent via email (AEintakeCT@pcyc) or fax (408-215-3500) to Pharmacyclics Drug Safety, or designee, within 15 days of the event. Pharmacyclics may request follow-up and other additional information from the Sponsor Investigator.

All serious adverse events (SAEs) CTCAE Grade 3 and above, and all subsequent follow-up reports will be reported to the Stanford Cancer Institute (SCI) Data and Safety Monitoring Committee (DSMC) using the study-specific CRF regardless of the event's relatedness to the investigation. Following review by the DSMC, events meeting the IRB definition of

"Unanticipated Problem" will be reported to the IRB using eProtocol within 10 working days of DSMC review, or within 5 working days for deaths or life-threatening experiences

AEs, serious or otherwise, will be attributed to study treatment as follows:

- **Definite**: The AE is clearly related to the study treatment.
- **Probable**: The AE is likely related to the study treatment.
- **Possible**: The AE may be related to the study treatment.
- **Unlikely**: The AE is doubtfully related to the study treatment.
- **Unrelated**: The AE is clearly NOT related to the study treatment.

All serious adverse events (SAEs) will be followed until the SAE(s) is(are) resolved, stabilized, returned to baseline, attributed to agents other than the study drugs or to factors unrelated to study conduct, or until additional information cannot 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), whichever is longer.

Adverse events that are serious and unexpected suspected adverse reactions, ie, are possibly, probably, or definitely related to the study drugs venetoclax and ibrutinib, will be reported to the FDA via IND Safety Report [21CFR§312.32] within 14 calendar days, or within 7 calendar days if the event is an unexpected fatal or life-threatening suspected adverse reaction.

7.3 Safety Monitoring

This study is monitored by the Stanford Data and Safety Monitoring Committee (DSMC). SAEs will be reported by the study team to Stanford DSMC per the current Stanford SOP. SAEs that meet the definition of an "Unanticipated Problem" per the Stanford DSMC will be reported to the Stanford IRB using eProtocol within 10 working days of the Stanford DSMC's report to the Protocol Director regarding the event (within 5 working days for deaths or life-threatening events). See also Section 10.3 Data and Safety Monitoring Plan.

All serious adverse events (SAEs) that are CTCAE Grade 3 and above, and all subsequent follow-up reports will be reported to the Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) using the study specific CRF regardless of the event's relatedness to the investigation.

All SAEs will be reported will be reporting to the IRB in the annual Continuing Review, or the Final Report, that is submitted to the IRB.

7.4 Adverse Events of Special Consideration

7.4.1 Second Malignancy vs Secondary Malignancy

7.4.1.1 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). All new malignant tumors including solid tumors, skin malignancies and hematologic malignancies will be reported as SAEs per the current Stanford SOP, for the duration of study treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival.

7.4.1.2 Secondary Malignancy

In the context of a clinical study, a secondary malignancy is a cancer caused by the investigational agent/intervention, radiation, or chemotherapy. A secondary malignancy is not considered a metastasis of the initial neoplasm. All secondary malignancies will be reported as SAEs per the current Stanford SOP. Three options/examples are available to describe the event:

- Leukemia secondary to oncology chemotherapy [eg, acute myeloid leukemia (AML)]
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

By definition, secondary malignancies are serious and related adverse events, and require expedited reporting.

7.4.2 Other Adverse Events of Special Considerations

7.4.2.1 Adverse Events of Special Interest (AESI)

Specific adverse events, or groups of adverse events, will be followed as part of standard safety monitoring activities. In addition to normal reporting, these events (regardless of seriousness) will be reported on the Serious Adverse Event Report Form and sent via email or fax to Pharmacyclics Drug Safety, Pharmacovigilance & Epidemiology (DSP&E), or designee within 15 days of awareness.

- Major Hemorrhage, as defined by any of the following:
  - Any treatment-emergent hemorrhagic adverse events 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.

7.4.2.2 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 worsens, should be evaluated by an ophthalmologist whose findings should be reported in the CRF.

7.4.2.3 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 must immediately inform the Investigator if she becomes pregnant from the time of consent to 90 days after the last dose of study drug. A male subject must immediately inform the Investigator if his partner becomes pregnant from the time of consent to 3 months after the last dose of study drug. 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.

Men should be advised not to father a child or donate sperm while receiving ibrutinib, and for 3 months following completion of treatment.

Although pregnancy itself is not regarded as an adverse event, the outcome will need to be documented. Any pregnancy occurring in a subject or subject's partner from the time of consent to 30 days after the last dose of study drug must be reported. Any occurrence of pregnancy must be reported to Pharmacyclics Drug Safety, or designee, per SAE reporting timelines. All pregnancies will be followed for outcome, which is defined as elective termination of the pregnancy, miscarriage, or delivery of the fetus. Pregnancies with an outcome of live birth, the newborn infant will be followed until 30 days old by completing will need to be reported to Pharmacyclics per SAE reporting timelines. Any congenital anomaly/birth defect noted in the infant must be reported as a serious adverse event.

7.5 Case Report Forms (CRFs) for Adverse Event Reporting

Both SAEs and non-serious AEs will be clearly described in source documentation and listed on study-specific Case Report Forms (CRFs or eCRFs).

8 CORRELATIVE / SPECIAL STUDIES

8.1 Pharmacokinetics Assessments: Collected at Stanford Cancer Institute Site ONLY

Ibrutinib:

Pharmacokinetic samples for ibrutinib will be collected pre-dose (window: 30 to 60 minutes before dose), then 1 hour (window: 45 to 75 minutes); 2 hours (window: 1.5 to 2.5 hours); 4 hours (window: 3.5 to 4.5 hours); and 6 hours (window 5.5 to 6.5 hours) post-ibrutinib administration on the first day of ibrutinib dosing (Week 1 Day 1) and each day when dosed in combination with newly-escalated dose of venetoclax in all subjects enrolled in the study.

Venetoclax:

Pharmacokinetic samples for venetoclax will be collected at 0, 8, 24 hours with each dose-escalation of venetoclax.

8.2 Biomarker Assessments

Blood for CLL FISH

Approximately 4 mL of blood will be collected by venipuncture into a heparin vacutainer from subjects at the following time point:

- Screening or Week 1 Day 1 pre-dose

Blood for Mutation Profiling

Approximately 10 mL of blood will be collected by venipuncture into ACD vacutainers from all subjects at the following time points:

- Week 1 Day 1 pre-dose
- Final Visit/Time of Relapse

Blood/Bone Marrow for ClonoSEQ Sequencing

Approximately 10 mL of blood will be collected by venipuncture into EDTA tube from all subjects at the following time points:

Blood:

- Week 1 Day 1 pre-dose or anytime between screening and start of treatment
- Within 1 month of completion of therapy at Week 117

Bone Marrow:

- Week 62

9 TREATMENT ASSESSMENTS AND STUDY CALENDAR

9.1 Study Treatment Schedule

9.1.1 Screening Phase

Subjects will undergo screening procedures as described within Section 3 and Section 9.2.1 within 28 days prior to first study drug administration. Signed informed consent will be obtained from the subject or the subject's legally acceptable representative before any study-specific procedures are undertaken or before any prohibited medications are withheld from the subject to participate in this study. After signing the informed consent form, screening and meeting inclusion/exclusion criteria for trial enrollment, Stanford will assign subjects a unique consecutive subject number.

9.1.2 Treatment Phase

Following completion of the Screening Visit and once eligibility has been confirmed, subjects are enrolled. Enrollment should occur as close to the time of the expected first dose as possible. During the treatment and follow-up periods, AE and assessment will occur on an ongoing basis. Local labs will be used to guide all dosing-related decisions.

Treatment will initiate on Week 1 Day 1 with ibrutinib 420 mg PO daily. For tumor lysis prophylaxis, all subjects will be classified into 3 risk categories based on the risk for developing TLS prior to venetoclax administration (ie, after 8 weeks of ibrutinib administration) as detailed in Section 4.3.1.

Subjects in low category and medium risk category with CrCl ≥ 80 mL/min and low tumor burden will begin treatment with venetoclax in the outpatient setting with an initial dose of 20 mg venetoclax on Week 9 Day 1. If no significant findings suggestive of clinical or lab TLS occur within 24 hours, the same dose will be continued until Day 7 in the outpatient setting. Subjects with no laboratory abnormalities suggestive of LTLS will escalate to a dose of 50 mg venetoclax on Week 10 Day 1 in the outpatient setting.

Medium risk subjects with CrCl < 80 mL/min and higher tumor burden may be admitted to the hospital at the investigator discretion to begin venetoclax with an initial dose of 20 mg on Week 9 Day 1. If no significant findings suggestive of clinical or lab TLS occur within 24 hours, the same dose will be continued until Day 7 in the outpatient setting. Subjects may be hospitalized prior to the first dose increment if they continue to have Cr Cl < 80 mL/min and higher tumor burden at the investigator's discretion. Subjects with no laboratory abnormalities suggestive of LTLS will escalate to a dose of 50 mg venetoclax on Week 10 Day 1 in the outpatient setting.

All high-risk subjects will be admitted to the hospital and begin treatment with venetoclax with an initial dose of 20 mg on Week 9 Day 1. If no significant findings suggestive of clinical or lab TLS occur within 24 hours, the same dose will be continued until Day 7 in the outpatient setting. Each subject's risk status will be reassessed prior to subsequent dose increments to determine the need for hospitalization.

If no significant findings occur within 24 hours at dose escalation, the study drug will be continued at the same dose from Days 2 through 7. If there is indication of lab or clinical TLS

the study drug dose will be held till resolution of all findings. TLS management will be implemented as appropriate.

A lower starting dose to the lead-in regimen may be implemented for individual subject(s) at particularly high-risk for TLS.

9.2 Study Procedures and Assessments

All study procedures are discussed in detail in this section except for adverse event information (discussed in Section 7). Procedures performed at Screening will serve as baseline unless repeated prior to dosing in which case the latest prior to dosing will serve as baseline.

9.2.1 Study Assessments

Medical and Oncologic History

Screening Visit assessment will include:

- Complete medical history, including documentation of any clinically significant medical condition
- History of tobacco and alcohol use
- Detailed oncology history including:
    - Histology
    - Cytogenetics
    - Date of CLL diagnosis
    - Stage at diagnosis
    - Any surgical procedures
    - Treatments administered (including dates, type of modality, response to treatment and reason for treatment discontinuation)
- Detailed prior and concomitant medication usage including dates of usage and dosing information for all medications and supplements taken

Week 1 Day 1: Any changes observed from the Screening assessments (prior to dosing) will be recorded in the subject's medical history.

Adverse Event and Concomitant Medication Assessment

Medication (prescription or over-the-counter, including vitamins and herbal supplements) will be recorded beginning with the Screening Visit through the end of the study. At each visit, including the Final Visit and the 30-Day Safety Follow-Up Visit, the subject's medical history will be reviewed and any changes from baseline will be recorded.

Vital Signs, Physical Examination, ECOG Performance Status

Body temperature (oral or tympanic), weight, blood pressure and heart rate, evaluation of ECOG performance status (see Appendix B) as well as a complete physical examination including evaluation of the head, eyes, ears, nose, throat, cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal and neurologic systems will be performed at screening, Week 1 Day 1, Week 5 Day 1, Weekly from Week 9 Day 1 through Week 14 Day 1, every 4 weeks from Week 18 Day 1 through Week 30 Day 1, and every 12 weeks starting on

Week 38 day 1. ECOG status, vital signs and a complete physical exam should be performed at the Final Visit and 30-Day Safety Follow-Up Visit.

Subject Calendars/Diaries

Subject calendars/diaries will be provided. Subjects will be instructed to bring their calendars/diaries for review at:

- Week 1 Day 1
- Week 5 Day 1
- Week 9-14 Day 1
- Week 18 Day 1
- Week 22 Day 1
- Week 26 Day 1
- Week 30 Day 1
- Week 38 Day 1 and every 12 weeks thereafter through Week 117

Subjects will be instructed to record the date and time each dose of study drug is taken, (indicating if any doses of study drug are missed) and the timing of each dose relative to the subject's first meal of the day. Subjects will also be instructed to record adverse events and concomitant medications.

The calendars/diaries are to be reviewed at each visit and relevant pages are to be photocopied by study staff. At the end of the subject's participation in the study, the calendars/diaries are to be returned to the site and appropriately filed with the subject's source documents for this study.

9.2.2 Efficacy Evaluations

Response will be assessed by the investigator based on analysis of clinical laboratory tests, complete physical examination, and CT scan of involved anatomic regions (or MRI if CT is medically contraindicated) as well as bone marrow aspirate and biopsy with MRD assessment. Subjects will be evaluated with documentation of response (CR/PR/SD/progressive disease) per 2008 Modified IWCLL NCI-WG Criteria for Tumor Response (Appendix D).

- Week 9 Day 1
- Week 14 Day 1, and every 4 weeks through Week 30 Day 1
- starting Week 38 Day 1, every 12 weeks thereafter

CT scans (or MRI) will be obtained

- Week 9 Day 1
- Week 38 Day 1
- Week 62 Day 1
- Within 1 month of completion of therapy

Bone marrow aspirate and biopsy will be obtained Week 62 and within 1 month of completion of therapy

Minimal Residual Disease (MRD) Assessment

Subjects will have MRD assessed in a bone marrow aspirate sample using sensitive flow cytometry as well as ClonoSEQ.

Survival Assessment(s)

Survival information will not be collected.

9.2.3 Study Diagnostics / Procedures

Clinical Laboratory Tests

Pregnancy Test

For female subjects of childbearing potential, pregnancy testing must be performed as follows:

- Screening – quantitative beta-human chorionic gonadotropin (β-hCG) serum pregnancy test.
- Week 1 Day 1: Urine test, if it has been > 7 days since obtaining the Screening serum pregnancy test results.

Pregnancy test results must be reviewed and determined to be negative prior to dosing.

Subjects considered not of childbearing potential must be documented as being surgically sterile or postmenopausal for at least ≥ 1 year.

Hematology and Chemistry

Chemistry and hematology samples will be collected at the following time points (refer to Table 5 for specific tests):

- Screening
- Week 1 Day 1
- Week 5 Day 1
- For Weeks 9-13 refer to Section 4.3.1 Prophylaxis and Management of Tumor Lysis Syndrome and Appendix E Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome (TLS) for monitoring during intra-patient dose escalation of venetoclax
- Week 14 Day 1
- Week 18 Day 1
- Week 22 Day 1
- Week 26 Day 1
- Week 30 Day 1
- Week 38 Day 1and every 12 weeks thereafter
- Final Visit
- 30-Day Safety Follow-Up Visit
- As needed throughout study

Coagulation Panel

PT/aPTT samples will be collected at the following time points:

- Screening
- Week 9 Day 1

Note: Coagulation panel may be collected within 72 hours prior to the scheduled visit.

Urinalysis

Urinalysis samples will be collected at:

- Screening

Note: Urinalysis may be collected within 72 hours prior to the scheduled visit.

Viral Serologies

A sample for viral serologies to identify Hepatitis B (HBsAg, anti-HBs, total anti-HBc, IgM anti-HBc), Hepatitis C (HCV) antibody or RNA, cytomegalovirus, varicella zoster virus, herpes simplex virus, and Epstein-Barr virus will be collected at the following time points:

- Screening
- As needed for suspicion of viral infection

Table 5. Clinical Laboratory Tests

Hematology	**Clinical Chemistry**
Hematocrit	Blood Urea Nitrogen (BUN)
Hemoglobin	Creatinine
Red Blood Cell (RBC) count	Total bilirubin
White Blood Cell (WBC) count	Serum glutamic-pyruvic transaminase (SGPT/ALT)
Neutrophils	Serum glutamic-oxaloacetic transaminase (SGOT/AST)
Bands	Alkaline phosphatase
Lymphocytes	Sodium
Monocytes	Potassium
Basophils	Calcium
Eosinophils	Inorganic phosphorus
Platelet count (estimate not acceptable)	Uric acid
Mean platelet volume (MPV)	Total protein
Mean corpuscular hemoglobin (MCH)	Glucose
Mean corpuscular volume (MCV)	Albumin
Mean corpuscular hemoglobin concentration (MCHC)	Lactate dehydrogenase (LDH)
	Magnesium
	Chloride
	Bicarbonate
	G6PD assay (prior to rasburicase only)

Urinalysis	**Coagulation**
Specific gravity Ketones pH Protein Blood Glucose	Prothrombin time (PT) Activated partial thromboplastin time (aPTT)

Note for samples from patients treated with rasburicase: rasburicase causes enzymatic degradation of the uric acid in blood/plasma/serum samples potentially resulting in spuriously low plasma uric acid assay readings. The following special sample handling procedure must be followed to avoid ex vivo uric acid degradation. Uric acid must be analyzed in plasma. Blood must be collected into pre-chilled tubes containing heparin anticoagulant. **Immediately immerse plasma samples for uric acid measurement in an ice water bath**. Plasma samples must be prepared by centrifugation in a pre-cooled centrifuge (4°C). Finally, the plasma must be maintained in an ice water bath and analyzed for uric acid within four hours of collection.

Computed Tomography (CT) or Magnetic Resonance Imaging (MRI)

A CT scan with contrast (unless medically contraindicated) must be performed within 28 days prior to study drug administration. A CT scan without contrast or a MRI may be substituted when clinically warranted. Subjects should have the same imaging test performed through the study for accurate comparison.

A CT scan will also be performed at the completion of Week 8, 37 and 61 and should be performed within 1 week of the Week 38 and Week 62 scheduled visits and within 1 month of the completion of therapy.

If a subject exhibits clinical signs of disease progression (increased lymphadenopathy, hepatosplenomegaly) without meeting laboratory criteria for progression, a CT scan will be performed within 2 weeks to confirm or rule out progressive disease as described in Appendix D according to the Modified IWCLL Criteria for Tumor Response.

Bone Marrow Aspirate and Biopsy

A bone marrow aspirate and biopsy will be done at Screening (within 28 days prior to the first dose of study drug). The bone marrow aspirate and biopsy should be performed after all other eligibility criteria have been met, unless otherwise obtained through standard of care. Bone marrow aspirates and biopsies, immunohistochemical analysis and cytogenetics performed as standard of care throughout the study should also be documented.

If the subject meets clinical/laboratory criteria and a confirmatory CT scan meets criteria for a CR, a bone marrow aspirate and biopsy should be repeated.

The order of collections from the bone marrow aspirate and biopsy should be 1) MRD assessment and 2) clinical assessment.

12-Lead Electrocardiogram

A 12-lead resting ECG will be obtained at the following:

- Screening
- As clinically indicated

The ECG results will be used by the investigator for subject safety assessments, including adverse event determination and management and termination of subjects from the study.

- ECG results will be summarized as follows:

- Normal ECG
- Abnormal ECG – not clinically significant
- Abnormal ECG – clinically significant
- Unable to evaluate

The QT interval measurement will be documented only if a "prolonged QT" is observed. Correction by the Fridericia formula (QTcF) is preferred. The original ECG tracing will be retained in the subject's records at the study site.

9.3 Table of Assessments / Study Calendar

Table 6: Schedule of Assessments

Study Visits	Screening Phase	Treatment Phase							
		Week 1 D1	Week 5 D1	Weeks 9-13 Day 1	Weeks 9-13 Day 2	Week 14, 18, 22, 26, 30 Day 1	Week 38 Day 1- Week 61 Q12 weeks	Wk 62 - Wk 117	Final visit
Study Visit Windows	-28 days			exact		± 7 days			+ 30 days
Procedures									
Informed consent	X								
Medical history	X								
Confirm eligibility and enroll		X							
Cumulative Illness Rating Scale (CIRS)		X							
Concomitant medications	X	X	X	X		X	X	X	X
Adverse events [b]	X	X	X	X		X	X	X	X
Study drug compliance review [c]			X	X		X	X	X	
Height	X								
Physical exam, vital signs, weight, ECOG	X	X	X	X		X	X	X	X
Disease assessment:									
CT/MRI scan	X [j]			X [f]			X [f]		X [f]
Bone marrow biopsy/aspirate [h]	X								X
Disease-related symptoms [i]	X	X	X	X		X	X	X	X
Overall response assessment				X		X	X	X	X
Hematology	X	X	X	X		X	X	X	X
Serum chemistry	X	X	X	X	X	X	X	X	X
Creatinine clearance (Cockcroft-Gault)	X			X					
Cytogenetic, CLL FISH panel	X								
Hepatitis serologies	X								
Coagulation panel	X			X [l]					
12-lead ECG [k]	X								
Any new anticancer therapy									

Study Visits	Screening Phase	Treatment Phase							
		Week 1 D1	Week 5 D1	Weeks 9-13		Week 14, 18, 22, 26, 30 Day 1	Week 38 Day 1- Week 61 Q12 weeks	Wk 62 - Wk 117	Final visit
				Day 1	Day 2				
PK sample collection		X [d]		X [d]					
Mutational profiling		X [a]							
MRD assessment [m]	X								X

Study Visits		Screening Phase	Treatment Phase		
Study Drug Administration and Dispensation					
	Venetoclax		Continuous daily dosing Dispensed weekly during dose ramp-up and every specified study visit thereafter through Week 117		
			Intra-patient dose ramp-up	400 mg daily	
	Ibrutinib 420 mg PO		Continuous daily dosing [g] Dispensed every 4 weeks from Week 1 through Week 30 and every specified study visit thereafter through Week 117		

D = day; Term = treatment termination; d/c = discontinuation; PD = progressive disease; FU = follow-up; (x) = not all visits or all subjects

a To be collected pre-dose

b AEs are reported from the time the patient signs the Informed Consent Form until 30 days following last dose of study drug. In addition to all routine AE reporting, all new malignant tumors including solid tumors, skin malignancies and hematologic malignancies are to be reported as adverse events for the duration of the study treatment and during any protocol-specified follow-up periods including post-progression follow-up for overall survival.

c Includes patient instruction and routine review of study drug diary and evaluation of contents of study drug containers from home administration

d At SCI only: Ibrutinib: Pre-dose (window: 30 to 60 minutes before dose), then 1 hour (window: 45 to 75 minutes), 2 hours (window: 1.5 to 2.5 hours), 4 hours (window: 3.5 to 4.5 hours), and 6 hours (window: 5.5 to 6.5 hours) post-dose on the first day of ibrutinib dose administration (Week 1 Day 1) and each day when dosed in combination with new dose of venetoclax. Venetoclax: 0 hour, then 8 hour and 24 hour post-dose with each Day 1 dose increase of venetoclax

f Between Week 8 Day 1 and prior to Week 9 Day 1; Week 38 Day 1 +/- 7 days; Week 62 Day 1 +/- 7 days; within 1 month after completion of therapy; within 2 weeks of suspected disease progression

g Day 1 dose of Cycle 1 and each PK day should be administered at the investigational site. Subsequent daily doses may be self-administered at home.

h Bone marrow biopsy and/or aspirate should be performed at Screening within 28 days before the first dose of study drug, Week 62, and within 1 month of completion of therapy. Marrow collected to confirm CR should have minimal residual disease (MRD) assessed by flow cytometry and ClonoSEQ on the aspirate

i Disease-related symptoms include weight loss, fatigue, fever, night sweats, abdominal pain/discomfort due to splenomegaly including early satiety, and anorexia.

j Baseline CT scan can be performed within 28 days prior to study drug administration

k ECG's may be performed at the investigator's discretion, particularly in subjects with arrhythmic symptoms (eg, palpitations, lightheadedness) or new onset dyspnea

l Coagulation test to be done Week 9, Day1 only

m Bone marrow aspirate for ClonoSEQ between Screening and start of therapy, at Week 62, and within 1 month of completion of therapy at Week 117. Bone marrow aspirate for MRD flow assessment at Week 62 and within 1 month of completion of therapy at Week 117.

9.4 End-of-Study

The study will end after the last subject completes therapy. This is expected to be up to 4 years total, depending on the accrual rate.

9.4.1 Study Discontinuation

Per the IST Agreement, the Investigator reserves the right to terminate the study at any time. Should this be necessary, both the Investigator will arrange discontinuation procedures in partnership with Pharmacyclics. In terminating the study, the Investigator will assure that adequate consideration is given to the protection of the subjects' interests. Pharmacyclics may terminate the study for reasons including, but not limited to: evidence that the PI or an involved investigator is unqualified to conduct research or fulfill sponsor responsibilities (eg, is listed on a debarment or ineligible investigator list); failure to meet timelines or achieve agreed upon milestones; a known or perceived risk to patient well-being is identified; or breach of contract. Additional grounds for termination are outlined in the IST Agreement.

9.4.2 Publication of Study Results

Per the IST Agreement, the Investigator is required to submit to Pharmacyclics a copy of a planned publication (abstract, poster, oral presentation or manuscript) prior to the submission thereof for publication or disclosure. Pharmacyclics may provide scientific comments and suggestions understanding that the Investigator has sole editorial responsibility,and retains the authority to make the final determination on whether or not to incorporate Pharmacyclics comments or requests for additional information.

9.5 Follow-up

For subjects who complete or discontinue therapy, follow up assessments will not be performed, except to assess resolution of therapy-related toxicities that led to discontinuation of therapy.

10 REGULATORY CONSIDERATIONS

10.1 Institutional Review Board (IRB) Approval of Protocol

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. This protocol; the proposed informed consent; and all forms of information related to the study that will be provided to the subjects (eg, questionnaires, handouts, written instructions, diaries, advertisements used to recruit participants, etc) will be submitted to and reviewed and approved by the Stanford IRB and Stanford Cancer Institute Scientific Review Committee (SRC). Any changes made to the protocol will be submitted as a modification and will be approved by the IRB prior to implementation. The Protocol Director will disseminate the protocol amendment information to all participating investigators. The IRB must comply with current United States (US) regulations (§21 CFR 56) as well as country-specific national regulations and/or local laws.

Per the IST Agreement, any amendments to the Protocol or Informed Consent Form must be sent to Pharmacyclics for review and approval prior to submission to the IRB. Written verification of IRB approval will be obtained before any amendment is implemented. The following documents must be provided to Pharmacyclics or its authorized representative before entering subjects in this study: (1) a copy of the IRB letter that grants formal approval; and (2) a copy of the IRB-approved ICF.

10.2 Protocol Compliance and Deviations

10.2.1 Compliance with the Protocol

No deviation or changes from the procedures and process described by the IRB-approved protocol, except those necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial [eg, change in study monitor(s), change of telephone number(s)], will be knowingly permitted without review and approval by the IRB.

10.2.2 Protocol Deviations

Any deviation from the IRB-approved protocol, including those that eliminate an immediate hazard or are administrative nature, will be documented and explained in the study site file.

In addition, any deviation from the approved protocol that meets the reporting requirements defined in the Stanford University HRPP Policy Guidance “Events and Information that Require Prompt Reporting to the IRB” GUI-P13 with be reported to the IRB within the defined timeframes.

10.2.3 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, 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 and its designees, regulatory agencies, and IRBs. As the study Sponsor,

Pharmacyclics 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.

10.3 Data and Safety Monitoring Plan

The Stanford Cancer Institute Data and Safety Monitoring Committee (DSMC) will be the monitoring entity for this study. The DSMC will audit study-related activities to determine whether the study has been conducted in accordance with the protocol, local standard operating procedures, FDA regulations, and Good Clinical Practice (GCP). This may include review of the following types of documents participating in the study: regulatory binders; case report forms; eligibility checklists; and source documents. In addition, the DSMC will regularly review serious adverse events and protocol deviations associated with the research to ensure the protection of human subjects. Results of the DSMC audit will be communicated to the IRB and the appropriate regulatory authorities at the time of continuing review, or in an expedited fashion, as needed.

10.3.1 Data Management Plan

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 time. At all times, the Investigator has final responsibility for the accuracy and authenticity of all clinical data. Study staff will be appropriately trained in the use of CRFs before the start of the study. 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.

10.3.1.1 Record Retention

The Investigator must keep a record that lists all subjects considered for enrollment (including those who did not undergo screening) 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 approval letters (dated), signed Form FDA 1572 and Financial Disclosures, signed ICFs (including subject confidentiality information), drug dispensing and accountability records, shipping records of investigational product and study-related materials, signed, dated and completed CRFs, and documentation of CRF corrections, SAE forms and notification of SAEs and related reports, source documentation, normal laboratory values, curricula vitae for study staff, and all relevant correspondence and other documents pertaining to the conduct of the study.

The Investigator must notify Pharmacyclics and obtain written approval from Pharmacyclics 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. Pharmacyclics will inform the Investigator of the date that study records may be destroyed or returned to Pharmacyclics. Pharmacyclics must be notified in advance of, and Pharmacyclics 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 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.

10.4 Investigator Responsibilities

A complete list of Investigator responsibilities is outlined in the clinical trial research agreement and the Statement of Investigator Form FDA 1572, 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 approval to conduct the study; will obtain informed consent from each study participant; will maintain and supply to, auditors and regulatory agencies adequate and accurate records of study activity and drug accountability for study-related monitoring, audits, IRB reviews and regulatory inspections; will report SAEs to Pharmacyclics and IRB 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.

10.5 Protocol Amendments

Per the IST Agreement, any amendments to the Protocol or Informed Consent Form protocol must be sent to Pharmacyclics for review and approval prior to submission to the IRB. Written verification of IRB approval will be obtained before any amendment is implemented.

10.6 Publication of Study Results

Per the IST Agreement, the Investigator is required to submit to Pharmacyclics a copy of a planned publication (abstract, poster, oral presentation or manuscript) prior to the submission thereof for publication or disclosure. Pharmacyclics may provide scientific comments and suggestions understanding that the Investigator has sole editorial responsibility, and retains the authority to make the final determination on whether or not to incorporate Pharmacyclics comments or requests for additional information.

11 STATISTICAL CONSIDERATIONS

11.1 Statistical Design

This study uses the FDA approved dose of ibrutinib 420 mg PO daily for CLL/SLL and intra-patient dose-escalation of venetoclax to establish the efficacy, safety, and tolerability of venetoclax when combined with ibrutinib in patients with relapsed and refractory CLL/SLL. A description of the statistical methods to be used to analyze the efficacy and safety data is outlined below.

11.1.1 Treatment Assignment

Not applicable for this single-arm study.

11.2 Endpoints

All endpoints will be assessed during treatment period only.

11.2.1 Primary Endpoint

Complete response rate (CRR)

11.2.1.1 Measurement Time Points

The time frame for assessment of the primary endpoint is 62 weeks.

11.2.2 Secondary Endpoint(s)

Secondary Endpoints include:

- Overall response rate (ORR)
- Duration of response (DOR)
- Time-to-progression (TTP)
- Progression-free survival (PFS)
- Overall survival (OS)
- Rate of minimal residual disease (MRD) negativity in the bone marrow
- Safety

Efficacy analyses will be performed on the intent-to-treat population but will also detail the response rates for evaluable patients (those who receive at least one dose of venetoclax).

11.2.2.1.1 Assessment Methods

Laboratory and clinical assessments gathered as directed in the Study Treatment Schedule (Section 9).

11.2.2.2 Overall Response Rate

The proportion of subjects with an overall response (per investigator assessment) will be calculated for all subjects based on IWCLL criteria.

11.2.2.3 Duration of Response

Duration of response will be defined as the number of days from the date of first response per investigator assessment to the earliest recurrence or progressive disease per investigator assessment. If a subject is still responding then the subject's data will be censored at the date of the subject's last available clinical disease assessment. For subjects who never experienced response, the subject's data will be censored on the date of enrollment.

11.2.2.4 Time-to-progression

Time-to-progression will be defined as the number of days from the date of first dose (date of enrollment if not dosed) to the date of earliest disease progression (per the investigator assessment). All disease progression will be included regardless whether the event occurred while the subject was taking study drug or had previously discontinued study drug. If the subject does not experience disease progression, then the data will be censored at the date of the last available disease assessment.

11.2.2.5 Progression-free Survival (PFS)

Progression-free Survival will be defined as the number of days from the date of first dose to the date of earliest disease progression (per the investigator assessment) or death. All disease progression will be included regardless whether the event occurred while the subject was taking study drug or had previously discontinued study drug. If the subject does not experience disease progression or death, then the data will be censored at the date of the last disease assessment.

11.2.2.6 Overall Survival (OS)

Overall survival will be defined as the number of days from the date of first dose to the date of death for all dosed subjects. For subjects who did not die, their data will be censored at the date of last study visit or the last known date to be alive, whichever is later.

11.2.2.7 Rate of Minimal Residual Disease (MRD) Negativity in the Bone Marrow

MRD negativity will be defined as less than one CLL cell per 10,000 leukocytes (or below 10-4) on bone marrow-based flow cytometry. Rate of MRD negativity will be defined as the proportion of subjects who achieve MRD negativity status.

11.2.3 Exploratory Endpoint(s)

Time to Next Anti-CLL Treatment (TTNT)

Time to next anti-CLL treatment will be defined as the number of days from the date of the first dose of ibrutinib to the date of first dose of new non-protocol anti-leukemia therapy (NPT) or death from any cause. For subjects who did not take NPT, the data will be censored at the last known date to be free of NPT.

11.3 Interim analyses

No interim analysis for efficacy is planned.

11.4 Primary Analysis

11.4.1 Primary Analysis Population

All enrolled subjects who receive at least one dose of ibrutinib will be included in the safety and response-evaluable populations.

11.4.2 Sample Size

The total number of patients needed for this Phase 2 intra-patient dose escalation study is estimated to be 22, to accommodate 1 early withdrawal, and simultaneous screening of 2 eligible subjects for the last accrual slot. Accrual of 1 to 2 patients a month is anticipated. The historical rate of complete response (CR) in this setting is on the order of 7 to 8%.[36] 8% will be taken as a null hypothesis for an informal power calculation to describe the precision furnished by this study. With a minimum of 20 patients evaluable for CR, there is 80% power to reject a CR rate of 8% with a one-sided significance level of 5%, if the true CR rate is 32% or better.

Efficacy Analysis

Efficacy analysis will be performed on the intent-to-treat population but will also detail the response rates for evaluable patients (those who receive at least one dose of venetoclax).

Overall Response Rate

A 95% confidence interval based on binomial distribution will be constructed for the calculated ORR.

Duration of Response

Duration of response will be analyzed by Kaplan-Meier methodology using data for all enrolled subjects. Median duration of response will be calculated and the corresponding 95% confidence interval will be presented.

Time-to-progression (TTP)

TTP will be analyzed by Kaplan-Meier methodology using data for all enrolled subjects. Median time TTP will be calculated and 95% confidence interval for median time TTP will be presented.

Progression-Free Survival

PFS will be analyzed by Kaplan Meier methodology using data for all dosed subjects. Median PFS time will be calculated and 95% confidence interval for median PFS time will be presented.

Overall Survival

OS will be analyzed by Kaplan-Meier methodology using data from all dosed subjects. Median time survival will be calculated and 95% confidence interval for the median time survival will be presented.

Rate of Minimal Residual Disease (MRD) Negativity in the Bone Marrow

Ninety-five percent (95%) confidence intervals based on the binomial distribution will be provided.

Time-to-Next Anti-CLL Treatment (TTNT)

TTNT will be analyzed by Kaplan-Meier methodology using data for all dosed subjects. Median TTNT time will be calculated.

11.4.3 Accrual estimates

It is anticipated that 1-2 patients a month will accrue.

11.4.4 Safety Analysis

Safety Endpoints:

- 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

All patient safety information collected will be summarized using descriptive statistics (number of non-missing values, mean, median, standard deviation, minimum and maximum) for continuous variables and counts and percentages for categorical variables, where applicable. All safety outcome information reported will be presented in data listings.

11.4.5 Pharmacokinetic Analysis

Values for the pharmacokinetic parameters for ibrutinib and venetoclax including the maximum observed plasma concentration (C_{max}), the time to C_{max} (peak time, T_{max}), the area under the plasma concentration-time curve (AUC) from 0 to the time of the last measurable concentration (AUC_t) and AUC over a 24-hour dose interval (AUC_{0-24}) will be determined using non-compartmental methods. Additional analyses may be performed if useful in the interpretation of the data.

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13 APPENDICES

13.1 Appendix A. Participant Eligibility Checklist

The following Participant Eligibility Checklist will be completed in its entirety for each subject prior to registration. The completed, signed, and dated checklist will be retained in the patient's study file, and the study's Regulatory Binder.

The Study Coordinator, treating Physician and an Independent Reviewer will verify that the participant's eligibility is accurate, complete, and legible in source records. A description of the eligibility verification process will be included in the EPIC or other Electronic Medical Record progress note.

I. Protocol Information

Protocol Title:	*An Open Label Phase 1-2 Trial of Venetoclax with Ibrutinib in Relapsed and Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Leukemia*
eProtocol Number:	IRB-36705
Principal Investigator:	Steven E Coutre, MD

II. Subject Information

Subject name / Study ID:		
Gender	Male ☐	Female ☐

III. Study Information

SRC-Approved ☐ IRB-Approved ☐ Contract signed ☐

IV. Inclusion / Exclusion Criteria

Inclusion Criteria (From IRB-approved protocol 3.1)	Yes	No	Supporting Documentation*
1. Voluntarily sign and date an informed consent form (ICF) with authorization to use protected health information (in accordance with national and local subject privacy regulations) and approved by the Institutional Review Board (IRB) prior to initiation of any study specific procedures	☐	☐	
2. Diagnosis of chronic lymphocytic leukemia CLL) or small lymphocytic leukemia (SLL) meeting IWCLL/NCI-WG criteria, and relapsed after or refractory to at least 1 prior treatment	☐	☐	

Inclusion Criteria (From IRB-approved protocol 3.1)	Yes	No	Supporting Documentation*
3. Measurable nodal disease by computed tomography (CT)	☐	☐	
4. Adequate hematologic function independent of transfusion and growth factor support for at least 7 days prior to screening [except for pegylated G-CSF (pegfilgrastim) and darbepoetin which require at least 14 days prior to screening] defined as the following. • Absolute neutrophil count > 750 cells/mm^3 (0.75×10^9/L) • Platelet count > 30,000 cells/mm^3 (30×10^9/L) without transfusion support; evidence of mucosal bleeding; a known bleeding episode within 3 months of screening; or a history of a bleeding disorder • Hemoglobin > 8.0 g/dL If the bone marrow evaluation shows heavy infiltration with underlying disease, growth factor support may be administered after screening and prior to the first dose of therapy.	☐	☐	
5. Adequate hepatic and renal function defined as: • Serum aspartate transaminase (AST) or alanine transaminase (ALT) ≤ 2.5 x upper limit of normal (ULN) • Estimated Creatinine Clearance ≥ 30 mL/min (Cockcroft-Gault) • Bilirubin ≤ 1.5 x ULN (unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin)	☐	☐	
6. PT/INR < 1.5 x ULN and PTT (aPTT) < 1.5 x ULN	☐	☐	
7. Men and women ≥ 18 years of age	☐	☐	
8. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2	☐	☐	
9. Female subjects who are of non-reproductive potential (ie, post-menopausal by history - no menses for ≥ 1 year; OR history of hysterectomy; OR history of bilateral tubal ligation; OR history of bilateral oophorectomy). OR Female subjects of childbearing potential must have a negative serum pregnancy test upon study entry.	☐	☐	

Inclusion Criteria (From IRB-approved protocol 3.1)	Yes	No	Supporting Documentation*
10. Male and female subjects who agree to use highly effective methods of birth control (eg, condoms, implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], sexual abstinence, or sterilized partner) during the period of therapy and for 90 days after the last dose of study drug.	☐	☐	

Exclusion Criteria (From IRB-approved protocol 3.2)	Yes	No	Supporting Documentation*
1. Prior treatment with either venetoclax or ibrutinib.	☐	☐	
2. Vaccinated with live, attenuated vaccine(s) within 28 days prior to first dose of study drug.	☐	☐	
3. Received an allogeneic stem cell transplant in the past 1 year and must not have active cGVHD if over 1 year post allogeneic transplant.	☐	☐	
4. Richter's transformation confirmed by biopsy.	☐	☐	
5. Active uncontrolled autoimmune cytopenias	☐	☐	
6. Chemotherapy ≤ 21 days prior to first administration of study treatment and/or monoclonal antibody ≤ 4 weeks prior to first administration of study treatment.	☐	☐	
7. 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.	☐	☐	
8. Concurrent systemic immunosuppressant therapy (eg, cyclosporine A, tacrolimus, etc, or chronic administration [> 14 days] of > 20 mg/day of prednisone) within 28 days of the first dose of study drug.	☐	☐	
9. Recent infection requiring systemic treatment that was completed ≤ 14 days before the first dose of study drug.	☐	☐	

Exclusion Criteria (From IRB-approved protocol 3.2)	Yes	No	Supporting Documentation*
10. Unresolved toxicities from prior anti-cancer therapy, defined as having not resolved to Common Terminology Criteria for Adverse Event (CTCAE, version 4.03), Grade ≤ 1, or to the levels dictated in the inclusion/exclusion criteria except for alopecia.	☐	☐	
11. Known bleeding disorders (eg, von Willebrand's disease) or hemophilia	☐	☐	
12. History of stroke or intracranial hemorrhage within 6 months prior to first dose of study drug.	☐	☐	
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 or hepatitis B surface antigen must have a negative polymerase chain reaction (PCR) result before enrollment. Those who are PCR-positive will be excluded.*	☐	☐	
14. Any uncontrolled active systemic infection.	☐	☐	
15. Major surgery within 4 weeks of first dose of study drug	☐	☐	
16. 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.	☐	☐	
17. 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 screening.	☐	☐	
18. Unable to swallow capsules; malabsorption syndrome; disease significantly affecting gastrointestinal function; resection of the stomach or small bowel; symptomatic inflammatory bowel disease or ulcerative colitis; or partial or complete bowel obstruction	☐	☐	
19. Concomitant use of warfarin or other Vitamin K antagonists	☐	☐	
20. Received a strong cytochrome P450 (CYP) 3A inhibitor or inducer within 7 days prior to the first dose of ibrutinib, OR subjects who require continuous treatment with a strong cytochrome P450 CYP3A inhibitor or inducer (see Appendix C)	☐	☐	

Exclusion Criteria (From IRB-approved protocol 3.2)	Yes	No	Supporting Documentation*
21. Lactating or pregnant.	☐	☐	
22. Unwilling or unable to participate in all required study evaluations and procedures.	☐	☐	
23. Unable to understand the purpose and risks of the study	☐	☐	
24. Subjects with chronic liver disease with hepatic impairment Child-Pugh class B or C	☐	☐	

* All subject files must include supporting documentation to confirm subject eligibility. The method of confirmation can include, but is not limited to, laboratory test results, radiology test results, subject self-report, and medical record review.

By signing this form of this trial I verify that this subject is: ☐ eligible / ☐ ineligible for participation in the study. This study is approved by the Stanford Cancer Institute Scientific Review Committee, the Stanford IRB, and has finalized financial and contractual agreements as required by Stanford School of Medicine's Research Management Group.

Treating Physician Signature:	Date:
Printed name:	

Secondary Reviewer Signature:	Date:
Printed name:	

Study Coordinator Signature:	Date:
Printed name:	

13.2 Appendix B. ECOG Status Scores

Status	Eastern Cooperative Oncology Group (ECOG) Performance Status**
0	Fully active, able to carry on all pre-disease 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*. 1982;5:649-655.

Available at: http://www.ecog.org/general/perf_stat.html. Accessed 4 January 2008.

13.3 Appendix C. Inhibitors and Inducers of CYP3A

Inhibitors and inducers of CYP3A are defined as follows.

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

Refer to Section 4.3.3.1 on instructions for concomitant use of CYP3A inhibitors and inducers with ibrutinib and venetoclax.

CYP3A inhibitors:		
Strong	**Moderate**	**Weak**
boceprevir	aprepitant	alprazolam
clarithromycin	amprenavir	amiodarone
cobicistat	atazanavir	amlodipine
conivaptan	ciprofloxacin	atorvastatin
indinavir	crizotinib	bicalutamide
itraconazole	darunavir/ritonavir	cilostazol
ketoconazole	dronedarone	cimetidine
lopinavir	erythromycin	cyclosporine
mibefradil	diltiazem	fluvoxamine
nefazodone	fluconazole	fluoxetine

CYP3A inhibitors:		
Strong	**Moderate**	**Weak**
nelfinavir	fosamprenavir	ginkgo
posaconazole	imatinib	goldenseal
ritonavir	verapamil	isoniazid
saquinavir		nilotinib
telaprevir		oral contraceptives
telithromycin		pazopanib
troleandomycin		ranitidine
voriconazole*		ranolazine
		suboxone
		tipranavir/ritonavir
		ticagrelor
		zileuton

CYP3A inducers:		
Strong	**Moderate**	**Weak**
avasimibe	bosentan	amprenavir
carbamazepine	efavirenz	aprepitant,
phenobarbital	etravirine	armodafinil
phenytoin	modafinil	clobazamechinacea
rifabutin	nafcillin	glucocorticoids (eg, prednisone)
rifampin	oxcarbazepine	nevirapine
St John's Wort	troglitazone	pioglitazone
		rufinamide
		vemurafenib

Substrates of P-gp		
aliskiren	fexofenadine	saxagliptin
ambrisentan	lapatinib	sirolimus
colchicines	loperamide	sitagliptin
dabigatran etexilate	maraviroc	talinolol
digoxin	nilotinib	tolvaptan
everolimus	ranolazine	topotecan

Inhibitors of P-gp (Venetoclax)		
amiodarone	cyclosporine	quinidine
azithromycin	dronedarone	ranolazine
captopril	felodipine	ticagrelor
carvedilol	quercetin	

BCRP (Venetoclax only)	
Substrates	**Inhibitors**
methotrexate	cyclosporine
mitoxantrone	geftinib
irrinotecan	
lapatinib	
rosuvastatin	
sulfasalazine	
topotecan	

OATP1B1/B3 (Venetoclax only)	
Substrates	**Inhibitors**
atrasentan	gemfibrozil
atorvastatin	eltrombopag
ezetimibe	cyclosporine
fluvastatin	tipranavir
glyburide	
olmesartan	
rosuvastatin	
simvastatin acid	
pitavastatin	
pravastatin	
repaglinide	
telmisartan	
valsartan	

* 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/ucm08 0499.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.

13.4 Appendix D. Modified 2008 IWCLL Criteria for Tumor Response

Parameter	Complete Remission (CR) All Criteria Must be Met[a]	Partial Remission (PR) at Least 2 Criteria from Group A AND at Least 1 Criterion from Group B Must be Met	Progressive Disease (PD) at Least 1 Criterion from Group A OR 1 Criterion from Group B Must be Met[b]	Stable Disease (SD) All Criteria Must be Met
Group A				
Lymphadenopathy	None > 1.5 cm	Decrease ≥ 50%[c]	Increase ≥ 50%[d] or any new LN > 1.5 cm	Change of –49% to +49%[e]
Blood Lymphocytes	< 4000/µL	Decrease ≥ 50% from baseline	Increase ≥ 50% over baseline (≥ 5000/µL)	Change of –49% to +49%
Hepatomegaly[f]	None	Decrease ≥ 50%	Increase ≥ 50%[g]	Change of –49% to +49%
Splenomegaly[f]	None	Decrease ≥ 50%	Increase ≥ 50%[g]	Change of –49% to +49%
Marrow	Normocellular, < 30% lymphocytes, no B lymphoid nodules; hypocellular marrow defines CRi	N/A	N/A	N/A
Group B				
Platelet Count	> 100,000/µL[h]	> 100,000/µL or increase ≥ 50% over baseline[h]	Decrease of ≥ 50% from baseline secondary to CLL	Change of –49% to +49%
Hemoglobin	> 11.0 g/dL[h]	> 11.0 g/dL or increase ≥ 50% over baseline[h]	Decrease of > 2 g/dL from baseline secondary to CLL	Increase to ≤ 11.0 g/dL over baseline, or decrease < 2 g/dL
Neutrophils	> 1500/µL[h]	> 1500/µL or increase ≥ 50% over baseline[h]	Decrease ≥ 50% from baseline secondary to CLL	N/A
Other Considerations				
New Lesions	None	None	Appearance of new palpable lymph nodes (> 1.5 cm in longest diameter) or any new extra nodal lesion (regardless of size) or transformation to a more aggressive histology, e.g., Richter Syndrome[d]	None

Parameter	Complete Remission (CR) All Criteria Must be Met[a]	Partial Remission (PR) at Least 2 Criteria from Group A AND at Least 1 Criterion from Group B Must be Met	Progressive Disease (PD) at Least 1 Criterion from Group A OR 1 Criterion from Group B Must be Met[b]	Stable Disease (SD) All Criteria Must be Met
Other Considerations				
Non-Target Lesions	Nodes must be normal size as visually estimated; extra nodal and other assessable disease should be absent	No change/decreased	Unequivocal progression	No change or decrease or non-substantial increase
Target Extra Nodal Disease	Absence of any extra nodal disease by physical examination (palpable, visualized extra nodal) and CT scan	≥ 50% decrease in SPD	≥ 50% increase in the longest diameter of any extra nodal lesion	Not CR, CRi, PR, or SD

CLL = chronic lymphocytic leukemia; LN = lymph nodes; N/A = Not applicable; SPD = sum of the products of diameters; CRi = complete remission with incomplete marrow recovery

a. CR also requires the lack of disease-related constitutional symptoms.

b. Transformation to a more aggressive histology (e.g., Richter Syndrome) would also qualify as a PD.

c. Sum of the products of multiple LNs (as evaluated by CT scans). Note in eCRF if by physical examination only.

d. Increase in SPD of multiple nodes, or in greatest diameter of any previous site, or appearance of any new lymphadenopathy or organomegaly. Degree of change in LN or lymphocyte counts should be measured from nadir (lowest post-treatment) values.

e. Sum products of up to 6 LNs or LN masses (target lesions), with no increase in an LN or new enlarged LN. Increase of < 25% in small LNs (< 2 cm) not significant. Decreases should be measured compared to baseline (pre-treatment) values.

f. If enlarged before therapy.

g. An increase in the previously noted enlargement of the liver or spleen by 50% or more or the de novo appearance of hepatomegaly or splenomegaly.

h. Without the need for exogenous growth factors or transfusions.

13.5 Appendix E. 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) must be consulted/contacted (per institutional standards to ensure emergency dialysis is available) upon 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 and 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 below, for patients receiving the first dose of venetoclax:

- 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.

<u>If Potassium ≥ 0.5 mmol/L increase from prior value (even if potassium within normal limits [WNL])</u>

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 the discretion of the 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.

<u>If Potassium > upper limit of normal</u>

Perform STAT ECG and commence telemetry.

Nephrology (or other acute dialysis service) 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 to 200 mg/kg IV slowly if there is ECG/telemetry evidence of life threatening arrhythmias.

Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT.

If potassium < ULN 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 1, 2 and 4 hours, if no other evidence of tumor lysis.

If 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.

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.

If Uric acid ≥ 8.0 mg/dL (476 µmol/L)

Consider rasburicase (dose based on local guidelines and/or institutional standards).

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.

If Uric acid ≥ 10 mg/dL (595 µmol/L) OR Uric acid ≥ 8.0 mg/dL(476 µmol/L) with 25% increase and creatinine increase ≥ 0.3 mg/dL (≥ 0.027 mmol/L) from pre-dose level

Administer rasburicase (dose based on local guidelines and/or institutional standards).

When rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation.

Notify 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.

If 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.

<u>If Phosphorus ≥ 5.0 mg/dL (1.615 mmol/L) with≥ 0.5 mg/dL (0.16 mmol/L) increase</u>

Administer a phosphate binder (eg, 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.

<u>If Creatinine Increase ≥ 25% from baseline</u>

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 prior section).
- 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 prior table).

13.6 Appendix F. Clinical and Laboratory Definition of Tumor Lysis Syndrome

Metabolic Abnormality	Criteria for Classification of Laboratory Tumor Lysis Syndrome	Criteria for Classification of Clinical Tumor Lysis Syndrome
Hyperruricemia	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 falure 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 < 0.5 ml/kg/hr for 6 hrs

† 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 definited as an increase in the creatinine level of at least 0.3 mg per deciliter (26.5 µmol per liter) or a period of oliguia lasting 6 hours or more. By definition, if acute kidney injury is present, the patient has clinical tumor lysis syndrome. Data about acute kidney injurt from Levin at al.

Note: In laboratory tumor lysis syndrome, 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 afterward. Clinical tumor lysis syndrome requires the presence of laboratory tumor lysis syndrome plus an increased creatinine level, seizures, cardiac dysrhythmia, or death.

13.7 Appendix G. Template for Protocol Amendments

Protocol Amendment < Arabic number> to Stanford IRB-< number>

< Date>

Retain this template for your files.

Please provide a list of changes from the previous IRB-approved version of the protocol. The list shall identify by page and section each change made to a protocol document with hyperlinks to the section in the protocol document. All changes shall be described in a point-by-point format (ie, Page 3, section 1.2, replace 'xyz' and insert 'abc'). When appropriate, a brief justification for the change should be included.

Item	Section	Page(s)	Change
1.			
2.			
3.			
4.			
5.			

13.8 Appendix H. Drug Order Form for Venetoclax

abbvie

Shipment Order for Clinical Studies

Submit completed form to: supplies.team@abbvie.com

Name of Requestor		**Date of request**	
Telephone		**Deliver to site by (date)**	
Study		**Delivery restrictions**	
Study as in Clinicopia			

Investigator	**RIC #**	**Site ID**	**Address / Phone # if not in Clinicopia**	**Country**

Note: Unused spaces on this form (below) may be left blank.

1. **Clinical Drug Supplies to be Shipped**

Lot Number	**Description**	**Quantity**	**Check all that apply**			
			Room Temp	Refrigerated	Controlled Substance	Unlabeled Material
			☐	☐	☐	☐
			☐	☐	☐	☐
			☐	☐	☐	☐
			☐	☐	☐	☐
			☐	☐	☐	☐

2. **Ancillary Materials to be Shipped**

Earliest Allowable Expiry (minimum 60 days from date of request): _____

MMID	**Description**	**Quantity**	**Check all that apply**	
			No Expiry	Compatibility Requirement
			☐	☐
			☐	☐
			☐	☐
			☐	☐
			☐	☐

3. **Additional Items to be Shipped**

☐ Bioretention Letter
☐ Blindbreakers – Numbers to be shipped:_____
☐ Randomization Envelopes – Numbers to be shipped:_____

4. **Additional Comments:** _____

13.9 Appendix I. Drug Order Form for Ibrutinib

pharmacyclics
An AbbVie Company

IST Drug Order Form

For PCYC Office Completion only
Form Received Date: - -
Received by:
CSRF#:

Local Site Protocol ID: CTMS #:

To request additional drug, please complete this form and email to ist.ctep@pcyc.com.

Please note that drug requests received before 12:00 (PST) will be shipped out the same day and requests after 12:00(PST) will be shipped the next business day. Orders are not shipped on Fridays or holidays.

PI Name: **Date of Request:** / /
Is this request for a subsite? ☐yes ☐no
If yes, please provide sub-investigator name:

Requestor Information	
Study Pharmacist Name	
Institution	
Address **Phone Number**	
Email	

Shipping Information (if different from Requestor)	
Receiver Name **Institution**	
Address	
Phone Number	
Email	

Please use the table below to determine the number of bottles:

Ibrutinib dosage	**30-day supply**
420mg	1 x 92 capsule bottle
560mg	1 x 120 capsule bottle
840mg	2 x 92 capsule bottles

Study Drug Requested	**Current Inventory on Site (Bottles)**	**Amount Requested (Bottles)**	**Need-By Date (dd/mm/yyyy)**	**Number of Enrolled/Active Patients as of Request Date**
PCI-32765 PO Hard Gelatin Capsule (140 mg-*92* capsules per bottle)			/ /	/
PCI-32765 PO Hard Gelatin Capsule (140 mg-*120* capsules per bottle)			/ /	/

13.10 Appendix J. Drug Diary for Ibrutinib

PATIENT DRUG DIARY INSTRUCTIONS

Instructions: The bottles with the study drug, ibrutinib, should be stored at room temperature and should not be stored in the bathroom. Please do not freeze or refrigerate the study drug. You will take 420 mg of study drug (3 x 140-mg capsules) by mouth once a day with 8 ounces (240 mL) of water (**do not take with grapefruit juice or Seville orange juice**). The capsules should be swallowed intact. Do not open capsules or dissolve them in water.

Each dose (**all 3 capsules**) should be taken at least 30 minutes before eating and at least 2 hours after a meal, at around the same time each day. If a dose is missed, it can be taken up to 6 hours after the scheduled time with a return to the normal schedule the following day. If it has been more than 6 hours, the dose should be skipped and you must take the next dose at the scheduled time the next day. The missed dose will not be made up and all the capsules from the missed dose must be returned to the clinic or hospital at the next visit.

Please complete the form attached when a dose is missed or reduced. The purpose of this form is to help you keep track and remember when/why a dose was missed or reduced. For each day a dose is missed or reduced, complete the **date** it was missed or reduced and specify the **reason** for the missed or reduced dose. If you experience any abnormal symptoms while taking the study drug, you can also record them on the attached form. It is mandatory that you return this form and your bottles of the study drug to the study staff at each visit to the clinic or hospital.

PATIENT DRUG DIARY - IBRUTINIB

Site #		Patient #:	
Date Dispensed		Date Returned	
PI Name			

☐ Initial here to confirm that the drug has been maintained at room temperature.

☐ Initial here to confirm that no doses of the study drug were missed or reduced.

☐ Initial here to confirm that no extra doses of the study drug were taken by mistake.

DIARY FOR MISSED OR REDUCED DOSES OF IBRUTINIB

Date Dose is Missed or Reduced	Number of capsules taken if Missed or Reduced	Reason for Missed or Reduced Dose	Abnormal Symptoms *(if applicable)*
Example: 10/1/2016	*0*	*Not feeling well*	*Nauseous*
Example: 10/1/2016	*2*	*Forgot to take all 3 capsules*	

Patient's Signature Date

13.11 Appendix K. Drug Diary for Venetoclax

Subject Calendar/Diary Venetoclax

Subject Number:

Date Calendar dispensed:

Week _____ Day 1

Venetoclax Study Drug Dosing Instructions

1. Take 1 dose of Study Drug, by mouth every day, within 30 minutes after completion of breakfast or your first meal of the day.
   a. Drink 1 glass of water (approximately 8 oz or 240 mL) when you take your Study Drug.
   b. Do NOT chew or crush the Study Drug tablets; tablets must be swallowed whole.
   c. Use all medication within a bottle before opening another bottle of the same dose strength. Bottle may contain more tablets than are needed. Return all bottles (including empty and partially full) to the clinic.
2. Record the doses you take in the Daily Calendar:
   a. Record dose information daily:
   1) Record Week of treatment.
   2) Record the Date (Month/Day/Year).
   3) Record your current dose.
   4) Record the time that you took your dose.
   5) Record whether your dose was taken within 30 minutes after completion of breakfast or your first meal of the day.

Note: Store study drug supplies as listed on the label. Keep out of the reach of children.

Subject Number:

WEEK_____DOSING DETAILS	**WEEK_____DOSING DETAILS**	**WEEK_____DOSING DETAILS**
Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No
Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No
Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No
Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No
Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No
Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No
Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No

Subject Number:

WEEK_____DOSING DETAILS	**WEEK_____DOSING DETAILS**	**WEEK_____DOSING DETAILS**
Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No
Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No
Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No
Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No
Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No
Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No
Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No

Subject Number:

WEEK_____DOSING DETAILS	WEEK_____DOSING DETAILS	WEEK_____DOSING DETAILS
Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No
Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No
Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No
Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No
Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No
Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No
Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No

Subject Number:

WEEK_____DOSING DETAILS	WEEK_____DOSING DETAILS	WEEK_____DOSING DETAILS
Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No
Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No
Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No
Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No
Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No
Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No
Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No	Date:___/___/_____ Dose:______mg Time of dose:_____:_____ am pm Dose within 30 min of first meal? Yes No