1.0 Title Page

Clinical Study Protocol M15-550

Open-Label, Single Arm, Phase 3b, Multi-Center Study Evaluating the Efficacy of Venetoclax (ABT-199) in Relapsed/Refractory Subjects with Chronic Lymphocytic Leukemia (CLL) (VENICE I)

Incorporating Administrative Change 1 (GLOBAL) and Amendments 0.02, 0.02.01, 0.02.01.01 (ROW), and 0.02.01.01.01 (ROW)

AbbVie Investigational Product:	Venetoclax (ABT-199, GDC-0199)
Date:	12 October 2020
Development Phase:	3b
Study Design:	Open-label, single arm, Phase IIIB, multi-center study
EudraCT Number:	2015-003667-11
Investigators:	Investigator Information on file at AbbVie
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* The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and in the Clinical Trial Application with the Competent Authority.

This study will be conducted in compliance with the protocol, Good Clinical Practice, with the latest version of the Declaration of Helsinki and all other applicable regulatory requirements, including the archiving of essential documents.

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	24 February 2016
Amendment 0.02	25 April 2016
Administrative Change 1 (GLOBAL)	30 June 2016
Amendment 0.02.01 (ROW)	22 May 2017
Amendment 0.02.01.01 (ROW)	23 July 2018

The purpose of this amendment is to:

- Revise the contact details on the front page of the protocol.

  Rationale: *To change the phone number to Sponsor/Emergency Contact Stan Fort, MD.*

- Revise Section 5.3.1.1 Study Procedures – Extended Access Phase

  Rationale: *To indicate that if a subject in the extended access phase of this study continues to derive benefit from Venetoclax after the 2-year extension, then per PI's assessment, subjects who are transferring to the venetoclax extension study, Study M19-388, may remain in Extended Access for up to additional 1 year or until the extension study is approved and initiated at the site, whichever is sooner.*

- Update Appendix B – List of signatories.

  Rationale: *To replace* [redacted] *as the Study Project Manager with* [redacted]. *To replace* [redacted] *as the Sr. Medical Director with* [redacted]. *To remove* [redacted] *as the Group Project Director. GPD is no longer required for protocol signature. To add* [redacted] *as the Evidence Generation Medical Lead/Director. To replace* [redacted] *as the Study Project Manager with* [redacted].

- Revise Appendix E Schedule of Extended Access Phase.

  Rationale: *To add an additional year to the Schedule of Extended Access Phase.*

An itemized list of all changes made to this protocol amendment can be found in Appendix J.

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M15-550
Name of Study Drug: Venetoclax (ABT-199, GDC-0199)	**Phase of Development:** 3b
Name of Active Ingredient: Venetoclax	**Date of Protocol Synopsis:** 12 October 2020
Protocol Title: Open-Label, Single Arm, Phase 3b, Multi-Center Study Evaluating the Efficacy of Venetoclax (ABT-199) in Relapsed/Refractory Subjects with Chronic Lymphocytic Leukemia (CLL) (VENICE I)	
Objectives: **Primary Objective:** The primary objective of this study is to evaluate the efficacy of venetoclax monotherapy in subjects with relapsed or refractory chronic lymphocytic leukemia (CLL). The primary efficacy endpoint will be measured by complete remission rate (Complete Remission Rate [CR] and Complete Remission with Incomplete Marrow Recovery [CRi]; CR + CRi) as assessed by the investigator, of the subjects who have not been previously treated with B-cell receptor inhibitor (BCRi) therapy. **Secondary Objectives:** The secondary objectives are to evaluate other efficacy parameters including the overall response rate (ORR), duration of overall response (DoR), time to progression (TTP), progression-free survival (PFS), overall survival (OS), and the CR rate in BCRi treated subjects. In addition, quality of life will be assessed using the following patient reported outcome (PRO) questionnaires: the EuroQoL 5 Dimensions (EQ-5D-5L) questionnaire, a measure of general health status, the Functional Assessment of Cancer Therapy – Leukemia Questionnaire (FACT-Leu), a leukemia-specific health related quality of life for acute and chronic disease, and the Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F). The safety and tolerability of venetoclax in subjects with relapsed/refractory CLL will also be evaluated. **Exploratory Objectives:** The exploratory objectives are to evaluate the level of Minimal Residual Disease (MRD) and the rate of MRD negativity in the peripheral blood.	
Investigators: Multi-center	
Study Sites: Approximately 7 sites in the United States and approximately 67 sites globally.	
Study Population: Subjects with relapsed/refractory (R/R) CLL with or without the 17p deletion or TP53 mutation, including subjects with an unknown status, as well as R/R CLL subjects who have been previously treated with B-cell receptor inhibitor (BCRi) therapy.	
Number of Subjects to be Enrolled: Approximately 250 subjects	

Methodology:

This is a Phase 3b, single arm, open-label, multi-center study evaluating the efficacy of venetoclax in subjects with R/R CLL. All screening procedures must be performed within 28 days prior to initial study drug administration. A contrast computed tomography (CT) scan (or magnetic resonance imaging [MRI] if a CT with contrast is medically contraindicated) will be accepted if previously performed within 35 days prior to study drug administration, otherwise a CT scan (or MRI) must be performed within the screening period of 28 days. The starting dose of venetoclax is 20 mg once daily. The dose must be gradually increased over a 5-week period up to the daily dose of 400 mg. For all subjects, study visits will be conducted within 72 hours of dosing and on the first and second day of Week 1 and Week 2 during the dose titration phase. Beginning on Week 3, through Week 5, study visits will be conducted within 72 hours of dosing and on Day 1 of each week. Additional study visits on Day 2 of each week should be performed for subjects who continue to be at risk for TLS, based on investigator assessment. Study visits will be reduced to a monthly frequency at Week 8, and at Week 48, they will be reduced to every 3 months until the end of study treatment (Week 108). In countries where venetoclax is not commercially available, subjects who continue to derive benefit after 2 years of treatment may be able to extend their treatment for up to 2 additional years. If a subject in the extended access phase of this study continues to derive benefit from Venetoclax after the 2-year extension, then per PI's assessment, subjects who are transferring to the venetoclax extension study, Study M19-388, may remain in Extended Access for up to additional 1 year or until the extension study is approved and initiated at the site, whichever is sooner. A Disease Assessment for clinical response by physical exam and hematologic assessments will be performed at Screening, Week 24, Week 36 and Week 48. To confirm the response, a CT scan will be performed at Week 48 on all subjects. Biospecimens will be collected at designated time points throughout the study to conduct research to better characterize the disease. MRD assessments will be performed by using peripheral blood specimens at Week 1 Day 1 (baseline), Week 24 and Week 48. When confirming a CR or CRi status per 2008 Modified International Workshop for Chronic Lymphocytic Leukemia National Cancer Institute Working Group (IWCLL NCI WG) criteria with a bone marrow (BM) biopsy and aspirate, MRD assessment of the BM aspirate should also be performed. After treatment discontinuation, a final visit will be performed. Subjects will be followed for disease progression (if progression has not already occurred) and survival. Post-treatment follow-up calls will be performed every 6 months until discontinuation from the study. Survival information (i.e., the date and cause of death, post-treatment cancer therapies, date of progression etc.) will be collected. This period will continue for 2 years following discontinuation of venetoclax.

The Data Monitoring Committee (DMC) will review safety data intermittently according to the DMC charter. Subsequent reviews may be conducted based on recommendations from the DMC or requests from the Sponsor. Details of the DMC review will be presented in the DMC charter.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

A subject will be eligible for study participation if he/she meets all of the following criteria:

1. Age ≥ 18 years.
2. Eastern Cooperative Oncology Group (ECOG) performance score of ≤ 2.
3. Subject has relapsed/refractory disease (received at least one prior therapy).

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Inclusion (Continued):

4. Diagnosis of CLL that meets published 2008 Modified IWCLL NCI-WG Guidelines and:
   - has an indication for treatment according to the 2008 Modified IWCLL NCI-WG criteria
   - has clinically measurable disease (lymphocytosis > 5×10^9/L and/or palpable and measurable nodes by physical exam and/or organomegaly assessed by physical exam)
   - subjects with or without the 17p deletion or TP53 mutation are eligible.
   - subjects who have received prior B-cell receptor inhibitor therapy are also eligible (up to 60 subjects total in the study will be enrolled).
5. Adequate bone marrow function as follows:
   - hemoglobin ≥ 8.0 g/dL
   - platelets ≥ 25,000/mm^3 without any of the following:
     - transfusion support within 14 days of Screening
     - evidence of mucosal bleeding
     - known history of major bleeding episode within 3 months of Screening

Main Exclusion:

A subject will not be eligible for study participation if he/she meets any of the following criteria:

1. Subject has developed Richter's transformation or Prolymphocytic leukemia (PLL)
2. Subject has previously received venetoclax.
3. History of active malignancies other than CLL within the past 2 years prior to first dose of venetoclax, with the exception of:
   - adequately treated in situ carcinoma of the cervix uteri
   - adequately treated basal cell carcinoma or localized squamous cell carcinoma of the skin
   - previous malignancy confined and surgically resected (or treated with other modalities) with curative intent.
4. Active and uncontrolled autoimmune cytopenias (within 2 weeks prior to Screening), including autoimmune hemolytic anemia (AIHA) or idiopathic thrombocytopenic purpura (ITP), despite low dose corticosteroids.
5. Prior allogeneic stem cell transplant.

Investigational Product:	Venetoclax: 10 mg, 50 mg and 100 mg tablet
Doses:	Venetoclax will be administered orally once daily (QD), continuously. The starting dose of venetoclax is 20 mg QD. After 1 week of treatment at 20 mg QD, the dose will be escalated to 50 mg QD followed by subsequent increases, each after 1 week, to 100 mg QD, 200 mg QD and the target dose of 400 mg QD.
Mode of Administration:	Oral
Reference Therapy:	Not applicable.
Doses:	Not applicable.
Mode of Administration:	Not applicable.

Duration of Treatment: Subjects may continue receiving venetoclax for up to 2 years provided they continue to tolerate the drug, have no evidence of disease progression (based on investigator assessment), do not have unacceptable toxicity and do not meet any of the criteria for subject discontinuation. After treatment discontinuation, subjects will be followed for disease progression (if progression has not already occurred) and survival. Post-treatment calls will be performed every 6 months until discontinuation from the study. Survival information (i.e., the date and cause of death, post-treatment cancer therapies, date of progression etc.) will be collected. This period will continue for 2 years following discontinuation of venetoclax.

In countries where venetoclax is not commercially available, subjects who continue to derive benefit after 2 years of treatment may be able to extend their treatment for up to 2 additional years. If a subject in the extended access phase of this study continues to derive benefit after the 2-year extension and venetoclax is still not commercially available in their country, they may continue their treatment for 1 additional year. Per PI's assessment, subjects who are unable to transfer to the venetoclax extension study, Study M19-388, may remain in Extended Access for the additional 1 year or until the extension study is approved and initiated at the site, whichever is sooner. AbbVie will work with the investigator on a case by case basis to consider the potential continuation of venetoclax therapy.

Criteria for Evaluation:

Efficacy:

Disease response will be assessed by the investigator, based on laboratory results and physical examinations using the 2008 Modified IWCLL NCI-WG criteria for Tumor Response including CT imaging and bone marrow biopsy and aspirate for subjects with CR to confirm the response (or MRI in the case CT is medically contraindicated).

All measurable disease must be documented at Screening by physical examination, laboratory testing, and CT scan (or MRI in the case CT is medically contraindicated). During the study, clinical disease assessments will take place at Week 24, Week 36, and Week 48. To confirm the response, a CT scan will be performed at Week 48.

Minimal Residual Disease (MRD):

A peripheral blood specimen will be collected from all subjects at Week 1 Day 1 (baseline), Week 24 and Week 48 to determine the level of minimal residual disease. When confirming a CR/CRi status per 2008 Modified IWCLL NCI-WG criteria with a bone marrow biopsy and aspirate, MRD assessment of the BM aspirate should also be performed. The level of MRD and MRD negativity will be assessed. MRD negativity in the 2008 Modified IWCLLNCI-WG criteria is defined as the presence of less than one CLL cell per 10,000 leukocytes (or below 10^{-4}).

Pharmacokinetics:

A single pharmacokinetic (PK) blood sample will be collected from each subject and analyzed for plasma venetoclax concentration.

Safety:

Adverse event monitoring, vital signs, physical examination, and laboratory assessments will be evaluated.

The study analyses will be descriptive. All subjects participating in the study who received at least one dose of venetoclax will be included in the analyses unless otherwise noted in the separate, statistical analysis plan (SAP).

Statistical Methods (Continued):

Efficacy:

The following efficacy endpoints will be analyzed: Complete Remission rate (CR + CRi), Overall Response Rate (ORR), Duration of Overall Response (DOR), Duration of Progression-Free Survival (PFS) and Overall Survival (OS):

Complete Remission Rate (CR) and Complete Remission with Incomplete Marrow Recovery (CRi)

Defined as the proportion of subjects who achieved a CR or CRi (all subjects and previously BCRi treated subjects).

Overall Response Rate (ORR)

Defined as the proportion of subjects with an overall response (complete remission plus partial remission).

Duration of Response (DOR)

Defined as the number of days from the date of first response (per the 2008 Modified IWCLL NCI-WG criteria) to the date of disease progression. All disease progression will be included regardless whether the event occurred while the subject was taking venetoclax or had previously discontinued venetoclax.

Time to Progression (TTP)

Defined as the number of days from the date of first dose of venetoclax to date of disease progression. All disease progression will be included regardless whether the event occurred while the subject was taking venetoclax or had previously discontinued venetoclax.

Duration of Progression-Free Survival (PFS)

Defined as the number of days from the date of first dose of venetoclax to the date of disease progression or death, whichever occurs first. All disease progression will be included regardless whether the event occurred while the subject was taking venetoclax or had previously discontinued venetoclax.

Overall Survival (OS)

Defined as number of days from the date of first dose of venetoclax to the date of death.

Additional Exploratory Analyses Include:

Minimal Residual Disease (MRD) Level and Negativity Status:

The level of MRD and the rate of MRD negativity will be assessed in the peripheral blood of all subjects at Week 1 Day 1 (baseline), Week 24 and Week 48. MRD negativity will be defined as less than one CLL cell per 10,000 leukocytes (or below 10^{-4}). Additionally, bone marrow samples collected from subjects achieving CR/CRi will also be assessed for both the level of MRD and the rate of MRD negativity. Rate of MRD status will be defined as the proportion of subjects who have MRD negativity status. Ninety-five percent (95%) confidence intervals based on the binomial distribution will be provided. The relationship between venetoclax PK and efficacy parameters including MRD level and CR will be evaluated.

Pharmacokinetics:

An analysis of venetoclax plasma concentrations will be performed using a population PK modeling approach.

Statistical Methods (Continued):

Health Economic and Patient Reported Outcome (PRO) Measures:

Quality of life will be assessed by using the following PROs: the EQ-5D-5L, FACT-Leu, and the FACIT-F.

Quality of life endpoints will be summarized based on the scoring manuals for the instrument.

Sample Size Estimation:

Using the CR rate of 6% reported for current therapies* 250 subjects would provide approximately 90% power (based on an exact test for single proportions using a two-sided alpha of 5%) to reject the null hypothesis of 6% in favor of an alternative hypothesis that the CR rate for venetoclax monotherapy is 12% (doubling of the CR rate).

In order to provide approximately 80% power (based on an exact test for single proportions using a two-sided alpha of 5%) to reject the null hypothesis of 6% CR rate in favor of an alternative hypothesis that the CR rate for venetoclax monotherapy is 12% (doubling of the CR rate), the study will enroll 190 subjects who have not been previously treated with BCRi therapy. Since there are approximately a total of 250 subjects, up to 60 subjects previously treated with BCRi therapy can be enrolled.

Safety:

A safety analysis will be performed for all subjects participating in the study who took at least one dose of study drug. For the study as a whole, adverse events will be evaluated and summarized. Laboratory test results and vital signs will be explored for trends and summarized.

* Resonate Trial. ASH. 2014. Abstract 3331.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

ABT-199	Study Drug Compound, "Venetoclax"
AE	Adverse Event
AIHA	Autoimmune Hemolytic Anemia
ALC	Absolute Lymphocyte Count
ALT	Alanine transaminase
AML	Acute Myeloid Leukemia
AST	Aspartate transaminase
aPTT	Activated Partial Thromboplastin Time
Bcl	B-Cell Lymphoma
BCR	B-Cell receptor
BCRi	B-Cell receptor inhibitor
BCR PI	B-cell receptor pathway inhibitor
BM	Bone Marrow
BUN	Blood Urea Nitrogen
CLL	Chronic Lymphocytic Leukemia
cm	Centimeter
CR	Complete Remission
CRi	Complete Remission with Incomplete Marrow Recovery
CT	Computed Tomography
CTLS	Clinical Tumor Lysis Syndrome
CYP3A	Cytochrome P450 3A
DNA	Deoxyribonucleic Acid
DMC	Data Monitoring Committee
DOR	Duration of Overall Response
ECOG	Eastern Cooperative Oncology Group
EQ-5D-5L	EuroQoL 5 Dimension 5 Level Questionnaire
eCCr	Estimated creatinine clearance rate using Cockcroft-Gault Formula
eCRF	Electronic Case Report Form
FACIT-F	Functional Assessment of Chronic Illness Therapy – Fatigue Scale
FACT-Leu	Functional Assessment of Cancer Therapy – Leukemia Questionnaire
FL	Follicular Lymphoma

G-CSF	Granulocyte-colony stimulating factor
GCP	Good Clinical Practice
GDC-0199	Venetoclax (ABT-199)
HDPE	High Density Polyethylene
HIV	Human Immunodeficiency Virus
Hr	Hour
HR	Hazard Ratio
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITP	Immune Thrombocytopenia
IV	Intravenous
IVIG	Intravenous immunoglobulins
IWCLL NCI WG	2008 Modified International Workshop for Chronic Lymphocytic Leukemia National Cancer Institute Working Group
Kg	Kilogram
LDi	Longest Diameter
LDH	Lactate Dehydrogenase
LN	Lymph Node
LTLS	Laboratory Tumor Lysis Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mL	Milliliter
MM	Multiple Myeloma
mm	Millimeter
µM	Micromolar
MRD	Minimal Residual Disease
MRI	Magnetic Resonance Imaging
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	Non-Hodgkin's Lymphoma
nM	Nanomolar
nPR	Nodular Partial Remission

ORR	Overall Response Rate
OS	Overall Survival
PB	Peripheral Blood
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression-free Survival
PR	Partial Remission
PRO	Patient-reported Outcomes
PT	Prothrombin Time
QD	Once Daily
RBC	Red Blood Cell
RNA	Ribonucleic Acid
R/R	Relapsed/Refractory
SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum Glutamic-oxaloacetic Transaminase
SLL	Small Lymphocytic Lymphoma
SPD	Sum of the products of the greatest diameters
STAT	Immediately
SUSAR	Suspected Unexpected Serious Adverse Reactions
TA MD	Therapeutic Area Medical Director
TLS	Tumor Lysis Syndrome
TTP	Time to progression
ULN	Upper Limit of Normal
US	Ultrasound
VAS	Visual Analog Scale
WBC	White Blood Cell
WOCP	Women of Childbearing Potential

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3.0 Introduction

Bcl-2 Family Proteins

The B-cell lymphoma-2 (Bcl-2) family proteins are important regulators of the intrinsic apoptosis pathway. The Bcl-2 oncogene was first identified in follicular lymphoma (FL) where the t(14;18) chromosomal translocation results in significant over-expression of the protein in B-cells. The Bcl-2 family of genes encodes a family of closely related proteins that possess either pro-apoptotic or anti-apoptotic activity and share up to four Bcl-2 Homology (BH) domains.[1-4] 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.[5,6]

Venetoclax (ABT-199)

Venetoclax, also known as ABT-199, is a novel, orally bioavailable, small molecule Bcl-2 family protein inhibitor that binds with high affinity (Ki < 0.010 nM) to antiapoptotic Bcl-2 and with lower affinity to other antiapoptotic Bcl-2 family proteins like B-cell lymphoma-extra large (Bcl-X_L) and B-cell lymphoma-Walter and Eliza Hall Institute (Bcl-w) (> 4,000-fold and > –2,000- to > 20,000-fold lower affinity than to Bcl-2, respectively).[8] Selective inhibition by venetoclax disrupts Bcl-2 signaling and rapidly induces multiple hallmarks of apoptotic cell death in Bcl-2-dependent human tumor cell lines.[8] Importantly, venetoclax inhibition of Bcl-2 is independent of p53 activity.

A detailed discussion of the non-clinical toxicology, metabolism, and pharmacology can be found in the Investigator's Brochure.[8]

Venetoclax Clinical Data

In the Investigator's Brochure,[8] a total of 2495 subjects received at least 1 dose of venetoclax in company sponsored studies as of 28 November 2017. 2473 of these

subjects are included in overall pooled analyses for reporting Reference Safety Information. The 2473 subjects in the overall pooled analysis include 2224 oncology subjects (987 in monotherapy studies and 1237 in combination therapy studies), 153 healthy volunteers, 23 subjects with hepatic impairment and 73 subjects with SLE. Of the 2224 oncology subjects, 1132 subjects had CLL/small lymphocytic lymphoma (SLL), 569 subjects had Non-Hodgkin's Lymphoma (NHL), 172 subjects had multiple myeloma (MM), 340 had Acute Myeloid Leukemia (AML), and 11 subjects had myelodysplastic syndrome (MDS). 787 subjects with blinded data have been treated with either venetoclax combination therapy or a comparator treatment in company-sponsored venetoclax oncology studies. Doses administered in venetoclax clinical studies have ranged from 20 mg to 1200 mg.

The most common adverse events reported in venetoclax monotherapy studies were neutropenia (39.3%), nausea (31.4%) and diarrhea (24.9%). The most common adverse events that were grade 3 and above were neutropenia (34.9%), anemia (13.8%) and thrombocytopenia (12.8%). The most common serious adverse events were febrile neutropenia (6.1%), pneumonia (5.4%), malignant neoplasm progression (3.4%), and pyrexia (3.3%).

Tumor lysis syndrome (TLS) is an important risk, particularly in subjects with R/R CLL. As a result of on-target effects, the potential for TLS with venetoclax was identified early in the program when the initial 3 subjects with CLL/SLL received starting doses of 100 mg or 200 mg and experienced TLS, which was reported as an adverse event for each. Subsequently, 2 fatal events in the setting of TLS and another event of clinical TLS in subjects with CLL/SLL occurred in December 2012. After comprehensive review of all safety data available from studies with venetoclax, a revised dosing regimen with a dose-titration phase of 5 weeks and enhanced TLS prophylaxis and monitoring measures were implemented in all CLL studies. A subsequent analysis of data from subjects with CLL/SLL following the implementation of prophylaxis measures, who completed monotherapy 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 nonserious event of clinical TLS (CTLS) or laboratory TLS (LTLS) or had study treatment discontinued because of TLS. Since May 2014, a more personalized approach for prophylaxis and monitoring measures, where subjects with lower tumor burden could receive venetoclax on an out-patient basis, has been evaluated with no cases of clinical TLS. Overall, the clinical data strongly support that the risk of TLS with venetoclax in CLL/SLL subjects is highest when initiating venetoclax dosing (5-week dose titration phase), as well as being greater in subjects with a large tumor burden.

The safety profile in combination studies is consistent with that observed in monotherapy studies and with known toxicity profile of combination agents. Preliminary efficacy data indicate that venetoclax, both as monotherapy and in combination with other therapeutic agents, continues to show promising efficacy in oncology subject populations. The overall response rate (ORR) in subjects with CLL/SLL was 75.0% to 81.7% (dose escalation and safety expansion cohorts, respectively), with a complete remission rate (CR + CRi) of 32.1% in dose escalation and 11.7% in the safety expansion cohort for venetoclax monotherapy (Study M12-175 as of 10 June 2016).[9]

Additional safety and efficacy data are described in detail in the Investigator Brochure.[8]

Chronic Lymphocytic Leukemia (CLL)

Chronic lymphocytic leukemia 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.[10] Chronic lymphocytic leukemia primarily affects elderly individuals; however, approximately one third of subjects are less than 60 years of age at diagnosis.[11] 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.[12] 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 – 2002.[10,13] The approximate 5-year survival rate for subjects with CLL is

73%.[14] CLL presents with a variable clinical course. Approximately one-third of subjects 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 subjects 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 subjects with CLL.[15]

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 subjects with CLL are made on the basis of 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 chemo immunotherapy. 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.

Chromosome 17p Deletions and TP53 Gene Mutations in Chronic Lymphocytic Leukemia

Chromosome 17p deletions and TP53 gene mutations are among a group of genetic defects that occur in subsets of subjects with CLL in addition to defects causing Bcl-2 dysregulation. The short arm of chromosome 17 contains the TP53 gene that encodes tumor protein p53, a tumor suppressor involved in deoxyribonucleic acid (DNA) repair activation, cell cycling regulation, and apoptosis signaling. Standard cytotoxic chemotherapies used in the treatment of CLL (i.e., fludarabine, cyclophosphamide, and bendamustine), act by inducing DNA damage and triggering apoptosis. The p53 tumor suppressor is essential for relaying the DNA damage signal to the apoptotic machinery. When p53 is functionally inactivated, either through mutation or deletion, these signals

are not effectively relayed and the efficacy of these agents is diminished. Chromosome 17p deletions and TP53 mutations occur over the course of the disease and expand under treatment selection pressure as a result of the resistance to chemotherapy and chemoimmunotherapy they confer.[16-18] Notably, over 80% of subjects with 17p deletions also carry a TP53 mutation.[17,19]

The decreased likelihood of subjects with 17p deletions and/or TP53 mutations responding to standard chemotherapy and chemoimmunotherapy regimens is accompanied by a greater risk of disease progression and a shorter overall survival (OS).[7,16-18,20] In a long-term follow up study of the effects of 17p deletions/TP53 mutations in CLL subjects treated according to standard practice outside of a clinical study, survival periods measured from date of study sampling were 7.6 months or less for subjects with 17p deletions and/or TP53 mutations compared to 69 months for subjects without TP53 loss or mutations.[21]

Poorer outcomes in subjects with these aberrations have also been demonstrated in large randomized clinical treatment trials. In the CLL8 trial (n = 817) comparing first-line chemoimmunotherapy (fludarabine/cyclophosphamide/rituximab) to chemotherapy alone (fludarabine/cyclophosphamide), multivariate analyses of prognostic indicators for survival at a median follow-up of 70 months found hazard ratios [HR] of 2.916 (confidence interval [CI]: 1.779 – 4.781) and 2.715 (CI: 1.602 – 4.602) for progression-free survival (PFS) and OS, respectively, for subjects with 17p deletions and 2.123 (CI: 1.400 – 3.218) and 3.014 (CI: 1.889 – 4.808), respectively, for subjects with TP53 mutations indicated.[19] Poorer response to first-line treatment and shorter survival in subjects with 17p deletions and/or TP53 mutations were also observed in the CLL4 trial of 777 subjects randomized to chlorambucil or fludarabine with or without cyclophosphamide and in subjects with 17p deletions treated in the E2997 trial (n = 278) of fludarabine with or without cyclophosphamide.[22,23]

Relatively improved treatment responses have been shown in 17p deletion/TP53 mutant first-line and relapsed patient populations with alemtuzumab, a monoclonal antibody specific for B-cell surface molecule CD52, in combination with steroids

(e.g., methylprednisolone, dexamethasone).[24,25] In a Phase 2 study (n = 39) the overall response rate, complete response (including with incomplete bone marrow recovery) rate (CR/CRi), median PFS, and median OS were 85%, 36%, 11.8 months, and 23.5 months, respectively, in the entire cohort and 88%, 65%, 18.3 months, and 38.9 months, respectively, in the 17 previously untreated subjects. Treatment-related death occurred in 5% of subjects, 67% of subjects experienced Grade 3/4 hematologic and glucocorticoid-associated toxicity, and 51% experienced Grade 3 infection.[24]

The tyrosine kinase inhibitors ibrutinib and idelalisib that act downstream of the B-cell receptor have also been shown to produce relatively improved responses compared to standard therapies and have been approved for use in some jurisdictions for the treatment of CLL subjects with 17p deletion (ibrutinib, idelalisib) or TP53 mutations (idelalisib only). Ibrutinib inhibits Bruton's tyrosine kinase, an enzyme involved in B-cell receptor signaling, homing, and adhesion. A Phase 3 relapsed or refractory CLL study comparing ofatumumab (an anti-CD20 monoclonal antibody) to ibrutinib included 127 subjects with the 17p deletion. In this cohort, the median duration of PFS was 5.8 months in the ofatumumab arm but was not reached in the ibrutinib arm (HR 0.25; 95% CI: 0.14, 0.45). The overall response rate was 47.6% with ibrutinib compared with 4.7% with ofatumumab. No complete responses were observed.[25] Overall, 57% of subjects in the ibrutinib arm had at least one ≥ Grade 3 adverse event (AE). The most frequent non-hematologic AEs (> 20% of subjects) with ibrutinib were diarrhea, fatigue, pyrexia, and nausea.[26] Grade 3/4 AEs reported in ≥ 5% of the 357 subjects with mantle cell lymphoma or CLL that received ibrutinib during clinical development were anemia, neutropenia, pneumonia and thrombocytopenia.[27]

Idelalisib targets the delta isoform of phosphatidylinositol 3-kinase (PI3Kδ) involved in signal transduction via multiple receptors including the B-cell receptor and chemokine receptors CXCR4 and CXCR5. A Phase 3 study comparing combined idelalisib/rituximab treatment with rituximab/placebo in previously treated subjects reported improved PFS in the idelalisib arm among the 96 subjects enrolled with 17p deletion or TP53 mutation (HR 0.12; CI: 0.05, 0.32). The majority of AEs in the

study were Grade 2 and the most common in the idelalisib arm were pyrexia, fatigue, nausea, chills, and diarrhea.[28] The overall safety profile determined in Phase 1 to 3 studies of idelalisib in hematologic malignancies as monotherapy or in combination with an anti-CD20 monoclonal antibody is characterized by a very common frequency (≥ 1/10 subjects) of ≥ Grade 3 infections, neutropenia, diarrhea/colitis and increased transaminase.[29]

CLL Subjects Who Have Received Prior B-Cell Receptor Inhibitor (BCRi) Therapy

Ibrutinib and idelalisib cause rapid response with reduction in lymph node size and splenic mass accompanied by increased peripheral blood (PB) lymphocytosis likely reflecting that microenvironment modulation could prevent these cells from receiving the survival signals delivered by the microenvironment.[30] In early trials of Ibrutinib, approximately 10% of the subjects developed progressive disease (PD). Few of these subjects developed resistance after achieving partial response lasting ≥ 6 months. Distinct single nucleotide variations were noted in these subjects.[31]

In addition, toxicities such as diarrhea, fatigue and pyrexia are common and can affect the subjects who receive these drugs.[26,28]

However, the mechanism of action of venetoclax is independent of the B-cell receptor (BCR) pathway.[32] Briefly, venetoclax inhibits Bcl-2 allowing the release of BIM, which includes oligomerization of pro-apoptotic molecules such as BAK and BAX which triggers rapid apoptosis. The clinical data to date with venetoclax monotherapy shows strong activity in refractory CLL indicating that it might be beneficial in a population that is refractory to these newer therapeutic agents.

Despite some improvement in disease outcomes in relapsed/refractory CLL subjects, including those who have received novel agents, significant toxicities remain a concern, complete disease responses are uncommon, and relapse is virtually inevitable. Subjects carrying TP53 aberrations and those who have received prior BCRi therapy continue to represent a significant unmet medical need and current treatment recommendations

include participation in investigative clinical trials proceeding to allogeneic hematopoietic stem cell transplantation in responding subjects eligible for transplant (e.g., younger age with no co-morbidities and a suitable donor).[16,33]

Further details of disease activity observed in clinical studies with venetoclax are provided in the Venetoclax Investigator's Brochure.[8]

3.1 Differences Statement

This is the first Phase 3b study to assess the efficacy of venetoclax monotherapy in relapsed or refractory CLL. The R/R CLL patient population will be enriched to include subjects who have previously received BCRi therapy. This will allow for the assessment of deep responses in this high risk/unmet need patient population. In this study, subjects will be assessed for efficacy with standard criteria.

3.2 Benefits and Risks

There is data that shows substantial efficacy of venetoclax monotherapy in the treatment of relapsed/refractory CLL characterized by 17p deletions. Venetoclax is expected to be as active in subject selected for TP53 mutations as these subject populations overlap and the oncogenic effect of both genetic defects occurs via p53 abrogation. In addition, there is limited data in the BCRi failure CLL population for subjects that subsequently receive venetoclax and also in subjects without the 17p deletion. Current CLL therapies do not reliably produce complete responses and are not curative in subjects with p53 aberrations or those refractory to BCRi. Furthermore, drugs more recently approved for these subjects are limited by toxicity.

Clinical safety data indicate that the adverse effects of venetoclax administered with appropriate measures are manageable and as expected from a treatment targeting hematologic cells including in subjects with 17p, TP53 mutation or subjects who have previously received BCRi therapy.

Additional safety and efficacy data can be found in the current Investigator Brochure.[8]

4.0 Study Objective

The primary objective of this study is to evaluate the efficacy of venetoclax monotherapy in subjects with relapsed or refractory chronic lymphocytic leukemia (CLL). The primary efficacy endpoint will be measured by complete remission rate (CR + CRi) of the subjects who have not been previously treated with BCRi therapy, as assessed by the investigator.

The secondary objectives are to evaluate other efficacy parameters including the overall response rate (ORR), duration of overall response (DoR), time to progression (TTP), progression-free survival (PFS), overall survival (OS), and the CR rate in previously BCRi treated subjects.

Additional secondary objectives will also be evaluated, as well. Quality of life will be assessed using the following patient reported outcomes (PRO) questionnaires: the EuroQoL 5 Dimensions (EQ-5D-5L), a measure of general health status, the Functional Assessment of Cancer Therapy – Leukemia Questionnaire (FACT-Leu), a leukemia-specific health related quality of life for acute and chronic disease, and the Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F).

The safety and tolerability of venetoclax in subjects with relapsed/refractory CLL will also be evaluated.

Additional exploratory objectives will be evaluated. Minimal Residual Disease (MRD) will be assessed in the peripheral blood and bone marrow (BM) by flow cytometry and PCR.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is an open-label, single arm, Phase 3b, multi-center study evaluating the efficacy of venetoclax monotherapy in relapsed/refractory CLL.

This study is designed to enroll approximately 250 subjects to meet scientific objectives without enrolling an undue number of subjects in alignment with ethical considerations. All efforts will be made to adhere to these specific enrollment numbers; however, it would not be ethical to deny treatment to eligible subjects already in screening as they may have undergone study related procedures.

Subjects in this study will be enrolled at approximately 67 research sites globally.

Subjects will undergo screening procedures within 28 days prior to initial venetoclax administration. For all subjects, a contrast computed tomography (CT) scan (or medically indicated alternative such as magnetic resonance imaging [MRI]) will be accepted if previously performed within 35 days prior to venetoclax administration. Otherwise, a CT scan (or MRI) must be performed within the screening period of 28 days. Following the 4-week Screening period, eligible subjects will initiate venetoclax and attend study visits within 72 hours of dosing and on the first and second day of Week 1 and Week 2 during the dose titration phase. Beginning on Week 3, through Week 5, study visits will be conducted within 72 hours of dosing and on Day 1 of each week. Additional study visits on Day 2 of each week should be performed for subjects who continue to be at risk for TLS, based on investigator assessment. Study visits will be reduced to a monthly frequency at Week 8, and at Week 48, they will be reduced to every 3 months until the end of study treatment (Week 108). As of Week 8, the visit window for scheduled visits is ± 2 days. A 30 day Safety Follow-up Visit should be performed approximately 30 days (± 3 days) following the last dose of venetoclax (to allow for AE collection 30 days following last dose of study drug). If a subject is discontinued from the study with an ongoing AE or an unresolved clinically significant laboratory result, the site will attempt to provide follow-up until the AE has resolved to a ≤ Grade 1 or baseline or it is the investigator's judgment that the event is unlikely to resolve.

Venetoclax will be administered orally once daily (QD), continuously. Venetoclax tablets should be taken with a meal and water in the morning at approximately the same time each day. To mitigate the risk for TLS, the first 5 weeks of treatment include a dose-titration phase where venetoclax will be dosed in increments as outlined in Figure 1. The

starting dose of venetoclax is 20 mg once daily. The dose will be gradually increased over a period of 5 weeks up to the daily dose of 400 mg.

Figure 1. 5-Week Dose-Titration Schedule

Week	VENETOCLAX Daily Dose
1	20 mg
2	50 mg
3	100 mg
4	200 mg
5 and beyond	400 mg

Disease response will be assessed by the investigator based on laboratory results and physical examinations using the 2008 Modified International Workshop on CLL National Cancer Institute – Working Group (IWCLL NCI-WG) Guidelines for Tumor Response with the addition of CT imaging (or MRI). A Disease Assessment for clinical response by physical exam and hematologic assessments will be performed at Screening, Week 24, Week 36 and Week 48. To confirm the response, a CT scan (or MRI if CT is medically contraindicated) will be performed at Week 48 on all subjects and BM samples will be collected for subjects with CR to confirm the response.

MRD assessments will be performed by using peripheral blood specimens at Week 1 Day 1 (baseline), Week 24 and Week 48. When confirming a CR status or complete remission with incomplete bone marrow recovery (CRi) status per IWCLL NCI-WG guidelines with a bone marrow aspirate and biopsy, MRD assessment of the bone marrow aspirate should also be performed.

Quality of life will be assessed by using the following patient reported outcome questionnaires: the EQ-5D-5L, the FACT-Leu, and the FACIT-F. Quality of life endpoints will be summarized based on the scoring manual for the instruments.

Subjects may continue to receive venetoclax for up to 2 years provided they continue to tolerate the drug, have no evidence of disease progression (based on investigator's assessment), do not have unacceptable toxicity and do not meet any of the criteria for discontinuation (see Section 5.4.1). A final visit will be conducted upon treatment discontinuation.

After treatment discontinuation, subjects will be followed for disease progression (if progression has not already occurred) and survival. Post-treatment calls will be performed every 6 months until discontinuation from the study. Survival information (i.e., the date and cause of death, post-treatment cancer therapies, date of progression, etc.) will be collected. This period will continue for two years following discontinuation of venetoclax.

All study procedures will be performed as outlined in Section 5.3.1.1 and Appendix D and Appendix E.

For subjects who continue to derive benefit after 2 years of treatment, AbbVie will work with the investigator on a case by case basis to consider the potential continuation of venetoclax therapy. In countries where venetoclax is commercially available, extension of therapy may not be allowed.

A safety analysis will be performed for all subjects participating in the study who took at least one dose of study drug. For the study as a whole, serious adverse events and adverse events will be evaluated and summarized. Laboratory test results and vital signs will be explored for trends and summarized.

5.2 Selection of Study Population

Subjects will undergo screening procedures within 28 days prior to initial venetoclax administration, with the exception of the CT scan (or MRI). A CT scan will be accepted if previously performed within 35 days prior to venetoclax administration.

Adult male and female subjects who meet the inclusion criteria and who do not meet any of the exclusion criteria will be eligible for enrollment into the study.

5.2.1 Inclusion Criteria

A subject will be eligible for study participation if he/she meets the following criteria:

1. Age ≥ 18 years.
2. Eastern Cooperative Oncology Group (ECOG) performance score of ≤ 2.
3. Subject has relapsed/refractory disease (received at least one line of prior therapy).
4. Diagnosis of CLL that meets published 2008 Modified IWCLL NCI-WG Guidelines and:
   - has an indication for treatment according to the 2008 Modified IWCLL NCI-WG criteria
   - has clinically measurable disease (lymphocytosis > 5×10^9/L and/or palpable and measurable nodes by physical exam and/or organomegaly assessed by physical exam)
   - subjects with or without the 17p deletion or TP53 mutation are eligible.
   - subjects who have received prior B-cell receptor inhibitor therapy are also eligible (up to 60 subjects total will be enrolled in the study).
5. Adequate bone marrow function as follows:
   - hemoglobin ≥ 8.0 g/dL
   - platelets ≥ 25,000/mm^3, without any of the following:
     - transfusion support within 14 days of Screening
     - evidence of mucosal bleeding
     - known history of bleeding episode within three months of Screening
6. Adequate coagulation parameters per local laboratory reference range as follows:
   - activated partial thromboplastin time (aPTT) and prothrombin time (PT) and/or International Normalized Ratio (INR) not to exceed 1.5 × the upper limit of normal (ULN)

7. Adequate renal function per local laboratory reference range as follows:

   - calculated creatinine clearance ≥ 50 mL/min using 24-hour creatinine clearance or estimated creatinine clearance using the modified Cockcroft-Gault equation:

$$\text{Estimated creatinine clearance (eCCr)} = \frac{(140 - \text{age}) \bullet \text{Weight(kg)} \bullet [0.85 \text{ if female}]}{72 \bullet \text{serum creatinine (mg/dL)}}$$

   or, if serum creatinine is in µmol/L:

$$\text{eCCr} = \frac{(140 - \text{Age}) \bullet \text{Weight(kg)} \bullet [1.23 \text{ if male, } 1.04 \text{ if female}]}{\text{serum creatinine (µmol/L)}}$$

8. Adequate hepatic function per local laboratory reference range as follows:

   - aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 3.0 × ULN
   - bilirubin ≤ 1.5 × ULN. Subjects with Gilbert's Syndrome may have a bilirubin > 1.5 × ULN per correspondence between the investigator and AbbVie Therapeutic Area Medical Director (TA MD).

9. If female, subject must be either postmenopausal defined as:

   - Age > 55 years with no menses for 12 or more months without an alternative medical cause.
   - Age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND an FSH level > 40 IU/L.

     OR

   - Permanently surgical sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

     OR

   A Women of Childbearing Potential (WOCP) practicing at least one protocol specified method of birth control (Refer to Section 5.2.4), starting at Study Day 1 through at least 30 days after the last dose of study drug.

10. Females of childbearing potential must have a negative serum pregnancy test result at Screening, and a negative urine pregnancy test at Study Day 1. Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as define above) at Screening do not require pregnancy testing.
11. Subject voluntarily signs and dates an informed consent form that has been approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB) prior to the initiation of any screening or study-specific procedures.

Rationale for Inclusion Criteria

1 – 4	To select the subject population
5 – 8	For the safety of the subjects
9 – 10	The impact of venetoclax on pregnancy is unknown
11	In accordance with Harmonized Good Clinical Practice (GCP)

5.2.2 Exclusion Criteria

A subject will not be eligible for study participation if he/she meets any of the following criteria:

1. Female subject who is pregnant, breastfeeding or is considering becoming pregnant during the study or for approximately 30 days after the last dose of study drug.
2. Subject has developed Richter's transformation or Prolymphocytic leukemia.
3. Subject has previously received venetoclax.
4. History of active malignancies other than CLL within the past 2 years prior to first dose of venetoclax, with the exception of:
    - adequately treated in situ carcinoma of the cervix uteri
    - adequately treated basal cell carcinoma or localized squamous cell carcinoma of the skin

- previous malignancy confined and surgically resected (or treated with other modalities) with curative intent.

5. Active and uncontrolled autoimmune cytopenias (within 2 weeks prior to Screening), including autoimmune hemolytic anemia (AIHA) or idiopathic thrombocytopenic purpura (ITP), despite low dose corticosteroids.
6. Prior allogeneic stem cell transplant.
7. Treatment with the following **within 30 days** prior to the first dose of venetoclax:
   - a biologic agent (i.e., monoclonal antibodies) with anti-neoplastic intent.
8. Treatment with any of the following **within five half-lives or 14 days** (if half-life unknown) as applicable prior to the first dose of venetoclax, or clinically significant adverse effect(s)/toxicity(s) of the previous therapy have not resolved to < National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03 Grade 2:
   - any anti-cancer therapy including chemotherapy or radiotherapy, with the exception of b-cell receptor pathway inhibitors (i.e., ibrutinib, idelalisib)
   - investigational therapy, including targeted small molecule agents
9. Treatment with any of the following **within 7 days** prior to the first dose of venetoclax:
   - Steroid therapy for anti-neoplastic intent.
   - Moderate or strong Cytochrome P450 3A (CYP3A) inducers (See Appendix C for examples)
10. Treatment, administration or consumption of any of the following **within 3 days** prior to the first dose of venetoclax.
    - Strong CYP3A inhibitors. (See Appendix C for examples)
    - Moderate CYP3A inhibitors (See Appendix C for examples)
    - B-cell receptor pathway inhibitors (i.e., ibrutinib, idelalisib)
    - grapefruit or grapefruit products
    - Seville oranges (including marmalade containing Seville oranges)

- Star fruit.

11. Subject is known to be positive for Human Immunodeficiency Virus (HIV) (due to potential drug-drug interactions between anti-retroviral medications and venetoclax, as well as anticipated venetoclax mechanism based lymphopenia that may potentially increase the risk of opportunistic infections).
12. Known allergy to xanthine oxidase inhibitors and/or rasburicase for subjects at risk for TLS.
13. Cardiovascular disability status of New York Heart Association Class ≥ 2. Class 2 is defined as cardiac disease in which subjects are comfortable at rest but ordinary physical activity, results in fatigue, palpitations, dyspnea or anginal pain.
14. Evidence of other clinically significant uncontrolled condition(s) including, but not limited to:
    - uncontrolled and/or active systemic infection (viral, bacterial or fungal)
    - chronic hepatitis B virus (HBV) or hepatitis C (HCV) requiring treatment.
    - febrile neutropenia.
15. Significant history of renal, pulmonary, neurologic, psychiatric, endocrinologic, metabolic, immunologic, cardiovascular or hepatic disease that in the opinion of the investigator would adversely affect the subject's participation in this study.
16. Malabsorption syndrome or other condition that precludes enteral route of administration.

Rationale for Exclusion Criteria

1	The impact of venetoclax on pregnancy is unknown
2 – 5, 7	To select the appropriate subject population
6, 8 – 16	For the safety of the subjects

5.2.3 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving at the time of enrollment, or receives during the study, must be recorded along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency.

The AbbVie TA MD should be contacted if there are any questions regarding concomitant or prior therapy(ies).

Subjects should receive full supportive care during study participation, including hematopoietic growth factors, transfusion of blood products, fluid and electrolyte replacement, and antibiotics when appropriate. Subjects who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

Steroid therapy for anti-neoplastic intent will not be allowed either during or within 7 days prior to the first dose of venetoclax.

Inhaled steroids for the treatment of asthma or COPD, topical steroids, replacement corticosteroid therapy for an inherited or acquired deficiency are allowed.

In addition, limited corticosteroid treatment is allowed while on study for significant active autoimmune cytopenias, e.g., autoimmune hemolytic anemia (AIHA) or immune thrombocytopenia (ITP). IVIG (intravenous immune globulin) is also allowable.

For additional guidance regarding medications for management of neutropenia, refer to Section 6.1.8.3.

The AbbVie TA MD identified in Section 6.1.3 should be contacted if there are any questions regarding concomitant or prior therapy(ies).

General guidelines regarding excluded, cautionary and allowed medications are summarized in Table 1 and Table 2 below.

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.

Table 1. Excluded and Cautionary Medications

Excluded
Anticancer therapies including chemotherapy, radiotherapy, or other investigational therapy, including targeted small molecule agents: Excluded 5 half-lives prior to first dose and throughout venetoclax administration **Biologic agents (e.g., monoclonal antibodies) for anti-neoplastic effect:** Excluded 30 days prior to first dose and throughout venetoclax administration
Excluded during initiation and the dose-titration phase and Cautionary at 400 mg Steady Daily Dose:
Strong CYP3A inhibitors Exclude during initiation and the dose-titration phase. If subject requires use of these medications after the dose titration phase at steady daily 400 mg doses, use with caution and reduce the venetoclax dose by at least 75% during co-administration. Resume the venetoclax dose that was used prior to initiating the CYP3A inhibitor 2 to 3 days after discontinuation of the inhibitor
Cautionary
Moderate CYP3A inhibitors Avoid concomitant use of venetoclax with moderate CYP3A inhibitors at initiation and during the dose-titration phase. Consider alternative treatments. If a moderate CYP3A inhibitor must be used, reduce the initiation dose, titration doses and the 400 mg steady daily dose of venetoclax by at least 50%. Resume the venetoclax dose that was used prior to initiating the CYP3A inhibitor 2 to 3 days after discontinuation of the inhibitor. **Strong and Moderate CYP3A inducers** Avoid concomitant use of venetoclax with strong or moderate CYP3A inducers. Consider alternative treatments with less CYP3A induction. **Warfarin** **P-gp substrates** **BCRP substrates** **OATP1B1/1B3 substrates** **P-gp inhibitors** **BCRP inhibitors**

Note: See Appendix C for Examples.

Table 2. Sample of Permitted Medications

Drug or Therapy	Comments
Colony stimulating factors e.g., G-CSF, GM-CSF	**Permitted**; per ASCO guidelines.[32] Notify AbbVie TA MD if subject requires use of these medications or recombinant human erythropoietin.
Best supportive care and treatment e.g., antiemetics, antibiotics, transfusions, nutritional support, pain control, etc.	**Permitted**
Antiherpes and anti-pneumocystis prophylaxis	**Permitted**; if clinically indicated.
Autoimmune thrombocytopenia and hemolytic anemia medications	**Permitted**; if clinically indicated.

A sample list of excluded medications and cautionary medications that fall into these categories is provided in Appendix C. It is not possible to produce a complete list of medications that fall into these categories, so if in question, please refer to the appropriate product label.

If the investigator determines that such a medication is medically necessary, the investigator will notify the AbbVie TA MD and discuss the investigator's use of these medications and the investigator's plans to medically monitor the study subject.

5.2.4 Contraception Recommendations

While participating in this research study, female subjects should not become pregnant or breastfeed a baby.

If female, subject must be either postmenopausal or permanently surgically sterile (refer to inclusion criteria for definitions of both) OR a Women of Childbearing Potential, practicing at least one of the following highly effective methods of birth control, on Study Day 1 (or earlier) through at least 30 days after the last dose of study drug.

- Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) associated with the inhibition of ovulation, initiated at least 1 month prior to Study Day 1. In addition to combined hormonal contraception, a barrier method must be used during this study from

initial study drug administration to 30 days after the last dose of study drug as drug-drug interaction with venetoclax upon the hormonal contraception is unknown.

- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 1 month prior to Study Day 1. In addition to a progestogen-only hormonal contraception, a barrier method must be used during this study from initial study drug administration to 30 days after the last dose of study drug as drug-drug interaction with venetoclax upon the hormonal contraception is unknown.
- Bilateral tubal occlusion/ligation at least 1 month prior to Study Day 1.
- Bilateral tubal occlusion via hysteroscopy (i.e., Essure), provided a hysterosalpingogram confirms success of the procedure at least 1 month before study participation.
- Vasectomized partner(s), provided the vasectomized partner verbally confirms receipt of medical assessment of the surgical success, and is the sole sexual partner of the WOCP trial participant.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- True abstinence: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject [periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable].

5.3 Efficacy and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Study procedures described are listed in the following section of this protocol and are summarized in tabular format in Appendix D and Appendix E.

Unless otherwise stated, the baseline measurement for any given variable will be defined as the last value obtained for the variable prior to the first dose of venetoclax.

5.3.1.1 Study Procedures

All study procedures outlined in Appendix D and Appendix E are discussed in detail in this section, with the exception of adverse event (AE) information (discussed in Section 6.1.1). All study data will be recorded on electronic case report forms (eCRFs).

Informed Consent

Subjects must voluntarily sign and date an informed consent form approved by an IEC/IRB, prior to the initiation of any screening, study-specific procedures, or before any prohibited medications are withheld from the subject in order to participate in the study. Details about how informed consent will be obtained and documented are provided in Section 9.3.

Screening

Procedures performed at Screening will serve as baseline, unless repeated on Week 1 Day 1 prior to dosing; in which case the latter will serve as baseline. Any abnormal laboratory or vital sign assessment between screening and prior to administration of study drug will be recorded in the subject's medical history and will also serve as the subject's baseline. The schedule of study visit procedures is based on subject study drug administration. Scheduled study visits and/or procedures will need to be altered if there is an interruption in study drug administration. If study drug administration is interrupted for more than 3 days (i.e., adverse event), the site will contact the AbbVie study team or AbbVie TA MD to adjust the subject's visit schedule, procedures and/or dosing on a case by case basis.

Subjects who signed informed consent, have had at least one study procedure conducted, and are determined to be a screen failure, will not proceed in study.

Re-Screening Procedures

Subjects that initially screen fail for the study may be permitted to re-screen following re-consent. All Screening procedures will need to be repeated. The subject must meet all

inclusion and none of the exclusion criteria at the time of re-screening in order to qualify for the study. There is no minimum period of time a subject must wait to re-screen for the study. If the subject had a complete initial screening evaluation including the CT scan and the re-screen visit is more than 35 days since the initial screening assessment, a CT scan should be repeated. As appropriate, sites are encouraged to contact the AbbVie TA MD to confirm if subjects should or should not be re-screened.

Detection of 17p Deletion or TP53 Mutation

Subjects may have 17p deletion and/or TP53 mutation as assessed by local laboratory (in bone marrow or peripheral blood) to be considered as having this deletion/mutation. However, the 17p deletion or TP53 mutation is not a protocol required test for subjects to be enrolled in this study. If a subject does have the 17p deletion or TP53 mutation, a recent test is desirable but any previous positive test is acceptable.

Medical and Oncology History

A complete medical history, including history of tobacco, nicotine-containing products and alcohol use, will be taken from each subject during the Screening visit, including:

- documentation of any clinically significant medical condition
- a detailed oncology history including:
  - histology
  - cytogenetics
  - date of CLL diagnosis
  - stage
  - any surgical procedures
  - treatments administered (including dates, type of modality, response to treatment and reason for treatment discontinuation)

On Week 1 Day 1, any additional medical history observed after signing of the informed consent but prior to initial venetoclax administration and not considered related to study-required procedures will be recorded in the subject's medical history.

Pregnancy Testing

- WOCP must have a negative serum pregnancy test result at Screening, and a negative urine pregnancy test at Study Day 1.
- 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.
- During the study a urine pregnancy test can be performed at the discretion of the investigator or per local guidelines.
- Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined in Inclusion Criterion 9) at Screening do not require pregnancy testing.

Adverse Event and Concomitant Medication Assessment

On Week 1 Day 1, any protocol-related events observed from the time of signing of the informed consent but prior to initial venetoclax administration will be recorded as a serious or nonserious adverse event, if considered by the investigator to be causally related to the study-required procedures (See Figure 3).

At each visit, including the Final Visit and the Post-Treatment Follow-Up, the subject's medical history will be reviewed and any changes from baseline will be recorded on the adverse event eCRF.

If a subject reports taking any over-the-counter or prescription medications, vitamins and/or herbal supplements or if administration of any medication becomes necessary beginning with Screening through the end of the study, the name of the medication, dosage information including dose, route and frequency, date(s) of administration including start and end dates, and reason for use must be recorded on the appropriate eCRF.

Vital Signs

Vital signs include body temperature (oral or tympanic), weight, blood pressure and pulse. On days when venetoclax is administered in the clinic, blood pressure and pulse rate will be measured after the subject has been sitting for at least 5 minutes.

NOTE: Starting with visit Week 8/Day 1, vital signs may be performed within 72 hours before or after the scheduled visit.

Physical Examination

At Screening, the subject should have a **complete physical examination**, including height and weight (height only performed during Screening). A complete physical examination should include the evaluation of head, eyes, ears, nose and throat (HEENT); cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal and neurological systems.

A **symptom directed physical examination** may be performed at all other visits (other than screening) and should be limited to systems of primary relevance: cardiovascular, respiratory, and those associated with symptoms.

Physical Examination (Disease Assessment)

Physical examinations performed as a part of Disease Assessments (Screening, Weeks 24, 36, 48) are to include the evaluation of the presence and degree of enlarged lymph nodes in two dimension (cervical, supraclavicular, axillary, inguinal and femoral nodes), hepatomegaly, and splenomegaly. These lymph node evaluations should be noted on all physical examinations irrespective of being present or absent. Refer to Disease Assessments (2008 Modified IWCLL NCI-WG Criteria) for additional information pertaining to methods of measurement.

Changes from baseline abnormalities should be recorded at each subsequent physical examination. New or worsened abnormalities should be recorded as AEs if appropriate.

If signs or symptoms suggestive of Richter's Syndrome are observed during physical examination, further assessments (i.e., nodes, Positron Emission Tomography [PET] scan) should be considered to exclude or confirm the transformation.

Please refer to Appendix D and Appendix E for timing of all physical examinations.

NOTE: Starting with Week 8 Day 1, all Physical examinations may be performed within 72 hours before or after the scheduled visit.

Tumor Lysis Syndrome (TLS) Risk Assessment

At Screening, all study subjects will be assessed for risk of developing TLS. The risk of TLS is a continuum based on multiple factors, including tumor burden and comorbidities. Subjects with high tumor burden (e.g., any lymph node with a diameter ≥ 5 cm or high absolute lymphocyte count [ALC] [ALC ≥ 25×10^9/L]) are at greater risk of TLS. Reduced renal function (estimated creatinine clearance [eCrCl] < 80 mL/min) further increases the risk. The risk may decrease as tumor burden decreases with venetoclax treatment.

Tumor burden assessments, including radiographic evaluation (e.g., CT scans) as well as chemistry/hematology assessments (refer to Table 4, Clinical Laboratory Tests) will be performed in all subjects prior to initiating venetoclax treatment.

Appropriate venetoclax dosing and management of subjects throughout their study treatment is guided by their individual risk for developing TLS. Risk-based TLS prophylaxis and management measures are described in Section 6.1.8.1.

Eastern Cooperative Oncology Group (ECOG) Performance Status

For all subjects, the ECOG performance status[47] will be performed as outlined in Appendix D and Appendix E.

It is recommended, where possible, that a subject's performance status will be assessed by the same person throughout the study. ECOG performance status will be assessed as follows:

Table 3. ECOG Performance Status

Grade	Description
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, e.g., 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.

NOTE: Starting at Week 24 Day 1, ECOG performance status may be performed within 72 hours before or after the scheduled visit.

Coagulation Panel

Prothrombin time (PT) and/or International Normalized Ratio (INR) and activated partial thromboplastin time (aPTT) will be collected and will be analyzed by the local laboratory during Screening only.

Hematology and Chemistry

Hematology and chemistry will be analyzed by the local laboratory. Required tests are listed in Table 4.

Table 4. Clinical Laboratory Tests

Hematology	Chemistry	Coagulation[a]
Hematocrit Hemoglobin Red Blood Cell (RBC) count White Blood Cell (WBC) count Neutrophils Lymphocytes Platelet count (estimate not acceptable) Reticulocyte count	Blood Urea Nitrogen (BUN)* Creatinine Total bilirubin Alanine Aminotransferase (ALT) Aspartate Aminotransferase (AST) Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphorus Uric acid[b] Glucose Albumin Lactate dehydrogenase (LDH)	Prothrombin time (PT) AND/OR International Normalized Ratio (INR) Activated partial thromboplastin time (aPTT)

* Urea may be reported instead of BUN.

a. Performed at Screening and as clinically indicated.

b. For samples from subjects treated with rasburicase: rasburicase causes enzymatic degradation of the uric acid in blood/plasma/serum samples left at room temperature, 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 4 hours of collection.

PRE-DOSE LABS:

Prior to the Initial Dose of Venetoclax, for all Subjects:

- During the Screening Period: For all subjects, the chemistry/hematology panel (see Table 4, Clinical Laboratory Tests) is required.
  - Pre-existing abnormalities should be corrected
- Within 72 hours of Week 1 Day 1: If the screening labs were done more than 72h before the planned first dose, the chemistry/hematology panel should be repeated. These results should be reviewed prior to dosing.
  - Labs should be assessed and pre-existing abnormalities should be corrected.

- On the day of Week 1 Day 1: Before dosing, the chemistry/hematology panel should be drawn.

  The results of the labs drawn on Week 1 Day 1 need to be reviewed prior to dosing **IF** an additional lab draw within 72 hours of the initial dose at Week 1 Day 1 was not drawn **AND** reviewed.

Prior to Each Subsequent Dose Increase, for all Subjects:

- Within 72 hours of each subsequent dose increase: The chemistry/hematology panel should be repeated. The results should be reviewed prior to dose increasing.
- Prior to dosing, on the day of each subsequent dose increase: Before dosing, the chemistry/hematology panel should be drawn. The results of the labs drawn on Day 1 of each dose increase need to be reviewed prior to dosing **IF** an additional lab draw within 72 hours of the dose increase was not drawn **AND** reviewed.

POST-DOSE LABS:

For all subjects, the chemistry/hematology panel (refer to Table 4, Clinical Laboratory Tests) should be monitored at 6 to 8 hours and at 24 hours after the first dose of venetoclax (20 mg) and after the first dose increase (50 mg). Electrolyte abnormalities should be corrected promptly. The next venetoclax doses (the Day 2 20 mg venetoclax dose and the Day 2 50 mg venetoclax dose) should not be administered until the 24 hour lab results have been evaluated. Electrolyte abnormalities should be corrected promptly. For subjects who continue to be at risk of TLS, the same lab monitoring schedule (i.e., 6 to 8 hour and 24-hr post dose) should be followed at the subsequent dose increases.

This monitoring is also recommended during the re-initiation of the therapy after a dose interruption.

Additional monitoring may be required based on the risk assessment by the investigator and as directed by the AbbVie TA MD.

Local laboratories will be utilized to process and provide results for clinical laboratory tests allowing for immediate subject medical management. The principal investigator or sub-investigator will review, initial, and date all laboratory results used for subject treatment management after receipt from the local laboratory. Local laboratory values will be entered by the site directly onto the appropriate eCRF and laboratory normal ranges for the laboratory that is used will be provided to the AbbVie Clinical Team.

A laboratory test value that requires a subject to be discontinued from the study, requires a subject to receive treatment, meets protocol specific criteria (see Section 6.1.8 regarding toxicity management), or if the Investigator considers clinically significant will be recorded as an adverse event.

NOTE: Starting with Week 8/Day 1, clinical laboratory tests may be collected within 72 hours prior to the scheduled visit.

Disease Assessments (2008 Modified IWCLL NCI-WG Criteria)

All measurable disease must be documented at Screening (baseline), prior to the first dose of venetoclax, for all subjects based on the analysis of clinical laboratory tests (hematology), disease assessment physical examination, contrast-enhanced CT scan of involved neck, chest, abdomen and pelvis (or MRI, if CT scan with contrast is medically contraindicated). Bone marrow examinations at screening are not required but results will be recorded if available.

For all subjects, clinical response will be assessed by the investigator at Week 24, Week 36 and Week 48. Disease response will be based on the analysis of clinical laboratory tests and a disease assessment physical examination. To confirm the response, a contrast-enhanced CT scan (or MRI, if CT scan with contrast is medically contraindicated) will be performed at Week 48 for all subjects. Subjects will be evaluated using the 2008 Modified IWCLL NCI-WG criteria for Tumor Response with the addition of CT imaging (or MRI).

For determination of complete remission (CR), the CT scan and bone marrow are required to be negative, per the IWCLL NCI-WG criteria. It is recommended that the CT scan is performed first; if it does confirm a clinical response, then a bone marrow biopsy will be obtained. If a CT scan is performed and does not confirm a clinical response, a bone marrow biopsy should not be obtained.

If a subject exhibits clinical signs of possible disease progression (i.e., increased or *de novo* enlargement of liver, spleen or lymph nodes on physical examination) without an increase in lymphocytes meeting the progression of disease criteria, then additional assessments including contrast-enhanced CT scan and/or bone marrow can be performed to confirm or rule out disease progression.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

For any subject who has not experienced progressive disease (PD) at the time of permanent discontinuation of venetoclax, follow-up phone calls will continue until death, discontinuation from the study or upon study completion.

Response criteria definitions are outlined in 2008 Modified IWCLL-WG Criteria for Tumor Response. See Table 5.

For patients with only Partial Remission at Week 48 an additional CT and a bone marrow examination can be done between Week 48 and Week 108 to confirm CR if there is a possibility that a patient is in Complete Remission based on laboratory tests and a disease assessment physical examination.

NOTE: Disease assessments may be performed approximately 7 days prior to the scheduled visit.

Computed Tomography Scans (or Magnetic Resonance Imaging)

A CT scan with contrast will be accepted if previously performed within 35 days prior to the first dose of venetoclax. Otherwise, a CT scan must be performed within the Screening window (28 days) for all subjects. A CT scan will be performed for all subjects at Week 48 to confirm disease response. Contrast-enhanced CT scans including neck, chest, abdomen, and pelvis will be performed to assess response to treatment. A contrast-enhanced MRI of the neck, chest, abdomen and pelvis with a non-contrast CT scan of the chest may be used for subjects in whom a contrast CT is medically contraindicated (i.e., subjects with a severe allergy to CT contrast agents or subjects with impaired renal clearance). Whichever method is used at Screening should be consistently used throughout the duration of the study.

Any CT scan (or MRI) performed as standard of care throughout the study should be captured on the eCRF.

NOTE: CT scans (or MRI) may be performed 7 days prior to the scheduled visit.

Bone Marrow Aspirate and Biopsy

At baseline, a bone marrow aspirate and biopsy are not required; however results should be recorded if available. If the subject achieves a CR by clinical criteria and confirmatory CT scan, a bone marrow aspirate and biopsy will be performed to confirm the CR. Whenever possible the bone marrow aspirate for biomarker MRD assessment should be split from this sample. If a CT scan is performed and does not confirm a CR, a bone marrow biopsy should not be obtained.

Bone marrow aspirates and biopsies performed as standard of care throughout the study should also be captured on an eCRF.

Subject Calendars/Diaries

For all subjects, subject calendars/diaries will be provided at the Week 20 visit. Subjects will be instructed to bring their calendars/diaries back to the site to be reviewed at the Week 24 visit.

Subjects will be instructed to record the date and time of each dose taken (indicating if any doses of study drug are missed) from Week 20 to Week 24, and whether or not the dose was taken with a meal. This information will be transcribed into the eCRF.

At the Week 24 visit, the calendars/diaries are to be returned to the site and appropriately filed with the subject's source documents for this study.

Health Economic and Patient Reported Outcome Measures

Quality of life will be assessed using the following questionnaires: the EQ-5D-5L the FACT-Leu and the FACIT-F.

Quality of life will be assessed at baseline (Week 1, Day 1 prior to the first dose), Week 4, Week 12, Week 24, and then every 3 months until the end of study treatment (Week 108). The Health Economic and Patient Reported Outcomes questionnaires should be administered and completed prior to any other study procedures being performed at these visits. Refer to Section 5.3.7, Health Economic and Patient-Reported Outcome Measures, for further information.

Final Visit

Upon treatment discontinuation (See Section 5.4.1), the reason(s) for discontinuation will be recorded in the eCRFs and a Final Visit will be performed. The Final Visit procedures as listed in Appendix D and Appendix E should be performed as soon as possible after study drug discontinuation.

At the Final Visit, all used/unused study drug and the subject's calendars/diaries, if applicable are to be returned to the site and drug accountability performed.

30-Day Safety Visit

A 30-Day Safety Follow-up Visit should be performed approximately 30 days (± 3 days) following the last dose of venetoclax (to allow for AE collection 30 days following last dose of study drug). Refer to Appendix D and Appendix E for procedures to be performed.

If a subject has an ongoing AE or an unresolved clinically significant laboratory result 30 days following last dose of study drug, the site will attempt to provide follow-up until the AE has resolved to a ≤ Grade 1 or baseline or it is the investigator's judgment that the event is unlikely to resolve.

Additionally, CT or MRI scans are not required, however if collected by the site as standard of care, the data should be recorded in EDC.

Post-Treatment and Survival Assessments

After treatment discontinuation, subjects will be followed for disease progression (if progression has not already occurred) and survival. Post-treatment calls will be performed every 6 months until discontinuation from the study. Survival information (i.e., the date and cause of death, post-treatment cancer therapies, date of progression etc.) will be collected. This period will continue for 2 years following discontinuation of venetoclax.

Extended Access Phase

In countries where venetoclax is not commercially available, subjects who continue to derive benefit after 2 years of treatment may be able to extend their treatment for up to 2 additional years. If a subject in the extended access phase of this study continues to derive benefit from Venetoclax after the 2-year extension, then per PI's assessment, subjects who are transferring to the venetoclax extension study, Study M19-388, may remain in Extended Access for up to additional 1 year or until the extension study is approved and initiated at the site, whichever is sooner. AbbVie will work with the

investigator on a case by case basis to consider the potential continuation of venetoclax therapy. The Extended Access Visits will include:

- Collection of Survival information
- AE/SAE/Con Med assessment
- Study drug reconciliation and dispensing

All other procedures should be performed as standard of care. The specific study assessments to be performed during these visits are detailed in Appendix E Study Activities.

Assignment of Subject Numbers

Subjects will be assigned unique consecutive subject numbers at screening, as described in Section 5.5.3. The results of all screening evaluations must be within clinically acceptable limits, upon review by the investigator before a subject can be administered study drug. Subjects will not be enrolled in the study if laboratory or other screening results are unacceptable.

5.3.1.2 Collection and Handling of Biomarker Research Samples

Biospecimens may be utilized to evaluate known and/or novel disease-related or drug-related biomarkers. The biomarker rationale will be discussed in the Biomarker Research Variables Section (Section 5.3.6).

Biomarker Samples

Minimal Residual Disease (MRD) Assessment

Peripheral blood for MRD will be collected from all subjects as outlined in Appendix D and Appendix E.

When confirming a CR or CRi status per the 2008 Modified IWCLL NCI-WG criteria with a bone marrow biopsy, whenever possible, a bone marrow aspirate should be

collected for MRD assessment. The bone marrow aspirate should be split and a sample sent to the Central Laboratory.

All biomarker samples should be labeled and shipped as outlined in the study-specific laboratory manual.

AbbVie (or people or companies working with AbbVie) will store the samples in a secure storage space with adequate measures to protect confidentiality. The samples may be retained while research on venetoclax, or drugs of this class, or this disease and related conditions continues, but for no longer than 20 years after study completion, or per local requirement.

5.3.2 Drug Concentration Measurements

5.3.2.1 Collection of Samples for Analysis

Blood samples for venetoclax and possible metabolite(s) will be collected by venipuncture per Appendix D and Appendix E. The date and time (to the nearest minute) of the last dose and second to last dose of venetoclax will be recorded on the eCRF. The date and time (to the nearest minute) of each blood sample collection will be recorded on the sample requisition form.

Blood samples (3 mL) for venetoclax assay will be collected at the following time:

- Week 24 Day 1: 0 hour (pre-dose)

A total of 1 blood sample is planned to be collected per subject for venetoclax PK analysis. Refer to the study specific laboratory manual for detailed instructions on sample collection, processing, and shipment.

5.3.2.2 Measurement Methods

Plasma concentrations of venetoclax will be determined by the Drug Analysis Department at AbbVie using validated methods. Plasma concentrations of other possible metabolites from venetoclax may be determined with validated or non-validated methods.

5.3.3 Efficacy Variables

The primary objective of this study is to evaluate the efficacy of venetoclax monotherapy in subjects with relapsed or refractory chronic lymphocytic leukemia (CLL). The primary efficacy endpoint will be measured by complete remission rate (CR + CRi) of the subjects who have not been previously treated with B-cell receptor inhibitor (BCRi) therapy, as assessed by the investigator.

The secondary objectives are to evaluate other efficacy parameters including the overall response rate (ORR), duration of overall response (DoR), time to progression, (TTP), progression-free survival (PFS), overall survival (OS), and the CR rate in BCRi treated subjects.

Additional secondary objectives will be evaluated. Health Economic and Patient-Reported Outcome Measures will include the EQ-5D-5L, the FACT-Leu and the FACIT-F. Minimal residual disease (MRD) and the rate of MRD negativity in the peripheral blood are assessed as exploratory objectives in the peripheral blood and bone marrow (BM) by flow cytometry, PCR and/or sequencing.

Analyses of these endpoints are described in Section 8.0.

5.3.3.1 Primary Variables

For disease assessments, response will be assessed by the investigator based on analysis of clinical laboratory tests (hematology laboratory values), disease assessment physical examination, CT scan including neck, chest, abdomen, and pelvis (or MRI if CT with contrast is medically contraindicated); bone marrow aspirate are not required but results will be recorded if available. Subjects will be evaluated against the 2008 Modified

IWCLL NCI-WG Criteria for Tumor Response[46] with CT imaging (or MRI). A BM sample assessment is required to confirm CR.

At screening (baseline), all measurable disease must be documented by laboratory testing (hematologic status), physical examination, and CT scan. All baseline evaluations should be performed as closely as possible to the beginning of treatment and not more than 4 weeks before the beginning of the treatment with the exception of the CT scan (or MRI) which will be accepted if previously performed within 35 days prior to study drug initiation. During the study, subjects will have a disease assessment at Week 24, Week 36 and Week 48. To confirm the response, a CT scan will be performed at Week 48 on all subjects. For subjects with CR as response at Week 48, a BM sample is required to confirm the response.

Methods of Measurement

Disease response and progression will be assessed by analysis of peripheral blood, clinical examination, radiographic scans and bone marrow aspirate and biopsy.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Details on the analysis of peripheral blood required to assess response are provided in Section 5.3.1.2.

A full disease assessment physical examination should be performed to assess the extent of disease involvement. Physical examinations should include the evaluation of the presence and degree of enlarged lymph nodes in two dimension (cervical, supraclavicular, axillary, inguinal and femoral nodes), hepatomegaly, and splenomegaly. These should be noted on all examinations irrespective of being present or absent. All measurements should be taken and recorded in metric notation using a ruler or calipers. Clinical lesions will only be considered measurable when they are superficial (e.g., palpable lymph nodes). The diameter, in two planes, of the largest palpable nodes in each of the

following sites should be measured: cervical, supraclavicular, axillary, inguinal, and femoral. The presence of hepatomegaly and splenomegaly should be performed.

The 12 largest bi-dimensional lesions should be recorded in the eCRF.

- Target Lesions: A maximum of 12 target lesions may be selected (up to 6 nodal and 6 extra nodal). Target nodal lesions must be abnormal (> 1.5 cm in LDi [Longest Diameter] at baseline), clearly measurable and suitable for consistent, reproducible measurement in at least two perpendicular dimensions. Target extra nodal lesions must be > 1 cm in two perpendicular diameters at baseline.
- Non-Target Lesions: Sites will be classified as non-target lesions where disease is present but not selected for target lesions. A maximum of 10 non-target lesions can be selected. Non-target nodal lesions must be abnormal (> 1.5 cm in LDi at baseline). Non-target extra nodal lesions must be > 1 cm in two perpendicular diameters. Nodal and extra nodal lesions that were not selected as target lesions at baseline can be followed as non-target lesions.

Computed tomography (CT) is the preferred method to measure lesions selected for response assessment. CT scans (with contrast) should include neck, chest, abdomen, and pelvis scans. CT scans for response assessment may be limited to areas of prior involvement only, if required by local regulatory authorities. A contrast-enhanced MRI of the neck, chest, abdomen and pelvis with a non-contrast CT scan of the chest may be used if CT with contrast is medically contraindicated (e.g., severe contrast allergy). If MRIs are used instead of CT scans, MRIs should be used consistently throughout the study. Conventional CT and MRI should be performed with cuts of 5 mm or less in slice thickness contiguously. Spiral CT should be performed by use of 5 mm contiguous reconstruction algorithm; this specification applies to the regions of the neck, chest, abdomen and pelvis at baseline and follow-ups. The 12 largest bi-dimensional lesions should be recorded in the eCRF (6 nodal and 6 extra nodal).

For accurate overall response evaluation, ultrasound (US) should not be used to measure tumor lesions.

Details on bone marrow biopsy and aspirate are provided in Section 5.3.1.1. Study Procedures.

Tumor Response Criteria

Complete Remission (CR)

CR requires all of the following criteria:

- Peripheral blood lymphocytes (evaluated by blood and differential count) below 4×10^9/L (4000/µL)
- Absence of lymphadenopathy (nodes > 15 mm in longest diameter or any extra nodal disease) by physical examination and CT scan
- No hepatomegaly or splenomegaly by physical examination (as determined by measurement below the relevant costal margin)
- Absence of disease or constitutional symptoms (B symptoms: unexplained fevers > 38°C or 100.4°F, drenching night sweats, > 10% body mass weight loss in the preceding 6 months)
- Blood counts above the following laboratory values:
  - Neutrophils > 1.5×10^9/L [1500/µL] (without the need for exogenous growth factors)
  - Platelets > 100×10^9/L [100,000/µL] (without the need for platelet transfusion or exogenous growth factors)
  - Hemoglobin > 110 g/L [11 g/dL] (without the need for blood transfusions or exogenous erythropoietin)
- Bone marrow at least normocellular for age, < 30% of nucleated cells being lymphocytes. Lymphoid nodules should be absent. Bone marrow aspirate and biopsy should be performed after CR/CRi has been achieved. If the bone marrow is hypocellular, a repeat determination should be made in 4 weeks or when peripheral blood counts have recovered. A marrow biopsy should be compared to a pre-treatment marrow if available. Subjects who are otherwise

in a complete remission, but bone marrow nodules can be identified histologically should be considered to be nodular PR (nPR). Immunohistochemistry (IHC) should be performed to define whether these nodules are composed of primarily T cells or lymphocytes other than CLL cells, or CLL cells.

Complete Remission with Incomplete Marrow Recovery (CRi)

Subjects who fulfill the criteria for CR (including bone marrow) but who have persistent cytopenia (anemia or thrombocytopenia or neutropenia) apparently unrelated to CLL but related to drug toxicity will be considered CRi. The marrow evaluation described above should be performed with scrutiny and not show any clonal infiltrate.

Partial Remission (PR)

To be considered a PR at least 2 of the following must be met:

- ≥ 50% decrease in peripheral blood lymphocyte count from the pretreatment baseline value.
- ≥ 50% reduction in lymphadenopathy.
- ≥ 50% reduction in the size of the liver and/or spleen (if abnormal prior to therapy).

In addition at least **one** of the following criteria must be met:

- Neutrophils > 1,500/μL or ≥ 50% improvement over baseline.
- Platelets > 100,000/μL or ≥ 50% improvement over baseline.
- Hemoglobin > 11.0 g/dL or ≥ 50% improvement over baseline without transfusions or exogenous growth factors.

Table 5. 2008 Modified IWCLL NCI-WG 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
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

Table 5. 2008 Modified IWCLL NCI-WG Criteria for Tumor Response (Continued)

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 PD

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.

5.3.3.2 Definition of Disease Progression

Disease progression according to 2008 Modified IWCLL NCI-WG Criteria for Tumor Response is characterized by at least one of the following:

- Appearance of any new lesion, such as enlarged lymph nodes (> 1.5 cm), splenomegaly, hepatomegaly, or other organ infiltrates. An increase by 50% or more in greatest determined diameter of any previous site.
- 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.
- An increase in the number of blood lymphocytes by 50% or more with at least 5,000 B lymphocytes per microliter. The increase should be assessed against the best response while on study.
- Transformation to a more aggressive histology (e.g., Richter's Syndrome). Whenever possible, this diagnosis should be confirmed by lymph node biopsy. For subjects experiencing disease progression due to Richter's Syndrome while on study, supplemental data may be collected.
- Occurrence of cytopenia (neutropenia, anemia or thrombocytopenia) attributable to CLL.

5.3.4 Safety Variables

The following safety evaluations will be performed during the study: serious adverse event and adverse event monitoring including AEs of special interest (Section 6.1.1.4), vital signs, physical examination, and laboratory assessments. Certain types of events require immediate reporting to the Sponsor, as outlined in Section 6.1.5. Safety will be monitored on an ongoing basis and summarize periodically in aggregate safety reports and end of study.

5.3.5 Pharmacokinetic Variables

Values for the PK parameters of venetoclax, including the apparent clearance (CL/F), will be determined using a population PK modeling approach. Additional parameters may be calculated if useful in the interpretation of the data.

5.3.6 Biomarker Variables

Biomarker Research Variables

Peripheral blood and/or bone marrow biospecimens will be collected to conduct exploratory analyses to investigate biomarkers. The types of biomarkers to be analyzed may include, but are not limited to, nucleic acids, proteins, lipids or metabolites. Cells isolated from the peripheral blood/bone marrow may be analyzed to assess specific genetic mutations within the tumor cells, or to track the tumor cells to determine the presence of minimal residual disease. Additionally, the expression levels (RNA or protein) of molecules involved in controlling the apoptosis machinery, including but not limited to BCL-2 family members, may also be correlated with efficacy.

Evaluations may include analyzing biomarkers related to the pathway(s) targeted by the study drug or those believed to be related to the disease or to drug response. The information learned from analyzing these samples may be used to investigate factors influencing response to treatment, scientific questions related to CLL, and/or in the development of new therapies and diagnostic tests. The results of biomarker testing may not be included with the study summary.

5.3.7 Health Economic and Patient-Reported Outcome Measures

5.3.7.1 Functional Assessment of Cancer Therapy – Leukemia (FACT-Leu) Questionnaire

The FACT-Leu is a 44-item, leukemia-specific questionnaire designed to assess subject health-related quality of life (HRQoL) and leukemia-specific symptoms using a 'core' set of questions (Functional Assessment of Cancer Therapy-General; FACT-G), as well as a cancer site-specific leukemia subscale.[34] The FACT-G is a 27-item compilation of general questions scored on a 5-point scale ranging from 0 = "not at all" to 4 = "very much."[35] The items are divided into 4 primary HRQOL domains: Physical Well-being (7 items; score range, 0 – 28), Social/Family Well-being (7 items; score range, 0 – 28), Emotional Well-being (6 items; score range, 0 – 24), Functional Well-being (7 items; score range, 0 – 28).[36]

The leukemia-specific subscale consists of 17 items (score range, 0 – 68) that assess subject concerns relating to leukemia. Three summary scales: FACT-Trial Outcome Index (score range, 0 – 124) a summary scale composed of the Physical Well-being, Functional Well-being, and leukemia-specific subscales; FACT-G (score range, 0 – 108) and the FACT-Leukemia Total (score range, 0 – 176) can also be calculated. Higher scores are reflective of better HRQOL. Minimally important differences (MIDs) have been identified for the different FACT-Leu scales: Physical Well-being, 2 – 3 points; Social/Family Well-being, not available; Emotional Well-being, 2 points; Functional Well-being, 2 – 3 points; FACT-G, 3 – 7 points; Leukemia-specific subscale, 4 – 7 points; FACT-Trial Outcome Index, 5 – 6 points; and FACT-Leukemia Total, 6 – 12 points.

Scores will be summarized descriptively at each assessment. The impact of treatment on quality of life over time will be assessed by calculating the change in scores from baseline at each assessment time point. Scores will be calculated according to the FACT-Leu scoring manual.

5.3.7.2 Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) Scale

The FACIT-F measures fatigue and its effect on functioning and daily activities.[37] The FACIT-F has 13 items answered on a 5-point rating scale based on a 7-day recall period. Scores range from 0 to 52, with lower scores reflecting greater fatigue. The instrument has shown good reliability and validity based on analyses of the general population in the United States, subjects with cancer, and subjects with rheumatoid arthritis.[37-39] The MID of the FACIT-F scale has been determined to be 3 points.[40]

Scores will be summarized descriptively at each assessment. The impact of treatment on fatigue over time will be assessed by calculating the change in score from baseline at each assessment time point. Scores will be calculated according to the FACIT-F scoring manual.

5.3.7.3 EuroQol 5 Dimensions (EQ-5D-5L)

The EuroQol 5 Dimensions (EQ-5D-5L) is a generic preference instrument that has been validated in numerous populations.[41,42] The EQ-5D-5L has five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. These dimensions are measured on a five level scale: no problems, slight problems, moderate problems, severe problems, and extreme problems. The scores for the 5 dimensions are used to compute a single utility index score ranging from zero (0.0) to 1 (1.0) representing the general health status of the individual. The EQ-5D-5L also contains a visual analog scale (VAS) to assess the subject's overall health. The MID for the EQ-5D utility index score in cancer subjects is 0.08, and the MID for EQ-5D VAS is 7.[43,44]

Each of the five dimensions of the EQ-5D-5L, the VAS and overall utility score will be calculated using the EuroQol scoring manual, and summarized (mean, std. dev., median) at each assessment. The impact of treatment over time will be assessed by calculating the change in score from baseline at each assessment time point.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

Each subject has the right to withdraw from the study and/or study drug treatment at any time. In addition, the investigator may discontinue a subject from study drug treatment at any time if the investigator considers it necessary for any reason including:

- The investigator believes it is in the best interest of the subject
- Subject's response to therapy is unsatisfactory, as evidenced by progression of disease while on study drug
- The subject requires other cancer treatment (e.g., radiotherapy, cancer-related surgery as a result of tumor progression, alternate anti-neoplastic agents) during the study period
- unacceptable toxicity
- The subject becomes pregnant while on the study

- drug/protocol non-compliance

The investigator will inform AbbVie prior to discontinuing a subject from the study by contacting the Clinical Team Leader as identified in Section 7.0. All subjects will be included for analysis of safety data. Subjects who withdraw from the study will not be replaced unless they are not evaluable.

Subjects will continue to be followed for unresolved AEs and survival information for any subject who has not experienced PD at the time of venetoclax discontinuation.

Final Visit

Upon study drug discontinuation and/or upon discontinuation from the study, the reason(s) for discontinuation will be recorded in electronic case report forms (eCRFs) and a final visit will be performed. The final visit procedures as listed in Appendix D should be performed as soon as possible after discontinuation from study drug.

30-Day Safety Follow-Up Visit

A 30-Day Safety Follow-up Visit should be performed approximately 30 days (± 3 days) following the last dose of venetoclax. The 30 day safety follow up procedures listed in Appendix D should be performed.

Post Treatment and Survival Follow-Up Calls

For subjects who discontinue venetoclax therapy, but do not discontinue the study, post treatment follow-up calls will be performed every 6 months (± 7 days) for survival information (i.e., disease progression, the date and cause of death, post-treatment cancer therapies, etc.) and will be collected via telephone calls for a period of 2 years and recorded in the eCRFs.

5.4.2 Discontinuation of Entire Study

AbbVie may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended

termination. The investigator may also terminate the study at his/her site for reasonable cause, after providing written notice to AbbVie in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will immediately notify the investigator by telephone and subsequently provide written instructions for study termination.

5.5 Treatments

5.5.1 Treatments Administered

Venetoclax tablets should be taken orally once daily with a meal and water in the morning at approximately the same time each day. Venetoclax tablets should be swallowed whole and not chewed, crushed, or broken prior to swallowing.

If the subject misses a dose of venetoclax within 8 hours of the time it is taken, the subject should take the missed dose as soon as possible on the same day and resume the normal daily dosing schedule the following day. If a subject misses a dose by more than 8 hours, the subject should not take the missed dose and resume the normal daily dosing schedule the following day.

In cases of vomiting after taking venetoclax, no additional dose (tablets) should be taken that day. The next dose should be taken at the usual time the following day.

5.5.2 Identity of Investigational Product

The individual study drug information is presented in Table 6.

Table 6. Identity of Investigational Product

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

Each site will be responsible for tracking the lot numbers and expiration dates for all non-investigational medicinal products (e.g., generic name and generic name) that are dispensed.

5.5.2.1 Packaging and Labeling

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

5.5.2.2 Storage and Disposition of Study Drug

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

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

5.5.3 Method of Assigning Subjects to Treatment Groups

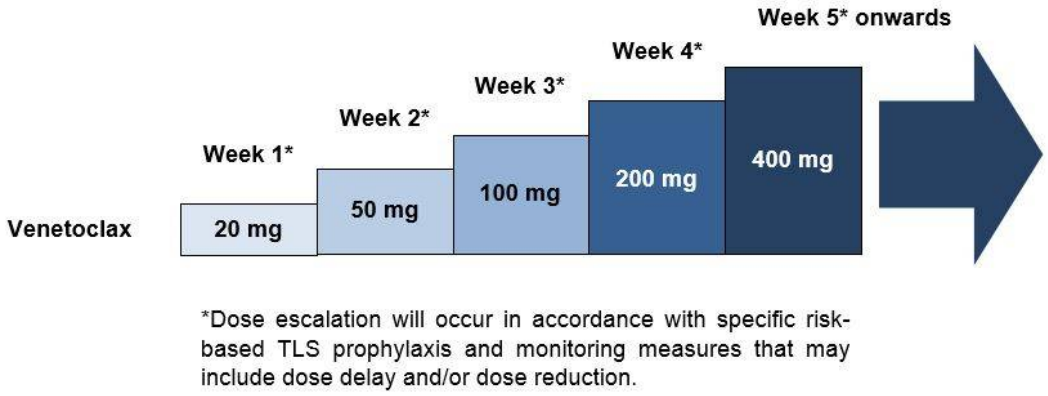
All subjects are assigned to the same treatment group in this single arm study. Subjects will be allocated a unique consecutive subject number at Screening. Subject numbers will consist of 5 digits (XXX01), with the first three digits denoting site number and the last

2 digits as the subject number, beginning with 01. All subjects will be enrolled using an (Interactive Response Technology) IRT. Before the study is initiated, each site will be provided with the IRT user instructions, which provides direction on how to use the IRT via the Web or the telephone. Since this is an open-label study, subjects will maintain the same subject number, regardless of the number of re-screens and through the duration of the study. The site, in conjunction with the Sponsor, will be responsible for assignment of all unique subject numbers at Screening and dose assignments if the subject is not a screening failure.

5.5.4 Selection and Timing of Dose for Each Subject

Venetoclax will be administered orally once daily (QD) beginning with a dose-titration phase. As shown in Figure 2, the initial venetoclax dose is 20 mg QD. After 1 week of treatment at 20 mg QD, the dose will be escalated to 50 mg QD followed by subsequent increases, each after 1 week, to 100 mg QD, 200 mg QD and the maximum dose of 400 mg QD. The maximum dose of venetoclax for this protocol will not exceed 400 mg per day. The 5-week dose-titration phase is designed to gradually reduce tumor burden (debulk) and decrease the risk of tumor lysis syndrome. All study subjects will be categorized at Screening according to their risk for developing TLS. Their dose management, including during the dose-titration phase, will be conducted in accordance with their risk for developing TLS (see Section 6.1.8.1) and may include dose delay and/or dose reduction as required for prophylaxis and management of TLS.

Figure 2. 5-Week Dose-Titration Schematic



5.5.5 Blinding

This is an open-label, single arm study.

5.5.6 Treatment Compliance

The investigator or his/her designated and qualified representatives will administer/dispense study drug only to subjects enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol.

To document compliance with the treatment regimen, subjects will be instructed to return all unused tablets and/or containers, even if empty and any other study related items as necessary, to the study coordinator at scheduled study visits. Compliance will be monitored and documented by the study coordinator on the appropriate form. The study coordinator will question the subject regarding adherence to the dosing regimen, record the number of tablets and/or containers returned, the date returned and determine treatment compliance before dispensing new venetoclax to the subject. Compliance below 80% will require counseling of the subject by study site personnel.

5.5.7 Drug Accountability

Investigator or representative will verify that study drug supplies are received intact and in the correct amounts. Documentation of the receipt of supplies will be supported by a signed and dated Proof of Receipt or similar shipping document in IRT. A current (running) and accurate inventory of venetoclax will be kept by the site and will include lot number, Proof of Receipt number(s), container numbers, blister pack numbers, subject initials, initials of person who dispensed the drug and the date study drug was administered for each subject. An overall accountability of study drug will be performed and verified by AbbVie monitor(s) throughout the study and at the study site closeout visit. All study drug unit doses must be inventoried, accounted for, and returned to AbbVie or destroyed per instructions from AbbVie and according to local regulations. All original containers (containing partially used or unused study drug) will be returned to AbbVie according to instructions from AbbVie or the designated monitor(s). If pre-arranged between AbbVie and the site, destruction of used and unused study drug containers will be performed at the site. Empty containers will be destroyed at the site. Labels must remain attached to the containers.

The investigator and/or named sub-investigators agree not to supply study medication to any persons not enrolled in the study.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

Study M15-550 is being conducted primarily to assess the efficacy of venetoclax monotherapy. This study is a single-arm trial; therefore, there is no control group or treatment blinding. The study will be conducted at multiple study centers globally to ensure a broad representation of the patient population and clinical care settings.

5.6.2 Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study.

5.6.3 Suitability of Subject Population

Venetoclax monotherapy has shown favorable activity in relapsed/refractory CLL subjects including subjects with 17p deletions. Venetoclax is expected to be as active in subjects selected for TP53 mutations as these patient populations overlap and the oncogenic effect of both genetic defects occurs via p53 abrogation. In addition, venetoclax has shown activity in subjects with relapsed or refractory CLL who have been previously treated with a B-cell receptor inhibitor. These subjects can participate in this study and may have relapsed or be refractory to ibrutinib, or idelalisib containing regimen.

All subjects enrolled in the study will have adequate performance status and hematologic, renal and hepatic function to undergo venetoclax treatment.

5.6.4 Selection of Doses in the Study

Venetoclax dosing will be introduced at an initial dose of 20 mg QD and escalated to a final dose of 400 mg QD. The maximum dose of venetoclax for this protocol will not exceed 400 mg per day. The daily dose will be titrated in the following weekly increments, as tolerated: 20 mg, 50 mg, 100 mg, 200 mg, and 400 mg. The 400 mg final dose was selected for the ongoing, Phase 2 study of venetoclax monotherapy in relapsed/refractory CLL subjects with 17p deletion (Study M13-982) based on time-to-response and logistic regression modelling of data from CLL/SLL subjects enrolled in the Phase 1 Study M12-175.

The initial 20 mg venetoclax dose and weekly incremental increases in the dose-titration phase were implemented for Study M13-982 to reduce the risk of TLS. Preliminary safety data from that study indicate the initial dose, the dose-titration phase and the final maximum dose are tolerable.

6.0 Complaints

A Complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability,

reliability, safety, effectiveness, or performance of a product/device after it is released for distribution.

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 6.2.2). For adverse events, please refer to Sections 6.1.1 through 6.1.6. For product complaints, please refer to Section 6.2.

6.1 Medical Complaints

The investigator will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The investigator will assess and record any adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the adverse event to study drug, and any action(s) taken. For serious adverse events considered as having "no reasonable possibility" of being associated with study drug, the investigator will provide an "Other" cause of the event. For adverse events to be considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All adverse events will be followed to a satisfactory conclusion.

6.1.1 Definitions

6.1.1.1 Adverse Event

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

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, meets protocol specific criteria (see Section 6.1.8 Toxicity Management) or if the investigator considers them to be adverse events.

For this protocol, disease progression is an efficacy endpoint. These data will be captured as efficacy assessment data only. Thus, events that are clearly consistent with the expected pattern of progression of the underlying disease (such as transformation to more aggressive histology) will result in discontinuation from the study and should not be recorded as adverse events but reported on the Study Completion eCRF. However, if a subject experiences an adverse event (e.g., pneumonia, pyrexia, fatigue, etc.) and is also found to have disease progression, report the adverse event. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

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

A treatment-emergent AE is defined as any AE reported by a subject with onset or worsening from the time that the first dose of venetoclax is administered until 30 days have elapsed following discontinuation of venetoclax administration.

6.1.1.2 Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to AbbVie as a serious adverse event (SAE) **within 24 hours** of the site being made aware of the serious adverse event.

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).

Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

For serious adverse events with the outcome of death, the date and cause of death will be recorded on the appropriate case report form. Deaths related to disease progression will not be recorded as serious adverse events (see Section 6.1.2.1.1).

Hospitalization of a subject to allow observation and management (e.g., for IV hydration) for the purpose of TLS prophylaxis will not be captured as an SAE, unless there is an additional reason for hospitalization or an additional criterion for seriousness other than hospitalization (e.g., abnormal post-dose TLS laboratories that necessitate therapeutic medical intervention, etc.).

Hospitalization of a subject following the 30-Day Safety Follow-Up visit due to a subsequent line of therapy will not be captured as a SAE.

6.1.1.3 Adverse Events Commonly Associated with CLL Study Population and/or Progression of CLL

Certain AEs are anticipated to occur in the study population at some frequency independent of drug exposure. Such events include known consequences of CLL (e.g., symptoms, disease progression) and events unlikely to be related to the underlying

disease under investigation but common in the study population independent of drug therapy (e.g., cardiovascular events in an elderly population).

These events are listed in Appendix I.

These AEs may occur alone or in various combinations and are considered expected for reporting purposes for this protocol.

Cytopenias (anemia, neutropenia, or thrombocytopenia) are part of the natural history of CLL. Persistent cytopenias at the same CTCAE grade as reported at baseline are not to be captured as adverse events, unless they fulfill a seriousness criteria, result in permanent discontinuation of a study drug, or the investigator had an identifiable cause other than the underlying disease. However, all laboratory data should be entered regardless of whether an adverse event is reported.

Although exempted from expedited reporting to certain Health Authorities and ECs/IRBs as individual cases, if an event commonly associated with CLL or progression of CLL meets seriousness criteria, it must be reported to AbbVie within 24 hours of the site being made aware of the SAE (as defined in Section 6.1.5). However, if the event was unequivocally due to disease progression, it should not be reported as an adverse event even if serious or fatal. For deaths related to disease progression, the date and cause of death will be recorded on the appropriate case report form, but the death will not be expedited as an individual case safety report (ICSR) to regulatory authorities.

6.1.1.4 Adverse Events of Special Interest

TLS and neutropenia are identified risks. Serious Infection is a potential risk.

6.1.2 Adverse Event Severity

The investigator will rate the severity of each AE according to the NCI CTCAE v4.03. If a reported AE increases in severity, the initial AE should be given an outcome date and a new AE must be reported on a different onset date than the end date of the previous adverse event to reflect the change in severity. The dates on the AEs cannot overlap. For

all reported SAEs that increase in severity, the supplemental eCRFs also need to be updated to reflect any changes due to the increase in severity.

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

Grade 1	The adverse event is transient and easily tolerated by the subject (mild).
Grade 2	The adverse event causes the subject discomfort and interrupts the subject's usual activities (moderate).
Grade 3	The adverse event causes considerable interference with the subject's usual activities and may be incapacitating (moderate to severe).
Grade 4	The adverse event is life-threatening requiring urgent intervention (severe).
Grade 5	The adverse event resulted in death of the subject (severe).

6.1.2.1 Adverse Events Expected Due to Study-Related Endpoints

6.1.2.1.1 Deaths

For this protocol, overall survival is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 6.1.4) that are attributed by the investigator solely to progression of CLL should be recorded ONLY on the Study Completion eCRF. All other on-study deaths, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 6.1.5). Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term "sudden death" should be used only for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a subject with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the subject was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be recorded on the Adverse Event eCRF. If the cause of

death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. During survival follow-up, deaths attributed to progression of CLL should be recorded only on the Survival eCRF.

6.1.2.1.2 Lack of Efficacy or Worsening of Disease

Events that are clearly consistent with the expected pattern of progression of the underlying disease are also considered an expected outcome for this study and will not be subject to expedited reporting.

6.1.3 Relationship to Study Drug

The investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug:

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

For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered "associated." Events assessed as having no reasonable possibility of being related to study drug will be considered "not associated." In addition, when the investigator has not reported causality or deemed it not assessable, AbbVie will consider the event associated.

If an investigator's opinion of no reasonable possibility of being related to study drug is given, an "Other Cause" of event must be provided by the investigator for the SAE.

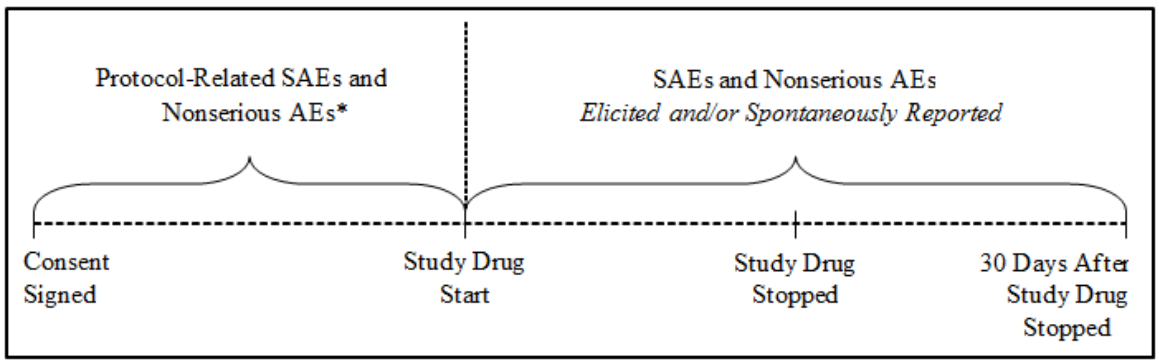
6.1.4 Adverse Event Collection Period

All adverse events reported from the time of venetoclax administration until 30 days, following discontinuation of venetoclax administration have elapsed will be collected, whether solicited or spontaneously reported by the subject. In addition, protocol related serious adverse events and nonserious adverse events will be collected from the time the subject signed the study-specific informed consent.

All AEs should be followed until resolution, return to baseline or determined to be stable per the investigator.

Adverse event information will be collected as shown in Figure 3.

Figure 3. Adverse Event Collection



* Only if considered by the investigator to be causally related to study-required procedures.

6.1.5 Adverse Event Reporting

In the event of a serious adverse event, whether associated with study drug or not, the investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event by entering the serious adverse event data into the electronic data capture (EDC) system. Serious adverse events that occur prior to the site having access to the RAVE® system, or if RAVE is not operable, should be documented on the SAE Non-CRF forms and emailed (preferred route) or faxed to Clinical

Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event.

Email: PPDINDPharmacovigilance@abbvie.com

FAX to: +1 (847) 938-0660

For safety concerns, contact the Oncology Safety Team at:

Dept. R48S, Bldg. AP30
AbbVie
1 North Waukegan Road
North Chicago, IL 60064

Safety Phone: (847) 935-2609
Safety Email: SafetyManagement_Oncology@abbvie.com

For any subject safety concerns, please contact the physician listed below:

[redacted] MD PhD
Medical Director
Oncology Global Medical Affairs
AbbVie
Neuhofstrasse 23
CH-6341 Baar
Switzerland

Office/Cell: [redacted]
Fax:
Email:

In emergency situations involving study subjects when the primary Therapeutic Area Medical Director (TA MD) is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated backup AbbVie TA MD:

Phone: +1 (973) 784-6402

The sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with Directive 2001/20/EC. The reference document used for SUSAR reporting in the EU countries will be the most current version of the Investigator's Brochure.

6.1.6 Pregnancy

Pregnancy in a study subject must be reported to AbbVie within 1 working day of the site becoming aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.4.1).

All subjects should be informed that contraceptive measures should be taken throughout the study and for 30 days after the last dose of venetoclax. Male subjects should be informed that contraceptive measures should be taken by their female partners.

Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected. In the event of a pregnancy occurring in the partner of an enrolled subject, written informed consent for release of medical information from the partner must be obtained prior to the collection of any pregnancy-specific information and the pregnancy will be followed to outcome.

Pregnancy in a study subject is not considered an adverse event. The medical outcome of either mother or infant, meeting any serious criteria including an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a serious adverse event and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

6.1.7 Data Monitoring Committee

A Data Monitoring Committee (DMC) will review safety data intermittently according to the DMC charter. Details of the DMC review are presented in the DMC charter. The separate charter has been created to provide detailed descriptions of the schedule of

analyses and the DMC meetings. DMC membership, responsibilities and the description of the data coordinating center are documented in the charter.

6.1.8 Toxicity Management

6.1.8.1 Prophylaxis and Management of Tumor Lysis Syndrome

Venetoclax can cause rapid reduction in tumor and thus poses a risk for TLS in the initial 5-week dose-titration phase. Changes in electrolytes consistent with TLS that require prompt management can occur as early as 6 – 8 hours following the first dose of venetoclax and at each dose increase.

Risk Assessment for tumor lysis syndrome: The risk of TLS is a continuum based on multiple factors, including tumor burden and comorbidities. Subjects with high tumor burden (e.g., any lymph node with a diameter ≥ 5 cm or high absolute lymphocyte count [ALC > 25×10^9/L]) are a greater risk of TLS. Reduced renal function (creatinine clearance [CrCl] < 80 mL/min) further increases the risk. The risk may decrease as tumor burden decreases with venetoclax treatment.

Additional comorbidities may further increase the risk for TLS.

Prior to initiating venetoclax, tumor burden assessment, including radiographic evaluation (refer to Section 5.3.1.1 Study Procedures – CT scans) must be performed for all subjects during Screening. The full blood chemistry/hematology panel (refer to Table 4 Clinical Laboratory Tests) should be performed in all subjects during the Screening period in order to assess eligibility and to correct pre-existing abnormalities.

If the chemistry/hematology panel was assessed more than 72 hours prior to the 1st dose of venetoclax, an additional full lab panel should be performed and reviewed within 72 hours prior to dosing in order to make a treatment decision.

Prophylaxis for tumor lysis syndrome: The prophylaxis measures listed below should be followed. More intensive measures (including hospitalization) should be employed as overall risk increases:

Hydration:

Subjects should be adequately hydrated prior to starting treatment with venetoclax and during the dose-titration phase. The recommended volume is 1.5 to 2.0 L (approximately 6 to 8 glasses) of water each day. Subjects should be instructed to drink water starting 2 days before and on the day of the first dose, and every time the dose is increased. Intravenous (IV) fluids should be administered as indicated based on overall risk of TLS or for those who cannot maintain an adequate level of oral hydration. For subjects for whom volume overload is considered a significant risk, hospitalization should be considered.

Anti-hyperuricemic agents: Anti-hyperuricemic agents should be administered 2 to 3 days prior to starting treatment with venetoclax and may be continued through the titration phase.

Laboratory Assessments:

PRE-DOSE LABS

Prior to the initial dose of venetoclax, for all subjects:

- During the Screening Period: For all subjects, the chemistry/hematology panel (see Table 4 Clinical Laboratory Tests) is required.
    - Pre-existing abnormalities should be corrected
- Within 72 hours of Week 1 Day 1: If the screening labs were more than 72h before the planned first dose, the chemistry/hematology panel should be repeated. These results should be reviewed before dosing.
    - Labs should be assessed and pre-existing abnormalities should be corrected
- On the day of Week 1 Day 1: Before dosing, the chemistry/hematology panel should be drawn. The results of the labs drawn on Week 1 Day 1 need to be reviewed prior to dosing **IF** an additional lab within 72 hours of the initial dose at Week 1 Day 1 was not drawn **AND** reviewed.

Prior to each subsequent dose increase, for all subjects:

- Within 72 hours of each subsequent dose increase: The chemistry/hematology panel should be repeated. The results should be reviewed prior to dose increasing.
- Prior to dosing, on the day of each subsequent dose increase: Before dosing, the chemistry/hematology panel should be drawn. The results of the labs drawn on Day 1 of each dose increase need to be reviewed prior to dosing **IF** an additional lab draw within 72 hours of the dose increase were not drawn **AND** reviewed.

POST-DOSE LABS:

For all subjects, the chemistry/hematology panel (refer to Table 4 Clinical Laboratory Tests) should be monitored at 6 to 8 hours and at 24 hours after the first dose of venetoclax (20 mg) and after the first dose increase (50 mg). Electrolyte abnormalities should be corrected promptly. The next venetoclax doses (Day 2 20 mg venetoclax dose and Day 2 50 mg venetoclax dose) should not be administered until the 24 hour lab results have been evaluated. Electrolyte abnormalities should be corrected promptly. For subjects who continue to be at risk of TLS, the same lab monitoring schedule (i.e., 6 to 8 hour and 24-hr post dose) should be followed at the subsequent dose increases.

This monitoring is also recommended during the re-initiation of the therapy after a dose interruption.

Hospitalization: Based on investigator assessment, some subjects, especially those at greater risk of TLS may require hospitalization on the day of the first dose of venetoclax for more intensive prophylaxis and monitoring through the first 24 hours. Hospitalization should be considered for subsequent dose increases based on reassessment of risk.

6.1.8.2 Dose Modifications Based on Toxicities

Dosing interruption and/or dose reduction may be required. See Table 7 for dose modifications for hematologic and other toxicities related to venetoclax. For subjects who have had a dosing interruption greater than 1 week during the first 5 weeks of dose titration or greater than 2 weeks when at the daily dose of 400 mg, TLS risk should be reassessed to determine if restarting at a reduced dose is necessary (e.g., all or some levels of the dose titration).

Tumor Lysis Syndrome

If a subject experiences blood chemistry changes suggestive of TLS, the following day's venetoclax dose should be withheld. If resolved within 24 to 48 hours of last dose, treatment with venetoclax can be resumed at the same dose. For events of clinical TLS or blood chemistry changes requiring more than 48 hours to resolve, treatment should be resumed at a reduced dose (see Table 7 and Table 8). When resuming treatment with venetoclax after interruption due to TLS, the instructions for Prophylaxis for tumor lysis syndrome should be followed.

Other Toxicities

Treatment with venetoclax should be withheld for any grade 3 or 4 non-haematological, grade 3 or 4 neutropenia with infection or fever, or grade 4 haematological toxicities, except lymphopenia. To reduce the risk of infection associated with neutropenia, granulocyte-colony stimulating factor (G-CSF) may be administered with venetoclax if clinically indicated. Once the toxicity has resolved to grade 1 or baseline level (recovery), therapy with venetoclax may be restarted at the same dose. If the toxicity recurs, and for any subsequent occurrences, the dose reduction guidelines in Table 7 and Table 8 should be followed when resuming treatment with venetoclax following resolution. A larger dose reduction may occur at the discretion of the investigator. For subjects who require dose reductions to less than 100 mg for more than 2 weeks due to adverse events, discontinuation of venetoclax should be considered.

Table 7. Recommended Dose Modifications for Toxicities

Event	Occurrence	Action
Tumor Lysis Syndrome		
Blood chemistry changes or symptoms suggestive of TLS	Any	Withhold the next day's dose. If resolved within 24 – 48 hours of last dose, resume at the same dose.
		For any blood chemistry changes requiring more than 48 hours to resolve, resume at a reduced dose (see Table 8).
		For any events of clinical TLS,[a] resume at a reduced dose following resolution (see Table 8).
Non-Hematologic Toxicities		
Grade 3 or 4 non-hematologic toxicities	1st occurrence	Interrupt venetoclax Once the toxicity has resolved to Grade 1 or baseline level, venetoclax therapy may be resumed at the same dose. No dose modification is required.
	2nd and subsequent occurrences	Interrupt venetoclax. Follow dose reduction guidelines in Table 8 when resuming treatment with venetoclax after resolution. A larger dose reduction may occur at the discretion of the investigator.
Hematologic Toxicities		
Grade 3 or 4 neutropenia with infection or fever; or Grade 4 hematologic toxicities (except lymphopenia)	1st occurrence	Interrupt venetoclax. To reduce the infection risks associated with neutropenia, granulocyte-colony stimulating factor (G-CSF) may be administered with venetoclax if clinically indicated. Once the toxicity has resolved to Grade 1 or baseline level, venetoclax therapy may be resumed at the same dose.
	2nd and subsequent occurrence	Interrupt venetoclax. Consider using G-CSF as clinically indicated. Follow dose reduction guidelines in Table 8 when resuming treatment with venetoclax after resolution. Additional dose reductions may occur at the discretion of the physician.
Consider discontinuing venetoclax for subjects who require dose reductions to less than 100 mg for more than 2 weeks.		

a. Clinical TLS was defined as laboratory TLS with clinical consequences such as acute renal failure, cardiac arrhythmias and/or seizures or sudden death.

Note: Adverse reactions were graded using NCI CTCAE version 4.03.

Table 8. Dose Modification for Toxicity During Venetoclax Treatment

Dose at Interruption, mg	Restart Dose, mg[a]
400	300
300	200
200	100
100	50
50	20
20	10

a. During the dose titration phase, continue the reduced dose for 1 week before increasing the dose.

Dose Modifications for Use with CYP3A Inhibitors

Concomitant use of venetoclax with strong or moderate CYP3A inhibitors increases venetoclax exposure and may increase the risk for TLS at initiation and during the dose-titration phase. Concomitant use of venetoclax with strong CYP3A inhibitors at initiation and during the dose-titration phase is contraindicated.

Concomitant use of venetoclax with moderate CYP3A inhibitors at initiation and during the dose-titration phase should be avoided. Alternative treatments should be considered. If a moderate CYP3A inhibitor must be used, the initiation and titration doses of venetoclax should be reduced by at least 50%. Subjects should be monitored more closely for signs of toxicities.

For subjects who have completed the dose-titration phase and are on a steady daily dose of venetoclax, the venetoclax dose should be reduced by at least 50% when used concomitantly with moderate CYP3A inhibitors and by at least 75% when used concomitantly with strong CYP3A inhibitors. Subjects should be monitored more closely for signs of toxicities. The venetoclax dose that was used prior to initiating the CYP3A inhibitor should be resumed 2 to 3 days after discontinuation of the CYP3A inhibitor.

Missed Dose

If a subject misses a dose of venetoclax within 8 hours of the time it is usually taken, the subject should take the missed dose as soon as possible and resume the normal daily dosing schedule. If a subject misses a dose by more than 8 hours, the subject should not take the missed dose and should resume the usual dosing schedule the following day.

If a subject vomits following dosing, no additional dose should be taken that day. The next prescribed dose should be taken at the usual time the following day.

6.1.8.3 Management of Neutropenia

Nonclinical and clinical experience indicates that venetoclax may cause neutropenia. Subjects with a history of neutropenia who have received multiple prior therapies and/or have significant bone marrow involvement may be at a particularly high risk.

Grade 3 or 4 neutropenia has been reported in subjects treated with venetoclax. Complete blood counts should be monitored throughout the treatment period. Dose interruptions or dose reductions are recommended for subjects with severe neutropenia. Supportive measures including antimicrobials for any signs of infection and prophylactic use of growth factors (e.g., G-CSF) should be considered.

6.1.8.4 Immunization

Live attenuated vaccines should not be administered prior to, during, or after treatment with venetoclax until B-cell recovery occurs. The safety and efficacy of immunization with live attenuated vaccines during or following venetoclax therapy have not been studied. Patients should be advised that vaccinations may be less effective.

6.1.8.5 Management of Hematologic Toxicities Other Than Neutropenia or Lymphopenia

Venetoclax treatment should be withheld for any Grade 4 hematologic toxicity. Once the toxicity has resolved to Grade 1 or baseline level (recovery), venetoclax may be re-started at the same dose. If the toxicity recurs, the dose reduction guidelines in Table 8 should be

followed when resuming study treatment following resolution. Additional dose reductions may occur at the discretion of the physician.

6.1.8.6 Management of Non-Hematologic Toxicity

Venetoclax treatment should be withheld for any clinically relevant ≥ Grade 3 non-hematologic toxicity. Once the toxicity has resolved to Grade 1 or baseline level (recovery), venetoclax may be re-started at the same dose. If the toxicity recurs, the dose reduction guidelines in Table 8 should be followed when resuming study treatment following resolution. Additional dose reductions may occur at the discretion of the physician.

6.2 Product Complaint

6.2.1 Definition

A Product Complaint is any Complaint (see Section 6.0 for the definition) related to the biologic or drug component of the product.

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (example: printing illegible), missing components/product, or packaging issues.

Any information available to help in the determination of causality to the events outlined directly above should be captured.

6.2.2 Reporting

Product Complaints concerning the investigational product must be reported to the Sponsor within 24 hours of the study site's knowledge of the event by entering the product complaint in RAVE, the EDC system. If the EDC system is not operable, the Product Complaint Form should be used and emailed to: RD_PQC_QA@abbvie.com **within 24 hours** of the study site's knowledge of the event. Product Complaints occurring during

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

Product Complaints may require return of the product with the alleged complaint condition. In instances where a return is requested, every effort should be made by the investigator to return the product within 30 days. If returns cannot be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

The description of the complaint is important for AbbVie in order to enable AbbVie to investigate and determine if any corrective actions are required.

7.0 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol unless when necessary to eliminate an immediate hazard to study subjects. The principal investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. If a protocol deviation occurs (or is identified) after a subject has been enrolled, the principal investigator is responsible for notifying Independent Ethics Committee (IEC)/Independent Review Board (IRB) regulatory authorities (as applicable), and their assigned AbbVie Clinical Monitor(s). In addition, the following AbbVie representatives should be contacted:

Primary Contact:

[redacted]
Study Project Manager I
AbbVie Oncology
Clinical Program Development
1 N. Waukegan Rd.
North Chicago, IL 60064
USA

Office: [redacted]
Email: [redacted]

Alternate Contact:

[redacted]
Study Management Associate II
AbbVie Oncology
Clinical Program Development
1 N. Waukegan Rd.
North Chicago, IL 60064
USA

Office: [redacted]
Email: [redacted]

Such contact must be made as soon as possible to permit a review by AbbVie to determine the impact of the deviation on the subject and/or the study.

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

Efficacy analyses will be performed on all subjects enrolled into the study, unless otherwise specified. The date of enrollment is defined as the date that the Interactive Response Technology (IRT) provided a subject number.

Safety analyses will be performed on all subjects who receive at least one dose of venetoclax.

Detailed analysis descriptions will be provided in a separate statistical analysis plan.

8.1.1 Baseline Characteristics

All baseline summary statistics will be based on characteristics prior to the initiation of study drug. Unless otherwise stated, baseline for a given variable will be defined as the last value for that variable obtained prior to the first dose of study drug.

8.1.1.1 Demographics

Descriptive statistics will be provided for baseline demographic variables. Age, height and weight will be summarized with means, medians, standard deviations and ranges. Frequencies and percentages will be provided for gender and race.

8.1.1.2 Medical Histories

Frequencies and percentages will be summarized for each medical history parameter.

8.1.2 Efficacy Endpoints

8.1.2.1 Primary Efficacy Endpoints

The primary efficacy endpoint will be complete remission rate (CR + CRi) of the subjects who have not been previously treated with BCRi therapy defined as the proportion of subjects achieving a CR or CRi as their best response (per the investigator assessment) based on IWCLL NCI-WG criteria.

In addition, the ninety-five percent (95%) confidence interval based on binomial distribution will be constructed for the calculated CR rate.

The assessment of response will be performed when all subjects enrolled have completed their Week 48 disease assessment, or after all enrolled subjects have discontinued venetoclax, whichever is earlier. Subjects who have not achieved complete remission (CR + CRi) prior to this time will be considered to be non-responders in the calculation of CR rate.

8.1.2.2 Secondary Efficacy Endpoints

Key secondary efficacy endpoints will include overall response rate, duration of response, time to progression, progression-free survival, overall survival, and the CR rate in previously BCRi treated subjects.

ORR will be assessed as the proportion of subjects with an overall response (CR + CRi + nPR + PR) based on the IWCLL NCI-WG criteria. The ninety-five percent (95%) confidence interval based on binomial distribution will be constructed for the calculated CR rate.

Duration of response will be defined as the number of days from the date of first response (CR, CRi, nPR, or PR) to the earliest recurrence or PD. If a subject is still responding, then the subject's data will be censored at the date of the subject's last available disease assessment. For subjects who never experience 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. Median duration of response will be calculated and the corresponding 95% confidence interval will be presented.

Time to progression (TTP) will be defined as the number of days from the date of first dose or enrollment if not dosed to the date of earliest disease progression. All disease progression will be included regardless whether the event occurred while the subject was taking the study drug or had previously discontinued the study drug. If the subject does not experience disease progression, then the data will be censored at the date of last available disease assessment. Data for subjects who receive non-protocol, CLL therapy prior to disease progression will be censored at the last disease assessment prior to receiving non-protocol therapy. Data for subjects without any disease assessments performed after the baseline visit will be censored at the time of enrollment plus 1 day. TTP will be analyzed by Kaplan-Meier methodology using data for all subjects enrolled. Median time TTP will be calculated and 95% confidence interval for median time TTP will be presented.

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

assessment. Data for subjects who receive non-protocol CLL therapy prior to disease progression will be censored at the last disease assessment prior to receiving non-protocol therapy. Data for subjects without any disease assessments performed after the baseline visit will be censored at the time of enrollment plus 1 day. PFS will be analyzed by Kaplan-Meier methodology using data for all subjects enrolled. Median time PFS will be calculated and 95% confidence interval for median time PFS will be presented.

Overall survival (OS) will be defined as 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. OS will be analyzed by Kaplan-Meier methodology using data from all enrolled subjects. Median time survival will be estimated and 95% confidence interval for the median time survival will be presented.

The CR rate (CR + CRi) in previously treated BCRi subjects will be assessed based on the 2008 Modified IWCLL NCI-WG criteria. The ninety-five percent (95%) confidence interval based on binomial distribution will be constructed for the calculated CR rate.

8.1.2.3 Exploratory Efficacy Endpoints

The rate of MRD negativity in subjects will be summarized. This rate will be defined as the proportion of subjects who had MRD negativity status. Ninety-five percent (95%) confidence intervals based on the binomial distribution will be provided. In addition, the relationship between venetoclax PK and efficacy parameters including MRD level and CR will be evaluated.

8.1.3 Timing of Efficacy Endpoints and Safety Evaluations

The date the last enrolled subjects has completed their Week 48 disease assessment, or after all enrolled subjects have discontinued venetoclax, whichever is earlier, will be defined as the data "cutoff" date for the efficacy analyses. Efficacy and safety data up to and including this date will be collected. Exact data cutoff date for the efficacy analysis will be detailed in a statistical analysis plan (SAP) which will be signed off prior to the

data cut-off date. During this data collection period, active subjects will continue to receive venetoclax, as applicable. When data collection is complete and all data management quality assurance (QA) and quality control (QC) procedures are performed, the clinical database data will be extracted for documentation and statistical analyses. Any active subjects will continue to receive venetoclax until they discontinue or for up to 2 years. Once the last enrolled subject discontinues/completes the study, the study will be considered complete and all remaining data will be collected and entered into the clinical database.

8.1.4 Additional Efficacy Analyses

Health Economic and Patient Reported Outcome measures will include the FACT-Leu, the FACIT-F, and the EQ-5D-5L.

For the FACT-Leu, scores will be summarized descriptively at each assessment. The impact of treatment on quality of life over time will be assessed by calculating the change in scores from baseline at each assessment time point. Scores will be calculated according to the FACT-Leu scoring manual.

For the FACIT-F, scores will be summarized descriptively at each assessment. The impact of treatment on fatigue over time will be assessed by calculating the change in score from baseline at each assessment time point. Scores will be calculated according to the FACIT-F scoring manual.

Each of the five dimensions of the EQ-5D-5L, the Visual Analog Scale (VAS) and overall utility score will be calculated using the EuroQol scoring manual, and summarized (mean, std. dev., median) at each assessment. The impact of treatment over time will be assessed by calculating the change in score from baseline to each assessment time point.

Alternative statistical analyses may be performed if deemed necessary and helpful in understanding the drug effect.

8.1.5 Safety

The safety of venetoclax will be assessed by evaluating study drug exposure, adverse events, serious adverse events, all deaths, and laboratory parameters.

Safety analyses will be performed for all subjects who take at least one dose of venetoclax.

8.1.5.1 Adverse Events

Analyses of adverse events will include only "treatment-emergent" events, i.e., those that have an onset on or after the day of the first dose of study drug.

Analyses will not include those that have an onset greater than 30 days after the last dose of study drug.

Treatment-emergent adverse events will be summarized by preferred terms within a System and Organ Class according to the most current MedDRA. In addition, the percentage of subjects experiencing an adverse event at a NCI CTCAE toxicity grade, and relationship to study drug will be provided.

8.1.5.2 Serious Adverse Events

Serious adverse events will be summarized using the same methods as Adverse Events described above.

8.1.5.3 Deaths

The number of subject deaths will be summarized (1) for deaths occurring within 30 days of the last dose of study drug, and (2) for deaths occurring more than 30 days of the last dose of study drug.

8.1.5.4 Analyses of Laboratory Data

Where applicable, blood chemistry and hematology determinations will be categorized according to NCI CTCAE version 4.03 grades, and shifts from baseline NCI CTCAE grades to maximum and final post-baseline grades will be assessed.

The baseline and final grades will be defined respectively as the grade of the last measurement collected prior to the first dose of study drug, and as the last post-baseline measurement collected no more than 30 days after the last dose of study drug. The percentage of subjects experiencing a shift from baseline grades of 0 to 2 to maximum post-baseline grades of 3 to 4, and from baseline grades of 0 to 2 to final post-baseline grades of 3 to 4 will be summarized. Detailed listings of data for subjects experiencing NCI CTCAE Grade 3 to 4 blood chemistry and hematology values will be provided. All measurements collected, regardless of the number of days after the last dose of study drug, will be included in these listings.

8.1.6 Pharmacokinetics

Plasma concentrations of venetoclax will be tabulated for each subject.

An analysis of venetoclax plasma concentrations will be performed using a nonlinear mixed-effect population PK modeling approach. The relationship between venetoclax PK and efficacy, including MRD level and CR, will also be evaluated. The results from the population PK analysis and evaluation of efficacy may not be reported within the clinical study report. Additional analyses may be performed if useful in the interpretation of the data.

8.2 Determination of Sample Size

Using the CR rate of 6% reported for current therapies[45] 250 subjects would provide approximately 90% power (based on an exact test for single proportions using a two-sided alpha of 5%) to reject the null hypothesis of 6% in favor of an alternative hypothesis that the CR rate for venetoclax monotherapy is 12% (doubling of the CR rate).

In order to provide approximately 80% power (based on an exact test for single proportions using a two-sided alpha of 5%) to reject the null hypothesis of 6% CR rate in favor of an alternative hypothesis that the CR rate for venetoclax monotherapy is 12% (doubling of the CR rate), the study will enroll 190 subjects who have not been previously treated with BCRi therapy. Since there are approximately a total of 250 subjects, up to 60 subjects previously treated with BCRi therapy can be enrolled.

9.0 Ethics

9.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any amendments to the protocol will require IEC/IRB approval and approval by Regulatory Authority(ies), if required by local regulations, prior to implementation of any changes made to the study design. The investigator will be required to submit, maintain and archive study essential documents according to International Conference on Harmonization (ICH) GCP and all other applicable regulatory requirements.

Any serious adverse events that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required by local regulations. During the conduct of the study, the investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that

affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to AbbVie.

9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, International Conference on Harmonization (ICH) guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the clinical investigator are specified in Appendix A.

9.3 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

Information regarding incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the study can be found in the informed consent form.

In the event a subject withdraws consent to participate from the study, stored biomarker samples will continue to be used for research and analysis. In the event that a subject would like to withdraw consent for research using these samples, the subject may request that their samples be withdrawn. Once AbbVie receives the request, remaining biomarker samples will be destroyed. If the subject changes his/her consent, and the samples have already been tested, those results will still remain as part of the overall research data.

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded on the appropriate source documents. The Investigator Awareness Date (SAE CRF) may serve as the source for this data point. This adverse event data point required for eCRF completion can be entered directly in the eCRF.

The following patient reported outcomes (PRO) assessments will be completed by the subject and will be considered source documentation:

- EQ-5D-5L
- FACT-Leu
- FACIT-F

The investigator(s)/institution(s) will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data documents.

10.2 Case Report Forms

Case report forms (CRF) must be completed for each subject screened/enrolled in this study. These forms will be used to transmit information collected during the study to AbbVie and regulatory authorities, as applicable. The CRF data for this study are being collected with an electronic data capture (EDC) system called Rave® provided by the technology vendor Medidata Solutions Incorporated, NY, USA. The EDC system and the study-specific electronic case report forms (eCRFs) will comply with Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available

through the vendor, Medidata, while the validation of the study-specific eCRFs will be conducted by AbbVie and will be maintained in the Trial Master File at AbbVie.

The investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will be recorded by investigative site personnel in the EDC system. All data entered into the eCRF will be supported by source documentation.

The investigator or an authorized member of the Investigator's staff will make any necessary corrections to the eCRF. All change information, including the date and person performing the corrections, will be available via the audit trail, which is part of the EDC system. For any correction, a reason for the alteration will be provided. The eCRFs will be reviewed periodically for completeness, legibility, and acceptability by AbbVie personnel (or their representatives). AbbVie (or their representatives) will also be allowed access to all source documents pertinent to the study in order to verify eCRF entries. The Principal Investigator will review the eCRFs for completeness and accuracy and provide his or her electronic signature and date to eCRFs as evidence thereof.

PRO data is collected directly onto paper source by the subjects. The completion of these forms is verified by the site staff. The forms are entered into the clinical database and then can be viewed within the EDC system by the site staff.

Medidata will provide access to the EDC system for the duration of the trial through a password-protected method of internet access. Such access will be removed from investigative sites at the end of the site's participation in the study. Data from the EDC system will be archived on appropriate data media (CD-ROM, etc.) and provided to the investigator at that time as a durable record of the site's eCRF data. It will be possible for the investigator to make paper printouts from that media.

11.0 Data Quality Assurance

To ensure data integrity and subject safety, a study monitor will continuously, throughout the study, verify that all subjects sign the informed consent prior to any study specific

procedures being conducted, that the protocol procedures are being followed appropriately, and that the information provided in the eCRF is complete, accurate, and supported by information in source documents. Computer logic and manual checks will be created to identify items such as inconsistent study dates. Any necessary corrections will be made to the eCRF.

12.0 Use of Information

Any research that may be done using research samples from this study will be experimental in nature and the results will not be suitable for clinical decision making or patient management. Hence, the subject will not be informed of individual results, should analyses be performed, nor will anyone not directly involved in this research. Correspondingly, researchers will have no access to subject identifiers. Individual results will not be reported to anyone not directly involved in this research other than for regulatory purposes. Data from research may be provided to investigators and used in scientific publications or presented at medical conventions. Research information will be published or presented only in a way that does not identify any individual subject.

13.0 Completion of the Study

The investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the investigator and AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by both the investigator and AbbVie. The investigator will provide a final report to the IEC/IRB following conclusion of the study, and will forward a copy of this report to AbbVie or their representative.

The investigator must submit, maintain and archive any records related to the study according to ICH GCP and all other applicable regulatory requirements. If the investigator is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

AbbVie will select the signatory investigator from the investigators who participate in the study. Selection criteria for this investigator will include level of participation as well as significant knowledge of the clinical research, investigational drug and study protocol. The signatory investigator for the study will review and sign the final study report in accordance with the European Agency for the Evaluation of Medicinal Products (EMEA) Guidance on Investigator's Signature for Study Reports.

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

14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for venetoclax.
2. I have read this protocol and agree that the study is ethical.
3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.
5. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

Protocol Title:	Open-Label, Single Arm, Phase 3b, Multi-Center Study Evaluating the Efficacy of Venetoclax (ABT-199) in Relapsed/Refractory Subjects with Chronic Lymphocytic Leukemia (CLL) (VENICE I)
Protocol Date:	12 October 2020

Signature of Principal Investigator _____ Date _____

Name of Principal Investigator (printed or typed) _____

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Appendix A. Responsibilities of the Clinical Investigator

Clinical research studies sponsored by AbbVie are subject to the Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement in Section 14.0 of this protocol, the investigator is agreeing to the following:

1. Conducting the study in accordance with the relevant, current protocol, making changes in a protocol only after notifying AbbVie, except when necessary to protect the safety, rights or welfare of subjects.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., independent ethics committee [IEC] or institutional review board [IRB]) review and approval of the protocol and amendments.
4. Reporting adverse experiences that occur in the course of the investigation(s) to AbbVie and the site director.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical investigation and all amendments.

9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.
10. Following the protocol and not make any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
[redacted]	Head of Statistics, Oncology	Statistics
[redacted]	Assistant Medical Director	Medical Affairs
[redacted]	Sr. Medical Director	Safety
[redacted]	Evidence Generation Medical Lead/Director	Medical Affairs
[redacted]	Study Project Manager I	Clinical
[redacted]	Associate Director	Clinical Pharmacology

Appendix C. Sample List of Excluded and Cautionary Medications

Excluded during initiation and the dose-titration phase and Cautionary at 400 mg Steady Daily Dose:
Strong CYP3A inhibitors Boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, elvitegravir/ritonavir, idelalisib*, indinavir, itraconazole, ketoconazole, mibefradil, lopinavir/ritonavir, nefazodone, nelfinavir, ritonavir, paritaprevir/ritonavir combinations, posaconazole, saquinavir, telaprevir, telithromycin, tipranavir/ritonavir, voriconazole
Cautionary
Moderate CYP3A inhibitors Amprenavir, aprepitant, atazanavir, cimetidine, ciprofloxacin, clotrimazole, crizotinib*, cyclosporine*, darunavir/ritonavir, diltiazem[1], erythromycin, fluconazole, fosamprenavir, imatinib*, isavuconazole, tofisopam, verapamil **Strong CYP3A inducers** Avasimibe, carbamazepine, enzalutamine, mitotane, phenytoin, rifampin, St. john's wort **Moderate CYP3A inducers** Bosentan, efavirenz, etravirine, modafinil, nafcillin **Warfarin**** **P-gp substrates** Aliskiren, ambrisentan, colchicine, dabigatran, etexilate, digoxin, everolimus*, fexofenadine, lapatinib*, loperamide, maraviroc, nilotinib*, ranolazine, saxagliptin, sirolimus*, sitagliptin, talinolol, tolvaptan, topotecan* **BCRP substrates** Methotrexate*, mitoxantrone*, irrinotecan*, lapatinib*, rosuvastatin, sulfasalazine, topotecan* **OATP1B1/1B3 substrates** Atrasentan, atorvastatin, ezetimibe, fluvastatin, glyburide, rosuvastatin, simvastatin acid, pitavastatin, pravastatin, repaglinide, telmisartan, valsartan, olmesartan **P-gp inhibitors** Amiodarone, azithromycin, captopril, carvedilol, dronedarone, felodipine, quercetin, quinidine, ronalzine, ticagrelor **BCRP inhibitors** Geftinib*

* These are anticancer agents; consult contact AbbVie TA MD before use.

** Closely monitor the international normalized ratio (INR).

1 Moderate CYP3A inhibitor per venetoclax FDA USPI.

Notes: that this is not an exhaustive list. For an updated list, see the following link:

http://www fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499 htm

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

Appendix D. Study Activities

Screening Through Week 5 Day 2

Activity	Scr[a]	Within 72 Hours of W1 D1	W1 D1	W1 D2	Within 72 Hours of W2 D1	W2 D1	W2 D2	Within 72 Hours of W3 D1	W3 D1	W3 D2	Within 72 Hours of W4 D1	W4 D1	W4 D2	Within 72 Hours of W5 D1	W5 D1	W5 D2
Informed Consent	X															
17p Deletion or TP53 Mutation	X[b]															
Medical History/Oncology History Assessment	X		X													
Pregnancy Test[c]	X		X													
Adverse Event/Concomitant Medication Assessment	X[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination[e]	X		X			X			X			X			X	
TLS Risk Assessment[f]	X															
ECOG Performance Status	X		X													
Coagulation Panel	X															
Hematology/Chemistry[g]	X	X[h]	X[i]	X[j]	X[k]	X[l]	X[j]	X[k]	X[l]	X[m]	X[k]	X[l]	X[m]	X[k]	X[l]	X[m]
Disease Assessments[n]	X															
Contrasted CT or MRI Scan[o]	X															
Bone Marrow Aspirate and Biopsy[p]																
MRD Assessment in Peripheral Blood[q]			X													

Activity	Scr[a]	Within 72 Hours of W1 D1	W1 D1	W1 D2	Within 72 Hours of W2 D1	W2 D1	W2 D2	Within 72 Hours of W3 D1	W3 D1	W3 D2	Within 72 Hours of W4 D1	W4 D1	W4 D2	Within 72 Hours of W5 D1	W5 D1	W5 D2
Venetoclax dispensation and accountability[r]			X	X		X	X		X	X		X	X		X	X
Quality of Life Questionnaires (FACT-Leu, FACIT-Fatigue, EQ-5D-5L)[s]			X									X				

Week 8 Through Post-Treatment Follow-Up

Activity	W8 D1	W12 D1	W16 D1	W20 D1	W24 D1	W28 D1	W32 D1	W36 D1	W40 D1	W44 D1	W48 D1	Every 12 Weeks Starting At W48	Week 108/ Final Visit	30 Day Safety Visit[t]	Post-Treatment Follow-Up[u]
Adverse Event/Concomitant Medication Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Examination[e]*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG Performance Status[v]					X							X	X	X	
Hematology/Chemistry**	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Disease Assessment[n]*					X			X			X				
Contrasted CT or MRI Scan[o]											X				
Bone Marrow Aspirate and Biopsy[p]											X[o]				
MRD Assessment in Peripheral Blood[q]					X						X				
PK sample[w]					X										
Venetoclax dispensation and accountability***	X	X	X	X	X	X	X	X	X	X	X	X	X[y]		
Dispense/Collect Subject Calendars/Diaries				X	X										
Quality of Life Questionnaires (FACT-Leu, FACIT-Fatigue, EQ 5D-5L)[s]		X			X			X			X	X	X		
Collection of Survival Information[x]														X	X

Scr = Screening; W = Wk = Week; D = Day; Post-Treat = Post-Treatment; FV = Final Visit

Study Windows:

* Within 72 hours before or after scheduled visit starting with Week 8 Day 1.

** Within 72 hours prior to scheduled visit starting with Week 8 Day 1.

*** As of Week 8 the visit window for scheduled visits is ± 2 days.

a. Subjects will undergo screening procedures within 28 days prior to the first study drug administration, except where otherwise indicated.

b. Subjects who have 17p deletion or TP53 mutation as assessed by local laboratory (in bone marrow or peripheral blood) may be considered for enrollment. A recent test is desirable but any previous positive test is acceptable. Subjects that do not have the 17p deletion or TP53 mutation or have an unknown status are also eligible.

c. For females of childbearing potential, as defined in the protocol, a urine pregnancy test must be obtained and processed locally at Week 1 Day 1, if it has been > 7 days since obtaining the serum pregnancy results at Screening. During the study, a urine pregnancy test can be performed at the discretion of the investigator or per local guidelines.

d. All protocol-related serious adverse events and nonserious adverse events must be collected from the signing of the study-specific informed consent until study drug administration.

e. A complete physical examination will be performed at Screening. A symptom directed physical examination may be performed as needed. Refer to Section 5.3.1.1 Physical Examination, for more details.

f. For subjects who have a dose interruption lasting more than 1 week during the first 5 weeks of dose-titration or more than 2 weeks when at the daily dose of 400 mg, the TLS risk should be reassessed to determine if restarting at a reduced dose is necessary.

g. All clinical laboratory tests will be analyzed by the local laboratory. Required tests are listed in Table 4 Clinical Laboratory Tests, refer to Section 5.3.1.1 Study Procedures, sub header Hematology and Chemistry as well as Section 6.1.8 Toxicity Management, for more details.

h. For all subjects, if the screening labs were done more than 72 hours before the planned first dose, the chemistry/hematology panel should be repeated and results reviewed prior to the initial dose in order to make a treatment decision. Labs should be assessed and pre-existing abnormalities should be corrected.

i. For all subjects, on the day of Week 1 Day 1, before dosing, the chemistry/hematology panel should be collected. The results of the labs drawn on Week 1 Day 1 need to be reviewed prior to dosing **IF** an additional lab within 72 hours of the initial dose at Week 1 Day 1 was not drawn **AND** reviewed.

j. For all subjects, the chemistry/hematology panel should be monitored at 6 to 8 hours and at 24 hours after the first dose of venetoclax (20 mg) and after the first dose increase (50 mg). The next venetoclax doses should not be administered until the 24 hour lab results have been evaluated. Electrolyte abnormalities should be corrected promptly. Note: There is a ± 2 hour window around the 24 hour lab draw.

k. For all subjects, within 72 hours of each subsequent dose increase, the chemistry/hematology panel should be repeated. The results should be reviewed prior to dose increasing.

l. Prior to dosing, on the day of each subsequent dose increase, the chemistry/hematology panel is required. The results of the labs drawn on Day 1 of each dose increase need to be reviewed prior to dosing **IF** additional labs within 72 hours of the dose increase were not drawn **AND** reviewed.

m. For subjects who continue to be at risk of TLS, the same lab monitoring schedule of 6 to 8 hour and 24-hr post dose should be followed at the subsequent dose increases. Note: There is a ± 2 hour window around the 24 hour lab draw.

n. All measurable disease must be documented at Screening by laboratory testing, physical examination and CT scans (or MRI if CT is medically contraindicated); bone marrow examinations are not required at screening but results will be recorded if available. All baseline evaluations should be performed as closely as possible to the beginning of treatment. For all subsequent disease assessments, disease response will be assessed by the investigator based on the analysis of clinical laboratory tests (hematology) and a complete physical examination at Week 24, Week 36 and Week 48.

o. CT scans with contrast (or MRI if CT is medically contraindicated) should include neck, chest, abdomen and pelvic sequences can be accepted if previously performed within 35 days prior to the initial venetoclax dose. Otherwise, CT scans (or MRI) must be performed within the 28 day screening period. To confirm response, a CT scan (or MRI) must be performed at Week 48 for all subjects. CT scans (or MRI) may be performed 7 days prior to the scheduled Week 48 visit. If a subject exhibits clinical signs of possible disease progression (i.e., increased or de novo enlargement of liver, spleen or lymph nodes on physical examination) without an increase in lymphocytes meeting the progression of disease criteria, then additional assessments including contrast-enhanced CT scan and/or bone marrow can be performed to confirm or rule out disease progression. Refer to Section 5.3.1.1 Computed Tomography Scans and Disease Assessments, for more details. For patients with only Partial Remission at Week 48, an additional CT and a bone marrow examination can be done between Week 48 and Week 108 to confirm CR if there is a possibility that a patient is in Complete Remission based on laboratory tests and a disease assessment physical exam.

p. For determination of complete remission (CR), the CT scan and bone marrow are required to be negative, per the IWCLL NCI-WG guidelines. If the subject achieves a CR by clinical criteria and confirmatory CT scan, a bone marrow aspirate and biopsy will be performed to confirm the CR. Whenever possible the bone marrow aspirate for biomarker MRD assessment should be split from this sample. Refer to Section 5.3.1.1 Disease Assessments and Bone Marrow Aspirate and Biopsy, for more details.

q. MRD will be assessed by using peripheral blood at Week 1 Day 1 (baseline), Week 24 and Week 48. Refer to Section 5.3.1.1 and Section 5.3.1.2 for more details. When confirming a complete remission (CR + CRi) status per 2008 Modified IWCLL NCI-WG criteria with a bone marrow biopsy and aspirate. The aspirate should be split and a sample sent to the central laboratory for MRD analysis.

r. Venetoclax tablets should be taken orally once daily with a meal and water in the morning at approximately the same time each day. Dosing may occur at study visits on Week 1 Days 1 & 2 through Week 5 Days 1 & 2.

s. The Quality of Life Questionnaires should be administered and completed prior to any other study procedures being performed at these visits. Refer to Section 5.3.7, Health Economic and Patient-Reported Outcome Measures, for further information.

t. 30-Day Safety Follow-up visit should occur approximately 30 days (± 3 days) after the last dose of venetoclax.

u. Upon discontinuation of study drug treatment, survival information (i.e., the date/cause of death, post treatment cancer therapies, etc.) will be collected every 6 months (± 7 days) for a period of 2 years.

v. ECOG performance status may be performed within 72 hours before or after the scheduled visit starting with Week 24.

w. Collect (immediately) prior to venetoclax dosing (0 hour) on Week 24 Day 1. The date and time (to the nearest minute) the venetoclax doses were taken, and whether or not the venetoclax doses were taken with a meal, will be recorded on the eCRF for the Week 24 Day 1 venetoclax PK day and for the 2 days prior to the Week 24 Day 1.

x. Survival information includes i.e., the date/cause of death, post treatment cancer therapies, etc.

y. In countries where venetoclax is not commercially available, subjects who continue to derive benefit after 2 years of treatment may be able to extend their treatment for up to 2 additional years AbbVie will work with the investigator on a case by case basis to consider the potential continuation of venetoclax therapy. Subjects who participate in the 2 year Extended Access phase will have study drug assigned at Week 108. For patients that are not participating in the 2 year Extended Access phase, the Week 108 visit is the Final visit. The specific study assessments to be performed at the Extended Access visits are detailed in Appendix E, Study Activities.

Appendix E. Schedule of Extended Access Phase*

Procedure	Week 108	Week 120	Week 132	Week 144	Week 156	Week 168	Week 180	Week 192	Week 204	Week 216	Week 228	Week 240	Week 252	Week 264	Final Visit	30 Day Safety Visit[d]	Post Treatment Follow up[e]
Vital signs**	X														X	X	
Physical Examination[a]**	X														X	X	
ECOG Performance Status**	X														X	X	
Hematology/ Chemistry***	X														X	X	
Adverse Event/ Concomitant Medication Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Venetoclax dispensation and accountability****	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Collection of Survival Information[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life Questionnaires (FACT-Leu, FACIT-Fatigue, EQ-5D-5L)[c]	X																

* In countries where venetoclax is not commercially available, subjects who continue to derive benefit after 2 years of treatment may be able to extend their treatment for up to 2 additional years. AbbVie will work with the investigator on a case by case basis to consider the potential continuation of venetoclax therapy.

** Within 72 hours before or after scheduled visit.

*** Within 72 hours prior to scheduled visit.

****The visit window for scheduled visits is ± 2 days.

a. Refer to Section 5.3.1.1 Physical Examination, for more details.

b. Survival information includes i.e., the date/cause of death, post treatment cancer therapies, etc.

c. The Quality of Life Questionnaires should be administered and completed prior to any other study procedures being performed at these visits. Refer to Section 5.3.7, Health Economic and Patient-Reported Outcome Measures, for further information.

d. 30-Day Safety Follow-up visit should occur approximately 30 days (± 3 days) after the last dose of venetoclax.

e. Upon discontinuation of study drug treatment, survival information (i.e., the date/cause of death, post treatment cancer therapies, etc.) will be collected every 6 months (± 7 days) for a period of 2 years.

Appendix F. Schedule of Biomarker Collection

Sample Collections (Sample Type)	Week 1 Day 1	Week 24 Day 1	Week 48 Day 1	Confirmation of CR/CRi	Comments
MRD Assessment					
Peripheral Blood	X	X	X	X	12 mL, EDTA Tube, Ship DOC
Bone Marrow Aspirate[a]				X	2 – 3 mL, EDTA Tube, Ship DOC

a. Whenever possible the bone marrow aspirate should be split and a sample sent to the central laboratory for biomarker MRD analysis.

Appendix G. Definitions of Laboratory and Clinical Tumor Lysis Syndrome

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

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 failure probably or definitely caused by hypocalcemia
Acute kidney injury‡	Not applicable	Increase in the serum creatinine level of 0.3 mg/dL (26.5 µmol/liter) (or a single value > 1.5 times the upper limit of the age-appropriate normal range if no baseline creatinine measurement is available) or the presence of oliguria, defined as an average urine output < 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 defined as an increase in the creatinine level of at least 0.3 mg per deciliter (26.5 µmol per liter) or a period of oliguria lasting 6 hours or more. By definition, if acute kidney injury is present, the subject has clinical tumor lysis syndrome. Data about acute kidney injury from Levin et 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.

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

Section 1: First Dose of Venetoclax or Dose Escalation

- Within the first 24 hours after either the first dose or dose escalation, if any laboratory criteria below are met, the subject should be hospitalized for monitoring and the investigator notified. No additional venetoclax doses should be administered until resolution. Rapidly rising serum potassium is a medical emergency.
- Nephrology (or other acute dialysis service) should be contacted/consulted (per institutional standards to ensure emergency dialysis is available) on admission for any subject hospitalized prophylactically or in response to laboratory changes.
- IV fluids (e.g., D5 1/2 normal saline) should be initiated at a rate of at least 1 mL/kg/hr rounded to the nearest 10 mL (target 150 to 200 mL/hr; not < 50 mL/hr). Modification of fluid rate should also be considered for individuals with specific medical needs.
- Monitor for symptoms or signs of TLS (e.g., 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 in the table below, for subjects 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.

Abnormality	**Management Recommendations**
Hyperkalemia (Including Rapidly Rising Potassium)	
Potassium ≥ 0.5 mmol/L increase from prior value (even if potassium within normal limits [WNL])	• Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. If further ≥ 0.2 mmol/L increase in potassium, but still < upper limit of normal (ULN), manage as per potassium ≥ ULN. Otherwise recheck in 1 hour. • Resume per protocol testing if change in potassium is < 0.2 mmol/L, and potassium < ULN, and no other evidence of tumor lysis. • At 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.
Potassium > upper limit of normal	• 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. o If potassium < ULN 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 1, 2 and 4 hrs., if no other evidence of tumor lysis.

Abnormality	Management Recommendations
Potassium ≥ 6.0 mmol/L (6.0 mEq/L) and/or symptomatic (e.g., muscle cramps, weakness, paresthesias, nausea, vomiting, diarrhea)	• Perform STAT ECG and commence telemetry. • Nephrology (or other acute dialysis service) assessment with consideration of initiating dialysis. • Administer Kayexalate 60 g (or Resonium A 60 g). • Administer furosemide 20 mg IV × 1. • Administer insulin 0.1 U/kg IV + D25 2 mL/kg IV. • Administer sodium bicarbonate 1 to 2 mEq/kg IV push. o If sodium bicarbonate is used, rasburicase should not be used as this may exacerbate calcium phosphate precipitation. • Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. Do not administer in same IV line as sodium bicarbonate. • Recheck potassium, phosphorus, uric acid, calcium and creatinine every hour STAT.
Hyperuricemia	
Uric acid ≥ 8.0 mg/dL (476 µmol/L)	• Consider rasburicase* (dose based on local guidelines and/or institutional standards). o If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hr STAT.
Uric acid ≥ 10 mg/dL (595 µmol/L) OR Uric acid ≥ 8.0 mg/dL (476 µmol/L) with 25% increase and creatinine increase ≥ 0.3 mg/dL (≥ 0.027 mmol/L) from pre-dose level	• Administer rasburicase* (dose based on local guidelines and/or institutional standards). o 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. o If uric acid < 8.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hrs., later, if no other evidence of tumor lysis.
Calcium ≤ 7.0 mg/dL (1.75 mmol/L) AND Subject symptomatic (e.g., muscle cramps, hypotension, tetany, cardiac arrhythmias)	• Administer calcium gluconate 50 to 100 mg/kg IV slowly with ECG monitoring. • Telemetry. • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hr STAT. o If calcium normalized 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hrs., later, if no other evidence of tumor lysis. • Calculate corrected calcium and check ionized calcium if albumin low.

Abnormality	Management Recommendations
Hyperphosphatemia	
Phosphorus ≥ 5.0 mg/dL (1.615 mmol/L) with ≥ 0.5 mg/dL (0.16 mmol/L) increase	• Administer a phosphate binder (e.g., aluminum hydroxide, calcium carbonate, sevelamer hydroxide, or lanthanum carbonate). • Nephrology (or other acute dialysis service) notification (dialysis required for phosphorus ≥ 10 mg/dL). • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hr STAT. ○ If phosphorus < 5.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hrs., later, if no other evidence of tumor lysis.
Creatinine	
Increase ≥ 25% from baseline	• Start or increase rate of IV fluids. • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 to 2 hours STAT.

* Check rasburicase label for contraindications.

Section 2: Ongoing Dosing of Venetoclax

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

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

- For potassium, admit subject 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 table).
- 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).

Appendix I. Adverse Events Commonly Associated with CLL Study Population and/or Progression of CLL

Disease-Related Events – CLL

Lymphadenopathy

Splenomegaly

Hepatomegaly

Leukemia cutis (macules, papules, plaques, nodules, ulcers, or blisters) Lymphocytosis

Cytopenias (neutropenia, anemia and thrombocytopenia)

Febrile neutropenia

Autoimmune hemolytic anemia

Autoimmune thrombocytopenia

Hypogammaglobulinemia

Infections (bacterial, viral, and fungal)

Second primary cancers, all types Fatigue

Unexplained weight loss

Pyrexia

Bruising

Minor hemorrhages

Pain, all types

Malignant neoplasm progression, including death

Population-Related Comorbidities

Hypertension

Rheumatoid arthritis/osteoarthritis

Hyperlipidemia

Peptic ulcer

Inflammatory bowel disease

Coronary artery disease

Peripheral vascular disease

Cardiomyopathy

Valvular disease

Atrial fibrillation

Diabetes mellitus

Chronic obstructive pulmonary disease

Cerebrovascular accident

Transient ischemia attack

Appendix J. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes:

Section 1.0 Title Page
"Sponsor/Emergency Contact:" previously read:

Sponsor/Emergency Contact:	[redacted], MD, PhD Medical Director, Oncology Global Medical Affairs AbbVie Neuhofstrasse 23 CH-6341 Baar Switzerland	Phone: [redacted] Fax: Email:
	AND	
	[redacted] MD Associate Medical Director AbbVie 26525 North Riverwoods Blvd. Mettawa, IL 60060 USA	Phone: [redacted] Email:

Has been changed to read:

Sponsor/Emergency Contact:	[redacted] MD Assistant Medical Director, Oncology Global Medical Affairs AbbVie 26525 North Riverwoods Blvd. Mettawa, IL 60045 USA	Phone: [redacted] Email:
	[redacted] MD Associate Medical Director AbbVie 26525 North Riverwoods Blvd. Mettawa, IL 60060 USA	Phone: [redacted] Email:

Section 1.2 Synopsis
Subsection Methodology:
First paragraph
Add: new eleventh sentence

If a subject in the extended access phase of this study continues to derive benefit from Venetoclax after the 2-year extension, then per PI's assessment, subjects who are transferring to the venetoclax extension study, Study M19-388, may remain in Extended Access for up to additional 1 year or until the extension study is approved and initiated at the site, whichever is sooner.

Section 1.2 Synopsis
Subsection Duration of Treatment:
Last paragraph
Add: new second and third sentence

If a subject in the extended access phase of this study continues to derive benefit after the 2-year extension and venetoclax is still not commercially available in their country, they may continue their treatment for 1 additional year. Per PI's assessment, subjects who are unable to transfer to the venetoclax extension study, Study M19-388, may remain in Extended Access for the additional 1 year or until the extension study is approved and initiated at the site, whichever is sooner.

Section 5.3.1.1 Study Procedures
Subsection Extended Access Phase
First paragraph
Add: new second sentence

If a subject in the extended access phase of this study continues to derive benefit from Venetoclax after the 2-year extension, then per PI's assessment, subjects who are transferring to the venetoclax extension study, Study M19-388, may remain in Extended Access for up to additional 1 year or until the extension study is approved and initiated at the site, whichever is sooner.

Appendix B. List of Protocol Signatories

Previously read:

Name	Title	Functional Area
[redacted]	Assistant Director	Statistics
[redacted]	Medical Director	Medical Affairs
[redacted]	Sr. Medical Director	Safety
[redacted]	Group Project Director	Clinical
[redacted]	Study Project Manager I	Clinical
[redacted]	Associate Director	Clinical Pharmacology

Has been changed to read:

Name	Title	Functional Area
[redacted]	Head of Statistics, Oncology	Statistics
[redacted]	Assistant Medical Director	Medical Affairs
[redacted]	Sr. Medical Director	Safety
[redacted]	Evidence Generation Medical Lead/Director	Medical Affairs
[redacted]	Study Project Manager I	Clinical
[redacted]	Associate Director	Clinical Pharmacology

Appendix E. Schedule of Extended Access Phase*
Previously read:

Procedure	Week 108	Week 120	Week 132	Week 144	Week 156	Week 168	Week 180	Week 192	Week 204	Week 216/ Final Visit	30 Day Safety Visit[d]	Post Treatment Follow up[e]
Vital signs**	X									X	X	
Physical Examination[a]**	X									X	X	
ECOG Performance Status**	X									X	X	
Hematology/Chemistry***	X									X	X	
Adverse Event/Concomitant Medication Assessment	X	X	X	X	X	X	X	X	X	X	X	X
Venetoclax dispensation and accountability****	X	X	X	X	X	X	X	X	X			
Collection of Survival Information[b]	X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life Questionnaires (FACT-Leu, FACIT-Fatigue, EQ-5D-5L)[c]	X											

* In countries where venetoclax is not commercially available, subjects who continue to derive benefit after 2 years of treatment may be able to extend their treatment for up to 2 additional years. AbbVie will work with the investigator on a case by case basis to consider the potential continuation of venetoclax therapy.

** Within 72 hours before or after scheduled visit.

*** Within 72 hours prior to scheduled visit.

****The visit window for scheduled visits is ± 2 days.

a. Refer to Section 5.3.1.1 Physical Examination, for more details.

b. Survival information includes i.e., the date/cause of death, post treatment cancer therapies, etc.

c. The Quality of Life Questionnaires should be administered and completed prior to any other study procedures being performed at these visits. Refer to Section 5.3.7, Health Economic and Patient-Reported Outcome Measures, for further information.

d. 30-Day Safety Follow-up visit should occur approximately 30 days (± 3 days) after the last dose of venetoclax.

e. Upon discontinuation of study drug treatment, survival information (i.e., the date/cause of death, post treatment cancer therapies, etc.) will be collected every 6 months (± 7 days) for a period of 2 years.

Has been changed to read:

Procedure	Week 108	Week 120	Week 132	Week 144	Week 156	Week 168	Week 180	Week 192	Week 204	Week 216	Week 228	Week 240	Week 252	Week 264	Final Visit	30 Day Safety Visit[d]	Post Treatment Follow up[e]
Vital signs**	X														X	X	
Physical Examination[a]**	X														X	X	
ECOG Performance Status**	X														X	X	
Hematology/ Chemistry***	X														X	X	
Adverse Event/ Concomitant Medication Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Venetoclax dispensation and accountability****	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Collection of Survival Information[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality of Life Questionnaires (FACT-Leu, FACIT-Fatigue, EQ-5D-5L)[c]	X																

* In countries where venetoclax is not commercially available, subjects who continue to derive benefit after 2 years of treatment may be able to extend their treatment for up to 2 additional years. AbbVie will work with the investigator on a case by case basis to consider the potential continuation of venetoclax therapy.

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*** Within 72 hours prior to scheduled visit.

****The visit window for scheduled visits is ± 2 days.

a. Refer to Section 5.3.1.1 Physical Examination, for more details.

b. Survival information includes i.e., the date/cause of death, post treatment cancer therapies, etc.

c. The Quality of Life Questionnaires should be administered and completed prior to any other study procedures being performed at these visits. Refer to Section 5.3.7, Health Economic and Patient-Reported Outcome Measures, for further information.

d. 30-Day Safety Follow-up visit should occur approximately 30 days (± 3 days) after the last dose of venetoclax.

e. Upon discontinuation of study drug treatment, survival information (i.e., the date/cause of death, post treatment cancer therapies, etc.) will be collected every 6 months (± 7 days) for a period of 2 years.