

abbvie Venetoclax (ABT-199, GDC-0199)
M15-889 Protocol Amendment 3
EudraCT 2016-001097-15

1.0 Title Page

Clinical Study Protocol M15-889

Open-Label, Single Arm, Phase 3b, Multi-Center Study Evaluating the Impact of Venetoclax on the Quality of Life of Relapsed/Refractory Subjects with Chronic Lymphocytic Leukemia (CLL) (VENICE II)

Incorporating Amendment 1, 2, and 3

AbbVie Investigational Product: Venetoclax (ABT-199, GDC-0199)

Date: 09 October 2018

Development Phase: 3b

Study Design: Open-label, single arm, phase 3B, multi-center study

EudraCT Number: 2016-001097-15

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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.

Confidential Information

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1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	04 May 2016
Amendment 1	11 July 2016
Amendment 2	30 January 2018

The purpose of this amendment is to:

- Revise Section 1.0 – Title page.
Rationale: To update new TA/MD name and contact information and back up TA/MD name and contact information.
- Revise Section 1.3 - List of Abbreviations and terms of definitions.
Rationale: To change 'absolute lymphocyte count' to 'Absolute Lymphocyte Count' with initial capital letters to be consistent with the other abbreviations.
Rationale: To correct 'Bone Marrow' to BM. It was inadvertently previously listed as BIM.
Rationale: To correct 'Bcl-2 interacting mediator' to BIM. It was inadvertently previously listed as BM.
Rationale: To add 'Bcl-2' (B-Cell Lymphoma 2) to list of abbreviations. It was inadvertently not listed previously.
Rationale: To delete Serum Glutamic Pyruvic Transaminase from the list of abbreviations since this abbreviation is not mentioned in the protocol.
- Revise Section 3.0 Introduction - Venetoclax Clinical Data
Rationale: To update the Venetoclax Clinical Data section to align with the most recent version of the Investigator's Brochure.
- Update Section 5.1, fourth paragraph.
Rationale: To add $a \pm 2$ day visit window as of Week 8.
- Update Section 5.1, sixth paragraph.
Rationale: To clarify that Bone Marrow samples will be collected for subjects with Complete Response to confirm response.

- Update Section 5.1, twelfth paragraph.
Rationale: *To add that in countries where venetoclax is commercially available extension of therapy may not be allowed.*
- Revise Section 5.3.1.1 - Study Procedures - Physical Examination (Disease Assessment).
Rationale: *To remove the requirement to evaluate lymph nodes at physical examinations at visits other than Screening and Weeks 24, 36 and 48.*
- Revise Section 5.3.1.1 - Study Procedures - Disease Assessments (2008 Modified IWCLL NCI-WG Criteria) - first paragraph.
Rationale: *To clarify that Bone marrow examinations at screening are not required but results will be recorded if available.*
- Revise Section 5.3.1.1 - Study Procedures - Disease Assessments (2008 Modified IWCLL NCI-WG Criteria) - third paragraph and Section 5.3.2.1 Primary Variables.
Rationale: *To clarify that if the CT is negative a bone marrow biopsy will be obtained to confirm clinical response. If a CT scan is performed and does not confirm a clinical response, a bone marrow biopsy should not be obtained.*
- Revise Section 5.3.1.1 - Study Procedures - Disease Assessments (2008 Modified IWCLL NCI-WG Criteria) - last paragraph.
Rationale: *To add that 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 Complete Response if there is a possibility that a patient is in Complete Remission based on laboratory tests and a disease assessment physical examination.*
- Revise Section 5.3.1.1 - Study Procedures - 30 Day Safety Visit.
Rationale: *To clarify that 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 \leq Grade 1 or baseline or it is the investigator's judgment that the event is unlikely to resolve.*
- Revise Section 5.3.1.1 - Study procedures - Extended Access Phase- and Synopsis - Methodology - Duration of Treatment.

Rationale: *To add a new paragraph on the Extended Access Phase to explain that 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. The specific study assessments to be performed during these visits are detailed in Appendix E.*

- Revise Section 5.4.1 - Discontinuation of individual subjects.

Rationale: *Clarify that each subject has the right to withdraw from the study and/or study drug treatment at any time.*

Rationale: *Update the pregnancy verbiage to be in line with AbbVie's latest standard pregnancy language.*

- Revise Section 5.4.1 - Post treatment follow up calls.

Rationale: *To clarify that subjects will be followed for survival information every 6 months even if subjects had an event of progression, they require alternate therapy, etc.*

- A window (± 7 days) was added to the post treatment calls.
- Revise Section 6.1.8 - Data Monitoring Committee and Synopsis - Methodology.

Rationale: *To explain that the Data Monitoring Committee (DMC) will review the 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.*

- Revise Section 6.1.9.2 - Dose Modifications Based on Toxicities - Table 7.

Rationale: *To revise the footnote "a." for clinical TLS to explain that Clinical TLS was defined as laboratory TLS with clinical consequences such as acute renal failure, cardiac arrhythmias, sudden death, and/or seizures.*

- Revise Section 15.0 - Reference list.

Rationale: *To add a reference for current version of Investigator's Brochure and remove the reference for Investigator's Brochure version 8.*

- Revise Appendix D study activities.

Rationale: *To add that Adverse Event/Concomitant medication assessment is to be done also at the following visits: within 72 hours of W2 D1, W3 D1, W4 D1 and W5 D1.*

Rationale: *To separate the study activities list for Extended Access Visits from the main study activities list [Appendix D](#). Appendix D is created to capture the main study activities and Appendix E is created to capture the Extended Access Study Activities.*

Rationale: *To be consistent with the changes and updates throughout the protocol.*

- Incorporate additional administrative changes.

An itemized list of all changes made to the protocol under this amendment can be found in [Appendix I](#).

1.2 Synopsis

AbbVie Inc.	Protocol Number: M15-889
Name of Study Drug: Venetoclax (ABT-199, GDC-0199)	Phase of Development: 3b
Name of Active Ingredient: Venetoclax	Date of Protocol Synopsis: 09 October 2018
Protocol Title: Open-Label, Single Arm, Phase 3b, Multi-Center Study Evaluating the Impact of Venetoclax on the Quality of Life of Relapsed/Refractory Subjects with Chronic Lymphocytic Leukemia (CLL) (VENICE II)	
Objectives: Primary Objective: The primary objective of this study is to evaluate the impact of venetoclax monotherapy on the quality of life of subjects with relapsed or refractory chronic lymphocytic leukemia (CLL). Quality of life will be assessed by the Global Health Status/Quality of Life (GHS/QoL) subscale of the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30). Secondary Objectives: The secondary objectives are to evaluate the impact of venetoclax monotherapy on quality of life based on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Chronic Lymphocytic Leukemia Module (EORTC QLQ-CLL16), EuroQoL 5 Dimension 5 Level Questionnaire (EQ-5D-5L), and the remaining subscales/items from the EORTC QLQ-C30; overall response rate (ORR); complete remission rate (CR + CRi); duration of overall response (DOR), time to progression (TTP), duration of progression-free survival (PFS); overall survival (OS); and CR rate in BCRi treated subjects. The safety and tolerability of venetoclax in subjects with relapsed/refractory CLL will also be evaluated.	
Investigators: Multi-center	
Study Sites: Approximately 43 sites in Latin America, Eastern Europe, and Asia-Pacific.	
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 200 subjects	

Methodology:

This is a Phase 3b, single arm, open-label, multi-center study evaluating the impact of venetoclax on the quality of life of subjects with relapsed/refractory 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. Quality of life assessments will be performed within 72 hours prior to the first dose of venetoclax, and at Week 4, Week 8, Week 12, Week 24, Week 36, and Week 48, then every 12 weeks thereafter until the end of study treatment (Week 108). A Disease Assessment for clinical response by physical exam and hematologic assessments will be performed at Week 24, Week 36 and Week 48. To confirm the response, a CT scan will be performed at Week 48 on all subjects. 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 a bone marrow (BM) biopsy and 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 \geq 18 years.
2. Eastern Cooperative Oncology Group (ECOG) performance score of \leq 2.
3. Subject has relapsed/refractory disease (received at least one 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 $> 5 \times 10^9/L$ 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.
5. Adequate bone marrow function as follows:
 - hemoglobin \geq 8.0 g/dL
 - platelets $\geq 25,000/mm^3$ 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:	<p>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.</p> <p>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.</p>
Criteria for Evaluation:	<p>Quality of Life: Quality of life will be assessed based on patient-reported outcome (PRO) measures, including the EORTC QLQ-C30, EORTC QLQ-CLL16, and EQ-5D-5L.</p> <p>Efficacy: Disease response will be assessed by the investigator, based on laboratory results, physical examinations, using the 2008 modified IWCLL NCI-WG Criteria for Tumor Response including CT imaging (or MRI in the case CT is medically contraindicated) and bone marrow biopsy and aspirate for subjects with CR to confirm the response.</p> <p>All measurable disease must be documented at Screening (baseline) 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.</p> <p>Safety: Adverse event monitoring, vital signs, physical examination, and laboratory assessments will be evaluated.</p>

Statistical Methods:

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).

Study Variables:

Quality of Life:

Quality of life will be evaluated by assessing change from baseline (within 72 hours prior to the first dose of venetoclax) to Week 48 in the GHS/QoL subscale of the EORTC QLQ-C30 (primary endpoint). Quality of life will be further evaluated by analyzing all multi-item scales and single-item scales from the EORTC QLQ-C30, EORTC QLQ-CLL16, and EQ-5D-5L. Scores will be calculated based on the scoring manual for each instrument.

Efficacy Analyses Include:

The following efficacy endpoints will be analyzed: Complete Remission rate (CR + CRi), Overall Response Rate (ORR), Duration of Overall Response (DOR), Time to Progression (TTP), 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 Overall 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 or death. 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 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.

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.

Statistical Methods (Continued):

Sample Size Estimation:

An improvement in the EORTC QLQ-C30 GHS/QoL subscale of 5 units is considered to be a clinically meaningful difference to subjects. From a prior study of venetoclax monotherapy in 17p del R/R CLL subjects (Study M13-982), the standard deviation was approximately 20.5 for the GHS/QoL subscale. Using a one-sided alpha of 0.025, 90% power, and a standard deviation of 20.5; 177 subjects are required to reject the null hypothesis in favor of the alternative hypothesis that venetoclax improves GHS/QoL by at least 5 units. To account for potential drop-outs at Week 48, a total of 200 subjects to be dosed.

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.

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
ASCO	American Society of Clinical Oncology
AST	Aspartate transaminase
aPTT	Activated Partial Thromboplastin Time
BAK	BCL-2 Antagonist/Killer
BAX	Bcl-2 associated X protein
Bcl	B-Cell Lymphoma
Bcl-2	B-Cell Lymphoma 2
Bcl-w	B-Cell Lymphoma protein W
Bcl-XL	B-Cell lymphoma-extra large
BCR	B-Cell receptor
BCRi	B-Cell receptor inhibitor
BCR PI	B-cell receptor pathway inhibitor
BH	Bcl-2 Homology
β -hCG	Beta-human chorionic gonadotropin
BM	Bone marrow
BIM	Bcl-2 interacting mediator
BUN	Blood Urea Nitrogen
CD	Cluster of differentiation
CLL	Chronic Lymphocytic Leukemia
CI	Confidence interval
cm	Centimeter
CR	Complete Remission
CRi	Complete Remission with Incomplete Marrow Recovery
CT	Computed Tomography
CTLS	Clinical Tumor Lysis Syndrome

CYP3A	Cytochrome P450 3A
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DOR	Duration of Overall Response
eCCr	Estimated creatinine clearance rate using Cockcroft-Gault Formula
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EMA	European Agency for the Evaluation Medicinal Products
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire
EORTC QLQ-CLL16	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Chronic Lymphocytic Leukemia Module
EQ-5D-5L	EuroQoL 5 Dimension 5 Level Questionnaire
EU	European Union
FL	Follicular Lymphoma
G-CSF	Granulocyte-colony stimulating factor
GCP	Good Clinical Practice
GDC-0199	Venetoclax (ABT-199)
g/dL	Grams per deciliter
GHS	Global Health Status
GM-CSF	Granulocyte macrophage colony-stimulating factor
HBs	Hepatitis B surface
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDPE	High Density Polyethylene
HIV	Human Immunodeficiency Virus
Hr	Hour
HR	Hazard Ratio
HRQoL	Health-related quality of life
ICH	International Conference on Harmonisation
ICSR	Individual case safety report
IEC	Independent Ethics Committee
IMP	Investigational medicinal product
INR	International Normalized Ratio

IRB	Institutional Review Board
IRT	Interactive Response Technology
ITP	Idiopathic thrombocytopenic purpura
IUD	Intrauterine device
IV	Intravenous
IVIG	Intravenous immunoglobulins
IWCLL NCI-WG	2008 Modified International Workshop on Chronic Lymphocytic Leukemia National Cancer Institute-Working Group Guidelines
kg	Kilogram
Ki	Kinetic inhibitor
LDH	Lactate Dehydrogenase
LDi	Longest Diameter
LN	Lymph Node
LTLS	Laboratory Tumor Lysis Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
µL	Microliter
mg	Milligram
MID	Minimum important difference
MiRNA	microRNA
mL	Milliliter
mL/min	Milliliter per minute
mmol	millimolar
MM	Multiple Myeloma
mm	Millimeter
µM	Micromolar
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Event
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
PLL	Prolymphocytic leukemia
PR	Partial Remission
PRO	Patient-reported Outcome
PT	Prothrombin Time
QA	Quality assurance
QC	Quality control
QD	Once Daily
QoL	Quality of Life
RBC	Red Blood Cell
RNA	Ribonucleic Acid
R/R	Relapsed Refractory
SAE	Serious Adverse Event
SAP	Statistical analysis plan
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
TP53	Tumor protein 53gene
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

B-Cell Lymphoma-2 (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 (Kinetic Inhibitor [K_i] < 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).⁷ 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.

For further details, please see findings from completed and ongoing studies, including safety data in the current Venetoclax Investigator's Brochure.⁸

Venetoclax Clinical Data

Tumor lysis syndrome (TLS) is an important risk, particularly in subjects with relapsed/refractory 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 safety expansion cohort for venetoclax monotherapy (Study M12-175 as of 10Jun2016).⁹

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

Chronic Lymphocytic Leukemia (CLL)

CLL 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 CLL 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 Deletion and TP53 Gene Mutation in Chronic Lymphocytic Leukemia

Chromosome 17p deletion and TP53 gene mutation 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 deletion and TP53 mutation 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 deletion also carry a TP53 mutation.^{17,19}

The decreased likelihood of subjects with 17p deletion and/or TP53 mutation 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 deletion/TP53 mutation 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 deletion and/or TP53 mutation 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 deletion and 2.123 (CI: 1.400 – 3.218) and 3.014 (CI: 1.889 – 4.808), respectively, for subjects with TP53 mutations indicated.¹⁸ Poorer response to first-line treatment and shorter survival in subjects with 17p deletion and/or TP53 mutation were also observed in the CLL4 trial of 777 subjects randomized to chlorambucil or fludarabine with or without cyclophosphamide and in subjects with 17p deletion 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 subject 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 II 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 (BCR) signaling, homing, and adhesion. A Phase III 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.²⁶ Overall, 57% of subjects in the ibrutinib arm had at least one \geq Grade 3 adverse event (AE). The most

frequent non-hematologic AEs (> 20% of subjects) with ibrutinib were diarrhea, fatigue, pyrexia, and nausea.²⁷ Grade 3/4 AEs reported in $\geq 5\%$ of the 357 subjects with mantle cell lymphoma or CLL that received ibrutinib during clinical development were anemia, neutropenia, pneumonia and thrombocytopenia.²⁸

Idelalisib targets the delta isoform of phosphatidylinositol 3-kinase (PI3K δ) involved in signal transduction via multiple receptors including the BCR and chemokine receptors CXCR4 and CXCR5. A Phase III 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.²⁹ The overall safety profile determined in Phase I to III studies of idelalisib in hematologic malignancies as monotherapy or in combination with an anti-CD20 monoclonal antibody is characterized by a very common frequency ($\geq 1/10$ subjects) of \geq Grade 3 infections, neutropenia, diarrhea/colitis and increased transaminase.³⁰

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.³¹ 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.³²

In addition, toxicities such as diarrhea, fatigue and pyrexia are common and can affect the subjects who receive these drugs.^{27,29}

However, the mechanism of action of venetoclax is independent of the B-cell receptor (BCR) pathway.³³ 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 a 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).^{16,34}

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 a Phase 3b study to assess the impact on quality of life of venetoclax monotherapy as a primary endpoint in relapsed or refractory CLL subjects. In this study, several PRO measures will be utilized to assess quality of life in subjects with relapsed or refractory CLL. This data will add to the quality of life data already collected from 17p deletion CLL subjects in Study M13-982.³⁵ In addition, the impact of venetoclax monotherapy on quality of life will be assessed in correlation with efficacy data (i.e., overall response rate [ORR], duration of overall response [DOR], etc). This will allow for an assessment of the relationship between quality of life and treatment outcomes in this high risk subject population.

3.2 Benefits and Risks

There is data from a previous study (Study M13-982) that shows there is substantial improvement in quality of life in addition to efficacy with venetoclax monotherapy in

subjects with relapsed/refractory CLL characterized by 17p deletion. 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 are 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 Venetoclax Investigator's Brochure.⁸

4.0 Study Objective

The primary objective of this study is to evaluate the impact of venetoclax monotherapy on the quality of life of subjects with relapsed or refractory chronic lymphocytic leukemia (CLL). Quality of life will be assessed by the Global Health Status/Quality of Life (GHS/QoL) subscale of the European Organization for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30).

The secondary objectives are to evaluate the impact of venetoclax monotherapy on quality of life based on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Chronic Lymphocytic Leukemia Module (EORTC QLQ-CLL16), EuroQoL 5 Dimension 5 Level Questionnaire (EQ-5D-5L), and the remaining subscales/items from the EORTC QLQ-C30; overall response rate (ORR); complete remission rate (CR + CRi); duration of overall response (DOR), time to progression

(TTP), duration of progression-free survival (PFS); overall survival (OS); and CR rate in BCRi treated subjects.

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

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 impact of venetoclax monotherapy on the quality of life in relapsed/refractory CLL.

This study is designed to enroll approximately 200 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 in screening as they may have undergone study related procedures.

Subjects in this study will be enrolled at approximately 43 research sites in Latin America, Eastern Europe, and Asia-Pacific.

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 \leq 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). Quality of Life Assessments will be performed within 72 hours prior to the first dose of venetoclax and at Week 4, Week 8, Week 12, Week 24, Week 36, and Week 48, then every 12 weeks thereafter until the end of study treatment (Week 108). 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.

When confirming a CR or Cri status per the 2008 IWCLL NCI-WG guidelines, a bone marrow biopsy and aspirate should also be performed.

Quality of life will primarily be assessed by using the GHS/QoL subscale of the EORTC QLQ-C30. Secondary objectives will evaluate the quality of life based on the EORTC QLQ-CLL16, EQ-5D-5L, and the remaining subscales/items from the EORTC QLQ-C30.

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 (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 2 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 if CT is medically contraindicated). 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 \geq 18 years.
2. Eastern Cooperative Oncology Group (ECOG) performance score of \leq 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 $> 5 \times 10^9/L$ 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

5. Adequate bone marrow function as follows:

- Hemoglobin ≥ 8.0 g/dL
- platelets $\geq 25,000/\text{mm}^3$, without any of the following:
 - transfusion support within 14 days of Screening
 - evidence of mucosal bleeding
 - known history of bleeding episode within 3 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 $1.5 \times$ 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:

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

or, if serum* creatinine is in $\mu\text{mol/L}$:

$$\text{eCCr} = \frac{(140 - \text{Age}) \cdot \text{Weight}(\text{kg}) \cdot [1.23 \text{ if male, } 1.04 \text{ if female}]}{\text{serum}^* \text{ creatinine } (\mu\text{mol/L})}$$

* plasma value may be used in place of serum depending on local laboratory standard testing

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

- aspartate transaminase (AST) and alanine transaminase (ALT) $\leq 3.0 \times$ ULN
- bilirubin $\leq 1.5 \times$ ULN. Subjects with Gilbert's Syndrome may have a bilirubin $> 1.5 \times$ 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 \leq 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 (PLL)
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 or 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 [6.1.9.3](#).

The AbbVie TA MD identified in Section [6.1.5](#) 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. ³³ Notify AbbVie medical monitor 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
Antih herpes 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 Study Assessments/Variables

5.3.1 Study Assessments 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 6.0](#)). All study data will be recorded on electronic case report forms (eCRFs) with the exception of the patient reported outcomes, which will be recorded on paper and considered source documents.

Informed Consent

Subjects must voluntarily sign and date an informed consent form approved by an IEC/IRB, prior to the initiation of any screening or 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.

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

Pregnancy Testing

- WOCB 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 non-serious adverse event, if considered by the Investigator to be causally related to the study-required procedures ([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 $\geq 25 \times 10^9/L$]) 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 [6.1.9.1](#).

Eastern Cooperative Oncology Group (ECOG) Performance Status

For all subjects, the ECOG performance status⁴⁷ 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/or 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 (Assessed by Local Laboratory)

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

* 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 four 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 72 hours 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. Only one set of labs is required prior to dosing as long as it is reviewed and corrected.

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.

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

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 6.7 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.

Quality of Life Assessments

Quality of life will be assessed using the EORTC QLQ-C30, the EORTC QLQ-CLL16, and EQ-5D-5L.

Quality of life will be assessed within 72 hours prior to the first dose of venetoclax, Week 4, Week 8, Week 12, Week 24, Week 36, and Week 48 then every 12 weeks thereafter until the end of treatment (Week 108). The quality of life questionnaires should be administered and completed prior to any other study procedures being performed at these visits. Refer to Section [5.3.2](#). Study Variables, for further information.

Analyses of these endpoints are described in Section [8.0](#).

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 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](#).

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

For patients with Partial Remission at Week 48 an additional CT scan 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 achieved Complete Remission based on laboratory tests and a disease assessment physical examination.

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. 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.

Final Visit

Upon treatment discontinuation (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 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 (\pm 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 \leq 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. 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.

5.3.2 Study Variables

The primary objective of this study is to evaluate the impact of venetoclax monotherapy on the quality of life of subjects with relapsed or refractory chronic lymphocytic leukemia (CLL). Quality of life will be assessed by the GHS/QoL subscale of the EORTC QLQ-C30.

The secondary objectives are to evaluate the impact of venetoclax monotherapy on quality of life based on the EORTC QLQ-CLL16, EQ-5D-5L, and the remaining subscales/items from the EORTC QLQ-C30; overall response rate (ORR); complete remission rate (CR + CRi); duration of overall response (DOR), time to progression (TTP), duration of progression-free survival (PFS); overall survival (OS); and CR rate in BCRi treated subjects.

Analyses of these endpoints are described in Section [8.0](#).

5.3.2.1 Primary Variable

The primary endpoint will be based on the mean change from baseline to Week 48 on the GHS/QoL subscale of the EORTC QLQ-C30. Subjects will complete the EORTC QLQ-C30, along with other PRO measures, at baseline (within 72 hours prior to the first dose of venetoclax), Week 4, Week 8, Week 12, Week 24, Week 36, and Week 48, then every 12 weeks thereafter until the end of treatment (Week 108). The GHS/QoL subscale will be calculated as per the EORTC scoring manual, and summarized (mean, std dev, median) at each visit.

5.3.2.2 Secondary Variables

Secondary variables include assessments of quality of life based on the EORTC QLQ-CLL16, EQ-5D-5L, and the remaining subscales/items from the EORTC QLQ-C30; overall response rate (ORR); complete remission rate (CR + CRi); duration of overall

response (DOR), time to progression (TTP), duration of progression-free survival (PFS); overall survival (OS); and the CR rate in BCRi treated subjects.

5.3.2.2.1 Quality of Life Assessments

EORTC QLQ-C30

Quality of life and symptoms will be assessed with the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (EORTC-QLQ-C30) version 3.³⁶ The QLQ-C30 is a 30-item subject self-report questionnaire composed of both multi-item and single scales, including five functional scales (physical, role, emotional, social, and cognitive), three symptom scales (fatigue, nausea and vomiting, and pain), a global health status/quality of life (GHS/QoL) scale, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Subjects rate items on a four-point scale, with 1 as "not at all" and 4 as "very much." The EORTC QLQ-C30 was developed and validated for use in a cancer subject population, and its reliability and validity is highly consistent across different language cultural groups. A change of 5 – 10 points is considered a small change, and the lower bound (5) is being used to define the minimum important difference (MID). A change of 10 – 20 points is considered a moderate change.

EORTC QLQ-CLL16

The EORTC QLQ-CLL16 was designed specifically for subjects with stage 0 to stage 4 CLL.³⁷ It is comprised of sixteen questions that address five domains of HRQoL important in CLL. There are three multi-item scales assessing Fatigue (2 items), Disease and Treatment Effects (7 items), and Infection (5 items), and two single-item scales assessing Social Activities and Future Health Worries. Subjects rate items on a four-point scale, with 1 as "not at all" and 4 as "very much." A negative change in score from baseline represents an improvement in symptoms. A change of 5 – 10 points is considered a small change, and the lower bound (5) is being used to define the minimum important difference (MID). A change of 10 – 20 points is considered a moderate change.³⁸⁻⁴⁰

EQ-5D-5L

The EuroQol 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.

5.3.2.2.2 Disease Assessments

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); a bone marrow aspirate and biopsy is not required but results will be recorded if available. Subjects will be evaluated against the 2008 Modified IWCLL NCI-WG Criteria for Tumor Response⁴⁶ with the addition of CT imaging (or MRI). A BM 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 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.

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 LD_i 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 $4 \times 10^9/L$ (4000/ μ L)
- 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 > $1.5 \times 10^9/L$ [1500/ μ L] (without the need for exogenous growth factors)
 - Platelets > $100 \times 10^9/L$ [100,000/ μ L] (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:

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

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

- Neutrophils $> 1,500/\mu\text{L}$ or $\geq 50\%$ improvement over baseline.
- Platelets $> 100,000/\mu\text{L}$ or $\geq 50\%$ improvement over baseline.
- Hemoglobin $> 11.0 \text{ g/dL}$ or $\geq 50\%$ 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 \geq 50% ^c	Increase \geq 50% ^d or any new LN > 1.5 cm	Change of -49% to +49% ^e
Blood Lymphocytes	< 4000/ μ L	Decrease \geq 50% from baseline	Increase \geq 50% over baseline (\geq 5000/ μ L)	Change of -49% to +49%
Hepatomegaly ^f	None	Decrease \geq 50%	Increase \geq 50% ^g	Change of -49% to +49%
Splenomegaly ^f	None	Decrease \geq 50%	Increase \geq 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/ μ L ^h	> 100,000/ μ L or increase \geq 50% over baseline ^h	Decrease of \geq 50% from baseline secondary to CLL	Change of -49% to +49%
Hemoglobin	> 11.0 g/dL ^h	> 11.0 g/dL or increase \geq 50% over baseline ^h	Decrease of > 2 g/dL from baseline secondary to CLL	Increase to \leq 11.0 g/dL over baseline, or decrease < 2 g/dL
Neutrophils	> 1500/ μ L ^h	> 1500/ μ L or increase \geq 50% over baseline ^h	Decrease \geq 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.

5.3.2.3 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.

5.3.3 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 6.1.6. Safety will be monitored on an ongoing basis and summarized periodically in aggregate safety reports and end of study.

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 (\pm 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 (\pm 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 usually 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).

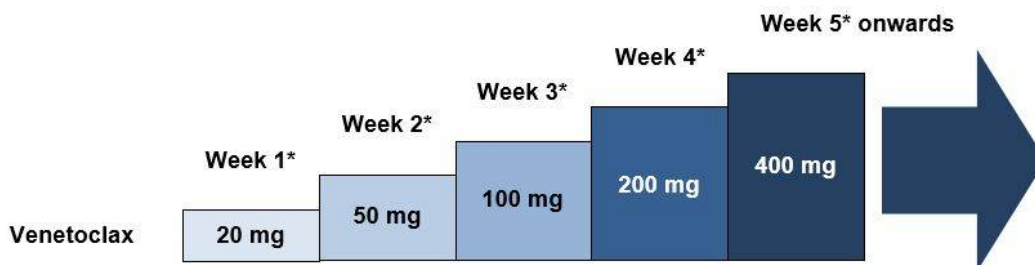
5.5.3 Method of Assigning Subjects to Treatment Groups

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 (Section [6.1.9.1](#)) and may include dose delay and/or dose reduction as required for prophylaxis and management of TLS.

Figure 2. 5-Week Dose-Titration Schematic



*Dose escalation will occur in accordance with specific risk-based TLS prophylaxis and monitoring measures that may include dose delay and/or dose reduction.

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 onsite. 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 M15-889 is being conducted primarily to assess the impact of venetoclax monotherapy on the quality of life of the participants. 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 subject population and clinical care settings.

5.6.2 Appropriateness of Measurements

The quality of life measures selected for this study include a cancer-specific questionnaire (EORTC QLQ-C30), a CLL-specific questionnaire (EORTC QLQ-CLL16), and a comprehensive generic health status/preference questionnaire (EQ-5D-5L). These measures have been used in previous CLL studies.^{45,48-52} Standard statistical, clinical, and laboratory

5.6.3 Suitability of Subject Population

Venetoclax monotherapy has shown favorable activity in relapsed/refractory CLL subjects including those with 17p deletion. Venetoclax is expected to be as active in subjects selected for TP53 mutations as these subject 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 II study of venetoclax monotherapy in relapsed/refractory CLL subjects with 17p deletion (Study M13-982) based on time-to-response and logistic regression modeling of data from CLL/SLL subjects enrolled in the Phase I 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 through 6.1.9. 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 6.1.9 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.
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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 (Section 6.1.3.1).

Hospitalization of a subject to allow observation and management (e.g., for intravenous (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 H](#).

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 6.1.6). However, if the event was unequivocally (clearly) due to disease progression, it should not be reported as an adverse event 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

Adverse events of special interest include TLS and neutropenia.

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 with 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).

6.1.3 Adverse Events Expected Due to Study-Related Endpoints

6.1.3.1 Deaths

For this protocol, overall survival is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (Section 6.1.5) 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 (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.

6.1.3.2 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.

6.1.4 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.

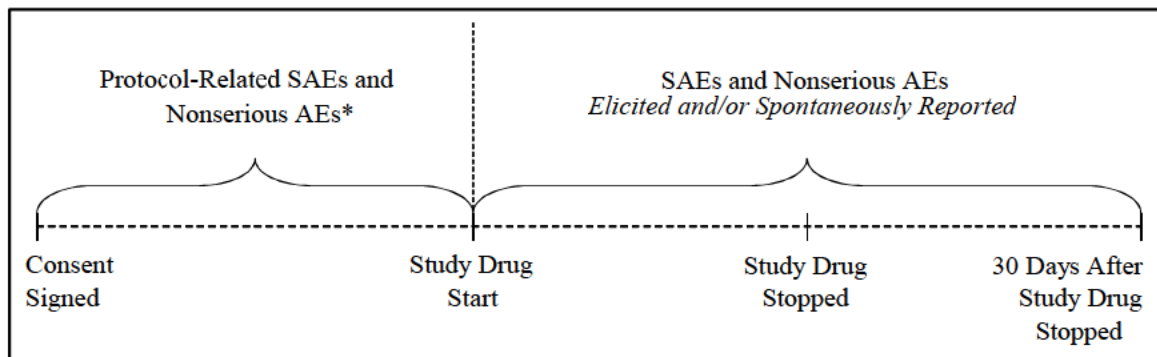
6.1.5 Adverse Event Collection Period

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 protocol-related 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.

6.1.6 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:

██████████ MD
Assistant Medical Director
Oncology Global Medical Affairs
AbbVie
████████████████████
26525 North Riverwoods Blvd.
Mettawa, IL 60045

Office: ████████████████████
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.

6.1.7 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.

6.1.8 Data Monitoring Committee

The 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 DMC 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.

6.1.9 Toxicity Management

6.1.9.1 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 to 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 $> 25 \times 10^9/L$]) are a 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.

Additional comorbidities may further increase the risk for TLS.

Prior to initiating venetoclax, tumor burden assessment, including radiographic evaluation (e.g., refer to Section 5.3.1.1 Study Procedures – Disease Assessment) 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 full 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:

- 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 72 hours 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 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 (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.

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

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.

6.1.9.2 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 ([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 (Table 8)
		For any events of clinical TLS, ^a resume at a reduced dose following resolution (Table 8).
Non-Hematologic Toxicities		
Grade 3 or 4 non-hematologic toxicities	1 st 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.
	2 nd 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)	1 st 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.
	2 nd 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 or sudden death and/or seizures.

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.

6.1.9.3 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.

6.1.9.4 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. Subjects should be advised that vaccinations may be less effective.

6.1.9.5 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.

6.1.9.6 Management of Non-Hematologic Toxicity

Venetoclax treatment should be withheld for any clinically relevant \geq 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 II
AbbVie Oncology
Clinical Program Development
1 N. Waukegan Rd.
North Chicago, IL 60064
USA

Office: [REDACTED]
Cell: [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]
Cell: [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

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 Study Endpoints

8.1.2.1 Primary Endpoint

The primary endpoint will be assessed by the GHS/QoL subscale of the EORTC QLQ-C30. The primary endpoint will be the mean change from baseline (within 72 hours prior to the first dose of venetoclax) to Week 48. Scores will be calculated based on the scoring manual.

8.1.2.2 Secondary Endpoints

Secondary quality of life endpoints will include all multi-item scales and single-item scales from the EORTC QLQ-C30, EORTC QLQ-CLL16, and EQ-5D-5L. Scores will be calculated based on the scoring manual for each instrument.

Key secondary efficacy endpoints will include Complete Remission rate (CR + CRi), Overall Response Rate (ORR), Duration of Overall Response (DOR), Time to Progression (TTP), Duration of Progression-Free Survival (PFS) and Overall Survival (OS).

Complete remission rate (CR + CRi) 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.

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 overall 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 overall response will be analyzed by Kaplan-Meier methodology using data for all enrolled subjects. Median duration of overall 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.

8.1.3 Timing of Study Endpoints and Safety Evaluations

The date the last enrolled subject has completed their Week 48 quality of life and disease assessments, or after all enrolled subjects have discontinued venetoclax, whichever is earlier, will be defined as the data "cutoff" date for the analyses. Quality of life, efficacy and safety data up to and including this date will be collected. Exact data cutoff date for the analysis will be detailed in the 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 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.

8.1.4.1 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 Medical Dictionary for Regulatory Activities (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.

8.1.4.2 Serious Adverse Events

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

8.1.4.3 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.

8.1.4.4 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.

8.2 Determination of Sample Size

An improvement in the EORTC QLQ-C30 GHS/QoL subscale of 5 units is considered to be a clinically meaningful difference to subjects. From a prior study of venetoclax monotherapy in 17p del R/R CLL subjects (Study M13-982), the standard deviation was approximately 20.5 for the GHS/QoL subscale. Using a one-sided alpha of 0.025, 90% power, and a standard deviation of 20.5; 177 subjects are required to reject the null hypothesis in favor of the alternative hypothesis that venetoclax improves GHS/QoL by at least 5 units. To account for potential drop-outs at Week 48, a total of 200 subjects to be dosed.

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 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 F](#).

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.

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, 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:

- EORTC QLQ-C30
- EORTC QLQ-CLL16
- EuroQoL EQ-5D-5L

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 subject 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 (EMA) 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 Impact of Venetoclax on the Quality of Life of Relapsed/Refractory Subjects with Chronic Lymphocytic Leukemia (CLL) (VENICE II)

Protocol Date: 09 October 2018

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]	Associate Director	Statistics
[REDACTED]	Assistant Medical Director	Medical Affairs
[REDACTED]	Group Project Director	Clinical
[REDACTED]	Study Project Manager II	Clinical

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
<p>Moderate CYP3A inhibitors Amprenavir, aprepitant, atazanavir, cimetidine, ciprofloxacin, clotrimazole, crizotinib*, cyclosporine*, darunavir/ritonavir, diltiazem¹, erythromycin, fluconazole, fosamprenavir, imatinib*, isavuconazole, tofisopam, verapamil</p> <p>Strong CYP3A inducers Avasimibe, carbamazepine, enzalutamine, mitotane, phenytoin, rifampin, St. john's wort</p> <p>Moderate CYP3A inducers Bosentan, efavirenz, etravirine, modafinil, nafcillin</p> <p>Warfarin**</p> <p>P-gp substrates Aliskiren, ambrisentan, colchicine, dabigatran, etexilate, digoxin, everolimus*, fexofenadine, lapatinib*, loperamide, maraviroc, nilotinib*, ranolazine, saxagliptin, sirolimus*, sitagliptin, talinolol, tolvaptan, topotecan*</p> <p>BCRP substrates Methotrexate*, mitoxantrone*, irrinotecan*, lapatinib*, rosuvastatin, sulfasalazine, topotecan*</p> <p>OATP1B1/1B3 substrates Atrasentan, atorvastatin, ezetimibe, fluvastatin, glyburide, rosuvastatin, simvastatin acid, pitavastatin, pravastatin, repaglinide, telmisartan, valsartan, olmesartan</p> <p>P-gp inhibitors Amiodarone, azithromycin, captopril, carvedilol, dronedarone, felodipine, quercetin, quinidine, ronalzine, ticagrelor</p> <p>BCRP inhibitors Gefitinib*</p>

Cautionary (continued)

* 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.

Note: 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																
Venetoclax dispensation and accountability ^q			X	X		X	X		X	X		X	X		X	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
Quality of Life Questionnaires (EORTC QLQ-30, EORTC QLQ-CLL16, EQ-5D-5L) ^f		X	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 W60	W108 / Final Visit	30 Day Safety Visit ^s	Post- Treatment Follow-Up ^t
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 ^{c*}	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG Performance Status ^u					X						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				
Venetoclax dispensation and accountability ^{***}	X	X	X	X	X	X	X	X	X	X	X	X	X ^w		
Quality of Life Questionnaires (EORTC QLQ-30, EORTC QLQ-CLL16, EQ-5D-5L) ^f	X	X			X			X			X	X	X		
Collection of Survival Information ^v														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 6.1.9 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 Disease Assessments and Computed Tomography Scans, 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. Refer to Section 5.3.1.1 Disease Assessments and Bone Marrow Aspirate and Biopsy, for more details.
- q. Venetoclax tablets should be taken orally once daily with a meal and water in the morning at approximately the same time each day. Dosing should occur at study visits on Week 1 Days 1 & 2 through Week 5 Days 1 & 2.
- r. The Quality of Life Questionnaires should be administered and completed prior to any other study procedures being performed at these visits. Refer to Section 5.3.1.1, Quality of Life Assessments for further information.
- s. 30-Day Safety Follow-up visit should occur approximately 30 days (\pm 3 days) after the last dose of venetoclax.
- t. 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 (\pm 7days) for a period of 2 years.
- u. ECOG performance status may be performed within 72 hours before or after the scheduled visit starting with Week 24.
- v. Survival information includes i.e., the date/cause of death, post treatment cancer therapies, etc.
- w. 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	W108 D1	W120 D1	W132 D1	W144 D1	W156 D1	W168 D1	W180 D1	W192 D1	W204 D1	W216/ 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 (EORTC QLQ-30, EORTC QLQ-CLL16, 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 \pm 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 [5.3.2.2.1](#) Health Economic and Patient-Reported Outcome Measures, for further information.
- d. 30-Day Safety Follow-up visit should occur approximately 30 days (\pm 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 (\pm 7 days) for a period of 2 years

Appendix F. 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 G. 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])	<ul style="list-style-type: none"> • 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 \geq 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	<ul style="list-style-type: none"> • 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 $\times 1$. • 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. <ul style="list-style-type: none"> ○ 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
Hyperkalemia (Including Rapidly Rising Potassium) (continued)	
Potassium ≥ 6.0 mmol/L (6.0 mEq/L) and/or symptomatic (e.g., muscle cramps, weakness, paresthesias, nausea, vomiting, diarrhea)	<ul style="list-style-type: none"> • 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 \times 1. • Administer insulin 0.1 U/kg IV + D25 2 mL/kg IV. • Administer sodium bicarbonate 1 to 2 mEq/kg IV push. <ul style="list-style-type: none"> ○ 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. <u>Do not administer in same IV line as sodium bicarbonate.</u> • Recheck potassium, phosphorus, uric acid, calcium and creatinine every hour STAT.
Hyperuricemia	
Uric acid ≥ 8.0 mg/dL (476 μ mol/L)	<ul style="list-style-type: none"> • Consider rasburicase* (dose based on local guidelines and/or institutional standards). <ul style="list-style-type: none"> ○ 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.
Hyperuricemia	
Uric acid ≥ 10 mg/dL (595 μ mol/L)	<ul style="list-style-type: none"> • Administer rasburicase* (dose based on local guidelines and/or institutional standards). <ul style="list-style-type: none"> ○ 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. <ul style="list-style-type: none"> ○ 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.
<u>OR</u>	
Uric acid ≥ 8.0 mg/dL (476 μ mol/L) with 25% increase and creatinine increase ≥ 0.3 mg/dL (≥ 0.027 mmol/L) from pre-dose level	

Abnormality	Management Recommendations
Hypocalcemia	
Calcium \leq 7.0 mg/dL (1.75 mmol/L)	<ul style="list-style-type: none"> • 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. <ul style="list-style-type: none"> ○ 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.
<p><u>AND</u></p> <p>Subject symptomatic (e.g., muscle cramps, hypotension, tetany, cardiac arrhythmias)</p>	
Hyperphosphatemia	
Phosphorus \geq 5.0 mg/dL (1.615 mmol/L) with \geq 0.5 mg/dL (0.16 mmol/L) increase	<ul style="list-style-type: none"> • 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 \geq 10 mg/dL). • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hr STAT. <ul style="list-style-type: none"> ○ 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 \geq 25% from baseline	<ul style="list-style-type: none"> • 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 H. 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 I. 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:	██████████ MD, PhD Medical Director, Oncology Global Medical Affairs AbbVie Neuhofstrasse 23 CH-6341 Baar Switzerland AND ██████████ MD Medical Director AbbVie 26525 North Riverwoods Blvd. Mettawa, IL 60060 USA	Phone: ██████████ Fax: ██████████ Email: ██████████ Phone: ██████████ Email: ██████████
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Has been changed to read:

Sponsor/Emergency Contact:	██████████ MD Assistant Medical Director, Oncology Global Medical Affairs AbbVie ██████████ 26525 North Riverwoods Blvd. Mettawa, IL 60045 AND ██████████ MD, PhD Medical Director, Oncology AbbVie Neuhofstrasse 23 CH-6341 Baar Switzerland	Phone: ██████████ Email: ██████████ Phone: ██████████ Fax: ██████████ Email: ██████████
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Section 1.2 Synopsis

Subsection Study Population:

Previously read:

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 therapy (BCRi).

Has been changed to read:

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.

Section 1.2 Synopsis

Subsection Methodology:

Second paragraph

Add: new second sentence

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.

Section 1.2 Synopsis

Subsection Methodology:

Last paragraph, first and second sentence previously read:

A Data Monitoring Committee (DMC) has been organized to support the review safety data associated with venetoclax monotherapy dosing. The DMC will review Study M15-889 safety data along with a data from a similar study, Study M15-550, with an initial review to occur when approximately 20 subjects have completed a minimum 12 weeks of treatment.

Has been changed to read:

The Data Monitoring Committee (DMC) will review safety data intermittently according to the DMC charter.

Section 1.2 Synopsis

Subsection Duration of Treatment:

Last paragraph previously read:

For subjects who continue to derive benefit after 2 years of treatment, AbbVie will work with the investigator to consider the potential continuation of venetoclax therapy.

Has been changed to read:

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.

Section 1.2 Synopsis

Subsection Criteria for Evaluation:

Heading "Efficacy:"

First paragraph previously read:

Disease response will be assessed by the investigator, based on laboratory results, physical examinations, using the 2008 modified IWCLL NCI-WG Criteria for Tumor Response with the addition of CT imaging (or MRI in the case CT is medically contraindicated) when available.

Has been changed to read:

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

Section 1.2 Synopsis

Subsection Statistical Methods:

First paragraph, last sentence previously read:

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.

Has been changed to read:

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).

Section 1.2 Synopsis

Subsection Statistical Methods:

Heading "Efficacy Analyses Include:"

Sub-heading "Duration of Overall Response (DOR):"

First sentence previously read:

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.

Has been changed to read:

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 or death.

Section 1.3 List of Abbreviations and Definition of Terms

Subsection Abbreviations

Add:

Bcl-2

B-Cell Lymphoma 2

Section 1.3 List of Abbreviations and Definition of Terms

Subsection Abbreviations

"BIM" and "BM" previously read:

BIM	Bone marrow
BM	Bcl-2 interacting mediator

Has been changed to read:

BM	Bone marrow
BIM	Bcl-2 interacting mediator

Section 1.3 List of Abbreviations and Definition of Terms

Subsection Abbreviations

Delete:

SGPT	Serum Glutamic-pyruvic Transaminase
------	-------------------------------------

Section 3.0 Introduction

Subsection Bcl-2 Family Proteins

Subsection title previously read:

Bcl-2 Family Proteins

Has been changed to read:

B-Cell Lymphoma-2 (Bcl-2) Family Proteins

Section 3.0 Introduction

Subsection Venetoclax (ABT-199)

Last paragraph previously read:

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

Has been changed to read:

For further details, please see findings from completed and ongoing studies, including safety data in the current Venetoclax Investigator's Brochure.⁸

Section 3.0 Introduction
Subsection Venetoclax Clinical Data
Delete: first and second paragraph

In the Investigator's Brochure,⁸ a total of over 2500 oncology subjects received at least 1 dose of venetoclax in AbbVie and Genentech/Roche studies and had data available as of 28 November 2016. Of these subjects, 1429 subjects had CLL/small lymphocytic lymphoma (SLL), 637 subjects had Non-Hodgkin's Lymphoma (NHL), 180 subjects had multiple myeloma (MM), 327 had acute myeloid leukemia (AML), and 114 were healthy volunteers. A total of 749 received the drug as monotherapy and 1922 received the drug in combination with other therapies. Doses administered in venetoclax clinical studies have ranged from 20 mg to 1200 mg.

The most common adverse events reported for all subjects in monotherapy studies were nausea (41.9%), diarrhea (41.1%), and neutropenia (31.1%). The most common adverse event that was grade 3 and above was neutropenia (22.4%). The most common serious adverse events were pneumonia (6.8%), febrile neutropenia (5.4%) and malignant neoplasm progression (5.9%).

Section 3.0 Introduction
Subsection Venetoclax Clinical Data
Fourth paragraph, last sentence previously read:

The overall response rate (ORR) in subjects with CLL/SLL was 77% to 82% (dose escalation and safety expansion cohorts, respectively), with a complete remission rate (CR + CRi) of 30% in dose escalation and 10% in safety expansion cohort for venetoclax monotherapy (Study M12-175).⁹

Has been changed to read:

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 safety expansion cohort for venetoclax monotherapy (Study M12-175 as of 10Jun2016).⁹

Section 3.0 Introduction

Subsection CLL Subjects Who Have Received Prior B-Cell Receptor Inhibitor Therapy

Subsection title previously read:

Subjects Who Have Received Prior B-Cell Receptor Inhibitor Therapy

Has been changed to read:

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

Section 3.0 Introduction

Subsection CLL Subjects Who Have Received Prior B-Cell Receptor Inhibitor Therapy

First paragraph, first sentence previously read:

Ibrutinib and idelalisib cause rapid response with reduction in lymph node size and splenic mass accompanied by increased peripheral blood lymphocytosis likely reflecting that microenvironment modulation could prevent these cells from receiving the survival signals delivered by the microenvironment.³¹

Has been changed to read:

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.³¹

Section 5.1 Overall Study Design and Plan: Description

Second paragraph, last sentence previously read:

All efforts will be made to adhere to these specific enrollment numbers; however, it might not be ethical to deny treatment to subjects in screening as they may have undergone study related procedures.

Has been changed to read:

All efforts will be made to adhere to these specific enrollment numbers; however, it would not be ethical to deny treatment to eligible subjects in screening as they may have undergone study related procedures.

Section 5.1 Overall Study Design and Plan: Description

Fourth paragraph

Add: new eighth sentence

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

Section 5.1 Overall Study Design and Plan: Description

Sixth paragraph, first sentence previously read:

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) when available.

Has been changed to read:

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).

Section 5.1 Overall Study Design and Plan: Description

Sixth paragraph, last sentence previously read:

To confirm the response, a CT scan (or MRI if CT is medically contraindicated) will be performed at Week 48 on all subjects.

Has been changed to read:

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.

Section 5.1 Overall Study Design and Plan: Description
Eleventh and twelfth paragraph previously read:

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

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.

Has been changed to read:

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.

Section 5.2.2 Exclusion Criteria
Criterion 11 previously read:

Subject is known to be positive for 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).

Has been changed to read:

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).

Section 5.3.1 Study Assessments and Flow Chart

First paragraph previously read:

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

Has been changed to read:

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

Section 5.3.1.1 Study Procedures

First paragraph, first sentence previously read:

All study procedures outlined in Appendix D are discussed in detail in this section, with the exception of adverse event (AE) information (discussed in Section 6.0).

Has been changed to read:

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 6.0).

Section 5.3.1.1 Study Procedures

Subsection Physical Examination (Disease Assessment)

First paragraph, first sentence previously read:

All physical examinations (complete or symptom-directed) 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.

Has been changed to read:

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.

Section 5.3.1.1 Study Procedures

Subsection Physical Examination (Disease Assessment)

Fifth paragraph previously read:

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

Has been changed to read:

Please refer to [Appendix D](#) and [Appendix E](#) for timing of all physical examinations.

Section 5.3.1.1 Study Procedures

Subsection Eastern Cooperative Oncology Group (ECOG) Performance Status

First paragraph previously read:

For all subjects, the ECOG performance status⁴⁷ will be performed as outlined in Appendix D.

Has been changed to read:

For all subjects, the ECOG performance status⁴⁷ will be performed as outlined in [Appendix D](#) and [Appendix E](#).

Section 5.3.1.1 Study Procedures

Subsection Hematology and Chemistry

Heading "PRE-DOSE LABS:"

Sub-heading "Prior to each subsequent dose ramp up, for all subjects:"

Sub-heading previously read:

Prior to each subsequent dose ramp up, for all subjects:

Has been changed to read:

Prior to Each Subsequent Dose Increase, for all Subjects:

Section 5.3.1.1 Study Procedures

Subsection Disease Assessments (2008 Modified IWCLL NCI-WG Criteria)

First paragraph, last sentence previously read:

Bone marrow examination is not required but results will be recorded if available.

Has been changed to read:

Bone marrow examinations at screening are not required but results will be recorded if available.

Section 5.3.1.1 Study Procedures

Subsection Disease Assessments (2008 Modified IWCLL NCI-WG Criteria)

Third paragraph, second sentence previously read:

It is recommended that the CT scan is performed first; if it does confirm a clinical response, then a bone marrow biopsy should be obtained.

Has been changed to read:

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.

Section 5.3.1.1 Study Procedures

Subsection Disease Assessments (2008 Modified IWCLL NCI-WG Criteria)

Add: new last paragraph

For patients with Partial Remission at Week 48 an additional CT scan 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 achieved Complete Remission based on laboratory tests and a disease assessment physical examination.

Section 5.3.1.1 Study Procedures

Subsection Bone Marrow Aspirate and Biopsy

First paragraph, second sentence previously read:

If the subject achieves a CR by clinical criteria and confirmatory CT scan, a bone marrow aspirate and biopsy should be performed to confirm the CR.

Has been changed to read:

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.

Section 5.3.1.1 Study Procedures

Subsection Final Visit

First paragraph, last sentence previously read:

The Final Visit procedures as listed in Appendix D should be performed as soon as possible after study drug discontinuation.

Has been changed to read:

The Final Visit procedures as listed in [Appendix D](#) and [Appendix E](#) should be performed as soon as possible after study drug discontinuation.

Section 5.3.1.1 Study Procedures

Subsection 30-Day Safety Visit

First paragraph, last sentence previously read:

Refer to Appendix D for procedures to be performed.

Has been changed to read:

Refer to [Appendix D](#) and [Appendix E](#) for procedures to be performed.

Section 5.3.1.1 Study Procedures

Subsection 30-Day Safety Visit

Second paragraph previously read:

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 \leq Grade 1 or baseline or it is the investigator's judgment that the event is unlikely to resolve.

Has been changed to read:

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 \leq Grade 1 or baseline or it is the investigator's judgment that the event is unlikely to resolve.

Section 5.3.1.1 Study Procedures

Subsection Extended Access Phase

Add: new subsection title and text

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. 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](#).

Section 5.3.2.2.2 Disease Assessments

First paragraph

Add: new last sentence

A BM assessment is required to confirm CR.

Section 5.3.2.2.2 Disease Assessments

Second paragraph

Add: new last sentence

For subjects with CR as response at Week 48, a BM is required to confirm the response.

Section 5.3.2.2.2 Disease Assessments

Subsection Methods of Measurement

First bullet, second sentence previously read:

Target nodal lesions must be abnormal (> 1.5 cm in longest diameter [LDi] at baseline), clearly measurable and suitable for consistent, reproducible measurement in at least two perpendicular dimensions.

Has been changed to read:

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.

Section 5.3.2.2.2 Disease Assessments

Subsection Tumor Response Criteria

Heading "Complete Remission (CR)"

Last bullet, last sentence previously read:

Immunohistochemistry should be performed to define whether these nodules are composed of primarily T cells or lymphocytes other than CLL cells, or CLL cells.

Has been changed to read:

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.

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

First page of table

Delete: subsection title "Other Considerations"

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				

Section 5.4.1 Discontinuation of Individual Subjects

First paragraph previously read:

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

Has been changed to read:

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:

Section 5.4.1 Discontinuation of Individual Subjects

Fifth and sixth bullet previously read:

- pregnancy
- protocol non-compliance

Has been changed to read:

- The subject becomes pregnant while on the study
- drug/protocol non-compliance

Section 5.4.1 Discontinuation of Individual Subjects
Subsection Post Treatment and Survival Follow-Up Calls

Previously read:

For subjects who discontinue venetoclax therapy, but do not discontinue the study (i.e., have not had an event of progression, do not require alternate therapy, etc.), post-treatment follow-up calls will be performed every 6 months 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.

Has been changed to read:

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.

Section 5.6.3 Suitability of Subject Population

First paragraph, third sentence previously read:

In addition, subjects with relapsed or refractory CLL who have been previously treated with a B-cell receptor inhibitor have shown to have activity when treated with venetoclax.

Has been changed to read:

In addition, venetoclax has shown activity in subjects with relapsed or refractory CLL who have been previously treated with a B-cell receptor inhibitor.

Section 6.1.6 Adverse Event Reporting
Third paragraph previously read:

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

██████████ MD PhD
Medical Director
Oncology Global Medical Affairs
AbbVie
Neuhofstrasse 23
CH-6341 Baar
Switzerland

Office/Cell: ██████████
Fax: ██████████
Email: ██████████

Has been changed to read:

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

██████████ MD
Assistant Medical Director
Oncology Global Medical Affairs
AbbVie
██████████
26525 North Riverwoods Blvd.
Mettawa, IL 60045

Office: ██████████
Email: ██████████

Section 6.1.8 Data Monitoring Committee
Previously read:

Data Monitoring Committee (DMC) has been organized to support the review of safety data associated with venetoclax monotherapy dosing. The DMC will review Study M15-889 safety data along with a data from a similar study, Study M15-550, with

an initial review to occur when approximately 20 subjects have completed a minimum 12 weeks of treatment.

A charter will be 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.

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.

Has been changed to read:

The 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 DMC 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.

Table 7. Recommended Dose Modifications for Toxicities

Table note "a." previously read:

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

Has been changed to read:

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

Section 7.0 Protocol Deviations

"Primary Contact;" title previously read:

Study Project Manager I

Has been changed to read:

Study Project Manager II

Section 8.1.3 Timing of Study Endpoints and Safety Evaluations

First paragraph, third sentence previously read:

Exact data cutoff date for the analysis will be detailed in the statistical analysis plan (SAP) which will be signed off prior to the data cut-off date.

Has been changed to read:

Exact data cutoff date for the analysis will be detailed in the SAP which will be signed off prior to the data cut-off date.

Section 10.1 Source Documents

Second paragraph previously read:

The following PRO assessments will be completed by the subject and will be considered source documentation:

Has been changed to read:

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

Section 15.0 Reference List

Reference 8 previously read:

AbbVie. Venetoclax Investigator's Brochure Edition 8. 03 May 2017.

Has been changed to read:

AbbVie. Venetoclax Investigator's Brochure. Current Version.

**Appendix B. List of Protocol Signatories
Previously read:**

Name	Title	Functional Area
[REDACTED]	Associate Director	Statistics
[REDACTED]	Medical Director	Medical Affairs
[REDACTED]	Group Project Director	Clinical
[REDACTED]	Study Project Manager I	Clinical

Has been changed to read:

Name	Title	Functional Area
[REDACTED]	Associate Director	Statistics
[REDACTED]	Assistant Medical Director	Medical Affairs
[REDACTED]	Group Project Director	Clinical
[REDACTED]	Study Project Manager II	Clinical

Appendix D. Study Activities: Screening Through Week 5 Day 2

Previously read:

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
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																
Dispense Venetoclax ^q			X	X		X	X		X	X		X	X		X	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
Quality of Life Questionnaires (EORTC QLQ-30, EORTC QLQ-CLL16, EQ-5D-5L) ^f		X	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 W60	W108 / Final Visit	30 Day Safety Visit ^s	Post- Treatment Follow-Up ^t
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 ^{c*}	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG Performance Status ^u					X						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															
Dispense Venetoclax	X	X	X	X	X	X	X	X	X	X	X	X			
Quality of Life Questionnaires (EORTC QLQ-30, EORTC QLQ-CLL16, EQ-5D-5L) ^r	X	X			X			X			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.

- 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 6.1.9 Toxicity Management, for more details.
- h. 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. 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 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. 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 Disease Assessments and Computed Tomography Scans, for more details.
- 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 should be performed to confirm the CR. Refer to Section 5.3.1.1 Disease Assessments and Bone Marrow Aspirate and Biopsy, for more details.
- q. Venetoclax tablets should be taken orally once daily with a meal and water in the morning at approximately the same time each day. Dosing should occur at study visits on Week 1 Days 1 & 2 through Week 5 Days 1 & 2.
- r. The Quality of Life Questionnaires should be administered and completed prior to any other study procedures being performed at these visits. Refer to Section 5.3.1.1, Quality of Life Assessments for further information.
- s. 30-Day Safety Follow-up visit should occur approximately 30 days (\pm 3 days) after the last dose of venetoclax.
- t. 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 for a period of 2 years.
- u. ECOG performance status may be performed within 72 hours before or after the scheduled visit starting with Week 24.

Has been changed to read:

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																
Venetoclax dispensation and accountability ^q			X	X		X	X		X	X		X	X		X	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
Quality of Life Questionnaires (EORTC QLQ-30, EORTC QLQ-CLL16, EQ-5D-5L) ^f		X	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 W60	W108 / Final Visit	30 Day Safety Visit ^s	Post- Treatment Follow-Up ^t
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 ^{c*}	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
ECOG Performance Status ^u					X						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				
Venetoclax dispensation and accountability ^{***}	X	X	X	X	X	X	X	X	X	X	X	X	X ^w		
Quality of Life Questionnaires (EORTC QLQ-30, EORTC QLQ-CLL16, EQ-5D-5L) ^f	X	X			X			X			X	X	X		
Collection of Survival Information ^v														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 6.1.9 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 Disease Assessments and Computed Tomography Scans, 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. Refer to Section 5.3.1.1 Disease Assessments and Bone Marrow Aspirate and Biopsy, for more details.
- q. Venetoclax tablets should be taken orally once daily with a meal and water in the morning at approximately the same time each day. Dosing should occur at study visits on Week 1 Days 1 & 2 through Week 5 Days 1 & 2.
- r. The Quality of Life Questionnaires should be administered and completed prior to any other study procedures being performed at these visits. Refer to Section 5.3.1.1, Quality of Life Assessments for further information.
- s. 30-Day Safety Follow-up visit should occur approximately 30 days (\pm 3 days) after the last dose of venetoclax.
- t. 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 (\pm 7days) for a period of 2 years.
- u. ECOG performance status may be performed within 72 hours before or after the scheduled visit starting with Week 24.
- v. Survival information includes i.e., the date/cause of death, post treatment cancer therapies, etc.
- w. 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*

Add: new appendix title and text

Appendix E. Schedule of Extended Access Phase*

Procedure	W108 D1	W120 D1	W132 D1	W144 D1	W156 D1	W168 D1	W180 D1	W192 D1	W204 D1	W216/ 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 (EORTC QLQ-30, EORTC QLQ-CLL16, 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 \pm 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 [5.3.2.2.1](#) Health Economic and Patient-Reported Outcome Measures, for further information.
- d. 30-Day Safety Follow-up visit should occur approximately 30 days (\pm 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 (\pm 7 days) for a period of 2 years