1.0 Title Page

Clinical Study Protocol M14-032

A Phase 2 Open-Label Study of the Efficacy and Safety of ABT-199 (GDC-0199) in Chronic Lymphocytic Leukemia Subjects with Relapse or Refractory to B-Cell Receptor Signaling Pathway Inhibitor Therapy

Incorporating Amendments 1, 2, 3, 4, 5, and 6 and Administrative Changes 1 and 2

AbbVie Investigational Product:	Venetoclax (ABT-199/GDC-0199)
Date:	15 December 2020
Development Phase:	2
Study Design:	This is an open-label, non-randomized, two arm study to determine the efficacy and safety of venetoclax (ABT-199/GDC-0199) in subjects with relapsed or refractory chronic lymphocytic leukemia.
Investigators:	Investigator information on file at AbbVie.
Sponsor:	AbbVie
Sponsor/Emergency Contact:	[redacted] MD, PhD Senior Medical Director [redacted] AbbVie 1 North Waukegan Road North Chicago, IL 60064 Phone: Cell: [redacted] Fax: Email: [redacted]

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

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	21 February 2014
Amendment 1	16 May 2014
Amendment 2	14 January 2015
Amendment 3	22 September 2015
Administrative Change 1	30 November 2015
Amendment 4	13 September 2016
Administrative Change 2	27 September 2016
Amendment 5	12 October 2018

The purpose of this amendment is to:

- Section 6.1.5, Adverse Event Reporting – to update medical director contact information for study.

  Rationale: *Provide current study team contacts.*
- Update Section 7.0, Protocol Deviations, to update the primary contact information.

  Rationale: *Provide current study team contacts.*
- Update Section 15.0, Reference List.

  Rationale: *Provide current Investigator Brochure edition.*
- Update Appendix B, List of Protocol Signatories.

  Rationale: *Provide current study team contacts.*
- Remove Appendix G, Protocol Amendment: List of Changes

  Rationale: *No longer required per AbbVie processes.*
- Add Appendix G, Summary of COVID-19 Changes

  Rationale: *To incorporate necessary protocol modifications in order to align with AbbVie's COVID-19 response strategies.*

- Update Section 1.3 List of Abbreviations and Definition of Terms, and correct typographical errors and minor language or word revisions throughout the document.

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M14-032
Name of Study Drug: Venetoclax	**Phase of Development:** 2
Name of Active Ingredient: Venetoclax	**Date of Protocol Synopsis:** 15 December 2020
Protocol Title: A Phase 2 Open-Label Study of the Efficacy and Safety of ABT-199 (GDC-0199) in Chronic Lymphocytic Leukemia Subjects with Relapse or Refractory to B-Cell Receptor Signaling Pathway Inhibitor Therapy	
Objectives: **Primary Objective:** The primary objective of this study is to evaluate the efficacy and safety of venetoclax monotherapy in subjects with Chronic Lymphocytic Leukemia (CLL) relapsed after or refractory to treatment with B-cell Receptor Signaling Pathway Inhibitors. Efficacy will be measured by overall response rate (ORR). **Secondary Objectives:** The secondary objectives are to evaluate the duration of response (DOR), time to progression (TTP), progression free survival (PFS), and overall survival (OS). **Exploratory Objectives:** Time to Next Anti-CLL Treatment (TNT) and Rate of Minimal Residual Disease (MRD) Status. Health Economic and Patient-Reported Outcome Measures will include the EORTC QLQ C30 and EORTC QLQ CLL16 (a measure of health-related quality of life specific to CLL) and the EQ-5D-5L (measure of general health status with visual analogue scale). **Note: Study objectives, with the exception of Safety, will not apply to the Extended Access period which will begin 2 years after last subject enrolled.**	
Investigators: Investigator information on file at AbbVie.	
Study Sites: Approximately 15 US research sites.	
Study Population: Relapsed or refractory CLL subjects after BCR Signaling Pathway Inhibitors.	
Number of Subjects to be Enrolled: Approximately 120.	

Methodology:

This is an open-label, non-randomized, multicenter, Phase 2 study evaluating the efficacy and safety of venetoclax in approximately 120 subjects with relapsed or refractory CLL after BCR Signaling Pathway Inhibitor (BCR PI) Treatment (specifically Ibrutinib, and Idelalisib). Two arms and an expansion cohort will be implemented: Arm A is designed to enroll approximately 40 subjects with relapsed or refractory CLL after Ibrutinib treatment, Arm B is designed to enroll approximately 20 subjects with relapsed or refractory CLL after Idelalisib treatment and the Expansion Cohort is designed to enroll approximately 60 subjects with relapsed or refractory CLL after either Ibrutinib or Idelalisib treatments. Screening must be performed within 28 days of study drug administration. PET/CT scans and bone marrow aspirate and biopsy must be performed within 28 days prior to study drug administration. For subjects enrolled under Arm A and Arm B, restaging CT/MRI scans will be performed at Week 8, Week 24 and every 12 weeks thereafter for a period of 1 year from enrollment and at the subject's Final Visit. For subjects enrolled under the Expansion Cohort, restaging CT/MRI scans will be performed at Week 12, Week 36 and at the subject's Final Visit. All subjects will have study visits conducted on Day 1 of each week from Week 1 through Week 5, Week 8, Week 12, Week 16, Week 24, and then every 12 weeks thereafter. A Disease Assessment for clinical response by physical exam and hematologic assessments will be performed at Screening, Week 5 Day 1 (or Day 1 of the initiation of 400 mg of venetoclax) and beyond. When an investigator has determined that a subject should discontinue the study, a Final Visit will be conducted as well as a 30-Day Safety Follow-Up. If the subject is discontinued from the study due to toxicities attributable to ABT-199, additional Follow-Up Visits will be conducted as clinically appropriate until a satisfactory clinical resolution of the adverse event is achieved and progression is documented.

Diagnosis and Main Criteria for Inclusion/Exclusion: CLL Subjects with Relapsed or Refractory to B-cell Receptor Signaling Pathway Inhibitor Therapy.

Main Inclusion:

- Subject must be ≥ 18 years of age.
- Subject must have diagnosis of CLL that meets published 2008 IWCLL NCI-WG criteria.
- Subject has relapsed/refractory disease with an indication for treatment.
- Subject has refractory disease or developed recurrence after therapy with a BCR signaling pathway inhibitor (BCR PI).
- Subject must have an Eastern Cooperative Oncology Group (ECOG) performance score of ≤ 2.

Main Exclusion:

- Subject has undergone an allogeneic stem cell transplant within the past 1 year.
- Subject has developed Richter's transformation confirmed by biopsy.
- Subject has active and uncontrolled autoimmune cytopenias.
- Subject has malabsorption syndrome or other condition that precludes enteral route of administration.
- Subject is tested positive for HIV or has chronic hepatitis B virus or hepatitis C virus requiring treatment.

Survival Assessment(s) Survival information will be collected up to 5 years after the last subject has been enrolled.	
Richter's Transformation and Second Primary Malignancies Assessment Richter's transformation and second primary malignancies information will be collected up to 5 years after the last subject has been enrolled. Extended Access: For subjects continuing into the Extended Access period of the trial, AbbVie will provide venetoclax until 5 years from the date of last subject enrolled, until disease progression, or until a subject chooses to receive commercial supply of VENCLEXTA.	
Investigational Product:	Venetoclax
Doses:	Single daily doses QD starting with 20 mg; dose increments will proceed weekly → 50 mg → 100 mg → 200 mg → 400 mg as tolerated. Expansion Cohort subjects with bulky disease who are non-responders at the Week 12 Disease Assessment may be permitted to escalate venetoclax to 600mg dose.
Mode of Administration:	Oral
Duration of Treatment: Subjects may continue receiving study drug for up to 5 years from the date of the last subject enrolled provided they continue to tolerate the drug, have no evidence of disease progression, and do not meet any of the criteria for subject discontinuation. The anticipated median treatment duration is ≥ 24 months.	
Criteria for Evaluation: **Efficacy:** Response will be assessed by the investigator, based on laboratory results, physical examinations, CT/MRI scans and bone marrow examinations, using the 2008 Modified IWCLL NCI-WG Criteria for Tumor Response. An Independent Review Committee (IRC) will evaluate disease progression and response based on overall response rate, duration of response, time to progression and progression free survival. Subject treatment management will be based on review by the local investigator and/or site staff. All measurable disease must be documented at screening by physical examination, laboratory testing, and PET/CT scan (or MRI if CT is medically contraindicated). During the study, subjects will be assessed at each visit by a physical examination and laboratory testing. Clinical Disease Assessments will take place at Screening (baseline), on Week 5 Day 1 (or Day 1 of initiation of 400 mg of venetoclax) Week 8, Week 12, Week 16, Week 24, Week 36 and then every 12 weeks thereafter until disease progression, death, discontinuation from the study or study completion.	

Criteria for Evaluation (Continued):

Efficacy (Continued):

Radiographic scans will be performed in addition as described below:

For subjects enrolled under Arm A and Arm B, a CT/MRI scan must be performed at Screening, Week 8, Week 24 and every 12 weeks thereafter for a period of 1 year from enrollment and at the subject's Final Visit – CT scan is not needed for subjects continuing in the Extended Access period of the trial. For subjects enrolled under the Expansion Cohort, a CT/MRI scan must be performed at Screening, Week 12, Week 36 and at the subject's Final Visit – CT scan is not needed for subjects continuing in the Extended Access period of the trial. If a subject has study drug interrupted for more than 3 days (i.e., adverse event), the site must contact the AbbVie study team or AbbVie medical monitor to adjust the subject's visit schedule, procedures and/or dosing on a case by case basis. Subjects should have the same method of imaging performed throughout the study for consistency. For determination of CR, both the CT/MRI and bone marrow are required to be free of disease. 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 exam and or changes in the peripheral blood count), a CT/MRI scan and/or bone marrow must be performed within 2 weeks to confirm or rule out PD.

Confirmation of CR by Bone Marrow Examination will be performed as described below:

Once CR is determined by clinical and radiographic criteria, a bone marrow aspiration and biopsy is performed for confirmation. If the marrow is hypocellular, a repeat examination should be performed after 4 weeks, or once the peripheral blood counts have recovered.

Exploratory MRD will be performed as described below:

A peripheral blood specimen will be collected at Screening from all subjects to determine individual disease characteristics, and follow up samples will be collected at Week 24 and after a confirmed CR/CRi/PR for analysis of MRD levels. MRD will be assessed using recommended methodologies (flow cytometry, PCR and/or sequencing). MRD negativity will be defined as the presence of less than one CLL cell per 10,000 leukocytes (or below 10^{-4}) in either peripheral blood and/or bone marrow.

Pharmacokinetic:

Pharmacokinetic samples will be collected for venetoclax at designated time points throughout the study. Values for the PK parameters of venetoclax, including the apparent clearance (CL/F) and the apparent volume of distribution (V/F), may be determined using a population PK approach. Additional parameters may be calculated if useful in the interpretation of the data.

Exploratory Biomarkers:

Several putative biomarkers of efficacy and response may be evaluated in this study with the goal of defining the relationship between various disease markers and disease status that may predict the subject's response to therapy. Assays to determine Bcl-2 gene amplifications and translocations, modifications of TP53 and NOTCH 1 and genomic profile for mutations before and after treatment may be performed. In addition, mutational analysis of genes that may be associated with resistance and response to ibrutinib and B-cell receptor targeted agents including but not limited to mutations of BTK (C481S), PLC gamma and other genes linked to B-cell receptor activation may also be evaluated. If necessary, aliquots from PK samples will be utilized for pharmacodynamics analyses. Exploratory research analyses may not be included in the clinical study report.

Pharmacogenetic:

DNA samples may be analyzed for genetic factors contributing to the subject's response to venetoclax.

Criteria for Evaluation (Continued):

Safety:

Adverse event monitoring, vital signs, physical examination, 12-lead ECG, and laboratory assessments will be evaluated. Guidelines for the management for TLS are provided.

Statistical Methods:

Efficacy:

The following efficacy endpoints will be analyzed: Overall Response Rate (ORR), Duration of Response (DOR), Time to Progression (TTP), Progression Free Survival (PFS), Overall Survival (OS) and Rate of Minimal Residual Disease (MRD) Negativity rate.

Overall Response Rate

The proportion of subjects with overall response (per the investigator assessment) will be calculated for all subjects based on IWCLL NCI-CWG criteria. In addition, a ninety-five percent (95%) confidence interval based on binomial distribution will be constructed for the calculated ORR.

Duration of Response

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

Time to Progression

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

Progression-Free Survival

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

Overall Survival

Overall survival will be defined as the number of days from the date of first dose to the date of death for all dosed subjects. 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 dosed subjects. Median time survival will be calculated and 95% confidence interval for the median time survival will be presented.

Statistical Methods (Continued):

Efficacy (Continued):

Additional Exploratory Efficacy Analyses

Rate of Minimal Residual Disease (MRD) Negativity Status

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

Time to Next Anti-CLL Treatment

Time to next anti-CLL treatment will be defined as the number of days from the date of the first dose of venetoclax to the date of first dose of new non-protocol anti-leukemia therapy (NPT) or death from any cause. For subjects who did not take NPT, the data will be censored at the last known date to be free of NPT. TTNT will be analyzed by Kaplan-Meier methodology using data for all dosed subjects. Median TTNT time will be calculated.

Pharmacokinetic/Pharmacodynamic:

An analysis may be performed using a nonlinear mixed-effect population modeling approach with NONMEM software to describe the disposition of venetoclax, to identify significant covariates and explore relationship between pharmacokinetics and pharmacodynamics by combining data from this study with other venetoclax clinical studies. Additional analyses may be performed if useful in the interpretation of the data.

Health Economic and Patient Reported Outcome (PRO) Measures

Descriptive statistics will be calculated for all scales of the EORTC QLQ-C30 and EORTC QLQ CLL16, the EQ-5D-5L utility score, and the EQ-5D-VAS score, including mean change from baseline to the visits identified in Table 5 (Week 1 Day 1, Week 24 Day 1, every 12 weeks starting with Week 24 and Final Visit). Only the EORTC QLQ C30 will be utilized in the Expansion Cohort.

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
ALL	Acute Lymphoblastic Leukemia
ALT	Alanine aminotransferase
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
aPTT	Activated Partial Thromboplastin Time
Bcl	B-Cell Lymphoma
BCR	B-cell receptor
BCR PI	B-cell receptor pathway inhibitor
BUN	Blood Urea Nitrogen
CLL	Chronic Lymphocytic Leukemia
cm	Centimeter
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
COVID-19	Coronavirus Disease - 2019
CR	Complete Remission
CRi	Complete Remission with Incomplete Marrow Recovery
CT	Computed Tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CTLS	Clinical Tumor Lysis Syndrome
CYP2B6	Cytochrome P450 2B6
CYP2C8	Cytochrome P450 2C8
CYP2C9	Cytochrome P450 2C9
CYP2C19	Cytochrome P450 2C19
CYP2D6	Cytochrome P450 2D6
CYP3A	Cytochrome P450 3A
DLBCL	Diffuse Large B-cell Lymphoma
DLT	Dose Limiting Toxicity

DNA	Deoxyribonucleic Acid
DTP	Direct-to-patient
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCCr	Estimated creatinine clearance rate using Cockcroft-Gault Formula
eCRF	Electronic Case Report Form
EDTA	Edetic acid (ethylenediaminetetraacetic acid)
EMA	European Medicines Agency
EP	European Pharmacopoeia
ERIC	European Research Initiative on CLL
FCR	Fludarabine, cyclophosphamide, and rituximab
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FFPE	Formalin Fixed, Paraffin Embedded
FISH	Fluorescence in situ Hybridization
FL	Follicular Lymphoma
G-CSF	Granulocyte-colony stimulating factor
GCP	Good Clinical Practice
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HAV-IgM	Hepatitis A virus immunoglobulin M
HBsAg	Hepatitis B Surface Antigen
HCV Ab	Hepatitis C virus antibody
HDPE	High Density Polyethylene
HIV	Human Immunodeficiency Virus
HNSTD	Highest Nonseverely Toxic Dose
hr	Hour
HT	Histologic transformation
IBM	Ideal Body Mass
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IRC	Independent Review Committee
IRB	Institutional Review Board

IV	Intravenous
IWCLL	International Workshop for Chronic Lymphocytic Leukemia
IxRS	Interactive Response System
kg	Kilogram
LDH	Lactate Dehydrogenase
LN	Lymph Node
LTLS	Laboratory Tumor Lysis Syndrome
LVEF	Left Ventricular Ejection Fraction
MCHC	Mean Corpuscular Hemoglobin Concentration
mRNA	Messenger Ribonucleic Acid
MCL	Mantle Cell Lymphoma
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
µg	Microgram
mg	Milligram
mL	Milliliter
µM	Micromolar
MPV	Mean Platelet Volume
MRD	Minimal Residual Disease
MRI	Magnetic Resonance Imaging
MUGA	Multi Gated Acquisition Scan
NCI	National Cancer Institute
NCI-WG	National Cancer Institute-Working Group
NDC	National Drug Code
NHL	Non-Hodgkin's Lymphoma
nM	Nanomolar
nPR	Nodular Partial Remission
ORR	Overall Response Rate
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic
PD	Progressive Disease
PET	Positron Emission Tomography
PG	Pharmacogenetic
PK	Pharmacokinetic

PR	Partial Remission
PT	Prothrombin Time
QD	Once Daily
qPCR	Quantitative Polymerase Chain Reaction
QTc	QT interval corrected for heart rate
QTcF	QT interval measurement corrected by Fridericia's formula
RBC	Red Blood Cell
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SD	Stable Disease
SGOT	Serum Glutamic-oxaloacetic Transaminase
SGPT	Serum Glutamic-pyruvic Transaminase
SLL	Small Lymphocytic Lymphoma
SPD	Sum of the products of the greatest diameters
STD	Severely Toxic Dose
TLS	Tumor Lysis Syndrome
TTP	Time to Tumor Progression
ULN	Upper Limit of Normal
US	Ultrasound
USP	United States Pharmacopoeia
VAS	Visual Analog Scale
WBC	White Blood Cell

Definition of Terms

AUC	Area under the plasma concentration-time curve
AUC_{0-24}	Area under the plasma concentration-time curve from time zero to hour 24
C_{max}	Maximum observed plasma concentration
CL/F	Apparent oral clearance
IC	Inhibitory concentration
K_i	Inhibition constant
nM	Nanomolar
QRS Duration	The interval between the beginning of the Q wave to the end of the S wave in an ECG
QT Interval	The interval between the beginning of the QRS complex to the end of the T wave in an ECG
$t_{1/2}$	Terminal phase elimination half-life
T_{max}	Time to maximum observed plasma concentration
V/F	Apparent volume of distribution

2.0 Table of Contents

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3.0 Introduction

Bcl-2 Family Proteins

The Bcl-2 family proteins are important regulators of the intrinsic apoptosis pathway. The Bcl-2 oncogene was first identified in follicular lymphoma where the t(14;18) chromosomal translocation results in significant over-expression of the protein in B-cells. The Bcl-2 family of genes encodes a family of closely related proteins that possess either pro-apoptotic or anti-apoptotic activity and share up to four Bcl-2 Homology (BH) domains.[1-4] Many hematologic malignancies are highly dependent upon the anti-apoptotic protein Bcl-2 for survival. Over-expression of Bcl-2 is associated with tumor initiation, disease progression, and drug resistance, and is thus a compelling target for anti-tumor therapy. Bcl-2 is 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 in vitro/in vivo Activity and Preclinical Pharmacokinetic Profile

Venetoclax is a potent, selective and orally bioavailable small molecule inhibitor of Bcl-2 that binds with > 1,000-fold higher affinity for Bcl-2 (K_i < 0.010 nM) than for Bcl-X_L (K_i – 48 nm) or Mcl-1 (K_i > 444 nM).[7]

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

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

The pharmacokinetic profile of venetoclax was evaluated in multiple animal species. In mouse, rat, monkey and dog, the venetoclax pharmacokinetic profile was characterized by low plasma clearance and low volumes of distribution. Half-lives ranged from 2.2 hours in monkey to 12 hours in dog. Food had a marked effect on the oral bioavailability in dog.

Venetoclax has high protein binding to human, rat, dog, and monkey plasma proteins (> 99.9%). In rats, venetoclax was widely distributed into liver, kidneys, spleen, heart, lungs, small intestine, and white fat, but was poorly distributed in testes, brain, muscle, and bone. Metabolism was the major route of elimination with biliary excretion of the parent drug playing the secondary role in rats. Venetoclax showed moderate metabolic stability in in vitro hepatic systems across species tested, except for low to moderate stability in dog hepatocytes.

Venetoclax is a CYP3A4 substrate and both venetoclax and its major human metabolite, M27, are predominately metabolized by CYP3A4 in vitro. Therefore, CYP3A4 inhibitors or inducers are expected to cause changes in venetoclax and M27 exposures. At the 400 mg QD dose, venetoclax and M27 are not predicted to be perpetrators of the major CYP or UGT enzymes, and venetoclax is predicted to weakly inhibit UGT1A1. Venetoclax and M27 are predicted to cause clinical interaction via inhibition with drugs that are substrates of P-gp (e.g., digoxin, dabigatran) and BCRP (e.g., rosuvastatin). Venetoclax is predicted to inhibit OATP1B1 and cause weak interaction with drugs that are substrates of this transporter (e.g., statins).

Venetoclax exhibited potent activity against patient-derived CLL cells treated ex vivo, killing these cells with an average concentration required for 50% effect (EC_{50}) of 0.006 μM (n = 35; note that not all subject samples are from venetoclax trials). Venetoclax was equally potent against the subset of CLL samples bearing the high-risk 17p deletion, with an average EC_{50} of 0.008 μM (n = 5), indicating that venetoclax may have a significant utility in treating subjects with this high-risk disease.

Venetoclax Preclinical Toxicology

The nonclinical toxicology of venetoclax has been evaluated in repeated-dose studies in mice and dogs with up to 4 weeks of once daily oral dosing (and with 4-week recovery periods) and in dogs with 2 weeks of dosing (18-week recovery period); safety pharmacology studies (cardiovascular, neurofunctional, and pulmonary); and in genetic toxicity tests (Ames and in vitro chromosome aberrations assays). The primary toxicities associated with venetoclax administration included effects on the hematologic system (lymphocytes and red blood cell parameters) in mice and dogs and on the male dog reproductive system. There was no evidence of genotoxicity of venetoclax. A severely toxic dose (STD10) was not identified in mice up to and including the top dose of 600 mg/kg/day (overall mean $AUC_{0\text{-}24}$ = 91.5 µg•hr/mL and C_{max} = 7.2 µg/mL). In dogs, the highest non-severely toxic dose (HNSTD) was 150 mg/kg/day, but due to overlapping exposures between the mid and high doses, the HNSTD was defined as the mid dose of 50 mg/kg/day (overall mean $AUC_{0\text{-}24}$ = 472 µg•hr/mL and C_{max} = 27.4 µg/mL).

Venetoclax causes decreases in circulating lymphocytes and lymphocytes in lymphoid tissue. After 4 weeks of dosing, the lymphocyte effects were reversible or partially reversible in the mouse but generally were less reversible in the dog at the end of a 4-week recovery period. However, in a 2-week dog study focused on lymphocyte recovery over an extended (18-week) period, reversibility of lymphocyte effects were demonstrated. Immunophenotyping was used to assess changes in peripheral blood lymphocyte subsets (i.e., mature T cells, helper T cells, cytotoxic T cells, and mature B cells). At the end of the 18-week recovery period, both total and lymphocyte subset counts returned to within range of baseline and control values, and all effects on lymphoid tissue reversed. The venetoclax-related decreases in lymphocytes in blood and lymphoid tissues are considered pharmacologically mediated and non-adverse.[8]

Additional hematological effects of venetoclax treatment included reversible decreases in red blood cell parameters (primarily, hematocrit and hemoglobin concentration) in mice and dogs.

The decreases in red cell parameters were adverse only at the high dose levels in the 4-week studies (i.e., at 600 mg/kg/day in mice and at 150 mg/kg/day in dogs, but all red cell parameters were reversible at the end of a 4-week recovery period.

Effects on both lymphocytes and red cell mass are readily monitored in subjects.

Male dog reproductive effects consisted of markedly reduced numbers of spermatogonia in the testes at all venetoclax dose levels after 4 weeks of dosing, with progression to severe decreases in the numbers of all germ cells in testes during the 4-week recovery period. Male mice did not have testicular changes associated with venetoclax administration. The translatability of the testicular findings in dogs to humans is unknown, but this change may be related to venetoclax pharmacology, as one or more members of the Bcl-2 family of proteins play a role in spermatogenesis.[9-11] In view of the potential treatment benefits of venetoclax, this finding is anticipated not to impact the treatment of subjects with advanced hematologic malignancies.

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

In an ongoing 9-month chronic toxicity study of dogs with venetoclax, hypopigmented (white) facial hair was observed after approximately 3 months of dosing (ongoing study AbbVie R&D/12/384). The finding was limited to the mid and high doses (6 and 20 mg/kg/day), and was observed in both males and females. Evidence from Bcl-2 knockout mouse (bcl-$2^{-/-}$) studies indicates that hair hypopigmentation is consistent with

the pharmacological effect of Bcl-2 functional loss, and occurs due to loss of hair follicle melanocytes dependent on Bcl-2 for survival.[12] A dedicated physical examination of the skin and extensive ophthalmic examinations determined that pigmentation of the skin and in the eye (particularly in the iris and fundus) appears unaffected. The potential for development of white (hypopigmented) hair in humans is unknown.

In an anesthetized dog cardiovascular model given intravenous doses of venetoclax, mild reductions in myocardial contractility (maximum rate of rise of left ventricular pressure [dP/dt_{max}]: –6% to –13%) and cardiac output (–11% to –19%) were observed at plasma concentrations of ≥ 16 µg/mL and ≥ 32 µg/mL, respectively. However, no effects on blood pressure, heart rate, or electrocardiogram (ECG) parameters were observed relative to baseline or controls in either the anesthetized dog study or in the conscious dog cardiovascular study using telemeterized animals at maximum drug concentrations of 46 µg/mL and 16 µg/mL, respectively.

Venetoclax was tested in a battery of safety pharmacology assays and produced no effects in central nervous system/neurobehavioral, or respiratory studies in mice at oral doses up to 600 mg/kg. In dogs, mild reductions in cardiac contractility and cardiac output were observed at plasma concentrations of ≥ 16 µg/mL. However, no effects on blood pressure, heart rate, or electrocardiogram (ECG) parameters were observed in dogs at a maximum drug concentration of 46 µg/mL.

On the basis of nonclinical safety pharmacology and toxicology evaluations of venetoclax, and on the basis of nonclinical and human studies of related antiapoptotic Bcl-2 family protein inhibitors, potential mechanism-based toxicities may include lymphopenia and neutropenia,[13] signs of tumor lysis, reduction in red cell mass, decreased spermatogenesis, skin swelling, and hair hypopigmentation. Thrombocytopenia has not been observed in toxicology studies in mice and dogs. These findings are consistent with venetoclax as a Bcl-2 specific (Bcl-X_L sparing) inhibitor. Consequently, thrombocytopenia is not expected to be a dose limiting toxicity (DLT) clinically.

Venetoclax is a CYP3A4 substrate and both venetoclax and its major human metabolite, M27, are predominately metabolized by CYP3A4 in vitro. Therefore, CYP3A4 inhibitors or inducers are expected to cause changes in venetoclax and M27 exposures.

A detailed discussion of the preclinical toxicology, metabolism, and pharmacology can be found in the current version of the Investigator's Brochure.[14]

Venetoclax Clinical Data

As of 28 November 2015, based on the available data in the AbbVie and Genentech/Roche clinical databases, a total of 1662 subjects have been exposed to at least 1 dose of venetoclax in the oncology and immunology development programs. A total of 1498 oncology subjects had data available in AbbVie and Genentech/Roche studies as of 28 November 2015. Of these 1498, 935 subjects had CLL/small lymphocytic leukemia (SLL), 346 subjects had NHL, 115 subjects had MM, and 102 had AML. An additional 66 subjects were healthy volunteers. A total of 564 oncology subjects received the drug as monotherapy, 933 received the drug in combination with other therapies, and 1 subject received venetoclax as a single dose in a DDI study who did not re-enroll into a subsequent monotherapy clinical study. As of 28 November 2015, an additional 98 subjects were exposed to at least 1 dose of venetoclax in the AbbVie immunology study, Study M13-093,

Venetoclax doses in clinical studies have ranged from 20 mg to 1200 mg. Multiple ongoing Phase 1/2 AbbVie and Phase 1/2/3 Genentech/Roche clinical studies are evaluating safety, tolerability, pharmacokinetics, and efficacy of venetoclax as monotherapy or in combination with other therapies (rituximab [R], obinutuzumab (GA101) [G], rituximab or obinutuzumab plus CHOP [cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHOP or G-CHOP, respectively], BR, bendamustine plus obinutuzumab [BG], bortezomib plus dexamethasone, azacitidine or decitabine, and cytarabine) in subjects with hematologic malignancies. Additionally, two Phase 3 studies are ongoing: one study in relapsed/refractory (R/R) CLL exploring the combination of venetoclax and rituximab against BR and one Phase 3 study in first-line CLL exploring

the combination of venetoclax and obinutuzumab against obinutuzumab plus chlorambucil.

Based on the mechanism of action, nonclinical and clinical data available to date, the safety profile of venetoclax is well described. The most common adverse drug reactions across all indications are nausea, diarrhea, hematological effects, and serious and/or opportunistic infections. The important risks identified with venetoclax administration based on nonclinical and clinical data are tumor lysis syndrome (TLS) and neutropenia, particularly in the CLL indication. Infection is a potential risk. Other adverse events commonly observed with venetoclax include nausea, diarrhea, and other hematological effects (including, anemia, thrombocytopenia, and lymphopenia). In addition, as venetoclax is being evaluated in subjects with relapsed/refractory (R/R) disease who had previously been treated with various cytotoxic agents, second primary malignancies are closely being monitored.

Tumor lysis syndrome (TLS) is an important risk, particularly in subjects with R/R CLL. As a result of on-target effects, the potential for TLS with venetoclax was identified early in the program when the initial 3 subjects with CLL/SLL received starting doses of 100 mg or 200 mg and experienced TLS, which was reported as an adverse event for each. Subsequently, 2 fatal events in the setting of TLS and another event of clinical TLS in subjects with CLL/SLL occurred in December 2012. After comprehensive review of all safety data available from studies with venetoclax, a revised dosing regimen with a ramp-up period 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. Overall, the clinical data strongly support that the risk of TLS with venetoclax in CLL/SLL subjects is highest when

initiating venetoclax dosing, especially with a higher initial dose of venetoclax, as well as being greater in subjects with a large tumor burden.

Additional safety and efficacy data are described in detail in the Investigator Brochure.[14]

Chronic Lymphocytic Leukemia (CLL)

Chronic lymphocytic leukemia is a lymphoproliferative disorder, characterized by progressive accumulation of monoclonal, small, mature-appearing $CD5^+$ B cells in peripheral blood, bone marrow, and secondary lymphoid organs. It is the most common form of leukemia in adults in the Western World, accounting for approximately 30% of all leukemias.[15] Chronic lymphocytic leukemia primarily affects elderly individuals; however, approximately one third of patients are less than 60 years of age at diagnosis.[16] 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.[17] 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.[15,18] The approximate 5-year survival rate for patients with CLL is 73%.[19] CLL presents with a variable clinical course. Approximately one-third of patients have indolent disease with prolonged median survival that does not require treatment, and die of causes unrelated to disease. Another third have an initial indolent phase that is followed by rapid progression of the disease requiring therapy. The remaining third have aggressive disease and require treatment at the time of diagnosis. Chronic lymphocytic leukemia patients will often have compromised bone marrow reserve due to their underlying disease. The principal complication of CLL is immunodeficiency related to myelosuppression and as a result, infection is the major cause of death in patients with CLL.[20]

Standard chemotherapeutic options for CLL cause significant immune suppression and myelosuppression, are not well-tolerated by the elderly population and have not consistently offered survival advantage. Treatment decisions for patients with CLL are made 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.

Study Rationale

During recent years, evidence accumulated suggesting that signaling via the BCR could have an important role in the development of CLL and that it could determine the clinical heterogeneity of the disease. The advent of new therapies that target the signalosome brings new evidence in favor of this view. Clinical trials with drugs that inhibit SYK kinase (Fostamatimib), reversible pan-Src kinase (Dasatinib), the BTK inhibitor AVL 292 and PI3Kinase inhibitor SF1126 and others, are underway. Ibrutinib (IMBURVICA) and idelalisib (Zydelig) are currently approved for relapsed CLL patients. These drugs cause rapid response with reduction in lymph node size and splenic mass accompanied by increased PB lymphocytosis likely reflecting that microenvironment modulation could prevent these cells from receiving the survival signals delivered by the microenvironment.[21] However, in early trials of Ibrutinib, approximately 10% of the patients developed progressive disease. Few of these patients developed resistance after achieving partial response lasting ≥ 6 months. Distinct single nucleotide variations were noted in these patients.[22]

The mechanism of action of venetoclax is independent of the BCR pathway.[23] 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.

3.1 Differences Statement

This is a Phase 2 study of venetoclax monotherapy for patients who have progressed or developed recurrence after treatment with BCR signaling kinase inhibitors. Safety data and preliminary efficacy responses in the CLL population from the Phase 1 trial support this Phase 2 trial. All subjects will be evaluated for histologic transformation (HT) to high grade lymphoma at screening with a positron emission tomography using 18F-fluorodeoxyglucose (FDG) and subsequent biopsy of PET avid areas to exclude subjects with histological and immunophenotypical confirmation of HT.

3.2 Benefits and Risks

The preliminary clinical data of venetoclax monotherapy in subjects with CLL/SLL, MCL and NHL have shown a favorable benefit to risk ratio drug during Study M12-175. In Arm A (CLL and SLL) 47 of 52 (90%) evaluable subjects achieved a best response of CR. CR with incomplete bone marrow recovery (CRi), or partial response (PR): 12 (21%) subjects experienced CR/CRi and 35 (63%) subjects experienced PR of which 30 were confirmed.

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

The encouraging preliminary data from the ongoing venetoclax studies in R/R CLL indicate that venetoclax may be beneficial in subjects with relapsed CLL after multiple treatment regimens.

Refer to Appendix G for COVID-19 (coronavirus disease 2019)-related processes.

4.0 Study Objectives

The primary objective of this study is to evaluate the efficacy and safety of venetoclax monotherapy in subjects with Chronic Lymphocytic Leukemia (CLL) relapsed after or refractory to treatment with B-cell Receptor Signaling Pathway Inhibitors (specifically Ibrutinib or Idelalisib). Efficacy will be measured by overall response rate (ORR).

The secondary objectives are to evaluate the duration of response, time to progression (TTP), progression free survival (PFS) and overall survival (OS).

Additional exploratory objectives will be evaluated. Time to next anti-CLL treatment (TNT) and minimal residual disease (MRD) will be assessed in the peripheral blood and bone marrow (BM) by flow cytometry and PCR. Health Economic and Patient-Reported Outcome Measures will include the EORTC QLQ-C30 and EORTC QLQ CLL16 (a measure of health-related quality of life specific to CLL) and the EQ 5D 5L (measure of general health status) including EQ-5D-VAS.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is an open-label, non-randomized, two arm, multicenter study to determine the efficacy and safety of venetoclax (GDC-0199) monotherapy in subjects with Chronic Lymphocytic Leukemia (CLL) relapsed/refractory to treatment with B-cell Receptor Signaling Pathway Inhibitors (specifically Ibrutinib and Idelalisib) sponsored by AbbVie in collaboration with Genentech/Roche.

This study is designed to enroll approximately 120 subjects who have CLL that is refractory to treatment with ibrutinib and/or idelalisib, has relapsed on treatment or experienced progression after discontinuation of either one of these agents.

Two arms and an expansion cohort will be implemented to enroll as follows:

- Arm A with approximately 40 subjects that have ibrutinib-resistant with relapsed or refractory CLL.
- Arm B with approximately 20 subjects that have idelalisib-resistant with relapsed or refractory CLL.
- Expansion Cohort with approximately 60 subjects that have either ibrutinib-resistant or idelalisib-resistant with relapsed or refractory CLL. Subjects who have received both agents and any additional interim therapy

will be enrolled into the corresponding arm based on their most recent treatment.

Subjects in this study will be enrolled at approximately 15 research sites.

The study was designed to enroll approximately 120 subjects to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. Therefore, if the target number of subjects has been enrolled, there is a possibility that additional subjects in screening will not be enrolled.

Dosing Schedule Overview (All Subjects)

Venetoclax will be administered orally once daily (QD), continuously. Each dose of venetoclax should be taken with approximately 240 mL of water within 30 minutes after the completion of breakfast or the subject's first meal of the day. To mitigate the risk for TLS, a lead-in period of 5 weeks will be employed with step wise dose increments. For tumor lysis syndrome prophylaxis, all subjects will be classified into 3 risk categories based on the risk for developing TLS prior to venetoclax administration.

Subjects in low risk category and medium risk category with CrCl ≥ 80 ml/min and low tumor burden will begin the lead-in period in the outpatient setting with an initial dose of 20 mg venetoclax on Week 1 Day 1. If no significant findings suggestive of clinical or lab TLS occur within 24 hours, the same dose will be continued until Day 7 in the outpatient setting. Subjects with no laboratory abnormalities suggestive of LTLS will escalate to a dose of 50 mg venetoclax on Week 2 Day 1 in the outpatient setting.

Medium risk subjects with CrCl < 80 mL/min and/or higher tumor burden (i.e., ALC $> 100 \times 10^9$/L or multiple bulky nodes) may be admitted to the hospital at the investigator discretion to begin the lead-in period with an initial dose of 20 mg venetoclax on Week 1 Day 1. If no significant findings suggestive of clinical or lab TLS occur within 24 hours, the same dose will be continued until Day 7 in the outpatient setting. Subjects with no laboratory abnormalities suggestive of LTLS will escalate to a dose of 50 mg venetoclax on Week 2 Day 1 in the outpatient setting. Subjects may be hospitalized prior to the

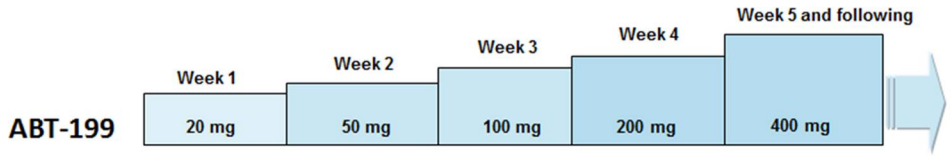
first dose of 50 mg if they continue to have Cr Cl < 80 mL/min and/or higher tumor burden (i.e., ALC > 100 × 10^9/L or multiple bulky nodes) at the investigator's discretion.

All high risk subjects will be admitted to the hospital and begin the lead-in period with an initial dose of 20 mg venetoclax on Week 1 Day 1. If no significant findings suggestive of clinical or lab TLS occur within 24 hours, the same dose will be continued until Day 7 in the outpatient setting. Subjects will be hospitalized prior to the first dose increment to 50 mg beginning on W2D1. Each subject's risk status may be reassessed prior to subsequent dose escalations per the guidelines in Section 6.1.7.1, Prophylaxis and Management of Tumor Lysis Syndrome.

If no significant findings occur within 24 hours at dose escalation, the study drug will be continued at the same dose from Days 2 through 7 in the outpatient setting. If there is indication of lab or clinical TLS, the study drug dose will be held until resolution of all findings. TLS management will be implemented as appropriate. If aggressive correction of electrolytes was performed, the next dose of venetoclax can only be given when electrolytes have been stable without any further treatment for at least 24 hours.

A lower starting dose to the lead-in regimen may be implemented for individual subject(s) at particularly high risk for TLS. For these individual cases, a discussion must occur between the investigator and the AbbVie medical monitor.

Figure 1. Lead-In Dosing Schematic



Dosing Schedule Details

Lead-In Period (All Subjects)

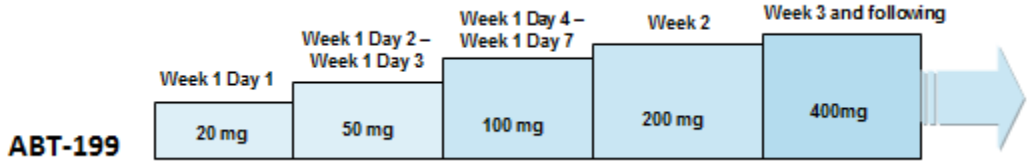
Every subject will receive an initial dose of 20 mg on Week 1, Day 1 of the lead-in period.

If one or more electrolyte changes (from the 0 hour pre-dose value) suggestive of TLS occurs within 24 hours of the 20 mg dose, no additional venetoclax doses will be administered until resolution. See Appendix D, Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome (TLS), for procedures to follow. If aggressive correction of electrolytes was performed, the subsequent dose of venetoclax can only be given when electrolytes have been stable without any further treatment for at least 24 hour. Upon resolution of laboratory abnormalities, the subject will remain on the 20 mg dose through Week 1 (e.g., Week 1 Day 2 – Week 1 Day 7).

Subjects who had drug interruptions may escalate to 50 mg after they have been on a 20 mg dose for 7 days.

After a week at 50 mg, weekly dose increments will be implemented as follows: 100 mg → 200 mg → 400 mg (or additional lead-in steps to designated 400 mg dose) as tolerated.

Figure 2. Expansion Cohort: Modified Dose Ramp-Up for Select High Risk Subjects Only



Expansion Cohort: Modified Dose Ramp-Up for Select High Risk Subjects Only

For subjects in the Expansion Cohort, a modified lead in period may be implemented if a high risk subject has clinical signs of progression during the screening period, to allow dose escalation to 400 mg by Week 3 Day 1. A discussion between the investigator and the AbbVie medical monitor must occur prior to approval of this modified lead-in period. These subjects will be admitted to the hospital and begin the lead-in period with an initial dose of 20 mg venetoclax on Week 1 Day 1. If no significant findings suggestive of clinical or lab TLS occur within 24 hours, the dose will be increased to 50 mg on Week 1 Day 2. If no significant findings suggestive of clinical or lab TLS occur within 24 hours the same dose will be administered for two days prior to the next dose increment. The dose of venetoclax will be further increased to 100 mg on Week 1 Day 4 and will be continued through Week 1 Day 7. If there are no significant findings suggestive of clinical or lab TLS that occur within 24 hours at this dose level, then the venetoclax dose will be increased to 200 mg on Week 2 Day 1. Subjects will remain in the hospital for at least 24 hours after reaching the 200 mg dose. If no significant findings suggestive of clinical or lab TLS occur within 24 hours, then the subject will continue at the 200 mg dose through Week 2 Day 7. Subjects will be hospitalized the night before venetoclax dose is to be increased to 400 mg on Week 3 Day 1 and remain in the hospital at least till the post dose 24 hours lab results are reviewed by the investigator and show no concerns for TLS related electrolyte changes.

Subjects enrolled into the Expansion Cohort with bulky disease at study entry who are non-responders or subjects who show signs of clinical progression after completing the ramp up to 400 mg either by clinical disease Assessment or by CT/MRI scan between Week 6 to Week 12 may be permitted to escalate venetoclax to 600 mg dose. A discussion between the investigator and the AbbVie medical monitor must occur prior to this dose escalation.

For all dose escalations, laboratory values for subject management must be reviewed in real time by the investigator and prior to the subject's next dose to ensure appropriate subject management. Based upon the laboratory values, the subject may continue dosing,

may need to hold dose until resolution, may require hospitalization for further monitoring or may need additional post-dose laboratory checks. (See Appendix D, Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome [TLS], for procedures to follow.)

Refer to Section 6.1.7.1, Prophylaxis and Management of Tumor Lysis Syndrome, for additional details on TLS prophylaxis.

Option to Continue Venetoclax Treatment

Subjects may continue receiving study drug for up to 2 years following the date of the last subject enrolled provided they continue to tolerate the drug, have no evidence of disease progression, and do not meet any of the criteria for subject discontinuation. (Section 5.4.1).

Extended Access

AbbVie will provide venetoclax for monotherapy use until 5 years from the date of the last subject enrolled, until disease progression, or until a subject chooses to receive commercial supply of VENCLEXTA.

For subjects continuing into the Extended Access period of the trial, venetoclax will be dispensed at the Final Visit that will occur prior to 31Dec2018. Extended Access visits will continue every 12 weeks (+/– 7 days) until disease progression or until a subject chooses to receive commercial supply of VENCLEXTA. Extended Access visits will include study drug administration, collection of AEs/SAEs and concomitant medication information, hemoglobin, hematocrit, absolute neutrophil count, absolute lymphocyte count, platelet counts and white blood cell counts, disease progression, and dispensing and collection of subject diaries. All other procedures for disease assessments will be performed as standard of care.

5.2 Selection of Study Population

Subjects must undergo screening procedures within 28 days prior to initial study drug administration including disease assessment with PET/CT and bone marrow aspirate.

Histologic transformation to high grade lymphoma needs to be excluded at screening with a positron emission tomography using 18F-fluorodeoxyglucose (FDG). Subjects with (FDG) uptake on PET scan above maximum standardized uptake value (SUV max) of 10 will be excluded, unless confirmed by biopsy of the suspicious area to rule out Richter's transformation and other malignancies. Additionally, subjects who have CD38+, ZAP 70+, TP 53 mutated and unmutated IGHV CLL whose PET has SUV max between 7 – 9 with at least one of the following parameters: B symptoms, nodal diameter > 5 cm, and/or unexplained lactate dehydrogenase (LDH) elevation will need biopsy of the suspicious site. If the biopsy is not feasible due to an inaccessible lesion or if the subject has declined to undergo the biopsy, the subject will be excluded from the study. Subjects with histological and immunophenotypical confirmation of Richter's transformation with a high grade lymphoproliferative disease will be excluded from the study.[24]

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. Subject must voluntarily sign and date an informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study specific procedures.
2. Subject must be ≥ 18 years of age.
3. Subject must have diagnosis of CLL that meets published 2008 IWCLL NCI-WG criteria.

4. Subject has relapsed/ refractory disease with an indication for treatment according to the 2008 IWCLL NCI-WG criteria.
5. Subject who has refractory disease or developed recurrence after therapy with either Ibrutinib or Idelalisib and meets one of the following:
    - treatment failure with either of the above agents;
    - progression during treatment or after discontinuation of either of the above agents.
6. Subject has an Eastern Cooperative Oncology Group (ECOG) performance score of ≤ 2.
7. Subject must have adequate bone marrow function at Screening as follows:
    - Absolute Neutrophil Count (ANC) ≥ 1000/μL;
        - An exception is for subjects with an ANC < 1000/μL at Screening; when bone marrow is heavily infiltrated with underlying disease (approximately 80% or more), G-CSF may be administered at the discretion of the investigator, after Screening and prior to the first dose of venetoclax to achieve the ANC eligibility criteria (≥ 1000/μL).
    - Platelets ≥ 30,000/mm^3 (without transfusion support, evidence of mucosal bleeding, known history of bleeding episode within 3 months of screening and history of bleeding disorder);
    - Hemoglobin ≥ 8.0 g/dL
        - For subjects with AIHA or ITP, hemoglobin of < 8 g/dL and platelet count of < 30,000/mm^3 without corticosteroid therapy a discussion between the investigator and the AbbVie medical monitor must occur.
8. Subject must have adequate coagulation profile, renal, and hepatic function, per laboratory reference range at Screening as follows:
    - aPTT and PT not to exceed 1.5 × the upper limit of normal (ULN).
    - AST and ALT ≤ 1.5 × the upper normal limit (ULN) of institution's normal range.

- Bilirubin ≤ 1.5 × ULN. Subjects with AIHA and Gilbert's syndrome may have a bilirubin > 1.5 × ULN, per discussion between the investigator and AbbVie medical monitor.
- Creatinine clearance ≥ 50 mL/min using 24-hour measured GFR **or** estimated by modified Cockcroft-Gault equation.

  Note: For subjects that have BMI of > 30 kg/m^2, 24-hour measured creatinine clearance is required.

$$\text{CrCl (mL/min)} = \frac{[(140\text{-age in years}) \times (\text{weight in kg}) \times (0.85 \text{ if patients is female})]}{[72 \times (\text{serum creatinine in mg/dL})]}$$

Or, if serum creatinine is µmol/L

$$\text{CrCl (mL/min)} = \frac{[(140\text{-age in years}) \times (\text{weight in kg}) \times (0.85 \text{ if patient is female})]}{[0.815 \times (\text{serum creatinine in mmol/L})]}$$

9. For high risk subjects (as defined in Section 6.1.7.1) a pre-approval by the AbbVie medical monitor is required prior to enrollment.

10. Female subjects of childbearing potential and non-sterile male subjects must practice at least one of the following methods of birth control with partner(s) beginning with initial study drug administration and continuing to 30 days after the last dose of study drug:

    - Total abstinence from sexual intercourse as the preferred lifestyle of the subject; periodic abstinence is not acceptable;
    - Intrauterine device (IUD);
    - Double-barrier method (contraceptive sponge, diaphragm or cervical cap with spermicidal jellies or cream AND a condom);
    - Hormonal contraceptives (oral, parenteral or transdermal) for at least 3 months prior to study drug administration;
    - Surgically sterile partner(s); acceptable sterility surgeries are: vasectomy, bilateral tubal ligation 3 months prior to screening, bilateral oophorectomy or hysterectomy.

If hormonal contraceptives are used, the specific contraceptive must have been used for at least 3 months prior to study drug administration. If the subject is currently using a hormonal contraceptive, she should also use a barrier method during this study from initial study drug administration to 30 days after the last dose of study drug. Any contraception method must be continued for 30 days after the last dose of study drug.

11. Females of childbearing potential (i.e., postmenopausal for at least 1 year with no alternative medical reason or surgically sterile) must have negative results for pregnancy test performed:
    - At Screening with a serum sample obtained within 14 days prior to the first study drug administration, and
    - Prior to dosing with urine sample obtained on Week 1 Day 1, if it has been > 7 days since obtaining the serum pregnancy test results.
12. Male subjects must agree to refrain from sperm donation, from initial study drug administration until 90 days after the last dose of study drug.

Rationale for Inclusion Criteria

(1) In accordance with Harmonized Good Clinical Practice (GCP)

(2 – 7) To select the subject population

(8 – 9) For the safety of the subjects

(10 – 12) The impact of venetoclax on pregnancy is unknown

5.2.2 Exclusion Criteria

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

1. Subject has previously received venetoclax.

2. Subject has undergone an allogeneic stem cell transplant within the past 1 year.
3. Subject has developed Richter's transformation confirmed by biopsy.
4. Subject has active and uncontrolled autoimmune cytopenias (for 2 weeks prior to screening), including autoimmune hemolytic anemia (AIHA) and idiopathic thrombocytopenic purpura (ITP) despite low dose corticosteroids.
5. Subject has tested 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).
6. Subject has chronic hepatitis B virus (HBV) or hepatitis C (HCV) requiring treatment. Note: Subjects with serologic evidence of prior vaccination to HBV (i.e., HBs Ag–, anti-HBs+ and anti-HBc–) and positive anti-HBc from IVIG may participate.
7. Subject has received any of the following **within 30 days** prior to the first dose of study drug with the exception of a BCR PI;
    - Any anti-cancer therapy including chemotherapy, immunotherapy or radiotherapy;
    - Investigational therapy, including targeted small molecule agents (with the exception of Ibrutinib and Idelalisib).
8. Subject has received the following **within 7 days** prior to the first dose of study drug:
    - Steroid therapy with anti-neoplastic intent;
    - Strong and Moderate CYP3A inhibitors (see Appendix C for examples).
9. Subject has consumed the following **within 3 days** prior to the first dose of study drug:
    - B-cell receptor pathway inhibitor (Ibrutinib or Idelalisib);
    - Grapefruit or grapefruit products;
    - Seville oranges (including marmalade containing Seville oranges);

- Star fruit.

10. Subject has known contraindication or allergy to both xanthine oxidase inhibitors and rasburicase.

11. Subject has malabsorption syndrome or other condition that precludes enteral route of administration.

12. Subject has a cardiovascular disability status of New York Heart Association Class ≥ 2. Class 2 is defined as cardiac disease in which patients are comfortable at rest but ordinary physical activity, results in fatigue, palpitations, dyspnea or angina pectoris.

13. Subject has a significant history of cardiovascular, pulmonary, renal, hepatic, neurologic, psychiatric, endocrinologic, metabolic or immunologic disease that in the opinion of the investigator would adversely affect his/her participation in this study or interpretation of study results. For subjects who have required an intervention for any above diseases within the past 6 months a discussion between the investigator and the AbbVie medical monitor must occur.

14. Subject has unresolved toxicities from prior anti-cancer therapy, defined as any grade 2 or higher clinically significant non-hematologic toxicity (excluding alopecia).

15. Subject exhibits evidence of other clinically significant uncontrolled condition(s) including, but not limited to:

    - Uncontrolled systemic infection (viral, bacterial, or fungal);
    - Febrile neutropenia.

16. Subject has a history of active malignancy other than CLL within the past 2 years prior to study entry, 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.

17. A female subject is pregnant or breast-feeding.

Rationale for Exclusion Criteria

(1 – 9) To select the appropriate subject population

(10 – 16) For the safety of the subjects

(17) The impact of venetoclax on pregnancy is unknown

5.2.3 Prior and Concomitant Therapy

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 the Screening visit 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 electronic case report form (eCRF).

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 study treatment with the exception of inhalational steroids for the treatment of asthma or COPD, topical steroids and replacement corticosteroid therapy for an inherited or acquired deficiency.

In addition, limited corticosteroid treatment (for no more than 14 days with rapid taper) is allowed while on study for subjects with clinically significant 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 and management of lymphopenia, refer to Section 6.1.7.3.

The AbbVie medical monitor identified in Section 7.0 should be contacted if there are any questions regarding concomitant or prior therapy(ies).

General guidelines regarding excluded and cautionary medications are summarized in Table 1.

Table 1. Excluded and Cautionary Medications/Food Items (See Appendix C for Examples of the Medications)

Excluded
Grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or starfruit
Excluded During Ramp-Up Phase and Cautionary Afterwards
• **Strong and Moderate CYP3A Inhibitors**
  ○ Exclude during ramp-up phase and consider alternative medications. If subject requires use of these medications after the ramp-up phase, use with caution and reduce the venetoclax dose 2-fold for moderate inhibitors and 4-fold for strong inhibitors during co-administration. After discontinuation of CYP3A inhibitor, wait for 3 days before venetoclax dose is increased back to the initial maintenance/target dose.
• Strong and Moderate CYP3A inducers
  ○ Exclude during ramp-up phase and consider alternative medications. If subject requires use of these medications after the ramp-up phase, use with caution and contact AbbVie medical monitor for guidance.

Cautionary • Warfarin • P-gp substrates • BCRP substrates • OATP1B1/1B3 substrates • P-gp inhibitors • BCRP inhibitors

Table 2. Sample of Permitted Medications

Drug or Therapy	Comments
Colony stimulating factors e.g., G-CSF, GM-CSF	**Permitted**; per ASCO guidelines.[32] Notify AbbVie 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**
Antiherpes and anti-pneumocystis prophylaxis	**Permitted**; if clinically indicated.
Autoimmune thrombocytopenia and hemolytic anemia medications	**Permitted**; if clinically indicated.

A sample list of excluded medications and cautionary medications that fall into these categories can be found in Appendix C. It is not possible to produce a 100% exhaustive 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 medical monitor and discuss the investigator's use of these medications and the investigator's plans to medically monitor the study subject.

5.3 Efficacy and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Table 3. Study Activities for Arm A and Arm B

Activity	Scr[a]	Within 72 Hours Prior to 1st Dose	W1 D1	W1 D2	W1 D3	W2 D1	W2 D2	W3 D1	W3 D2	W4 D1	W4 D2	W5 D1	W5 D2
Informed Consent	X												
Medical History/Oncology History Assessment	X		X										
Adverse Event/Concomitant Medication Assessment	X[b]	X[b]	X	X	X	X	X	X	X	X	X	X	X
Physical Examination[c]*	X		X			X		X		X		X	
Vital Signs*	X		X			X		X		X		X	
ECOG Performance Status*	X		X										
Pregnancy Test[d]	X		X										
Hematology/Chemistry	X	X	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]
Coagulation Panel**	X												
Urinalysis**	X												
Viral Serologies	X												
Viral Polymerase Chain Reaction	X												
12-Lead ECG	X												

Table 3. Study Activities for Arm A and Arm B (Continued)

Activity	W8 D1	W12 D1	W16 D1	W20 D1	W24 D1	W36 D1	Every 12 Weeks Starting After W36	After 1st CR, CRi, or PR	FV	30 Day Safety Visit	Post-Treat[f]	Extended Access Period[p]
Informed Consent												
Medical History/ Oncology History Assessment												
Adverse Event/ Concomitant Medication Assessment	X	X	X	X	X		X	X	X	X	X	X
Physical Examination[c]*	X	X	X	X	X		X	X	X	X	X	
Vital Signs*	X	X	X	X	X		X		X	X	X	
ECOG Performance Status*					X		X		X	X		
Pregnancy Test[d]												
Hematology/Chemistry**	X	X	X	X	X		X	X	X	X	X	
Hematology (Extended Access period)[q]												X
Coagulation Panel**		X			X				X		X	
Urinalysis**					X				X			
Viral Serologies												
Viral Polymerase Chain Reaction												
12-Lead ECG									X			

Table 3. Study Activities for Arm A and Arm B (Continued)

Activity	Scr[a]	Within 72 Hours Prior to 1st Dose	W1 D1	W1 D2	W1 D3	W2 D1	W2 D2	W3 D1	W3 D2	W4 D1	W4 D2	W5 D1	W5 D2
Echocardiogram or a Multi Gated Acquisition Scan (MUGA)[g]	X												
CT or MRI Scan[h]****	X												
PET CT	X												
Bone Marrow Aspirate and Biopsy	X												
Disease Assessments[i]*	X											X	
MRD Assessment[j]	X												
Survival Assessment													
Dispense/Collect Venetoclax and Subject Calendars/Diaries			X			X		X		X		X	
EORTC QLQ C30 and EORTC QLQ CLL16[k]			X										
EQ-5D-5L and EQ-5D-VAS[k]			X										

Table 3. Study Activities for Arm A and Arm B (Continued)

Activity	W8 D1	W12 D1	W16 D1	W20 D1	W24 D1	W36 D1	Every 12 Weeks Starting After W36	After 1st CR, CRi, or PR	FV	30 Day Safety Visit	Post-Treat[f]	Extended Access Period[p]
Echocardiogram or a Multi Gated Acquisition Scan (MUGA)[g]												
CT or MRI Scan[h]****	X				X[l]	X[l]	X	X[m]	X[r]		X[l]	
PET CT												
Bone Marrow Aspirate and Biopsy								X[n]				
Disease Assessments[i]*	X	X	X	X	X	X	X	X	X		X	
MRD Assessment[j]					X			X				
Survival Assessment											X[o]	X
Dispense/Collect Venetoclax and Subject Calendars/Diaries	X	X	X	X	X	X	X					X
EORTC QLQ C30 and EORTC QLQ CLL16[k]					X	X	X		X			
EQ-5D-5L and EQ-5D-VAS[k]					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;

** within 72 hours prior to scheduled visit starting with Week 8 Day 1;

Table 3. Study Activities for Arm A and Arm B (Continued)

*** within 72 hours prior to scheduled visit;

**** within 3 days of the scheduled visit.

a. Subjects will undergo screening procedures within 28 days prior to the first study drug administration.

b. 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.

c. A complete physical examination will be performed at Screening and the 30 Day Follow-Up Visit. A symptom directed physical examination may be performed at every other visit. Refer to Section 5.3.1.1 Physical Examination, for more details.

d. Urine pregnancy test must be obtained at Week 1 Day 1, if it has been > 7 days since obtaining the serum pregnancy results at Screening.

e. There is no 72 hour window for these samples. Refer to Section 6.1.7.1, Prophylaxis and Management of Tumor Lysis Syndrome and Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome (TLS).

f. For subjects who discontinue venetoclax monotherapy but have not had an event of disease progression, post treatment follow-up visits will be performed every 3 months for a period of 3 years after the last subject has enrolled in the study until discontinuation from the study due to disease progression requiring alternative therapy or upon a subject's refusal of the Post-Treatment visits.

g. Assessment of ejection fraction will be made at screening at the discretion of the investigator. Subsequent evaluation of Left Ventricular Ejection Fraction (LVEF) will be made as clinically indicated for subjects who develop signs of cardiac compromise.

h. 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 PD criteria), a CT/MRI scan may be performed within 2 weeks to confirm or rule out PD as described in Section 5.3.3.2.

i. All measurable disease must be documented at screening by laboratory testing, physical examination, CT scans (or MRI if CT is medically contraindicated), and bone marrow examinations. For all subsequent disease assessments, only PE and laboratory testing is required unless confirmation of CR is required. If confirmation of CR is required a CT/MRI and Bone Marrow will also be completed.

j. Screening sample will assess individual disease characteristics and the Week 24 sample will measure disease burden. MRD will be assessed in peripheral blood and bone marrow for subjects achieving CR/CRi at the 8 week confirmatory visit. After Week 24, for subjects that achieve a radiographic PR, MRD will be assessed in peripheral blood. MRD for these subjects (radiographic PR/CR/CRi) will continue to be assessed in the peripheral blood at 12 weeks interval visits until 2 consecutive negative MRD levels are reported. A final MRD status will be assessed in bone marrow aspirate once MRD negativity is achieved in two consecutive peripheral blood samples.

k. The Health Economic and Patient Reported Outcomes questionnaires should be administered and completed prior to any other study procedures being performed at these visits. Refer to Section 5.3.8, Health Economic and Patient-Reported Outcome Measures, for further information. Subjects will be asked to complete a questionnaire assessing the information they were provided for the Patient Information Card and the Tumor Lysis Syndrome Patient Information Brochure, at the Week 2 Day 1 visit.

Table 3. Study Activities for Arm A and Arm B (Continued)

l. The Week 24 scan may be performed within 2 weeks before or after the Week 24 scheduled visit provided that it has been at least 8 weeks since the subject's last scan. CT/MRI scans should be performed at Week 24 and every 12 weeks thereafter for a period of 1 year from enrollment. Post-treatment CT or MRI scans are collected only if they are performed by the PI's discretion or as part of standard of care. MRI should be performed if CT with contrast is contraindicated (refer to Section 5.3.1.1).

m. A CT/MRI scan will be performed after a response of CR/CRi is determined by clinical criteria (PE/labs) for confirmation. For confirmation of CR, both the CT and/or MRI scan and bone marrow are required to be negative. It is recommended that the CT scan is performed first, and if this does not confirm a CR, then a BM biopsy should not be obtained.

n. For subjects who meet all criteria for CR/CRi (with the exception of a node(s) that is enlarged around 1.5 – 2 cm) may also have a bone marrow performed. If bone marrow was performed to confirm a CR or for any clinical indication close to Week 24, then it should be performed within a week of the Week 24 Day 1 CT/MRI scans. Subjects who have MRD negativity confirmed in peripheral blood on 2 consecutive peripheral blood samples need to have a confirmation by bone marrow.

o. Survival information (i.e., the date/cause of death, post treatment cancer therapies, etc.) will be collected every 3 months for a period of 5 years after the last subject has enrolled into the study.

p. For subjects continuing into the Extended Access period of the trial, visits will include study drug administration, AEs/SAEs and concomitant medication information, hemoglobin, hematocrit, absolute neutrophil count, absolute lymphocyte count, platelet counts and white blood cell counts, disease progression and dispensing and collection of subject diaries. All other procedures for disease assessments will be performed as standard of care.

q. Hematology will include hemoglobin, hematocrit, absolute neutrophil count, absolute lymphocyte count, platelet counts and white blood counts for subjects continuing into the Extended Access period of the trial.

r. CT scan not needed for subjects continuing into the Extended Access period of the trial.

Table 4. Study Activities for Expansion Cohort Standard Lead-In

Activity	Scr[a]	Within 72 Hours Prior to 1st Dose	W1 D1	W1 D2	W1 D3	W2 D1	W2 D2	W3 D1	W3 D2	W4 D1	W4 D2	W5 D1	W5 D2
Informed Consent	X												
Medical History/Oncology History Assessment	X		X										
Adverse Event/Concomitant Medication Assessment	X[b]	X[b]	X	X	X	X	X	X	X	X	X	X	X
Physical Examination[c]*	X		X			X		X		X		X	
Vital Signs*	X		X			X		X		X		X	
ECOG Performance Status*	X		X										
Pregnancy Test[d]	X		X										
Hematology/Chemistry**	X	X	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]
Coagulation Panel**	X												
Urinalysis**	X												
Viral Serologies	X												
Viral Polymerase Chain Reaction	X												
12-Lead ECG	X												

Table 4. Study Activities for Expansion Cohort Standard Lead-In (Continued)

Activity	W8 D1	W12 D1	W16 D1	W24 D1	W36 D1	Every 12 Weeks Starting After W36	After 1st CR, CRi, or PR	FV	30 Day Safety Visit	Post-Treat[f]	Extended Access Period[o]
Informed Consent											
Medical History/Oncology History Assessment											
Adverse Event/Concomitant Medication Assessment	X	X	X	X	X	X	X	X	X	X	X
Physical Examination[c]*	X	X	X	X	X	X	X	X	X	X	
Vital Signs*	X	X	X	X	X	X		X	X	X	
ECOG Performance Status*				X	X	X		X	X		
Pregnancy Test[e]											
Hematology/Chemistry	X	X	X	X	X	X	X	X	X	X	
Hematology (Extended Access period)[q]											X
Coagulation Panel**		X		X				X		X	
Urinalysis**				X				X			
Viral Serologies											
Viral Polymerase Chain Reaction											
12-Lead ECG								X			

Table 4. Study Activities for Expansion Cohort Standard Lead-In (Continued)

Activity	Scr[a]	Within 72 Hours Prior to 1st Dose	W1 D1	W1 D2	W1 D3	W2 D1	W2 D2	W3 D1	W3 D2	W4 D1	W4 D2	W5 D1	W5 D2
Echocardiogram or a Multi Gated Acquisition Scan (MUGA)[g]	X												
CT or MRI Scan[h]****	X												
PET CT	X												
Bone Marrow Aspirate and Biopsy	X												
Disease Assessments[i]*	X											X	
MRD Assessment[j]	X												
Survival Assessment													
Dispense/Collect Venetoclax and Subject Calendars/Diaries			X			X		X		X		X	
EORTC QLQ C30[k]			X										

Table 4. Study Activities for Expansion Cohort Standard Lead-In (Continued)

Activity	W8 D1	W12 D1	W16 D1	W24 D1	W36 D1	Every 12 Wks Starting After W36	After 1st CR, CRi, or PR	FV	30 Day Safety Visit	Post-Treat[f]	Extended Access Period[o]
Echocardiogram or a Multi Gated Acquisition Scan (MUGA)[g]											
CT or MRI Scan[h]****		X			X[l]		X[l]	X[q]			
PET CT											
Bone Marrow Aspirate and Biopsy							X[m]				
Disease Assessments[i]*	X	X	X	X	X	X	X	X		X	
MRD Assessment[j]				X	X		X				
Survival Assessment										X[n]	X
Dispense/Collect Venetoclax and Subject Calendars/Diaries	X	X	X	X	X	X					X
EORTC QLQ C30[k]				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;

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

*** Within 72 hours prior to scheduled visit;

**** Within 3 days of the scheduled visit.

a. Subjects will undergo screening procedures within 28 days prior to the first study drug administration.

b. 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.

c. A complete physical examination will be performed at Screening and the 30 Day Follow-Up Visit. A symptom directed physical examination may be performed at every other visit. Refer to Section 5.3.1.1 Physical Examination, for more details.

Table 4. Study Activities for Expansion Cohort Standard Lead-In (Continued)

d. Urine pregnancy test must be obtained at Week 1 Day 1, if it has been > 7 days since obtaining the serum pregnancy results at Screening.

e. There is no 72 hour window for these samples. Refer to Section 6.1.7.1, Prophylaxis and Management of Tumor Lysis Syndrome and Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome (TLS).

f. For subjects who discontinue venetoclax monotherapy but have not had an event of disease progression, post treatment follow-up visits will be performed every 3 months for a period of 3 years after the last subject has enrolled in the study until discontinuation from the study due to disease progression requiring alternative therapy or upon a subject's refusal of the Post-Treatment visits.

g. Assessment of ejection fraction will be made at screening at the discretion of the investigator. Subsequent evaluation of Left Ventricular Ejection Fraction (LVEF) will be made as clinically indicated for subjects who develop signs of cardiac compromise.

h. 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 PD criteria), a CT/MRI scan may be performed within 2 weeks to confirm or rule out PD as described in Section 5.3.3.2.

i. All measurable disease must be documented at screening by laboratory testing, physical examination, CT scans (or MRI if CT is medically contraindicated), and bone marrow examinations. For all subsequent disease assessments, only PE and laboratory testing is required unless confirmation of CR is required. If confirmation of CR is required a CT/MRI and Bone Marrow will also be completed.

j. Screening sample will assess individual disease characteristics and the Week 24 sample will measure disease burden. MRD will be assessed in peripheral blood and bone marrow for subjects achieving CR/CRi at the 8 week confirmatory visit. After Week 24, for subjects that achieve a radiographic PR, MRD will be assessed in peripheral blood. MRD for these subjects (radiographic PR/CR/CRi) will continue to be assessed in the peripheral blood at 12 weeks interval visits until 2 consecutive negative MRD levels are reported. A final MRD status will be assessed in bone marrow aspirate once MRD negativity is achieved in two consecutive peripheral blood samples.

k. The Health Economic and Patient Reported Outcomes questionnaires should be administered and completed prior to any other study procedures being performed at these visits. Refer to Section 5.3.8, Health Economic and Patient-Reported Outcome Measures, for further information. Subjects will be asked to complete a questionnaire assessing the information they were provided for the Patient Information Card and the Tumor Lysis Syndrome Patient Information Brochure, at the Week 2 Day 1 visit.

l. A CT/MRI scan will be performed after a response of CR/CRi is determined by clinical criteria (PE/labs) for confirmation. For confirmation of CR, both the CT and/or MRI scan and bone marrow are required to be negative. It is recommended that the CT scan is performed first, and if this does not confirm a CR, then a BM biopsy should not be obtained.

m. For subjects who meet all criteria for CR/CRi (with the exception of a node(s) that is enlarged around 1.5 – 2 cm) may also have a bone marrow performed. If bone marrow was performed to confirm a CR or for any clinical indication close to Week 24, then it should be performed within a week of the Week 24 Day 1 CT/MRI scans. Subjects who have MRD negativity confirmed in peripheral blood on 2 consecutive peripheral blood samples need to have a confirmation by bone marrow.

n. Survival information (i.e., the date/cause of death, post treatment cancer therapies, etc.) will be collected every 3 months for a period of 5 years after the last subject has enrolled into the study.

Table 4. Study Activities for Expansion Cohort Standard Lead-In (Continued)

o. For subjects continuing into the Extended Access period of the trial, visits will include study drug administration, AEs/SAEs and concomitant medication information, hemoglobin, hematocrit, absolute neutrophil count, absolute lymphocyte count, platelet counts and white blood cell counts, disease progression and dispensing and collection of subject diaries. All other procedures for disease assessments will be performed as standard of care.

p. Hematology will include hemoglobin, hematocrit, absolute neutrophil count, absolute lymphocyte count, platelet counts and white blood cell counts for subjects continuing into the Extended Access period of the trial.

q. CT scan not needed for subjects continuing into the Extended Access period of the trial.

Table 5. Study Activities for Expansion Cohort Modified Lead-In

Activity	Scr[a]	Within 72 Hours Prior to 1st Dose	W1 D1	W1 D2	W1 D3	W2 D1	W2 D2	W2 D3	W2 D4	W3 D1	W3 D2	W3 D3	W3 D4
Informed Consent	X												
Medical History/Oncology History Assessment	X		X										
Adverse Event/Concomitant Medication Assessment	X[b]	X[b]	X	X	X	X	X	X	X	X	X	X	X
Physical Examination[c]*	X		X			X				X			
Vital Signs*	X		X			X				X			
ECOG Performance Status*	X		X										
Pregnancy Test[d]	X		X										
Hematology/Chemistry**	X	X	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	X[e]
Coagulation Panel**	X												
Urinalysis**	X												
Viral Serologies	X												
Viral Polymerase Chain Reaction	X												
12-Lead ECG	X												

Table 5. Study Activities for Expansion Cohort Modified Lead-In (Continued)

Activity	W8 D1	W12 D1	W16 D1	W24 D1	W36 D1	Every 12 Weeks Starting After W36	After 1st CR, CRi, or PR	FV	30 Day Safety Visit	Post-Treat[f]	Extended Access Period[o]
Informed Consent											
Medical History/Oncology History Assessment											
Adverse Event/Concomitant Medication Assessment	X	X	X	X	X	X	X	X	X	X	X
Physical Examination[c]*	X	X	X	X	X	X	X	X	X	X	
Vital Signs*	X	X	X	X	X	X		X	X	X	
ECOG Performance Status*				X	X	X		X	X		
Pregnancy Test[e]											
Hematology/Chemistry	X	X	X	X	X	X	X	X	X	X	
Hematology (Extended Access period)[p]											X
Coagulation Panel**		X		X				X		X	
Urinalysis**				X				X			
Viral Serologies											
Viral Polymerase Chain Reaction											
12-Lead ECG								X			

Table 5. Study Activities for Expansion Cohort Modified Lead-In (Continued)

Activity	Scr[a]	Within 72 Hours Prior to 1st Dose	W1 D1	W1 D2	W1 D3	W2 D1	W2 D2	W2 D3	W2 D4	W3 D1	W3 D2	W3 D3	W3 D4
Echocardiogram or a Multi Gated Acquisition Scan (MUGA)[g]	X												
CT or MRI Scan[h]****	X												
PET CT	X												
Bone Marrow Aspirate and Biopsy	X												
Disease Assessments[i]*	X												
MRD Assessment[j]	X												
Survival Assessment													
Dispense/Collect Venetoclax and Subject Calendars/Diaries			X			X				X			
EORTC QLQ C30[k]			X										

Table 5. Study Activities for Expansion Cohort Modified Lead-In (Continued)

Activity	W8 D1	W12 D1	W16 D1	W24 D1	W36 D1	Every 12 Wks Starting After W36	After 1st CR, CRi, or PR	FV	30 Day Safety Visit	Post-Treat[f]	Extended Access Period[o]
Echocardiogram or a Multi Gated Acquisition Scan (MUGA)[g]											
CT or MRI Scan[h]****		X			X[l]		X[l]	X[q]			
PET CT											
Bone Marrow Aspirate and Biopsy							X[m]				
Disease Assessments[i]*	X	X	X	X	X	X	X	X		X	
MRD Assessment[j]				X	X		X				
Survival Assessment										X[n]	X
Dispense/Collect Venetoclax and Subject Calendars/Diaries	X	X	X	X	X	X					X
EORTC QLQ C30[k]				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;

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

*** Within 72 hours prior to scheduled visit;

**** Within 3 days of the scheduled visit.

a. Subjects will undergo screening procedures within 28 days prior to the first study drug administration.

b. 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.

c. A complete physical examination will be performed at Screening and the 30 Day Follow-Up Visit. A symptom directed physical examination may be performed at every other visit. Refer to Section 5.3.1.1 Physical Examination, for more details.

Table 5. Study Activities for Expansion Cohort Modified Lead-In (Continued)

d. Urine pregnancy test must be obtained at Week 1 Day 1, if it has been > 7 days since obtaining the serum pregnancy results at Screening.

e. There is no 72 hour window for these samples. Refer to Section 6.1.7.1, Prophylaxis and Management of Tumor Lysis Syndrome and Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome (TLS).

f. For subjects who discontinue venetoclax monotherapy but have not had an event of disease progression, post treatment follow-up visits will be performed every 3 months for a period of 3 years after the last subject has enrolled in the study until discontinuation from the study due to disease progression requiring alternative therapy or upon a subject's refusal of the Post-Treatment visits.

g. Assessment of ejection fraction will be made at screening at the discretion of the investigator. Subsequent evaluation of Left Ventricular Ejection Fraction (LVEF) will be made as clinically indicated for subjects who develop signs of cardiac compromise.

h. 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 PD criteria), a CT/MRI scan may be performed within 2 weeks to confirm or rule out PD as described in Section 5.3.3.2.

i. All measurable disease must be documented at screening by laboratory testing, physical examination, CT scans (or MRI if CT is medically contraindicated), and bone marrow examinations. For all subsequent disease assessments, only PE and laboratory testing is required unless confirmation of CR is required. If confirmation of CR is required a CT/MRI and Bone Marrow will also be completed.

j. Screening sample will assess individual disease characteristics and the Week 24 sample will measure disease burden. MRD will be assessed in peripheral blood and bone marrow for subjects achieving CR/CRi at the 8 week confirmatory visit. After Week 24, for subjects that achieve a radiographic PR, MRD will be assessed in peripheral blood. MRD for these subjects (radiographic PR/CR/CRi) will continue to be assessed in the peripheral blood at 12 weeks interval visits until 2 consecutive negative MRD levels are reported. A final MRD status will be assessed in bone marrow aspirate once MRD negativity is achieved in two consecutive peripheral blood samples.

k. The Health Economic and Patient Reported Outcomes questionnaires should be administered and completed prior to any other study procedures being performed at these visits. Refer to Section 5.3.8, Health Economic and Patient-Reported Outcome Measures, for further information. Subjects will be asked to complete a questionnaire assessing the information they were provided for the Patient Information Card and the Tumor Lysis Syndrome Patient Information Brochure, at the Week 2 Day 1 visit.

l. A CT/MRI scan will be performed after a response of CR/CRi is determined by clinical criteria (PE/labs) for confirmation. For confirmation of CR, both the CT and/or MRI scan and bone marrow are required to be negative. It is recommended that the CT scan is performed first, and if this does not confirm a CR, then a BM biopsy should not be obtained.

m. For subjects who meet all criteria for CR/CRi (with the exception of a node(s) that is enlarged around 1.5 – 2 cm) may also have a bone marrow performed. If bone marrow was performed to confirm a CR or for any clinical indication close to Week 24, then it should be performed within a week of the Week 24 Day 1 CT/MRI scans. Subjects who have MRD negativity confirmed in peripheral blood on 2 consecutive peripheral blood samples need to have a confirmation by bone marrow.

n. Survival information (i.e., the date/cause of death, post treatment cancer therapies, etc.) will be collected every 3 months for a period of 5 years after the last subject has enrolled into the study.

Table 5. Study Activities for Expansion Cohort Modified Lead-In (Continued)

o. For subjects continuing into the Extended Access period of the trial, visits will include study drug administration, AEs/SAEs and concomitant medication information, hemoglobin, hematocrit, absolute neutrophil count, absolute lymphocyte count, platelet counts and white blood cell counts, disease progression and dispensing and collection of subject diaries. All other procedures for disease assessments will be performed as standard of care.

p. Hematology will include hemoglobin, hematocrit, absolute neutrophil count, absolute lymphocyte count, platelet counts and white blood cell counts for subjects continuing into the Extended Access period of the trial.

q. CT scan not needed for subjects continuing into the Extended Access period of the trial.

Table 6. Schedule of PK Blood Collection for Venetoclax (and Possible Metabolite[s]) for All Subjects

Study Visit	Week 1 Day 1	Weeks 2, 3, 4 and 5 Day 1	Weeks 8, 12, 16, 24, Day 1
Collection Times	8 hours post dose	8 hours post dose once started at a new dose level	0 hours (pre-dose)

Notes: The PK collection performed 8 hours post-dose after each increment to a new level of venetoclax may be taken up to 1 hour prior or up to 20 minutes after to allow for processing, if necessary.

The date and time (to the nearest minute) of each study drug dose taken and whether or not the dose was taken within 30 minutes after completing breakfast (or the subject's first meal of the day) will be recorded on the eCRF for each scheduled venetoclax PK day and for the 2 days prior to every scheduled venetoclax PK day.

Table 7. Schedule of Biomarker and Pharmacogenetic Sample Collection for Arm A and Arm B

Sample Collections	Screening	Week 1 Day 1	Week 1 Day 2	Week 2 Day 1	Week 4 Day 1	Week 24 Day 1	After 1st CR or CRi	Final Visit or Time of Relapse[k]	Comments
Pharmacogenetics (Optional)	X[a,f]								4 mL Blood
Serum Markers	X[a]		X[b]		X[b]			X	3.5 mL Blood
Blood for CD19 Cell Isolation Bcl-2 Family Analysis	X[a]							X	8 mL Blood
Blood for CLL FISH	X[a]								4mL Blood
Blood for Mutation and Expression Profiling		X		X					20 mL Blood
Blood for Plasma Markers		X		X				X	4 mL Blood
Bone Marrow Aspirate for Bcl-2 Protein Analysis[c]	X[a]							X	1 mL Bone Marrow Aspirate
Bone Marrow Aspirate for CD19 Isolation[c]	X[a]							X	4 mL Bone Marrow Aspirate

Table 7. Schedule of Biomarker and Pharmacogenetic Sample Collection for Arm A and Arm B (Continued)

Sample Collections	Screening	Week 1 Day 1	Week 1 Day 2	Week 2 Day 1	Week 4 Day 1	Week 24 Day 1	After 1st CR or CRi	Final Visit or Time of Relapse[k]	Comments
Tissue for IHC/FISH[c,e]	X[a,d,e,g]							X[e,g]	FFPE Tissue
Peripheral Blood and Bone Marrow Aspirate for Disease Assessment by PCR	X[h]					X[h]	X[i,j]		3 mL Bone Marrow Aspirate and/or 10 mL Blood
Non-tumor DNA Control	X[f]								Buccal Swab

a. Perform once at either Screening or prior to dosing on Week 1 Day 1.

b. Obtain sample prior to dosing.

c. Biopsy and aspirate (8 mL) samples should be split from samples obtained for 2008 Modified IWCLL NCI-WG Criteria for Tumor Response assessment whenever possible. If additional bone marrow aspirates or biopsies are collected by the site per standard of care, a sample should be provided for this study. Subjects should not be subjected to additional bone marrow sampling only for this purpose.

d. Archive sample may be used at Screening if obtained within 28 days of starting study drug without intervening treatment and representative of subject's current disease state.

e. Lymph node collections will be performed for all subjects with Richter's transformation. Samples should be sent to AbbVie.

f. If the sample is not collected at either of these visits, the sample can be collected at any visit during the study.

g. This collection is optional for all Screening and optional at Final Visit or Time of Relapse for subjects that discontinue for reasons other than Richter's transformation.

h. Only peripheral blood is required for the Screening and Week 24 samples.

i. Both peripheral blood and bone marrow aspirates should be collected after 1st CR/CRi. Bone marrow aspirate should be the first sample drawn.

j. Baseline sample will assess individual disease characteristics and the Week 24 sample will measure disease burden. MRD will be assessed in peripheral blood and bone marrow for subjects achieving CR/CRi at the 8 week confirmatory visit. After Week 24, for subjects that achieve a radiographic PR, MRD will be assessed in peripheral blood. MRD for these subjects (radiographic PR/CR/CRi) will continue to be assessed in the peripheral blood at 12 weeks interval visits until 2 consecutive negative MRD levels are reported. A final MRD status will be assessed in bone marrow aspirate once MRD negativity is achieved in two consecutive peripheral blood samples.

k. No final visit biomarker specimens are required for subjects continuing in the extended assess period of the trial.

Table 8. Schedule of Biomarker and Pharmacogenetic Sample Collection for Expansion Cohort

Sample Collections	Screening	Week 1 Day 1	Week 1 Day 2	Week 2 Day 1	Week 4 Day 1	Week 24 Day 1	Week 36 Day 1	After 1st CR or CRi	Final Visit or Time of Relapse[k]	Comments
Pharmacogenetics (Optional)	X[a,b]									4 mL Blood
Serum Markers	X[a]		X[c]		X[c]				X	3.5 mL Blood
Blood for CD19 Cell Isolation Bcl-2 Family Analysis	X[a]								X	8 mL Blood
Blood for CLL FISH	X[a]									4mL Blood
Blood for Mutation and Expression Profiling		X		X						20 mL Blood
Blood for Plasma Markers		X		X					X	4 mL Blood
Bone Marrow Aspirate for Bcl-2 Protein Analysis[d]	X[a]								X	1 mL Bone Marrow Aspirate
Bone Marrow Aspirate for CD19 Isolation[d]	X[a]								X	4 mL Bone Marrow Aspirate
Tissue for IHC/FISH[c,e]	X[a,e,f,g]								X[e,g]	FFPE Tissue
Peripheral Blood and Bone Marrow Aspirate for Disease Assessment by PCR	X[h]					X[h]	X[h]	X[i,j]		3 mL Bone Marrow Aspirate and/or 10 mL Blood
Non-tumor DNA Control	X[b]									Buccal Swab

a. Perform once at either Screening or prior to dosing on Week 1 Day 1.

b. If the sample is not collected at either of these visits, the sample can be collected at any visit during the study.

c. Obtain sample prior to dosing.

Table 8. Schedule of Biomarker and Pharmacogenetic Sample Collection for Expansion Cohort (Continued)

d. Biopsy and aspirate (8 mL) samples should be split from samples obtained for 2008 Modified IWCLL NCI-WG Criteria for Tumor Response assessment whenever possible. If additional bone marrow aspirates or biopsies are collected by the site per standard of care, a sample should be provided for this study. Subjects should not be subjected to additional bone marrow sampling only for this purpose.

e. Lymph node collections will be performed for all subjects with Richter's transformation. Samples should be sent to AbbVie.

f. Archive sample may be used at Screening if obtained within 28 days of starting study drug without intervening treatment and representative of subject's current disease state.

g. This collection is optional for all Screening and optional at Final Visit or Time of Relapse for subjects that discontinue for reasons other than Richter's transformation.

h. Only peripheral blood is required for the Screening, Week 24 and Week 36 samples.

i. Both peripheral blood and bone marrow aspirates should be collected after 1st CR/CRi. Bone marrow aspirate should be the first sample drawn.

j. Baseline sample will assess individual disease characteristics and the Week 24 and Week 36 samples will measure disease burden. MRD will be assessed in peripheral blood and bone marrow for subjects achieving CR/CRi at the 8 week confirmatory visit. After Week 36, for subjects that achieve a radiographic PR, MRD will be assessed in peripheral blood. MRD for these subjects (radiographic PR/CR/CRi) will continue to be assessed in the peripheral blood at 12 weeks interval visits until 2 consecutive negative MRD levels are reported. A final MRD status will be assessed in bone marrow aspirate once MRD negativity is achieved in two consecutive peripheral blood samples.

k. No final visit biomarker specimens are required for subjects continuing in the extended assess period of the trial.

5.3.1.1 Study Procedures

All study procedures outlined in Table 4 and Table 6 are discussed in detail in this section, with the exception of adverse event information (discussed in Section 6.0). All study data will be recorded on eCRFs with the exception of the pregnancy reporting forms, which will be recorded on paper CRFs.

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. 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 Medical Monitor 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. All of the data from the screening procedures will be collected into the EDC regardless of subjects' enrollment into the study.

Refer to Appendix G for COVID-19-related processes for this section.

Informed Consent

Signed informed consent will be obtained from the subject or the subject's legally acceptable representative before any study-specific procedures are undertaken or before any prohibited medications are withheld from the subject in order to participate in this study. Informed consent is also required for pharmacogenetic (PG) sampling and a portion of the pharmacodynamic (PD) sample collections. Details about how informed consent will be obtained and documented are provided in Section 9.3.

Medical History

The following will be collected during the Screening Visit:

- Complete medical history, including documentation of any clinically significant medical condition
- History of tobacco and alcohol use

Detailed Oncology History:

The following will be collected during the Screening Visit:

- 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)
- Detailed prior and concomitant medication usage including dates of usage and dosing information for all medications and supplements taken

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

Adverse Event and Concomitant Medication Assessment

Medication (prescription or over-the-counter, including vitamins and herbal supplements) will be recorded beginning with the Screening Visit through the end of the study.

At each visit, including the Final Visit and the 30-Day Safety Follow-Up Visit, the subject's medical history will be reviewed and any changes from baseline will be recorded on the adverse event eCRF.

Physical Examination

A **complete physical examination**, including height, will be performed at Screening and at the 30-Day Follow-Up Visit. The complete PE should include an evaluation of head, eyes, ears, nose, and throat (HEENT); cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems.

Clinically significant changes from baseline that are unrelated to disease will be documented in the source documentation and eCRFs as Adverse Events.

A **symptom directed physical examination** may be performed at all other visits (other than Screening and 30 Day Follow-Up visit) and should be limited to systems of primary relevance-that is, cardiovascular, respiratory and/or those associated with symptoms.

Physical Examination (Disease Assessment)

All Physical Examinations (complete or symptom-directed) should also 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. Refer to Section 5.3.3.1 for additional information pertaining to methods of measurement.

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

All physical examinations may be performed within 72 hours before or after the scheduled visit starting with Week 8 Day 1.

Vital Signs

For all subjects, body temperature (oral or tympanic), weight, blood pressure and pulse will be measured at:

- Screening
- Week 1 Day 1
- Week 2 Day 1
- Week 3 Day 1
- Week 4 Day 1
- Week 5 Day 1
- Week 8 Day 1
- Week 12 Day 1
- Week 16 Day 1
- Week 24 Day 1
- Week 36 Day 1 and every 12 weeks thereafter (e.g., Weeks 48, 60, 72, etc.)
- Final Visit
- 30-Day Safety Follow-Up Visit
- Post Treatment Follow-Up Visit

  Note: Vital signs may be performed within 72 hours before or after the scheduled visit starting with Week 8 Day 1.

Blood pressure and pulse rate will be measured after the subject has been sitting for at least 5 minutes on days when study drug is administered in the clinic.

ECOG Performance Status

For all subjects, the ECOG performance status[25] will be performed as follows:

- Screening
- Week 1 Day 1
- Week 24 Day 1
- Week 36 Day 1 and every 12 weeks thereafter (e.g., Weeks 48, 60, 72, etc.)
- Final Visit
- 30-Day Safety Follow-Up Visit

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:

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.

Clinical Laboratory Tests

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 after receipt from the local laboratory. The central laboratory will be utilized for special diagnostic testing only (refer to Table 9, and Section 5.3.1.2, Section 5.3.1.3 and Section 5.3.2.3).

Pregnancy Test

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

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

Pregnancy test results must be reviewed and determined to be negative prior to dosing. Subjects considered not of childbearing potential must be documented as being surgically sterile or postmenopausal for at least 2 years.

Hematology and Chemistry

For all subjects, chemistry and hematology samples will be collected at the following time points.

- Screening
- Baseline within 72 hours of dosing for W1 to W5
- Week 1 Days 1, 2 and 3
- Weeks 2, 3, 4, 5 Days 1 and 2
- Week 8 Day 1
- Week 12 Day 1
- Week 16 Day 1
- Week 24 Day 1
- Week 36 Day 1 and every 12 weeks thereafter (e.g., Weeks 48, 60, 72, etc.)
- Approximately 8 weeks after the CR, CRi or PR criteria for tumor response are first met
- Final Visit
- 30-Day Safety Follow-Up Visit
- Post Treatment Follow-Up Visit
- As needed throughout study

  Note: Chemistry and hematology samples may be collected within 72 hours prior to the scheduled visit starting with Week 8 Day 1. There is no 72 hour window permitted for the chemistry and hematology samples collected Week 1 Day 1 through Week 5 Day 1.

Refer to Table 9 for a special sample handling procedure that must be followed to avoid ex vivo uric acid degradation in the presence of rasburicase for samples analyzed locally.

For chemistry and hematology laboratories performed during Weeks 1 – 5 (lead-in period), refer to Section 6.1.7.1, Prophylaxis and Management of Tumor Lysis Syndrome, and Appendix D, Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome (TLS), for specific requirements.

Additional monitoring as needed based on risk assessment by the investigator and discussion with the AbbVie medical monitor.

Coagulation Panel

For all subjects, PT/aPTT samples will be collected at the following time points:

- Screening
- Week 12 Day 1
- Week 24 Day 1
- Final Visit
- Post Treatment

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

Urinalysis

For all subjects, urinalysis samples will be collected at:

- Screening
- Week 24 Day 1
- Final Visit

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

Viral Polymerase Chain Reaction (PCR)

Approximately 4 mL of blood will be collected by venipuncture into an appropriately labeled tube at the following time points:

- Screening
- As needed throughout study

Viral polymerase chain reaction (PCR) samples are to be collected and sent to the central laboratory for archiving and will only be analyzed if needed due to manifestations of possible infections during the treatment period.

Viral Serologies

- Viral serologies to identify hepatitis B (HBsAg, anti-HBs, total anti-HBc, IgM anti-HBc), hepatitis C (HCV) antibody or RNA, cytomegalovirus, varicella zoster virus, herpes simplex virus, and Epstein-Barr virus will be collected at Screening

Samples for viral serologies are to be collected and sent to the central laboratory for archiving and will only be analyzed if needed for any manifestations of possible infections during the treatment period.

Table 9. Clinical Laboratory Tests for All Subjects

Hematology	Clinical Chemistry	Urinalysis
Hematocrit Hemoglobin Red Blood Cell (RBC) count White Blood Cell (WBC) count Absolute Neutrophilc Count Bands Absolute Lymphocyte Count Monocytes Platelet count (estimate not acceptable) Reticulocyte count[a]	Blood Urea Nitrogen (BUN) Creatinine Clearance Creatinine[b] Total bilirubin Serum glutamic-pyruvic transaminase (SGPT/ALT) Serum glutamic-oxaloacetic transaminase (SGOT/AST) Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphate Uric acid[c] Total protein Glucose Albumin Lactate dehydrogenase (LDH) Magnesium Chloride Bicarbonate/CO2 G6PD assay[d]	Specific gravity Ketones pH Protein Blood Glucose
Coagulation		**Viral Analysis**
Prothrombin time (PT) Activated partial thromboplastin time (aPTT)		Viral Polymerase Chain Reaction (PCR)[e] Viral Serologies

a. To be performed at screening and Week 36.

b. Creatinine clearance should be assessed using Cockcroft-Gault equation or a 24-hour urine collection.

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

d. Prior to rasburicase administration per protocol, test to be performed per label.

e. Viral polymerase chain reaction (PCR) samples are to be collected and sent to the central laboratory for archiving and will only be analyzed if needed due to manifestations of possible infections during the treatment period.

12-Lead Electrocardiogram

For all subjects, a 12-lead resting ECG will be obtained at the following:

- Screening

- Final Visit
- As clinically indicated

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

- normal ECG
- abnormal ECG – not clinically significant
- abnormal ECG – clinically significant
- unable to evaluate

Any ECG report that is both abnormal and clinically significant will be faxed to the Oncology Safety Management Team via the contact information provided in Section 6.1.5 within 5 business days of obtaining the results. The QT interval measurement will be documented in the eCRF only if a "prolonged QT" is observed. Correction by the Fridericia formula (QTcF) is preferred; however, correction by other methods may be acceptable based on discussion with the AbbVie medical monitor. The original ECG tracing will be retained in the subject's records at the study site.

Assessment of Left Ventricular Ejection Fraction (LVEF)

Assessment of ejection fraction will be made at screening by either two-dimensional echocardiogram or a Multi Gated Acquisition Scan (MUGA) at the discretion of the investigator. Subsequent evaluation of LVEF will be made as clinically indicated for subjects who develop signs of cardiac compromise.

Disease Assessments

For all subjects, clinical response will be assessed by the investigator based on analysis of clinical laboratory tests (hematology laboratory values) and physical examination. In addition, upon achieving a clinical response of (CR/CRi), a CT scan of involved anatomic regions (or MRI if CT is medically contraindicated) and bone marrow aspirate and biopsy

will be performed for confirmation. Subjects will be evaluated against the 2008 Modified IWCLL NCI-WG Criteria for Tumor Response including CT imaging (or MRI).

Disease Assessment will be performed at the following visits:

- Screening
- Week 5 Day 1 (or Day 1 of initiation of 400 mg dose)
- Week 8 Day 1
- Week 12 Day 1
- Week 16 Day 1
- Week 24 Day 1
- Week 36 Day 1 and every 12 weeks thereafter (e.g., Weeks 48, 60, 72, etc.) until disease progression, death, discontinuation from the study or study completion.
- Approximately 8 weeks after the CR/CRi criteria is first met (if applicable)
- Final Visit
- Post Treatment Follow-Up Visits

Response criteria definitions are outlined in Section 5.3.3.1.

Note: Disease assessments may be performed 72 hours before or after, starting with Week 8 Day 1.

Radiographic Imaging

A PET and CT scan with contrast must be performed within 28 days prior to study drug administration for all subjects. CT must be of diagnostic quality with contrast to serve as a baseline for future comparisons. CT scans (with contrast) including neck, chest, abdomen, and pelvis will be performed to assess response to treatment. MRI of the abdomen and pelvis with a non-contrast CT scan of the neck and chest may be used instead in subjects for whom CT scan with contrast is contraindicated (i.e., subjects with contrast allergy and impaired renal clearance). Subjects should have the same imaging modality performed throughout the study for consistency and direct comparison.

Interpretation of the PET-CT scans for all subjects including screen failures will be collected in the EDC.

When CR/CRi is determined by clinical criteria at any time during the study, a CT/MRI scan must be performed for confirmation (refer to Table 10). If the CT/MRI scan confirms a CR, then a BM biopsy is also required. For confirmation of CR, both the CT/MRI scan and bone marrow are required to be negative.

When PR is determined by clinical criteria by changes in disease assessment they must be confirmed by a repeat clinical assessment at least 8 weeks after the clinical criteria for response are first met.

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 PD criteria, a CT/MRI scan must be performed within 2 weeks to confirm or rule out PD, as described in Section 5.3.3.2 according to Modified IWCLL NCI-WG Criteria for Tumor Response.

Clinical data and radiographic scans will be interpreted according to 2008 Modified IWCLL NCI-WG Criteria for Tumor Response (refer to Table 10). In addition to being reviewed by the investigator and/or site staff, an independent review will be performed to assess tumor response and disease progression. The independent review facility will provide instructions regarding the preparation and shipment of the data. Interpretations from the independent review will not be sent to the site. Subject treatment management will be based on review by the local investigator and/or site staff. Local assessments will be used for endpoints.

If a subject has study drug interrupted for more than 3 days (i.e., adverse event), the site must contact the AbbVie study team or AbbVie medical monitor to adjust the subject's visit schedule, procedures and/or dosing on a case by case basis. CT/MRI scans will be performed within 3 days of the following visits:

Arm A and Arm B Subjects:

- Screening (PET/CT with contrast of neck, chest, abdomen and pelvis)
- An MRI of the abdomen and pelvis with a non-contrast CT scan of the neck and chest may be used instead in subjects for whom CT scan with contrast is contraindicated
- Week 8
- Week 24
- Every 12 weeks after Week 24 for a period of 1 year from enrollment
- Final Visit* (if the most recent scan is ≥ 8 weeks prior to this visit)
    - *CT scan not needed at Final Visit for subjects entering the Extended Access period.

Expansion Cohort Subjects:

- Screening (PET/CT with contrast of neck, chest, abdomen and pelvis)
- An MRI of the abdomen and pelvis with a non-contrast CT scan of the neck and chest may be used instead in subjects for whom CT scan with contrast is contraindicated
- Week 12
- Week 36
- Final Visit* (if the most recent scan is ≥ 8 weeks prior to this visit)
    - *CT scan not needed at Final Visit for subjects entering the Extended Access period.

Bone Marrow Aspirate and Biopsy

A bone marrow aspirate and biopsy will be done at the following timepoints:

- Screening (within 28 days prior to the first dose of study drug). The bone marrow aspirate and biopsy should be performed after all other eligibility criteria have been met, unless otherwise obtained through standard of care.

- Upon meeting all clinical/laboratory criteria for CR/CRi and having a confirmatory CT/MRI scan that meets the criteria for CR/CRi (with the exception of a node(s) that is enlarged around 1.5 – 2 cm.
- Upon having MRD negativity confirmed in peripheral blood on 2 consecutive samples.

Bone marrow aspirates and biopsies, immunohistochemical analysis and cytogenetics performed as standard of care throughout the study should be captured in EDC. All bone marrow aspirate and biopsy reports (done as standard of care or per protocol) with complete immunohistochemical analysis and cytogenetics must be faxed to the AbbVie primary contact listed in Section 7.0 or designee. All reports must be fully de-identified prior to sending to AbbVie.

Bone marrow aspirates and biopsies for biomarker assessments should be split from this sample whenever possible and when deemed feasible by the investigator. If the subject wishes to participate in the optional biomarker testing, a separate consent form will need to be signed.

The order of collections from the bone marrow aspirate and biopsy should be 1) clinical assessment, 2) MRD assessment and, 3) biomarker assessment.

Minimal Residual Disease (MRD) Assessment

MRD[28] will be assessed in peripheral blood and/or bone marrow aspirate using a recommended methodology (flow cytometry, PCR, and/or sequencing) to define CLL event for all subjects at:

- Screening for baseline assessment (peripheral blood and bone marrow aspirate)
- Week 24 (Peripheral Blood, All Subjects)
- Week 36 (peripheral blood **Expansion Cohort subjects only**)
- Upon achieving CR/CRi (peripheral blood and bone marrow) at the 8 week confirmatory visit. After Week 24 (Week 36 for Expansion Cohort subjects), for subjects that achieve a radiographic PR, MRD will be assessed in

peripheral blood only. For subjects who meet all laboratory criteria for CR with the exception of a node(s) that are enlarged around 1.5 – 2 cm should also have MRD assessed (peripheral blood and bone marrow aspirate).

- MRD for subjects achieving a radiographic PR/CR/CRi will continue to have MRD assessed in the peripheral blood at 12 weeks intervals until two consecutive negative MRD levels are reported.
- Once MRD negativity is achieved and confirmed in peripheral blood (by two consecutive peripheral blood samples), a bone marrow aspirate specimen will be collected for analysis and confirmation of MRD negativity.

  Note: The bone marrow aspirate for MRD assessments (flow cytometry, PCR and/or sequencing) should be the first samples collected. Only peripheral blood is required for the baseline MRD assessment by PCR.

Dispense/Collect Venetoclax and Subject Calendars/Diaries

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

- Week 1 Day 1
- Week 2 Day 1
- Week 3 Day 1
- Week 4 Day 1
- Week 5 Day 1
- Week 8 Day 1
- Week 12 Day 1
- Week 16 Day 1
- Week 24 Day 1
- Week 36 Day 1 and every 12 weeks thereafter (e.g., Weeks 48, 60, 72, etc.)
- Extended Access Period: Every 12 weeks (+/– 7 days)

Subjects will be instructed to record the date and time each dose of study drug is taken, (indicating if any doses of study drug are missed) and whether or not doses were taken

within 30 minutes after completing breakfast or the subject's first meal of the day. The date and time (to the nearest minute) of each dose taken and whether or not the dose was taken within 30 minutes after completing breakfast or the subject's first meal of the day will be recorded on the eCRF on the scheduled venetoclax PK days and for the 2 days prior to every scheduled venetoclax PK day.

Subjects will also be instructed to record adverse events and concomitant medications in the subject calendars/diaries.

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

Health Economic and Patient Reported Outcome Measures

The EORTC QLQ-C30 and EORTC QLQ CLL16 (a measure of health related quality of life), and the EQ-5D-5L and EQ-5D-VAS (measure of general health status) are the measures of quality of life as they pertain to symptomology and treatment that will be assessed in the study.

Arm A and Arm B Subjects

The EORTC QLQ-C30 and EORTC QLQ CLL16 assessment will take place at:

- Week 1 Day 1
- Week 24 Day 1 and every 12 weeks thereafter
- Final Visit
- Post Treatment Follow-Up Visits

The EQ-5D-5L and EQ-5D-VAS assessments will take place at:

- Week 1 Day 1
- Week 24 Day 1 and every 12 weeks thereafter

- Final Visit

Expansion Cohort Subjects:

The EORTC QLQ-C30 assessment will take place at:

- Week 1 Day 1
- Week 24 Day 1
- Week 36 Day 1 and every 12 weeks thereafter
- Final Visit
- Post Treatment Follow-Up Visits

The Health Economic and Patient Reported Outcomes questionnaires should be administered and completed prior to any other study procedures being performed at these visits. Refer to Section 5.3.8, Health Economic and Patient-Reported Outcome Measures, for further information.

Subjects will be asked to complete a questionnaire assessing the information they were provided for the Patient Information Card and the Tumor Lysis Syndrome Patient Information Brochure, at the Week 2 Day 1 visit.

Post-Treatment Follow-Up Visit(s)

Subjects who discontinue venetoclax monotherapy, and have not had an event of disease progression, will remain on study for Post Treatment Follow-Up Visits. During Post Treatment Follow-Up, the following assessments will be performed every 3 months until discontinuation from the study (e.g., disease progression, alternative therapy is required, or a subject's refusal of the Post-Treatment visits) for a period of 3 years after the last subject has enrolled on the study:

- Adverse Event/Concomitant Medication Assessment
- Physical Examination
- Vital Signs

- Hematology and Chemistry
- Coagulation
- Disease Assessments
- The EORTC QLQ-C30 and EORTC QLQ CLL16 Assessment (only the EORTC QLQ C30 will be utilized in the Expansion Cohort)
- CT or MRI scans are not required during Post Treatment Follow-Up, however if collected by the site as standard of care, the data must be recorded in EDC

Note: Effective with protocol Amendment 5, subjects being followed in Post-Treatment as of 08Nov2018 will switch to being assessed per the Survival Assessments below. No new subjects will enter the Post-Treatment period.

Survival Assessment(s)

Survival information (i.e., the date and cause of death, post treatment cancer therapies, disease status etc.) will be collected via clinic visits, telephone calls, or through public records at approximately 3-month intervals (+/– 7 days) after the last study visit for a period of 5 years after the last subject has enrolled on the study.

Extended Access

For subjects continuing into the Extended Access period of the trial, venetoclax will be dispensed at the Final Visit, followed by Extended Access visits every 12 weeks (+/– 7 days) until disease progression, or until a subject chooses to receive commercial supply of VENCLEXTA. Extended Access visits will include:

- AE/SAE/ConMed assessment
- Study drug reconciliation and dispensing
- Hemoglobin, hematocrit, absolute neutrophil count, absolute lymphocyte count, platelet counts and white blood cell counts
- Dispense/Collect subject diaries

All other procedures for disease assessments will be performed as standard of care.

Richter's Transformation and Second Primary Malignancies Assessment

Richter's transformation and second primary malignancies information (i.e., confirmation if the subject developed Richter's transformation and/or second primary malignancies and any post study treatment for CLL, etc.) will be collected via clinic visits or telephone calls at 3 month intervals after the last study visit for a period of up to 5 years after the last subject has been enrolled, for those subjects who have consented for this follow-up procedure.

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 and AbbVie medical monitor before a subject can be administered study drug. Subjects will not be enrolled in the study if laboratory or other screening results are unacceptable.

Confinement

All high risk subjects will be hospitalized for TLS prophylaxis and observation prior to their first dose of venetoclax at 20 mg and at 50 mg. Additionally, subjects who continue to meet the criteria for high risk of TLS will be hospitalized for prophylaxis and monitoring at each subsequent dose increment.

Subjects in the Medium Risk category who have creatinine clearance of < 80 mL/min and/or higher tumor burden (i.e., ALC > 100×10^9/L or multiple bulky nodes) may be handled as high risk subjects per investigator discretion for the first dose of venetoclax at 20 mg and 50 mg.

Meals and Dietary Requirements

Each dose of venetoclax will be taken with approximately 240 mL of water within 30 minutes after the completion of breakfast or the subject's first meal of the day. 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 study drug administration and until the last day of treatment is completed due to possible CYP3A mediated metabolic interaction.

5.3.1.2 Blood Samples for Pharmacogenetic Analysis (Optional)

One 4 mL whole blood sample for DNA isolation will be collected at Screening or prior to first dose of study drug on Week 1 Day 1 from each subject who consents to provide samples for pharmacogenetic analysis. If the sample is not collected at either of these visits, it may be collected at any visit during the study. The procedure for obtaining and documenting informed consent is discussed in Section 9.3.

Whole blood will be collected by standard phlebotomy techniques as described below:

- Collect approximately 4 mL of blood into an appropriately labeled EDTA tube.
- Immediately invert the collection tube 8 to 10 times to reduce the likelihood of clot formation.
- Store samples at –20°C or colder within 30 minutes of the blood draw until shipped/transported to AbbVie on dry ice sufficient to last during shipment/transport.

Samples will be shipped frozen to central laboratory. The central laboratory or AbbVie will maintain the samples for DNA extraction and long-term storage. Samples should not be allowed to thaw prior to arrival at the central laboratory. Arrangements will be made with AbbVie for the shipment of samples to:

Attn: AbbVie Sample Receiving
D-R43F, Bldg. AP13A, Rm. 2310
c/o: Delivery Services
1150 S. Northpoint Blvd.
Waukegan, IL 60085
Phone: (847) 937-0889
Fax: (847) 938-9898
E-mail: sample.receiving@abbvie.com

The sample collection tubes will minimally be labeled with "PG-DNA blood," the drug number, protocol number, subject number and the study day. AbbVie or designee will store the DNA samples in a secure space with adequate measures to protect confidentiality. The samples will be retained while research on venetoclax (or drugs of this class) continues but no longer than 20 years or per country requirement.

5.3.1.3 Collection and Handling of Biomarker Testing

Mandatory Collections

Serum Markers

Approximately 3.5 mL of blood will be collected by venipuncture into an appropriately labeled 3.5 mL SST (gold top) tube from all subjects at the following time points:

- Screening or Week 1 Day 1 pre-dose
- Week 1 Day 2
- Week 4 Day 1
- Final Visit/Time of Relapse

Serum Marker samples will be processed and shipped to the central laboratory from the site per the current laboratory manual.

Blood for CLL FISH

Approximately 4 mL of blood will be collected by venipuncture into a heparin vacutainer from subjects with unknown 17p deletion status at the following time point:

- Screening or Week 1 Day 1 pre-dose

Blood for CD19 Cell Isolation Bcl-2 Family Analysis

Approximately 8 mL of blood will be collected by venipuncture into an ACD vacutainer from all subjects at the following time points:

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

Blood for CD19 Isolation Bcl-2 Family Analysis samples will be processed and shipped to the central laboratory from the site per the current laboratory manual.

Blood for Mutation and Expression Profiling

Approximately 20 mL of blood will be collected by venipuncture into ACD vacutainers from all subjects at the following time points:

- Week 1 Day 1 pre-dose
- Week 2 Day 1 pre-dose

Bone Marrow Aspirate for Bcl-2 Protein Analysis

Approximately 1 mL of bone marrow aspirate will be collected and placed into a sodium heparin vacutainer. Bone marrow aspirate must be split for this analysis from samples obtained for 2008 Modified IWCLL NCI-WG Criteria for Tumor Response whenever feasible, but should not require the subject to undergo a second bone marrow collection if sample is insufficient. Samples should be collected at the following time points:

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

Bone Marrow Aspirate Bcl-2 Protein Analysis samples will be processed and shipped directly to the central laboratory from the site per the current laboratory manual.

Bone Marrow Aspirate for CD19 Isolation

Approximately 4 mL of bone marrow aspirate each will be collected and placed into a ACD vacutainer. Bone marrow aspirate must be split for this analysis from samples obtained for 2008 Modified IWCLL NCI-WG Criteria for Tumor Response whenever feasible, but should not require the subject to undergo a second bone marrow collection if sample is insufficient. Samples should be collected at the following time points:

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

Bone Marrow Aspirate for CD19 Isolation samples will be processed and shipped to the central laboratory from the site per the current laboratory manual.

Peripheral Blood and Bone Marrow Aspirate for Disease Assessment by PCR

Approximately 10 mL of blood will be collected in a sodium heparin vacutainer and Approximately 3 mL of bone marrow aspirate will be collected and placed into a sodium heparin vacutainer. Bone marrow aspirate must be split for this analysis from samples obtained for 2008 Modified IWCLL NCI-WG Criteria for Tumor Response whenever feasible, but should not require the subject to undergo a second bone marrow collection if sample is insufficient. Samples should be collected at the following time points:

- Screening or Week 1 Day 1 pre-dose (Peripheral Blood only)
- Week 24 (Peripheral Blood only, All Subjects)
- Week 36 (Peripheral Blood **Expansion Cohort subjects only**)
- After the 1st CR (Peripheral Blood and Bone Marrow Aspirate)*
  - * Specimens will continue to be collected for these subjects in the peripheral blood only at the 12 weeks interval visits until 2 negative MRD levels are reported. A final specimen will be assessed in bone marrow aspirate once MRD negativity (as indicated by Flow cytometry) is achieved in two consecutive peripheral blood samples.

The Peripheral Blood and Bone Marrow Aspirate for MRD assessment by PCR samples will be processed and shipped directly to the central laboratory from the site per the current laboratory manual.

Non-Tumor DNA for Mutational Profiling (Control Specimen)

A buccal swab will be collected at the following time point:

- Screening (preferred) or prior to the first dose of study drug
  Note, if the sample is not collected at either visit. It can be collected at any subsequent visit.

Tissue for IHC and FISH

Optional for all subjects:

Screening or Week 1 Day 1 pre-dose

Subjects who undergo Richter's transformation while taking venetoclax will require a mandatory biopsy from the new lesion (when deemed feasible by the investigator). If the subject discontinues for any other reason, the collection is optional.

Final Visit/Time of Relapse (when feasible)

Either archived diagnostic formalin fixed paraffin embedded (FFPE) tissue blocks and/or formalin fixed core needle biopsy should be completed at Screening for all subjects who provide consent. A formalin-fixed core needle biopsy should be completed at the Final Visit or time of disease progression for all subjects who have consented. Tissue specimen for IHC and FISH testing should be split from samples obtained for 2008 Modified IWCLL NCI-WG Criteria for Tumor Response whenever possible. If feasible, it is preferred that tissue specimens from both locations be submitted for analysis from subjects with lymph node and bone marrow involvement.

Formalin Fixed, Paraffin Embedded Samples (Archived Tissues are Acceptable at Screening Only)

Immunohistochemistry (IHC), fluorescence in situ hybridization (FISH) and/or nucleic acid analysis, for example, quantitative polymerase chain reaction (qPCR), or micro RNA quantitation may be performed on tissue slides from archived, diagnostic, formalin fixed, paraffin embedded FFPE tissue blocks from all subjects who consent in the study.

The tissue may be processed according to the institutional standard procedures or per the most current version of the Laboratory Manual for this study. If a procedure other than what is described in the most current version of the Laboratory Manual for this study is used, a description of the procedure should be provided to AbbVie.

Core Needle Biopsy – Formalin Fixed (Prior to Therapy if FFPE Block is Not Available or if Investigator Prefers; and at Time of Disease Progression)

Formalin-fixed core needle biopsies will be obtained prior to therapy and at time of disease progression, when feasible, for all subjects in the study who consent and who have readily accessible tumor tissue. Biopsies will be performed after consent, prior to study drug administration and after the subject has progressed on therapy. Lymph node collections will be performed for all subjects with Richter's transformation.

The needle biopsy should be at least 18 gauge in diameter and at least 1 cm in length. It is estimated that there will be between 2 to 5 million cells from each biopsy. The biopsy may be processed according to the institutional standard procedures or per the most current version of the Laboratory Manual for this study. If a procedure other than what is described in the most current version of the Laboratory Manual for this study is used, a description of the procedure should be provided to AbbVie.

Recollection of biopsy samples prior to the first dose of venetoclax may occur as necessary due to technical failures such as inadequate sampling in screening.

Tissue for IHC and FISH should be shipped to the central laboratory from the site per the current laboratory manual.

5.3.2 Drug Concentration Measurements

5.3.2.1 Collection of Samples for Analysis

Blood samples (3 mL) for venetoclax (and possible metabolite[s]) assay will be collected in K_2EDTA containing tubes by venipuncture in appropriately labeled tubes at the times listed in Table 6.

A total of approximately 11 blood samples (approximately 33 mL) will be collected. The PK collection performed 8 hours post dose after each dose increment, may be taken up to 1 hour before or up to 20 minutes after, to allow for processing if necessary.

The date and time of each blood sample collection will be recorded to the nearest minute on the eCRF. The date and time (to the nearest minute) of each venetoclax dose and whether or not the venetoclax dose was taken within 30 minutes after the completion of breakfast (or subject's first meal of the day) will be recorded on the scheduled venetoclax PK days and for the 2 days prior to every scheduled venetoclax PK day. Sites will ensure that all information is captured through source documents (site or subject calendar/diary provided by AbbVie).

5.3.2.2 Handling/Processing of Samples

Blood and plasma samples must be protected from direct sunlight during collection, processing and storage. Immediately after collection, the blood samples for venetoclax will be inverted 8 to 10 times to ensure good mixing of the blood and anticoagulant, and will be placed in an ice bath. Within 1 hour of blood draw, the blood samples will be centrifuged using a refrigerated centrifuge (2° to 8°C) to separate the plasma at 1100 to 1600 × g for approximately 10 to 15 minutes. The plasma samples will be transferred using plastic pipettes into a 2 mL Greiner tube labeled with the drug number name, assay type, type of sample (plasma), the protocol number, the subject number, the study week and day, and the planned time of sampling relative to dosing and then frozen at –20°C or colder. The entire process should be completed within 2 hours of draw. Samples should be maintained at –20°C or colder until shipped to the central laboratory.

5.3.2.3 Disposition of Samples

The frozen plasma samples for venetoclax (and possible metabolite[s]) assay will be packed in dry ice sufficient to last during transport and shipped from the study site to the central laboratory according to instructions included in the Laboratory Manual for this study. An inventory of the samples included will accompany the package. The central laboratory will be responsible for shipping the plasma samples to AbbVie or designated laboratory for testing.

5.3.2.4 Measurement Methods

Plasma concentrations of venetoclax will be determined by the Drug Analysis Department at AbbVie using a validated method. Other potential metabolites of venetoclax may be analyzed with either a validated or non-validated assay.

5.3.3 Efficacy Variables

The primary objective of this study is to evaluate the efficacy and safety of venetoclax monotherapy in subjects with Chronic Lymphocytic Leukemia (CLL) relapsed after or refractory to treatment with B-cell Receptor Signaling Pathway Inhibitors. Efficacy will be measured by overall response rate (ORR).

The secondary objectives are to evaluate the duration of response (DOR), time to progression (TTP) progression free survival (PFS), and overall survival (OS).

Additional exploratory objectives will be evaluated. Minimal residual disease (MRD) is assessed in the peripheral blood and bone marrow (BM) by flow cytometry, PCR and/or sequencing. Health Economic and Patient-Reported Outcome Measures will include the EORTC QLQ-C30 and EORTC QLQ CLL16 (a measure of health related quality of life specific to CLL) and the EQ-5D-5L (measure of general health status) including EQ-5D-VAS. For Expansion Cohort subjects, only the EORTC QLQ-C30 will be performed.

Analyses of these endpoints are described in Section 8.0.

5.3.3.1 Primary Variables

For disease assessments, response will be assessed by the investigator based on analysis of clinical laboratory tests (hematology laboratory values), complete physical examination, CT scan of involved anatomic regions (or MRI if CT is medically contraindicated), bone marrow aspirate and biopsy. Subjects will be evaluated against the 2008 Modified IWCLL NCI-WG Criteria for Tumor Response[27] with the addition of CT imaging (or MRI).

At Screening, all measurable disease must be documented by laboratory testing (hematologic status), physical examination, PET/CT and bone marrow. All baseline evaluations should be performed no more than 4 weeks before the beginning of the treatment. All the other tumor assessments after baseline should be performed within 7 days after the scheduled visit. During the study, subjects will have a disease assessment at Screening, Week 5 Day 1 (or Day 1 of initiation of 400 mg dose) and beyond by a physical examination and laboratory testing. When a CR/CRi response is determined by clinical criteria at any time during the study, a CT scan or MRI must be performed within 8 weeks for confirmation. For determination of CR, both the CT/MRI scan and bone marrow are required to be negative. If the scans confirm a CR, then a BM biopsy is required for confirmation of the CR.

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 PD criteria, then additional assessments including contrast enhanced CT scan (or MRI) and/or bone marrow must be performed within 2 weeks to confirm or rule out PD.

Methods of Measurement

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

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

Details on the analysis of peripheral blood required to assess response are provided in Section 5.3.1.1, Study Procedures.

A full physical examination should be performed to assess the extent of disease involvement. 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 extranodal). Target nodal lesions must be abnormal (> 1.5 cm in LDi at baseline), clearly measurable and suitable for consistent, reproducible measurement in at least two perpendicular dimensions. Target extranodal lesions must be > 1 cm in two perpendicular diameters at baseline.
- Non-Target Lesions: A maximum of 10 non-target lesions can be selected. Non-target nodal lesions must be abnormal (> 1.5 cm in LDi at baseline). Non-target extranodal lesions must be > 1 cm in two perpendicular diameters. Nodal and extranodal 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. Magnetic Resonance Imaging (MRI) may be used if CT 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.

In addition to being reviewed by the investigator and/or site staff, an independent review will be performed to assess tumor response and disease progression. Clinical data and radiographic scans will be interpreted according to 2008 Modified IWCLL NCI-WG Criteria for Tumor Response (refer to Table 10). The independent review facility will provide instructions regarding the preparation and shipment of the imaging data. Interpretations from the independent review for individual subjects will not be sent to the site. Subject treatment management will be based on review by the local investigator and/or site staff.

Tumor Response Criteria

Complete Remission (CR)

CR requires all of the following criteria:

- Peripheral blood lymphocytes (evaluated by blood and differential count) below 4×10^9/L (4000/μL)
- Absence of lymphadenopathy (nodes > 15 mm in longest diameter or any extra nodal disease) by physical examination and CT scan
- No hepatomegaly or splenomegaly by physical examination (as determined by measurement below the relevant costal margin)

- Absence of disease or constitutional symptoms (B symptoms: unexplained fevers > 38°C or 100.4°F, drenching night sweats, > 10% body mass weight loss in the preceding 6 months)
- Blood counts above the following laboratory values:
  - Neutrophils > 1.5×10^9/L [1500/μL] (without the need for exogenous growth factors)
  - Platelets > 100×10^9/L [100,000/μL] (without the need for platelet transfusion or exogenous growth factors)
  - Hemoglobin > 110 g/L [11 g/dL] (without the need for blood transfusions or exogenous erythropoietin)
- Bone marrow at least normocellular for age, < 30% of nucleated cells being lymphocytes. Lymphoid nodules should be absent. Bone marrow aspirate and biopsy should be performed after CR/CRi has been achieved. If the bone marrow is hypocellular, a repeat determination should be made in 4 weeks or when peripheral blood counts have recovered. A marrow biopsy should be compared to a pre-treatment marrow if available. Subjects who are otherwise in a complete remission, but bone marrow nodules can be identified histologically should be considered to be nodular PR (nPR). Immunohistochemistry should be performed to define whether these nodules are composed of primarily T cells or lymphocytes other than CLL cells, or CLL cells.

Complete Remission with Incomplete Marrow Recovery (CRi)

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

Partial Remission (PR)

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

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

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

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

Table 10. 2008 Modified IWCLL NCI-WG Criteria for Tumor Response

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

Table 10. 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 SD

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

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

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

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

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

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

f. If enlarged before therapy.

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

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

The goal of confirmation of overall response is to avoid overestimating responses. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome that the response(s) is (are) not confirmed.

To be assigned a status of PR changes in tumor measurements must be confirmed by repeat assessments. These must be performed at least 8 weeks after the clinical criteria for response are first met.

5.3.3.2 Secondary Variables

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

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

5.3.4 Safety Variables

The following safety evaluations will be performed during the study: adverse event monitoring, vital signs, physical examination, 12-lead ECG, and laboratory assessments.

5.3.5 Pharmacokinetic Variables

Plasma concentration of venetoclax will be tabulated. Values for the PK parameters of venetoclax, including the apparent clearance (CL/F), and the apparent volume of

distribution (V/F), may be determined using a population PK approach. Additional parameters may be calculated if useful in the interpretation of the data.

5.3.6 Pharmacogenetic Variables

DNA samples may be analyzed for genetic factors contributing to the subject's response to venetoclax in terms of pharmacokinetics, efficacy and safety. Such genetic factors may include, for example, drug metabolizing enzymes, drug transport proteins, CLL prognostic markers and Bcl-2 family members. Some genes currently insufficiently characterized or unknown may be understood to be important at the time of analysis. These samples may be analyzed as part of a multicenter, multi-study project to identify genetic factors involved in the response to study drugs. The samples may also be used for the development of diagnostic tests related to venetoclax (or drugs of this class). The results of pharmacogenetic analyses may not be reported with the study summary.

5.3.7 Biomarker Variables

Several putative biomarkers of efficacy and response may be evaluated in this protocol with the goal of defining the relationship between various disease markers and disease status. Biospecimens collected during the course of this study will be banked and used in the future to investigate new scientific questions related to this study. The samples may also be used for diagnostic test development. AbbVie (or a designated laboratory) will store the samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on venetoclax (or drugs of this class) continues but no longer than 20 years.

Examination of the plasma and serum components of subjects on this venetoclax clinical trial may reveal patterns of cell-free nucleic acids, proteins/peptides or metabolites that may be further evaluated in future clinical studies to determine any prognostic value and any correlation with clinical response. Plasma and serum samples may also be analyzed for predictive or drug-responsive markers. In the event that any plasma and serum samples are unused, remaining samples will be banked for use in diagnostic test development efforts.

DNA methylation regulates gene expression (inactivates certain genes and their normal role); aberrant methylation of specific genes is associated with cancer development and poor clinical outcome. Genes with variable methylation status that are known to have prognostic implications may be assessed in the trial. These analyses may examine putative stratification markers for correlation for efficacy.

Genetic amplification, chromosomal loss and/or mutational/methylation status of various genes represent genetic lesions potentially associated with subject outcome. Nucleic acids, protein expression, and/or mutational/methylation analysis may be conducted on CLL cells isolated from blood, tissue from tumor samples and/or DNA/RNA extracted from serum from subjects participating in this study to assess modifications in genes (e.g., which may include but will not be limited to the Bcl-2 family, p53, notch and other genes associated with resistance to B-cell receptor targeted agents such as BTK and PLCγ), which may prove to be informative. Additionally, comprehensive sequencing of CLL cells isolated from the blood or bone marrow aspirate may also be performed. The sequencing may be used to identify the mutation status of genes associated with CLL as well as sequencing of the tumor associated immunoglobulin gene as a method to monitor disease burden. FISH may be conducted on tissue from tumor samples and/or CLL cells from subjects participating in this study to assess amplifications and translocations in the Bcl-2 gene and other alteration in genes associated with CLL, which may prove to be informative. The potential relationship between amplification/loss/mutation/methylation of these genes and the clinical outcome in these subjects may be examined as a subject stratification tool. Biospecimens collected during the course of this study may be banked and used in the future to investigate new scientific questions related to this study.

5.3.8 Health Economic and Patient-Reported Outcome Measures

The EORTC QLQ-C30 consists of a Global Health Status/QoL scale, a Financial Difficulties scale, five Functional scales (Cognitive Functioning, Social Functioning, Physical Functioning, Emotional Functioning, and Role Functioning), and eight Symptom scales/items (Fatigue, Insomnia, Appetite Loss, Pain, Constipation, Diarrhea, Dyspnea,

and Nausea and Vomiting). For Expansion Cohort subjects, only the EORTC QLQ-C30 will be performed.

Each of these domains will be calculated as per the EORTC scoring manual, and summarized (mean, std. dev., median) at each assessment; in addition mean change in each of these values (final assessment versus baseline) will be calculated to identify any statistically significant differences versus baseline.

The five EORTC QLQ CLL16 domains (Fatigue, Treatment Side Effects and Disease Symptoms, Infection, Social Activities, Future Health Worries) will be summarized (mean, std. dev., median) at each assessment; in addition mean change in each of these values (final assessment versus baseline) will be calculated to identify any statistically significant differences versus baseline.[29]

EQ-5D-5L and EQ-5D-VAS

The EuroQol 5 Dimensions (EQ-5D-5L) is a generic preference instrument that has been validated in numerous populations. 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 EQ-5D-5L also contains a visual analog scale (VAS) to assess the subject's overall health.[30]

Each of the five dimensions of the EQ-5D-5L, the Visual Analog Scale (VAS) and overall utility score will be calculated using the EuroQol scoring manual, and summarized (mean, std. dev., median) at each assessment; in addition mean change in each of these values (final assessment versus baseline) will be calculated to identify any statistically significant differences versus baseline.[30]

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 at any time. In addition, the investigator will discontinue a subject from the study 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;
- The subject's response to therapy is unsatisfactory, as evidenced by progression of disease while on study drug;
- The subject requires radiotherapy, cancer-related surgery as a result of tumor progression, or alternate anti-neoplastic agents during the study period;
- Noncompliance with the protocol.

Subjects with disease progression may continue to receive study treatment when, in the opinion of the investigator, it is in the subject's best interest to stay on the study drug. Disease progression will be captured in EDC per iWCLL NCI-WG criteria as described in Section 5.3.3.2 of the protocol. The subject will be monitored per study procedures described in Section 5.3.1.1 or more often if the investigator considers it necessary.

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.

Refer to Appendix G for COVID-19-related processes for this section.

Post Treatment Follow-Up Visits

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 visits will be performed every 3 months until discontinuation from the study (e.g., disease progression, alternative therapy is required, or a subject's refusal of

the Post-Treatment visits) for a period of 3 years after the last subject has enrolled on the study.

Final Visit

Upon discontinuation from the study, the reason(s) for discontinuation will be recorded in EDC and a Final Visit will be performed. The Final Visit procedures as listed in Table 4 and Table 6 should be performed as soon as possible after discontinuation from the study.

At the Final Visit, the subject's calendars/diaries are to be returned to the site and appropriately filed with the subject's source documents.

30 Day Safety Follow-Up Visit

A Safety Follow-Up Visit should be performed for all subjects approximately 30 days following discontinuation of study drug and then as clinically appropriate for safety assessment. The subject will be followed until a satisfactory clinical resolution of the adverse event is achieved.

A Safety Follow-Up Visit does not need to be performed for subjects who had a Final Visit conducted > 30 days after discontinuation of study drug and did not require additional adverse event follow-up. If the subject refuses or is unable to attend the Safety Follow-Up Visit, this should be noted in the subject's source documentation.

Survival Follow-Up

Survival information (i.e., the date and cause of death, post-treatment cancer therapies, etc.) will be collected via telephone calls and/or clinical visits at 3-month intervals after the last study visit for a period of 5 years after the last subject has enrolled on the study.

In the event that a positive result is obtained on a pregnancy test for a subject or a subject reports becoming pregnant during the study, the administration of study drug must be discontinued immediately. The investigator must report a pregnancy within 1 working

day of the site being aware to one of the AbbVie representatives listed in Section 6.1.5 or Section 7.0.

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

Each dose of venetoclax will be taken with approximately 240 mL of water within 30 minutes after the completion of breakfast or the subject's first meal of the day.

In cases of vomiting, if vomiting occurs within 15 minutes of taking the dose and all tablets are intact, another dose may be given. Otherwise, no replacement dose is to be given. In cases where a dose is missed or forgotten, the subject should take the dose as soon as possible, ensuring the dose is taken within 8 hours of the missed dose with food. Otherwise, the dose should not be taken.

Refer to Appendix G for COVID-19-related processes for this section.

5.5.2 Identity of Investigational Product

The individual study drug information is presented in Table 11.

Table 11. Identity of Investigational Product

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

5.5.2.1 Packaging and Labeling

The venetoclax tablets will be packaged in high density polyethylene (HDPE) plastic bottles or blister packs to accommodate the study design. Each container will be labeled per local regulatory requirements.

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

5.5.2.2 Storage and Disposition of Study Drugs

The investigational product supplied in this study is for investigational use only, and are to be used only within this study. All clinical supplies must be maintained under adequate security and stored under conditions specified on the label.

The tablets must be stored at 15° to 25°C (59° to 77°F).

5.5.3 Method of Assigning Subjects to Treatment Groups

There is no randomization schedule for this study. Subjects will be assigned at Screening, a unique consecutive subject number. All subjects will be enrolled using an IxRS. Before the study is initiated, each site will be provided with the IxRS user instructions, which provides direction on how to use the IxRS 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 screen failure.

5.5.4 Selection and Timing of Dose for Each Subject

Selection of the dose for this study is discussed in Section 5.6.4. Each dose of venetoclax will be taken with approximately 240 mL of water. All subjects will be trained to self-administer venetoclax orally QD within 30 minutes after the completion of breakfast or the subject's first meal of the day.

5.5.5 Blinding

This is an open-label, two 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 study drug to the subject. Compliance below 80% will require counseling of the subject by study site personnel.

5.5.7 Drug Accountability

Documentation of the receipt of supplies will be supported by a signed and dated Proof of Receipt or similar shipping document in IxRS. A current (running) and accurate

inventory of study drug will be kept by the site and will include lot number, Proof of Receipt number(s), container numbers, blister pack numbers, and the date on which study drug is administered to the subject.

An overall accountability of study drug will be performed in IxRS and verified by AbbVie or the designated monitor(s) throughout the study and at the study site closeout visit. Upon completion or termination of the study, all original containers (containing partially used or unused study drug) will be returned to AbbVie according to instructions from AbbVie or the designated monitor(s). If pre-arranged between AbbVie and the site, destruction of used and unused study drug containers will be performed at the site. Empty containers will be destroyed at the site. Labels must remain attached to the containers.

5.6 Discussion and Justification of Study Design

Antiapoptotic BCL-2 family members are associated with tumor initiation, disease progression, and drug resistance, and thus are compelling targets for antitumor therapy. Venetoclax is a novel orally bioavailable small molecule BCL-2 family protein inhibitor that binds with high affinity to Bcl-2 and with lower affinity to other Bcl-2 family proteins BCL-xL and BCL-w. The mechanism of action of venetoclax is independent of the BCR signaling and TP53 pathway. 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 independent of *TP*53 and BCR pathways.

Preliminary data indicate that ongoing venetoclax first-in-human Study M12-175 had a strong efficacy signal in oncology subjects. In the CLL Arm A, 47 of 52 (90.2%) evaluable subjects achieved a best response of complete response (CR), CR with incomplete bone marrow recovery (CRi), or partial response (PR): 12 (21%) subjects experienced CR/CRi, and 36 (63%) subjects experienced PR (of which 30 were confirmed). Subjects with high-risk CLL had a response rate of 82% in del (17p) and 78% in fludarabine-refractory disease. Three of the 4 high-risk disease subjects who achieved CR/CRi had no detectable MRD. One subject with SLL after disease progression on Idelalisib had PR on venetoclax for 11 months prior to developing PD.

5.6.1 Discussion of Study Design and Choice of Control Groups

There are no control groups in this study.

5.6.2 Appropriateness of Measurements

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

5.6.3 Suitability of Subject Population

Subjects with relapsed or refractory CLL will be selected to participate in this study. Subjects must have relapsed or be refractory to Ibrutinib or Idelalisib containing regimen.

5.6.4 Selection of Doses in the Study

The dose of 400 mg was selected on the basis of the data in relapsed/refractory CLL/SLL subjects from the ongoing venetoclax first-in-human Study M12-175. A time-to-response model and a logistic-regression model were developed using data from Study M12-175 to understand the relationship between the response outcome and the final target venetoclax dose. Both models found that a faster response was achieved with a higher final target dose. Further analysis focused on comparing 400 mg and 600 mg as the final target dose showed a minimum difference on the overall response rate (i.e., percentage of subjects with partial response or better). With doses below 400 mg QD, however, a longer (and clinically unfavorable) duration will be needed to achieve the same response rate. Since there is no strong difference between 400 mg and 600 mg as the final dose, the 400 mg dose was selected as the minimum effective dose.

To mitigate the risk for TLS, a lead-in period of 5 weeks will be employed to escalate venetoclax dose to the final treatment dose of 400 mg. All high risk subjects will be admitted to the hospital and begin the lead-in period with an initial dose of 20 mg venetoclax on Week 1 Day 1 and first dose of 50 mg on Week 2 Day 1. Low risk subjects and medium risk subjects with Cr Cl $\geq$ 80 mL/min will begin lead-in-period as outpatients. If no significant findings suggestive of clinical or lab TLS occur within

24 hours, the same dose will be continued until Day 7 in the outpatient setting. A dose of 50 mg venetoclax will be administered on Week 2 Day 1. After a week at 50 mg, weekly dose increments will be implemented as follows: 100 mg → 200 mg → 400 mg (or additional lead-in steps to designated 400 mg dose) as tolerated. Expansion Cohort subjects with bulky disease that are non-responders either by clinical or radiographic Disease Assessment between Week 6 to Week 12 or subjects who show signs of clinical progression after completing the ramp up to 400 mg may be permitted to escalate venetoclax to a 600 mg dose.

The maximum dose in this study is 400 mg, however currently the established maximum clinical dose of venetoclax is not to exceed 1200 mg/day for a duration not to exceed 48 months based on genotoxicity studies.

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. Medical complaints are further detailed in the Adverse Events Section. For adverse events, please refer to Sections 6.1 through 6.1.7.4.

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 patient 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 6.1.7 regarding toxicity management]) and/or if the investigator considers them to be adverse events.

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 adverse event is defined as any adverse event 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 study drug administration.

6.1.1.2 Serious Adverse Events

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

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

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

For serious adverse events with the outcome of death, the date and cause of death will be recorded on the appropriate case report form. For deaths related to disease progression (coded to malignant neoplasm progression), the date and cause of death will be recorded on the appropriate case report form, however, the event will be considered expected for the purpose of determining expedited reporting requirements to regulatory authorities. If the cause of death is unknown at the time of reporting, "unexplained death" should be recorded on the eCRF. If the cause of death later becomes available "unexplained death" should be replaced by the established cause of death.

Hospitalization of a subject to allow observation and management (e.g., for IV hydration) for the purpose of TLS prophylaxis will not be captured as a serious adverse event (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.).

Certain adverse events are anticipated to occur in the study population (CLL) at some frequency independent of drug exposure. These are discussed here as Adverse Events commonly associated with CLL or progression of CLL. Such events include known consequences of the underlying disease or condition under investigation (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 E.

These adverse events may occur alone or in various combinations and are considered expected for reporting purposes.

Although exempted from expedited reporting to Health Authorities and IRBs as individual cases, if an event commonly associated with CLL or progression of CLL meets seriousness criteria (as defined in Section 6.1.1.2) it must be reported to AbbVie *within 24 hours* of the site being made aware of the serious adverse event. For deaths related to disease progression (coded to malignant neoplasm progression), the date and cause of death will be recorded on the appropriate case report form, but the event will not be expedited as an individual case safety report (ICSR) to regulatory authorities.

6.1.2 Adverse Event Severity

The investigator will rate the severity of each adverse event according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE Version 4.0).[27] If a reported adverse event increases in severity, the initial adverse event should be given final outcome date and a new adverse event must be reported to reflect the change in severity. The dates on the AE's cannot overlap. For all reported serious adverse events that increase in severity, the supplemental eCRFs also need to be updated to reflect any changes due to the increase in severity. For adverse events not captured by the Common Terminology Criteria, 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 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	An adverse event where there is evidence to suggest a causal relationship between the study drug and the adverse event.
No Reasonable Possibility	An adverse event where there is no evidence to suggest a causal relationship between the study drug and the adverse event.

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 a 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 serious adverse event.

6.1.4 Adverse Event Collection Period

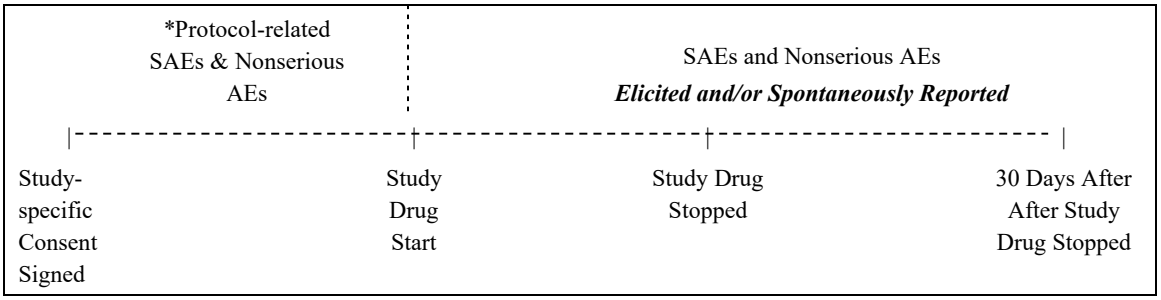
All protocol-related serious adverse events and nonserious adverse events must be collected from the signing of the study-specific informed consent until study drug administration.

In addition, all adverse events reported from the time of study drug administration until 30 days following discontinuation of study drug administration have elapsed will be collected, whether solicited or spontaneously reported by the subject.

Serious and nonserious adverse events occurring after the study-specific informed consent is signed but prior to the initial dose of venetoclax will be collected only if they are considered by the Investigator to be causally related to the study-required procedures.

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

Figure 3. Adverse Event Collection



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

6.1.5 Adverse Event Reporting

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

Refer to Appendix G for COVID-19-related processes for this section.

Email (preferred method):
PPDINDPharmacovigilance@abbvie.com
and CC:
SafetyManagement_Oncology@abbvie.com
Or
FAX to: +1 (847) 938-0660 & +1 (847) 785-8224

For safety concerns, contact the Oncology Safety Management Team at:

Oncology Safety Management Team
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 emergent subject safety concerns, please contact the AbbVie medical monitor:

[redacted] MD, PhD
Senior Medical Director
[redacted]
AbbVie
1 North Waukegan Road
North Chicago, IL 60064

Office:
Cell:
Fax:
Email:
[redacted]

In emergency situations involving study subjects when the primary Study Designated Physician (SDP) 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 SDP.

Phone: +1-973-784-6402

6.1.6 Pregnancy

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

All subjects should be informed that contraceptive measures should be taken throughout the study and for 30 days after discontinuing study drug. 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.

Male subjects should be informed that contraceptive measures should be taken by their female partners. If the subject's partner should become pregnant during the study, this should also be reported and data may be collected.

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

6.1.7 Toxicity Management

6.1.7.1 Prophylaxis and Management of Tumor Lysis Syndrome (TLS)

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

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

A detailed description of risk factors for developing tumor lysis following treatment with venetoclax is available in the current Investigator's Brochure.

A "TLS Prophylaxis and Monitoring Checklist" will be completed throughout the lead-in period to ensure proper TLS prophylaxis measures.

Refer to table in Appendix F for laboratory and clinical TLS.

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

6.1.7.1.1 Risk Categories for Developing TLS

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

6.1.7.1.2 TLS Prophylaxis Guidelines

The section below describes the management of subjects throughout dosing based on their risk factors for developing TLS identified upon study entry.

First Dose of Venetoclax at 20 mg and at 50 mg

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

- An oral agent to reduce the uric acid level (e.g., allopurinol) to be initiated at least 72 hours prior to dosing. Treatment may need to be continued for up to 5 weeks based on the ongoing risk of TLS development. Subjects allergic to allopurinol must use another uric acid reducer.
- Oral hydration consisting of fluid intake of 1.5 to 2 L per day starting at least 48 hours prior to the start of treatment for all subjects prior to first dose, at all subsequent dose increment steps and continued for at least 24 hours after dosing until all of the chemistry laboratory values remain within ULN. Oral hydration is recommended beyond 24 hours post-dose for subjects who demonstrate any laboratory changes.

- Serum chemistry and hematology laboratory samples (low risk and medium risk subjects to be treated in the outpatient setting) must be drawn anytime within 72 hours prior to first dose. For subjects who will receive outpatient dosing, the 0 hour pre-dose chemistry and hematology lab results may be used for dosing decisions on Day 1 of each week during the lead-in period. For subjects who will be hospitalized and will receive inpatient dosing, the chemistry and hematology labs must be drawn upon admission the night before first dose of venetoclax. All electrolyte values should be reviewed and not demonstrate any clinically significant abnormalities prior to the first dose of venetoclax in order to keep the treatment on schedule.
- If clinically significant laboratory abnormalities are observed in this baseline laboratory assessment, the first dose of venetoclax must be delayed until resolution and initiate TLS management per the protocol Appendix D, Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome (TLS) must be initiated. If aggressive correction of electrolytes was performed, the initial dose of venetoclax can only be given when electrolytes have been stable without any further treatment for at least 24 hours. If needed, subjects may continue to receive additional prophylactic treatment prior to the initiation of dosing.

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

Subjects in Low Risk Category

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

- For subjects who are unable to maintain adequate oral hydration, IV hydration of 1.5 to 2 L is recommended in the outpatient setting on D1 of the 20 mg and 50 mg dose to assure the full amount of hydration is achieved. For subjects in whom volume overload is considered a significant risk, hospitalization should be considered.

- Chemistry and hematology laboratory tests are to be performed within 72 hours before the first dose of venetoclax. These laboratory values must be reviewed by the investigator. The investigator's decision to proceed with the initiation of venetoclax treatment may be based on these laboratory values.
- Chemistry laboratory tests must be performed STAT at 0 hour (pre-dose, within 4 hours before venetoclax administration), 8, and 24* hours post-dose after the first dose of venetoclax at 20 mg and at 50 mg. These laboratory values must be reviewed in real time by the investigator. Results from 0 hour (pre-dose) laboratory values will be collected and used as baseline to assess potential electrolyte abnormalities occurring post venetoclax administration. Results from STAT 0 hour (pre-dose) laboratory values are not required to be available prior to initiating venetoclax treatment. Subjects must remain at the hospital, or clinic, until the 8 hour laboratory values have been reviewed by the investigator.
- The Day 2 dose of venetoclax should not be administered until the 24 hour post-dose chemistry laboratory values are reviewed by the investigator.
- If no significant findings suggestive of clinical or lab TLS occur within 24 hours, the same dose will be continued until Day 7 in the outpatient setting.
- If any significant laboratory changes are observed within the first 24 hours after the first dose, refer to Appendix D (Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome [TLS]) for procedures to follow. These laboratory values must be reviewed in real time by the investigator.
    - Additional laboratory assessments may be performed per investigator discretion.
- Hematology laboratory tests must be performed 24* hours post-dose after the first dose of venetoclax at 20 mg and at 50 mg.

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

Subjects in Medium Risk Category

- Subjects in the Medium Risk category who have creatinine clearance ≥ 80 mL/min may receive their initial doses of venetoclax at 20 and 50 mg in the outpatient setting.
- Subjects in the Medium Risk category who have creatinine clearance of < 80 mL/min and/or higher tumor burden (i.e., ALC > 100×10^9/L or multiple bulky nodes) may be handled as high risk subjects per investigator discretion for the first dose of venetoclax at 20 mg and 50 mg (Refer to section for high risk subjects below).
- Subjects will receive IV hydration of 1.5 to 2 L in the outpatient setting on Day 1 of the 20 mg and 50 mg dose in addition to oral hydration as outlined above. For subjects in whom volume overload is considered a significant risk, hospitalization should be considered.
- Chemistry and hematology laboratory tests are to be performed within 72 hours before the first dose of venetoclax. These laboratory values must be reviewed by the investigator. The investigator's decision to proceed with the initiation of venetoclax treatment may be based on these laboratory values.
- Chemistry laboratory tests must be performed STAT at 0 hour (pre-dose, within 4 hours before venetoclax administration), 8, and 24* hours after the first dose of venetoclax at 20 mg and at 50 mg. These laboratory values must be reviewed in real time by the investigator. Results from 0 hour (pre-dose) laboratory values will be collected and used as baseline to assess potential electrolyte abnormalities occurring post venetoclax administration. Results from STAT 0 hour (pre-dose) laboratory values are not required to be available prior to initiating venetoclax treatment. Subjects must remain at the hospital, or clinic, until the 8 hour laboratory values have been reviewed by the investigator.
- The Day 2 dose of venetoclax should not be administered until the 24 hour post-dose chemistry laboratory values are reviewed by the investigator.
- If no significant findings suggestive of clinical or lab TLS occur within 24 hours, the same dose will be continued until Day 7 in the outpatient setting.

- If any significant laboratory changes are observed within the first 24 hours after the first dose, refer to Appendix D, (Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome [TLS]) for procedures to follow.
  - Additional laboratory assessments may be performed per investigator discretion.
- Hematology laboratory tests must be performed 24* hours post-dose after the first dose of venetoclax at 20 mg and at 50 mg.
  * All 24 hours post-dose laboratory assessments may be taken within a 2 hour window if necessary.

Subjects in High Risk Category

High-risk subjects will be hospitalized to receive their initial doses of 20 and 50 mg of venetoclax. Hospitalization and monitoring will start the night before administration of the first dose of 20 mg and 50 mg of venetoclax and will be continued until the 24 hour post-dose chemistry laboratory values are reviewed by the investigator.

- Chemistry and hematology laboratory tests are to be performed upon admission the night before the first dose of venetoclax. The investigator's decision to proceed with venetoclax treatment initiation will be based on these laboratory values.
- Nephrology (or other acute dialysis service) consultation should be considered upon admission per institutional standards at investigators' discretion to ensure emergency dialysis is available and the appropriate staff is aware and prepared to handle any necessary intervention for TLS. Telemetry should also be considered.
- IV hydration must be started the night before the first dose of 20 mg and first dose of 50 mg, with a target of approximately 1.5 – 2 L/day, or as clinically appropriate, and continued for at least 24 hours after dosing.

- Rasburicase must be administered prior to the first dose of venetoclax (per regional standards or institutional guidelines) for subjects with elevated uric acid level at baseline (> ULN) or > Cairo-Bishop threshold of 476 μmol/L) as prophylaxis. For subjects with a contraindication to rasburicase (i.e., glucose-6-phosphate dehydrogenase [G6PD] deficiency), the TLS risk-mitigation plan must be reviewed with AbbVie medical monitor prior to initiating treatment.
- Chemistry laboratory tests must be performed STAT at 0 (pre-dose, within 4 hours before venetoclax administration), 4, 8, 12 and 24* hours after the first dose of venetoclax at 20 mg and 50 mg. These laboratory values must be reviewed in real time by the investigator. Results from 0 hour (pre-dose) laboratory values will be collected and used as baseline to assess potential electrolyte abnormalities occurring post venetoclax administration. Results from 0 hour (pre-dose) laboratory values are not required to be available prior to initiating venetoclax treatment.
- If any significant laboratory changes are observed within the first 24 hours after initiation of dosing, refer to Appendix D, (Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome [TLS]), for additional laboratory assessments and management guidelines. If aggressive correction of electrolytes abnormalities was performed, the next dose of venetoclax can only be given when electrolytes have been stable without any further treatment for at least 24 hours.
- Hematology laboratory tests will be performed pre-dose (within 4 hours before venetoclax administration), and 24* hours after the first dose of venetoclax at 20 mg and 50 mg.
- The Day 2 dose should not be administered until the 24 hour post-dose laboratory values are reviewed by the investigator.
- If no significant findings suggestive of clinical or lab TLS occur within 24 hours, the same dose will be continued until Day 7 in the outpatient setting.

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

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

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

- Continue administration of an oral uric acid reducer as indicated above.
- Oral hydration consisting of fluid intake of approximately 1.5 to 2 L/day starting at least 48 hours days prior to each dose increment. IV hydration is encouraged at subsequent dose increases for subjects who are unable to maintain such oral hydration. IV hydration will be in the outpatient setting on the day of dose increment. For subjects in whom volume overload is considered a significant risk, hospitalization should be considered.
- Chemistry and Hematology laboratory tests for all subjects treated in the outpatient setting must be performed within 72 hours and results must be reviewed by the investigator prior to each dose escalation. For subjects demonstrating any clinically significant laboratory abnormalities, additional prophylactic treatment should be administered prior to dosing (see Appendix D; Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome [TLS]). If aggressive correction of electrolytes was performed, the next dose of venetoclax can only be given when electrolytes have been stable without any further treatment for at least 24 hours.

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

Subjects Low Risk Category

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

- Chemistry laboratory tests will be performed at STAT at 0 hour (pre-dose, within 4 hours before venetoclax administration), 8 and 24* hours after dose administration. Hematology laboratory tests must be performed STAT at 0 hour (pre-dose, within 4 hours before venetoclax administration) and 24* hours post-dose. These laboratory values must be reviewed in real time by the investigator. Results from 0 hour (pre-dose) laboratory values will be collected and used as baseline to assess potential electrolyte abnormalities occurring post venetoclax administration. Results from 0 hour (pre-dose) laboratory values are not required to be available prior to administering venetoclax treatment unless these results are used for dosing decisions.
  - * All 24 hours laboratory assessments may be taken within 2 hour window if necessary.
- Subjects must remain at the hospital, or clinic, until the 8 hour laboratory values have been reviewed by the investigator.
- The Day 2 dose should not be administered until the 24 hours post-dose chemistry laboratory values are reviewed by the investigator.
- If no significant findings suggestive of clinical or lab TLS occur within 24 hours, the same dose will be continued until Day 7 in the outpatient setting.
  - Additional laboratory assessments may be performed per investigator discretion.

Subjects in Medium Risk Category

- Subjects in the Medium Risk category who have creatinine clearance ≥ 80 mL/min may receive their subsequent dose escalations in the outpatient setting.
- Subjects with creatinine clearance < 80 mL/min and/or higher tumor burden (i.e., ALC > 100×10^9/L or multiple bulky nodes) may be hospitalized per investigator's discretion. Hospitalization will begin the evening prior to administering venetoclax and will continue for 24 hours after dose administration.
- For subjects who receive their subsequent dose escalations in the outpatient setting, Chemistry laboratory tests will be performed 0 (pre-dose, within

4 hours before venetoclax administration), 8 and 24* hours post dose administration. Hematology laboratory tests must be performed STAT at 0 hour (pre-dose, within 4 hours before venetoclax administration) and 24* hours post-dose. These laboratory values must be reviewed in real time by the investigator. Results from 0 hour (pre-dose) laboratory values will be collected and used as baseline to assess potential electrolyte abnormalities occurring post venetoclax administration. Results from 0 hour (pre-dose) laboratory values are not required to be available prior to initiating venetoclax treatment unless these results are used for dosing decisions.

- Subjects must remain at the hospital, or clinic, until the 8 hour laboratory values have been reviewed by the investigator.
- The Day 2 dose should not be administered until the 24 hours post-dose chemistry laboratory values are reviewed by the investigator.
- If no significant findings suggestive of clinical or lab TLS occur within 24 hours, the same dose will be continued until Day 7 in the outpatient setting.
- Additional laboratory assessments may be performed per investigator discretion.

- For subjects who are hospitalized during subsequent dose escalations, Chemistry and Hematology laboratory tests will be performed upon admission. Chemistry tests will be performed STAT at 0 hour (pre-dose, within 4 hours before venetoclax administration), 4, 8, 12 and 24 hours post dose. These laboratory values must be reviewed in real time by the investigator. Results from 0 hour (pre-dose) laboratory values will be collected and used as baseline to assess potential electrolyte abnormalities occurring post venetoclax administration.
  - IV hydration should be started with a target of approximately 1.5 – 2 L per day or as clinically appropriate for subjects who are hospitalized.
  - Nephrology (or acute dialysis service) consultation may be considered on admission (based on investigator discretion) for hospitalized subjects.
  - Hematology laboratory tests will be performed 24 hours post-dose.
  - The 24-hour post-dose laboratory results must be reviewed by the investigator prior to the subject leaving the hospital.

- The Day 2 dose should not be administered until the 24 hours post-dose chemistry laboratory values are reviewed by the investigator.
- If no significant findings suggestive of clinical or lab TLS occur within 24 hours, the same dose will be continued until Day 7 in the outpatient setting.

- Additional laboratory assessments may be performed per investigator discretion.
  * All 24 hours laboratory assessments may be taken within 2 hour window if necessary.

Subjects in High Risk Category

- High risk subjects may receive the subsequent dose increases as outpatients. Subjects with creatinine clearance < 80 mL/min and/or higher tumor burden (i.e., ALC > 100×10^9/L or multiple bulky nodes) may be hospitalized per investigator discretion. Hospitalization will begin the night prior to administration of venetoclax and continue for 24 hours after dose administration.
- For subjects who are hospitalized during subsequent dose escalations, Chemistry and Hematology laboratory tests will be performed upon admission. Chemistry tests will be performed STAT at 0 hour (pre-dose, within 4 hours before venetoclax administration), 4, 8, 12 and 24 hours post-dose. These laboratory values must be reviewed in real time by the investigator. Results from 0 hour (pre-dose) laboratory values will be collected and used as baseline to assess potential electrolyte abnormalities occurring post venetoclax administration.
  - IV hydration should be started with a target of approximately 1.5 – 2 L per day or as clinically appropriate for subjects who are hospitalized.
  - Nephrology (or acute dialysis service) consultation may be considered on admission (based on investigator discretion) for hospitalized subjects.
  - Hematology laboratory tests will be performed 24 hours post-dose.
  - The 24-hour post-dose laboratory results must be reviewed by the investigator prior to the subject leaving the hospital.

- For subjects who are not hospitalized, Chemistry laboratory tests will be performed at 0 hours (pre-dose, within 4 hours before venetoclax administration), 8 and 24 hours post dose administration. Hematology laboratory tests must be performed STAT at 0 hour (pre-dose, within 4 hours before venetoclax administration) and 24* hours post-dose. These laboratory values must be reviewed in real time by the investigator. Results from 0 hour (pre-dose) laboratory values will be collected and used as baseline to assess potential electrolyte abnormalities occurring post venetoclax administration. Results from 0 hour (pre-dose) laboratory values are not required to be available prior to initiating venetoclax treatment.
    - Intravenous hydration of approximately 1.5 to 2 L or as clinically appropriate will be given in the outpatient setting.
    - Subjects must remain at the hospital, or clinic, until the 8 hour laboratory values have been reviewed by the investigator.
- The Day 2 dose should not be administered until the 24 hours post-dose chemistry laboratory values are reviewed by the investigator.
- If no significant findings suggestive of clinical or lab TLS occur within 24 hours, the same dose will be continued until Day 7 in the outpatient setting.
- Additional laboratory assessments may be performed per investigator discretion.

Re-Assessment of Risk Category for Subjects with Lymph Nodes < 10 cm:

Subjects classified in the high-risk TLS category at Screening due to an absolute lymphocyte count $\geq 25 \times 10^9$/L AND a measurable lymph node with the largest diameter ≥ 5 cm but less than 10 cm by radiologic assessment may have a re-evaluation of their TLS risk category based on their most recent ALC for dose escalations after 50 mg. Based on those results, one of the following two options may be implemented:

- If the subject's ALC decreases to $< 25 \times 10^9$/L, the subject may be re-categorized as medium-risk for TLS and follow the TLS management guidelines for the medium-risk category for subsequent dose escalations of venetoclax during the Lead-In Period.

- If the subject's ALC remains ≥ 25 × 10^9/L, the subject will remain in the high-risk TLS category and continue to follow TLS management guidelines for high-risk subjects for subsequent dose escalations of venetoclax during the Lead-In Period.

Re-assessment of the subject's TLS risk category can occur prior to each subsequent dose escalation.

Expansion Cohort: Modified Dose Ramp-Up for Select High Risk Subjects Only

First Dose of Venetoclax at 20 mg and Dose Escalation

Subjects who have signs of clinical progression at Screening and who are categorized as high-risk for TLS may participate in a Modified Lead-In Period allowing them to more rapidly escalate to higher doses of venetoclax.

A discussion between the investigator and the AbbVie medical monitor must occur before beginning the modified lead-in period.

- Hospitalization is required for these subjects starting the night before the initial dose of venetoclax and for a minimum of 24 hours after any dose escalation. All of the TLS prophylaxis measures described in Section 6.1.7.1.2 for the high risk category must be implemented before the first dose of venetoclax.
- Chemistry and hematology laboratory tests to be performed upon admission to the hospital the night before first dose of venetoclax. The investigator's decision to proceed with venetoclax treatment initiation will be based on these laboratory values.
- Nephrology (or other acute dialysis service) consultation should be considered upon admission per institutional standards at investigators' discretion to ensure emergency dialysis is available and the appropriate staff is aware and prepared to handle any necessary intervention for TLS. Telemetry should also be considered.
- IV hydration must be started the night before the first dose of 20 mg with a target of approximately 1.5 – 2 L/day, or as clinically appropriate, and

continued for at least 24 hours after administration of the 100 mg dose of venetoclax.

- Rasburicase must be administered prior to the first dose of venetoclax (per regional standards or institutional guidelines) for subjects with elevated uric acid level at baseline (> ULN) or > Cairo-Bishop threshold of 476 µmol/L) as prophylaxis. For subjects with a contraindication to rasburicase (i.e., glucose 6 phosphate dehydrogenase [G6PD] deficiency), the TLS risk mitigation plan must be reviewed with AbbVie medical monitor.
- Chemistry and Hematology laboratory tests will be performed upon admission and daily at 0 hour. Chemistry tests will be performed STAT at 0 hour (pre-dose, within 4 hours before venetoclax administration), 4, 8, 12 and 24 hours post dose. These laboratory values must be reviewed in real time by the investigator. Results from 0 hour (pre-dose) laboratory values will be collected and used as baseline to assess potential electrolyte abnormalities occurring post venetoclax administration.
- The first dose of 20 mg venetoclax will be administered on Week 1 Day 1.
- If no significant findings suggestive of clinical or lab TLS occur within 24 hours then dose increments will be implemented as follows:
  - 50 mg (Week 1 Day 2 and Week 1 Day 3).
  - 100 mg (Week 1 Day 4 – Week 1 Day 7) Subjects will remain in the hospital for at least 24 hours after reaching the 100 mg dose.
  - 200 mg (Week 2 Day 1 – Week 2 Day 7) Subjects will remain in the hospital for at least 24 hours after reaching the 200 mg dose.
  - 400 mg (Week 3 Day 1) Subjects will remain in the hospital for at least 24 hours after reaching the 400 mg dose.

If there is indication of lab or clinical TLS the study drug dose will be interrupted until resolution of all findings. If a subject has study drug interrupted for more than 3 days (i.e., adverse event), the site will contact the AbbVie study team or AbbVie medical monitor to adjust the subject's visit schedule, procedures and/or dosing on a case by case basis. TLS management will be implemented as appropriate (per Appendix F). If aggressive correction of electrolytes was performed, the subsequent dose of venetoclax

can only be given when electrolytes have been stable without any further treatment for at least 24 hours.

Additional laboratory assessments may be performed per investigator discretion

- The Week 2 Day 2 dose should not be administered until the 24 hours post-dose chemistry laboratory values are reviewed by the investigator.
- If no significant findings suggestive of clinical or lab TLS occur within 24 hours after the Week 2 Day 2 dose, the same dose will be continued in the outpatient setting.
- TLS Chemistry labs will be performed at Week 2 Day 3 and Week 2 Day 4 after reaching the 200 mg dose in the outpatient setting.
- Week 3 Day 2 dose should not be administered until the 24 hours post-dose chemistry laboratory values are reviewed by the investigator.
- If no significant findings suggestive of clinical or lab TLS occur within 24 hours after Week 3 Day 2 dose, the same dose will be continued in the outpatient setting.
- **TLS Chemistry labs must be performed at Week 3 Day 3 and Week 3 Day 4 after reaching the 400 mg dose in the outpatient setting.**

Subjects with bulky disease who are non-responders either by clinical or radiographic Disease Assessment between Week 6 to Week 12 or subjects who show signs of clinical progression after completing the ramp up to 400 mg who are permitted to escalate venetoclax to 600 mg dose must be hospitalized and follow all of the high risk TLS prophylaxis guidelines below:

- Venetoclax dose escalation to 600 mg may occur once approved by AbbVie Medical Monitor. Subjects will remain in the hospital for at least 24 hours after reaching the 600 mg dose.
- Chemistry and Hematology laboratory tests will be performed upon admission and daily at 0 hour. Chemistry tests will be performed STAT at 0 hour (pre-dose, within 4 hours before venetoclax administration), 4, 8, 12 and 24 hours post dose. These laboratory values must be reviewed in real time by

the investigator. Results from 0 hour (pre-dose) laboratory values will be collected and used as baseline to assess potential electrolyte abnormalities occurring post venetoclax administration.

- IV hydration should be started with a target of approximately 1.5 – 2 L per day or as clinically appropriate upon admission to the hospital and continued for at least 24 hours after the administration of the escalated dose.
- Nephrology (or acute dialysis service) consultation may be considered on admission (based on investigator discretion).
- Chemistry and Hematology laboratory tests will be performed 24 hours post-dose.
- The 24-hour post-dose laboratory results must be reviewed by the investigator prior to the subject receiving the dose on W13 D2 and leaving the hospital.
- The Day 2 dose should not be administered until the 24 hours post-dose chemistry laboratory values are reviewed by the investigator.
- If no significant findings suggestive of clinical or lab TLS occur within 24 hours, the same dose will be continued in the outpatient setting.
- Additional laboratory assessments may be performed per investigator discretion.
- **TLS Chemistry labs must be performed on Day 3, Day 4 and Day 5 after reaching the 600 mg dose in the outpatient setting.**

Any subject, who at any dose level develops clinically significant electrolyte abnormalities must have their subsequent venetoclax dose interrupted until the electrolyte abnormalities resolve. Electrolyte changes should undergo aggressive management and further monitoring as per Appendix D, Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome (TLS). If aggressive correction of electrolytes was performed, the next dose of venetoclax can only be given when electrolytes have been stable without any further treatment for at least 24 hours. The subject may resume dosing based on a risk assessment (including tumor burden status), as determined by the investigator. All subjects must receive the intended dose for at least 7 consecutive days before increasing to the next higher dose.

6.1.7.2 Management of Neutropenia

Based on clinical observations with the 1st generation Bcl-2 inhibitor, navitoclax and in vitro colony-forming assays to assess Bcl-2-selective inhibitor effects on granulocyte precursors, it is possible that subjects treated with venetoclax might experience neutropenia. Subjects with a history of neutropenia, who have received multiple prior therapies and/or have significant bone marrow involvement, may be at particular high risk. If determined to be clinically indicated by the treating physician in compliance with ASCO guidelines,[32] G-CSF may be administered during dosing of venetoclax. The use of G-CSF support is strongly recommended for subjects with Grade 4 neutropenia (ANC < 500/μL). If the subject presents with febrile neutropenia or Grade 4 neutropenia for more than one week despite the use of optimal G-CSF support, venetoclax dosing should be interrupted until ANC recovery to > 500/μL. Venetoclax may then be re-initiated at a lower dose as defined in the following table. Subjects not responding to G-CSF despite venetoclax interruption should undergo further evaluation to determine the etiology of the neutropenia. If study drug administration is interrupted (i.e., adverse event), the site will contact the AbbVie study team or AbbVie Medical Monitor to adjust the subject's visit schedule, procedures and/or dosing on a case by case basis.

Table 12. Dose Reduction Guidelines for Management of Neutropenia

Venetoclax Dose	Reduced Dose
600 mg	400 mg
400 mg	200 mg
200 mg	100 mg
100 mg	50 mg
50 mg	Re-challenge at 20 mg[a]

a. Subjects who do not tolerate 50 mg will discontinue venetoclax, but remain on study for Post Treatment Follow-Up Visits to assess for progression.

6.1.7.3 Management of Lymphopenia

There is a potential for clinically significant lymphopenia in this study. If clinically indicated, anti-infective prophylaxis should be implemented at the investigator's

discretion, including appropriate prophylaxis for viral, fungal, bacterial or Pneumocystis infections. Potential for drug-drug interactions should be considered. Most anti-fungals are excluded and other commonly used agents may be cautionary or prohibited due to drug-drug interactions. Please refer to Table 1 and Appendix C for a description of excluded and cautionary medications/food items.

6.1.7.4 Management of Decrease in Spermatogenesis

Based on findings in a preclinical study, there is a potential for decreased spermatogenesis. Male subjects should consider sperm banking before treatment with venetoclax if they are considering preservation of fertility.

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 CRO Clinical Monitor or the following AbbVie Clinical Monitor(s):

Primary Contact:

[redacted]
Study Project Manager
[redacted]
AbbVie
1 North Waukegan Road
North Chicago, IL 60064

Office: [redacted]
Cell:
Fax:
Email: [redacted]

Alternate Contact:

[redacted] MD, PhD
Senior Medical Director
[redacted]
AbbVie
1 North Waukegan Road
North Chicago, IL 60064

Office: [redacted]
Cell:
Fax:
Email:

Program Lead:

[redacted]
Clinical Program Lead I
[redacted]
AbbVie
1 North Waukegan Road
North Chicago, IL 60064

Contact Information:
Office: [redacted]
Email:

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.

Refer to Appendix G for COVID-19-related processes for this section.

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

Unless otherwise noted, statistical analyses will be two-sided *using alpha* = 0.05 (one-sided alpha = 0.025 where applicable).

The primary and secondary efficacy analyses will be performed on all subjects enrolled unless otherwise specified. The date of enrollment is defined as the date that the IxRS 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 errors, standard deviations and ranges. Frequencies and percentages will be provided for gender and race.

8.1.1.2 Medical Histories

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

8.1.2 Efficacy Endpoints Per Investigator Assessment

8.1.2.1 Primary Efficacy Endpoints

The primary efficacy endpoint will be overall response rate (ORR) – the proportion of subjects with an overall response (per the investigator assessment) will be calculated for all subjects 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 ORR.

The assessment of ORR will be performed independently for Arm A, Arm B and the Expansion Cohort. In the Expansion Cohort assessment of ORR will be performed independently for ibrutinib failure and idelalisib failure subjects. Subjects who have not had a confirmed response prior to the data "cutoff" date defined in Section 8.1.3 will be considered to be non-responders.

8.1.2.2 Secondary Efficacy Endpoints

Key secondary efficacy endpoints will include duration of response, time to progression, progression-free survival, and overall survival.

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

Time to progression (TTP) will be defined as the number of days from the date of first dose or enrollment if not dosed to the date of earliest disease progression. All disease progression will be included regardless whether the event occurred while the subject was

taking the study drug or had previously discontinued the study drug. If the subject does not experience disease progression, then the data will be censored at the date of last available disease assessment. Data for patients 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 patients 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 Efficacy Endpoints Per Independent Review Committee

An Independent Review Committee (IRC) will evaluate disease progression and response. The following efficacy endpoints, described in Section 8.1.2, will be summarized based on this IRC review: overall response rate, duration of response, time to progression, and progression-free survival.

8.1.4 Timing of Efficacy Endpoints and Safety Evaluations

The date when 60 subjects in the Expansion Cohort have completed their Week 36 disease assessment, or after all enrolled subjects have discontinued venetoclax, whichever is earlier, will be defined as the data "cutoff" date for the efficacy analyses. Efficacy and safety data up to and including this date will be collected. Exact data cutoff date for the efficacy analysis will be detailed in a statistical analysis plan (SAP) which will be signed off prior to the data cut-off date. During this data collection period, active subjects will continue to receive venetoclax, as applicable. When data collection is complete and all data management quality assurance (QA) and quality control (QC) procedures are performed, the clinical database data will be extracted for documentation and statistical analyses. Any active subjects will continue to receive venetoclax until they discontinue or for up to 2 years from the date of the last subject enrolled in study. 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.

8.1.5 Pharmacokinetics

An analysis may be performed using a nonlinear mixed-effect population modeling approach with NONMEM software to describe the disposition of venetoclax, to identify significant covariates and explore relationship between pharmacokinetics and pharmacodynamics by combining data from this study with other venetoclax clinical studies. Additional analyses may be performed if useful in the interpretation of the data.

8.1.6 Additional Exploratory Efficacy Analyses

Time to next anti-CLL treatment will be defined as the number of days from the date of the first dose of venetoclax to the date of first dose of new non-protocol anti-lymphoma therapy (NPT) or death from any cause. For subjects who did not take NPT, the data will be censored at the last known date to be free of NPT. TTNT will be analyzed by Kaplan-Meier methodology using data for all enrolled subjects. Median TTNT time will be calculated and 95% confidence interval for median TTNT time will be presented.

The rate of MRD negativity in subjects will be an exploratory endpoint. This rate will be defined as the proportion of subjects who had MRD negativity status. Ninety-five percent (95%) confidence intervals based on the binomial distribution will be provided.

Health Economic and Patient Reported Outcome measures will include the EORTC QLQ-C30 and QLQ CLL16 (a measure of health related quality of life specific to CLL) and the EQ-5D-5L (measure of general health status) and EQ-5D-VAS. Descriptive statistics will be calculated for the EORTC QLQ-C30 and EORTC QLQ CLL16, the EQ-5D-5L utility score, and the EQ-5D-VAS score including mean change from baseline to each assessment as well as the final visit. Additionally, the EORTC QLQ-C30 and EORTC QLQ CLL16 will be administered through post-treatment. The results obtained for each instrument will be explored for trends and summarized as appropriate.

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

8.1.7 Safety

The safety of venetoclax will be assessed by evaluation study drug exposure, adverse events, serious adverse events, all deaths, as well as changes in laboratory values and vital sign parameters.

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

8.1.7.1 Adverse Events

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

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

Treatment-emergent adverse events will be summarized by preferred terms within a System and Organ Class according to the most current MedDRA dictionary. In addition, the percentage of subjects experiencing an adverse event at a NCI CTCAE Version 4.0 toxicity grade, and relationship to study drug will be provided.

8.1.7.2 Serious Adverse Events

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

8.1.7.3 Deaths

The number of subject deaths will be summarized (1) for deaths occurring within 30 days of the last dose of study drug, (2) for deaths occurring more than 30 days of the last dose of study drug, and (3) for all deaths in this study regardless of the number of days after the last dose of study drug.

8.1.7.4 Longitudinal Analyses of Laboratory and Vital Signs Data

Changes from baseline will be analyzed for each scheduled post-baseline visit and for the final visit for blood chemistry and hematology parameters, as well as urinalysis and vital sign parameters. If more than one measurement exists for a subject on a particular day, then an arithmetic average will be calculated. This average will be considered to be that subject's measurement for that day. Post-baseline measurements more than 30 days after the last dose of study drug will not be included. Subjects that do not have a baseline measurement or do not have any post-baseline measurements will not be included.

8.1.7.5 Analyses of Laboratory Data Using NCI CTCAE

Where applicable, blood chemistry, hematology and lymphocyte enumeration determinations will be categorized according to NCI CTCAE version 4.0 grades or higher, 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. An exception will be used for those subjects enrolled with a baseline value of neutrophils less than 1,000/μL requiring G-CSF support to meet entry criteria. For these subjects, the last value pre-G-CSF administration will be the baseline. 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

There is no planned hypotheses testing on the primary endpoint overall response rate (ORR). ORR will be presented by a point estimate and its corresponding 95% confidence interval. A sample size of 20 subjects would ensure that the distance of true rate will be within 23% of the observed rate with 95% confidence and a sample size of 60 subjects would ensure that the distance of true rate will be within 14% of the observed rate with 95% confidence.

Table 13. Sample Size Calculation

Number of Subjects (N)	Distance of True Rate from Observed Rate
20	23%
40	17%
60	14%

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 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.

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.

Refer to Appendix G for COVID-19-related processes for this section.

9.2 Ethical Conduct of the Study

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

9.3 Subject Information and Consent

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

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

Pharmacogenetic analysis will only be performed if the subject has voluntarily signed and dated a separate pharmacogenetic informed consent, approved by an IRB/IEC, after the nature of the testing has been explained and the subject has had an opportunity to ask questions. The separate pharmacogenetic informed consent must be signed before the pharmacogenetic testing is performed. If the subject does not consent to the pharmacogenetic testing, it will not impact the subject's participation in the study.

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded on the appropriate source documents.

The investigator(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.

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 investigator 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.

Refer to Appendix G for COVID-19-related processes for this section.

11.0 Data Quality Assurance

Prior to enrolling any subject in the study, a Site Initiation Visit will be held with AbbVie personnel (and/or their representatives), the investigators, and the appropriate site personnel. This meeting will include a detailed discussion and review of the protocol and essential documents, performance of study procedures, eCRF completion, and specimen collection methods. The personnel at the study site will be trained on the study procedures, when applicable, by an AbbVie monitor or designee.

The AbbVie monitor or designee will monitor the study site throughout the study. A source document review will be performed against entries on the eCRFs and a quality assurance check will be performed to ensure that the investigator is complying with the protocol and regulations. In addition, ongoing review of the data will be conducted by a physician or representative at AbbVie.

Data entered into eCRFs will be electronically transferred to AbbVie and imported into the database using validated software throughout the study. Computer logic checks will be run to identify such items as inconsistent study dates. Any necessary corrections will be made to the eCRF.

Routine hematology, serum chemistry and serology, and urinalysis will be conducted using the local laboratory.

A review of all laboratory results will be conducted by a physician and clinical review team at AbbVie, the AbbVie monitors (or their representatives), the investigator, and other appropriate personnel from AbbVie.

12.0 Use of Information

All information concerning venetoclax and AbbVie operations, such as AbbVie patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by AbbVie and not previously published is considered confidential information.

The information developed during the conduct of this clinical study is also considered confidential and will be used by AbbVie in connection with the development of venetoclax. This information may be disclosed as deemed necessary by AbbVie to other clinical investigators, other pharmaceutical companies, and to governmental agencies. To allow for the use of the information derived from this clinical study and to ensure complete and thorough analysis, the investigator is obligated to provide AbbVie with complete test results and all data developed in this study and to provide direct access to source data/documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection.

This confidential information shall remain the sole property of AbbVie, shall not be disclosed to others without the written consent of AbbVie, and shall not be used except in the performance of this study.

The investigator will maintain a confidential subject identification code list of all subjects enrolled in the study, including each subject's name and subject number. This list will be maintained at the study site with other study records under adequate security and restricted access and will not be retrieved by AbbVie.

Any pharmacogenetic research that may be done using DNA samples from this study will be experimental in nature and the results will not be suitable for clinical decision making or patient management. Hence, neither the investigator, the subject, nor the subject's physician (if different from the investigator) will be informed of individual subject pharmacogenetic results, should analyses be performed, nor will anyone not directly involved in this research. Correspondingly, genetic 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. Aggregate pharmacogenetic information from this study may be used in scientific publications or presented at medical conventions. Pharmacogenetic 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 retain any records related to the study according to local requirements. If the investigator is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

AbbVie will select the signatory investigator from the investigators who participate in the study. Selection criteria for this investigator will include level of participation as well as

significant knowledge of the clinical research, investigational drug and study protocol. The signatory investigator for the study will review and sign the final study report in accordance with the European Agency for the Evaluation of Medicinal Products (EMEA) Guidance on Investigator's Signature for Study Reports.

The end-of-study is defined as the date of the last subject's last visit.

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:	A Phase 2 Open-Label Study of the Efficacy and Safety of ABT-199 (GDC-0199) in Chronic Lymphocytic Leukemia Subjects with Relapse or Refractory to B-Cell Receptor Signaling Pathway Inhibitor Therapy
Protocol Date:	15 December 2020

Signature of Principal Investigator _____ Date _____

Name of Principal Investigator (printed or typed) _____

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Appendix A. Responsibilities of the Clinical Investigator

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

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

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

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
[redacted]	Study Project Manager	Clinical
[redacted]	Head of Statistics	Statistics
[redacted]	Senior Consultant, Clinical Supply	Global Drug Supply Management
[redacted]	Senior Medical Director	Clinical
[redacted]	Director	Clinical Pharmacokinetics
[redacted]	Senior Scientist III	Discovery
[redacted]	Principle Bioanalytical Investigator	Bioanalysis

Appendix C. Sample List of Excluded and Cautionary Medications

Excluded During Ramp-Up Phase and Cautionary Afterwards: (Additional Guidance Noted):
Strong CYP3A inducers – avasimibe, carbamazepine, enzalutamine, mitotane, phenytoin, rifampin, St. John's wort
Moderate CYP3A inducers^ – bosentan, efavirenz, etravirine, modafinil, nafcillin
Strong CYP3A inhibitors† – Boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, elvitegravir/ritonavir, idelalisib,* indinavir, itraconazole, ketoconazole, mibefradil, lopinavir/ritonavir, nefazodone, nelfinavir, paritaprevir/ritonavir combinations, ritonavir, posaconazole, saquinavir, telaprevir, telithromycin, tipranavir/ritonavir, troleandomycin, voriconazole
Moderate CYP3A inhibitors†† – Amprenavir, aprepitant, atazanavir, cimetidine, ciprofloxacin, clotrimazole, crizotinib,* cyclosporine,* darunavir/ritonavir, diltiazem,[1] dronedarone, erythromycin, fluconazole, fluvoxamine, fosamprenavir, imatinib,* isavuconazole, tofisopam, verapamil
Cautionary
Coumarins (vitamin K antagonists):
Warfarin (Coumadin)**
phenprocoumon (Marcumar)**
P-gp substrates
Aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus,* fexofenadine, lapatinib,* loperamide, maraviroc, nilotinib,* ranolazine, saxagliptin, sirolimus,* sitagliptin, talinolol, tolvaptan, topotecan*
BCRP substrates
Methotrexate,* mitoxantrone,* irrinotecan,* lapatinib,* rosuvastatin, sulfasalazine, topotecan*
OATP1B1/1B3 substrates
Asunaprevir, atrasentan, atorvastatin, certivastatin, docetaxel, ezetimibe, fluvastatin, glyburide, nateglinide, paclitaxel, rosuvastatin, simvastatin acid, pitavastatin, pravastatin, repaglinide, telmisartan, valsartan, olmesartan
P-gp inhibitors
Amiodarone, captopril, carvedilol, , felodipine, propafenone, quercetin, ronalzine, ticagrelor
BCRP inhibitors
Geftinib*, curcumin

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 Starfruits.

* These are anticancer agents; contact AbbVie medical monitor before use.

** Closely monitor international normalized ratio (INR).

^ If subject requires use of these medications, use with caution and contact AbbVie Primary TA MD or designee for guidance.

† If subject requires use of these medications, use with caution and reduce the venetoclax dose at least by 4-fold. After discontinuation of CYP3A inhibitor, wait for 3 days before venetoclax dose is increased back to the target dose.

†† If subject requires use of these medications, use with caution and reduce the venetoclax dose at least by 2-fold. After discontinuation of CYP3A inhibitor, wait for 3 days before venetoclax dose is increased back to the target dose.

1 Moderate CYP3A inhibitor per venetoclax FDA USPI.

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

Section 1: First Dose of Venetoclax or Dose Escalation

- Within the first 24 hours after either the first dose or dose escalation, if any laboratory criteria below are met, the patient should be hospitalized for monitoring and the investigator notified. No additional venetoclax doses should be administered until resolution. A rapidly rising serum potassium is a medical emergency.
- Nephrology (or other acute dialysis service) must be consulted/contacted (per institutional standards to ensure emergency dialysis is available) upon admission for any subject hospitalized prophylactically or in response to laboratory changes.
- IV fluids (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.
- Rasburicase must be administered/considered per regional standards or institutional guidelines for subjects with rapidly rising uric acid level.
- 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 patients receiving the first dose of venetoclax:

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

Abnormality	Management Recommendations
Hyperkalemia (including rapidly rising potassium)	
Potassium ≥ 0.5 mmol/L increase from prior value (even if potassium within normal limits [WNL])	Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. If further ≥ 0.2 mmol/L increase in potassium, but still < upper limit of normal (ULN), manage as per potassium ≥ ULN. Otherwise recheck in 1 hour. Resume per protocol testing if change in potassium is < 0.2 mmol/L, and potassium < ULN, and no other evidence of tumor lysis. At the discretion of the investigator, may recheck prior to hospitalization. If stable or decreased, and still WNL, hospitalization is at the discretion of the investigator. Potassium, phosphorus, uric acid, calcium and creatinine must be rechecked within 24 hours.
Potassium > upper limit of normal	Perform STAT ECG and commence telemetry. Nephrology (or other acute dialysis service) notification with consideration of initiating dialysis. Administer Kayexalate 60 g (or Resonium A 60 g). Administer furosemide 20 mg IV × 1. Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is ECG/telemetry evidence of life threatening arrhythmias. Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. If potassium < ULN 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 1, 2 and 4 hours, if no other evidence of tumor lysis.

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)	Perform STAT ECG and commence telemetry. Nephrology (or other acute dialysis service) assessment with consideration of initiating dialysis. Administer Kayexalate 60 g (or Resonium A 60 g). Administer furosemide 20 mg IV × 1. Administer insulin 0.1 U/kg IV + D25 2 mL/kg IV. Administer sodium bicarbonate 1 to 2 mEq/kg IV push. If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is ECG/telemetry evidence of life threatening arrhythmias. Do not administer in same IV line as sodium bicarbonate. Recheck potassium, phosphorus, uric acid, calcium and creatinine every hour STAT.
Hyperuricemia	
Uric acid ≥ 8.0 mg/dL (476 µmol/L)	Consider rasburicase (dose based on local guidelines and/or institutional standards). If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT.
Uric acid ≥ 10 mg/dL (595 µmol/L) OR Uric acid ≥ 8.0 mg/dL (476 µmol/L) with 25% increase and creatinine increase ≥ 0.3 mg/dL (≥ 0.027 mmol/L) from pre-dose level	Administer rasburicase (dose based on local guidelines and/or institutional standards). When rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. Notify nephrology (or other acute dialysis service). Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. If uric acid < 8.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours, later, if no other evidence of tumor lysis.

Abnormality	Management Recommendations
Hypocalcemia	
Calcium ≤ 7.0 mg/dL (1.75 mmol/L) AND Patient symptomatic (e.g., muscle cramps, hypotension, tetany, cardiac arrhythmias)	Administer calcium gluconate 50 to 100 mg/kg IV slowly with ECG monitoring. Telemetry. Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. If calcium normalized 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours, later, if no other evidence of tumor lysis. Calculate corrected calcium and check ionized calcium if albumin low.
Hyperphosphatemia	
Phosphorus ≥ 5.0 mg/dL (1.615 mmol/L) with ≥ 0.5 mg/dL (0.16 mmol/L) increase	Administer a phosphate binder (e.g., aluminum hydroxide, calcium carbonate, sevelamer hydroxide, or lanthanum carbonate). Nephrology (or other acute dialysis service) notification (dialysis required for phosphorus ≥ 10 mg/dL). Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. If phosphorus < 5.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours, later, if no other evidence of tumor lysis.
Creatinine	
Increase ≥ 25% from baseline	Start or increase rate of IV fluids. Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 to 2 hours STAT.

Section 2: Ongoing Dosing of Venetoclax

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

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

- For potassium, admit patient for any increase ≥ 1.0 mmol/L (1.0 mEq/L), or any level > upper limit of normal.
    - Refer to the management guidelines for electrolyte changes observed within the first 24 hours after either the first dose or dose escalation (see 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 E. 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)
Secondary 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 F. Definitions of Laboratory and Clinical Tumor Lysis Syndrome

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

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

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

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

Appendix G. Summary of COVID-19 Processes

Section	Title	Language Added
3.2	Benefits and Risks	Considering the coronavirus (COVID-19) pandemic, the benefit and risk to subjects participating in this study has been re-evaluated. Subjects receiving venetoclax may be at an increased risk for COVID-19 infection or experience serious illness if infected. Management of these adverse events will be made on a case-by-case basis with consideration of benefit/risk. However, based on the population and disease being studied and the anticipation that COVID-19 related risks are not expected to differ substantially between study subjects and the broader population of subjects receiving treatment for CLL, no change to the benefit/risk balance for subjects in this study is expected.
5.2.3	Prior and Concomitant Therapy	A vaccine for COVID-19, though not yet available at the time of protocol amendment version 6.0, may be allowed when available after documented communication with the AbbVie TA MD.
5.3.1.1	Study Procedures	During the COVID-19 pandemic, it has been necessary to employ mitigation strategies to enable the investigator to ensure patient safety and continuity of care. Acceptable mitigation strategies are identified below and throughout the protocol. Study visits may be impacted due to the COVID-19 pandemic. This may include changes such as phone or virtual visits, visits at alternative locations, or changes in the visit frequency and timing of study procedures, among others. Additional details are provided in the subsequent section. Every effort should be made to ensure the safety of subjects and site staff, while maintaining the integrity of the study. If visits cannot be conducted onsite due to travel restrictions or other pandemic-related reasons, follow the updates below on how to proceed. **COVID-19 Pandemic-Related Acceptable Protocol Modifications** During the COVID-19 pandemic, if it is not possible for all study procedures to be performed as specified due to travel restrictions or other reasons, the following modifications are allowed: • Some study visits and/or activities may be performed by phone/virtually. • Some study visits and/or activities may be performed by a local clinic/hospital/laboratory. All procedures performed at local facilities must be performed by appropriately qualified personnel. • Study visits and/or activities should be performed as scheduled whenever possible. If it is not possible to do so due to the pandemic, the following modifications are allowed: o If an activity is missed during a virtual visit, perform the activity at the earliest feasible opportunity. o **NOTE:** If a subject tests positive for COVID-19 or if there is

Section	Title	Language Added
		strong suspicion of COVID-19 (based on symptoms, travel history, or close contact with a case), the investigator should evaluate the benefit/risk of venetoclax being interrupted until the infection has resolved or has been ruled out. There are no time limits for venetoclax interruption as long as no permanent study discontinuation criteria have been met. The investigator should contact the AbbVie TA MD prior to reintroducing venetoclax in research participants previously diagnosed with COVID-19. See also Section 5.4.1, Discontinuation of Individual Subjects, for additional detail. **Informed Consent** Due to the COVID-19 pandemic, it is possible that additional protocol modifications not outlined in this protocol may become necessary. If this situation arises, in addition to the study informed consent, additional verbal consent may be obtained prior to these adaptations or substantial changes in study conduct in accordance with local regulations. Clinical Laboratory Testing • If travel restrictions or other changes in local regulations in light of the COVID-19 pandemic prevent the subject from having blood drawn for laboratory testing at the study site, if possible, arrange for subjects to have laboratory work done at a local lab, hospital, or other facility. Local lab results should be obtained along with reference ranges and kept within the subjects' source documentation. Local lab results should be reviewed by the investigator as soon as possible and before venetoclax is administered. • If laboratory samples cannot be obtained, study drug administration may be continued provided the investigator has reviewed all prior laboratory results and confirms and discusses with the subject that there is no safety concern for the subject to continue use of the study drug in the absence of current labs. The subject should be scheduled for laboratory draws as soon as feasible.
5.4.1	Discontinuation of Individual Subjects	**COVID-19 Pandemic-Related Acceptable Protocol Modification** The investigator should contact the sponsor medical contact before discontinuing a subject from the study for a reason other than "planned per protocol," to ensure all acceptable mitigation steps have been explored. Interruption/Discontinuation of Study Drug Due to COVID-19 Infection During the Study Drug Dosing Period, a subject with confirmed (viral test positive) or suspected COVID-19 infection can only be dosed with study drug if the following COVID-19 viral clearance criteria are met: • Symptomatic subjects: At least 2 negative viral tests in a row, ≥ 24 hours apart after at least 10 days have passed since recovery, defined as resolution of fever without use of antipyretics and

Section	Title	Language Added
		improvement in respiratory symptoms (e.g., cough, shortness of breath) • Asymptomatic subjects: At least 2 negative viral tests in a row, ≥ 24 hours apart after at least 10 days have passed since prior positive result (note: subjects who develop symptoms will follow guidance above for symptomatic subjects) Delays in study drug dosing due to the above COVID-19 testing guidance for subjects must be discussed with the AbbVie medical contact, along with the possibility of premature discontinuation from the study drug dosing period. Frequency or timing of COVID-19 testing and intervals between testing for the above viral clearance criteria may be adjusted to account for epidemiologic trends, updated information regarding infectivity, and local/institutional guidelines.
5.5.1	Treatments Administered	**Direct-to-patient (DTP) Shipment of Study Drug** If a subject is unable to come to the study site to pick up their study drug due to COVID-19, a direct-to-patient (DTP) study drug shipment can be made from the study site to the subject if allowed by local regulations. AbbVie will submit any required notifications to the regulatory authority as applicable. Study drug may be shipped from the study site directly to the study subject's home if all the following criteria are met: • Direct-to-patient (DTP) shipment of study drug is allowed by local regulations and the relevant ethics committee • Study drug can be administered by the subject (or subject's caregiver) at home • Subject agrees to have the study drug shipped directly to their home o Shipments may also include other study supplies (e.g., drug dosing diaries). Instructions will be provided by AbbVie as to how a study site can initiate a DTP shipment using Marken, a global vendor selected by AbbVie to provide this service when necessary. Shipments of study drugs from the study site to a subject's home will be appropriately temperature controlled (qualified shipper or temperature monitoring) within the labeled storage conditions. Signature is required upon delivery; due to COVID-19 related social distancing, this may be provided by the courier after delivery. Documentation of the shipment is to be retained by the clinical site. • AbbVie will not receive subject identifying information related to these shipments, as the site will work directly with the courier. The study site is responsible for meeting IRB/IEC reporting requirements related to DTP shipments of study drug, and for obtaining consent to provide delivery information to the courier and documenting

Section	Title	Language Added
		this consent in source documents.
6.1.5	Adverse Event Reporting	**Adverse Event Reporting** Supplemental study case report forms should be completed in the event of COVID-19 related missed/virtual visits, study drug interruptions or discontinuations, or adverse events (including capture of specific signs/symptoms of infection and testing results). COVID-19 infections should be captured as adverse events. If the event meets the criteria for a serious adverse event (SAE), then follow the SAE reporting directions per the protocol and above. The following COVID-19 related supplemental eCRFs should be completed (for both serious and non-serious events): • COVID-19 Supplemental Signs/Symptoms • COVID-19 Status Form If a subject has a confirmed or suspected COVID-19 infection and study drug was interrupted, the investigator should contact the sponsor emergency medical contact listed above before reintroducing study drug.
7.0	Protocol Deviations	Protocol deviations may include modifications due to COVID-19.
9.1	Independent Ethics Committee (IEC) or Institutional Review Board (IRB)	In the event of a state of emergency due to the COVID-19 pandemic leading to difficulties in performing protocol-specific procedures, AbbVie will engage with study site personnel in efforts to ensure the safety of subjects, maintain protocol compliance, and minimize risks to the integrity of the study while trying to best manage subject continuity of care. This may include alternative methods for assessments (e.g., phone contacts or virtual site visits), alternative locations for data collection (e.g., use of a local lab instead of a central lab), and shipping investigational product and/or supplies direct to subjects to ensure continuity of treatment where allowed. Refer to Section 5.3.1.1 and Section 5.5.1 for additional details. In all cases, these alternative measures must be allowed by local regulations and permitted by IRB/IEC. Investigators should notify AbbVie if any urgent safety measures are taken to protect the subjects against any immediate hazard.
11.0	Source Documents and Case Report Form Completion	During the COVID-19 pandemic, remote monitoring of data may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.