1.0 Title Page

Clinical Study Protocol M13-982

A Phase 2 Open-Label Study of the Efficacy of ABT-199 (GDC-0199) in Subjects with Relapsed/Refractory or Previously Untreated Chronic Lymphocytic Leukemia Harboring the 17p Deletion

Incorporating Amendments 1, 2, 3, 4, 5, 6, and Amendments 3.01 and 3.02 (Germany Only)

AbbVie Investigational Product:	Venetoclax (ABT-199/GDC-0199)
Date:	28 February 2017
Development Phase:	2
Study Design:	This is an open-label, single arm study to determine the efficacy of venetoclax (ABT-199/GDC-0199) in subjects with relapsed/refractory or previously untreated chronic lymphocytic leukemia harboring 17p deletion.
EudraCT Number:	2012-004027-20
Investigator:	Investigator information on file at AbbVie.
Sponsor:	AbbVie*
Sponsor/Emergency Contact:	[redacted] AbbVie 1 North Waukegan Road North Chicago, IL 60064 Phone: [redacted] Cell: Fax:

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.

*The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and the Clinical Trial Application with the Competent Authority.

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	15 October 2012
Amendment 1	10 May 2013
Amendment 2	25 July 2014
Amendment 3	19 December 2014
Amendment 3.01 (Germany only)	15 April 2015
Amendment 3.02 (Germany only)	28 May 2015
Amendment 4	16 May 2016
Amendment 5	08 September 2016

The purpose of this amendment is to:

- Update Section 1.2, Synopsis, Section 5.1, Overall Study Design and Plan: Description, and Section 5.3.1.1, Study Procedures, to add a Survival Extended Access period to the trial.

  Rationale: *AbbVie feels it is an ethical approach to continue to offer venetoclax in the study setting to those subjects who are continuing to derive clinical benefit and have not withdrawn consent. The original study design allowed subjects to remain on study drug only up to 2 years following last subject first dose. The Extended Access period will allow subjects to continue on venetoclax until disease progression; up to 5 years following last subject first dose (12 May 2020); or until a subject chooses to switch to commercial supply.*

- Update Section 1.2, Synopsis, to clarify that study objectives, with the exception of Safety, will cease to be evaluated beyond 2 years after last subject first dose.

  Rationale: *The Survival Extended Access period is intended only to collect safety and long-term MRD data for analyses.*

- Update Section 5.1, Overall Study Design and Plan: Description, Post-Treatment Visits, and Section 5.3.1.1, Study Procedures, Post-Treatment, to discontinue post-treatment visits effective 12 May 2017.

  Rationale: *As very few subjects entered the Post-Treatment period, there is little data to provide any meaningful, Statistical analyses. Subjects will continue to be followed in Survival until disease progression or withdrawal of consent.*

- Update Table 2, Excluded and Cautionary Medications/Food Items.

  Rationale: *Additional information has been added regarding excluded and cautionary medications/food.*

- Update Table 4, Study Activities, to include the activities to be performed during the Survival period.

  Rationale: *The Survival period was not previously included in the table, so it has been updated to include the activities to be performed during the Survival Extended Access visits.*

- Update Section 5.3.1.1, Study Procedures, Quantitative Minimal Residual Disease (MRD) Assessment, to add the collection of blood specimen for MRD PCR every 12 weeks during the Survival Extended Access period for subjects who qualify.

  Rationale: *AbbVie would like to obtain additional, long-term MRD data for analysis.*

- Update Section 5.4.1, Discontinuation of Individual Subjects, to allow subjects with progressive disease who remain on venetoclax the ability to receive other approved treatment agents for CLL in addition to venetoclax.

  Rationale: *CLL patients with 17p deletion have limited options for treatment. The addition of other approved CLL agents may aid to slow the disease progression and extend the life of the subject.*

- Update Section 6.0, Adverse Events, to reflect changes made to the AbbVie protocol template.

  Rationale: *Additional information has been added regarding medical and product complaints.*

- Update Section 6.1.3, Relationship to Study Drug.

Rationale: *Definitions for adverse event causality have been updated to provide a more robust description.*

- Update Section 6.1.6, Adverse Event Reporting.

  Rationale: *Updated to reflect change in AbbVie medical monitor and to remove the Oncology Safety Management phone contact number.*

- Update Section 7.0, Protocol Deviations.

  Rationale: *Updated to reflect changes in AbbVie Program Lead and medical monitor.*

- Update Section 8.1.1.2.7, Additional Exploratory Efficacy Analyses, and Section 8.1.4.1, Additional Exploratory Efficacy Analyses, to confirm that MRD-Flow data for exploratory analysis will not be collected during the survival extended access portion of the study.

  Rationale: *Only safety and MRD-PCR will be assessed during the extended access portion of the study.*

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

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M13-982
Name of Study Drug: Venetoclax	**Phase of Development:** 2
Name of Active Ingredient: Not available	**Date of Protocol Synopsis:** 28 February 2017
Protocol Title: A Phase 2 Open-Label Study of the Efficacy of ABT-199 (GDC-0199) in Subjects with Relapsed/Refractory or Previously Untreated Chronic Lymphocytic Leukemia Harboring the 17p Deletion	
Main Cohort Objectives: **Primary objective:** The primary objective of this cohort is to evaluate the efficacy of venetoclax monotherapy in subjects with relapsed or refractory chronic lymphocytic leukemia (CLL) harboring the 17p deletion. Efficacy will be measured by overall response rate (ORR). **Secondary objectives:** The secondary objectives are to evaluate the complete remission rate (CR), partial remission rate (PR), duration of overall response (DOR), progression-free survival (PFS), time to progression (TTP), overall survival (OS) and percent of subjects who move on to stem cell transplant. The safety and tolerability of venetoclax in subjects with relapsed or refractory CLL harboring 17p deletion will also be evaluated. **Safety Expansion Cohort Objectives:** **Primary objective:** A safety expansion cohort is being added with the primary objective of evaluating the safety of venetoclax in approximately 50 subjects with relapsed/refractory or previously untreated CLL harboring 17p deletion per the updated TLS prophylaxis and management measures. **Secondary objectives:** The secondary objectives are to evaluate ORR, CR rate, PR rate, duration of overall response (DOR), progression-free survival (PFS), time to progression (TTP), overall survival (OS), and percent of subjects who move on to stem cell transplant. **Exploratory objectives (both main and safety expansion cohorts):** Time to next anti-CLL treatment (TTNT), minimal residual disease (MRD) assessed in the peripheral blood and/or bone marrow (BM), pharmacokinetics, pharmacogenetics and biomarkers will be evaluated as exploratory objectives. Health Economic and Patient-Reported Outcome Measures will include the MDASI (measure of subject reported symptoms), 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) and EQ-5D-VAS. *Note: All study objectives, with the exception of Safety and MRD analyses, will cease to be evaluated beyond 2 years after last subject first dose.*	
Investigators: Multicenter	
Study Sites: Approximately 60 research sites globally.	
Study Population: Main Cohort: Relapsed or refractory CLL subjects harboring 17p deletion Safety Expansion Cohort: Relapsed/refractory or previously untreated CLL subjects harboring 17p deletion (previously untreated chronic lymphocytic leukemia harboring 17p deletion patients will not be enrolled in Germany)	
Number of Subjects to be Enrolled: Approximately 150 (100 subjects in the main cohort and 50 subjects in the safety expansion cohort)	

Methodology: This is a Phase 2, open label, multicenter, study evaluating the efficacy of venetoclax in relapsed/refractory or previously untreated subjects with CLL harboring 17p13 deletion. The main cohort will enroll approximately 100 subjects with relapsed/refractory CLL harboring 17p13 deletion to assess efficacy and safety of venetoclax. The safety expansion cohort will enroll approximately 50 subjects with relapsed/refractory or previously untreated CLL harboring 17p13 deletion to assess the updated TLS prophylaxis measures. The detection of 17p13 deletion (17p del) will be determined by the local laboratory and/or by the central laboratory which uses the Vysis CLL FISH probe kit. Screening must be performed within 28 days of study drug administration. CT scan must be performed within 35 days prior to study drug administration. A bone marrow biopsy and aspirate will also be performed at Screening (within 35 days prior to study drug administration), and again in coordination with CT scans, to confirm complete remission. Study visits will be conducted on Days 1 and 2 of each week through Week 5, then on Day 1 of every 4 weeks thereafter, beginning with Week 8 (e.g., Weeks 8, 12, 16, 20, 24, etc.) until Week 36, and then Day 1 of every 12 weeks thereafter.

Diagnosis and Main Criteria for Inclusion/Exclusion

Main Inclusion:

A subject will be eligible for participation in the safety expansion cohort of the study 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 Modified IWCLL NCI-WG Guidelines.
    - Subject has an indication for treatment according to the 2008 Modified IWCLL NCI-WG Guidelines;
    - Subject has clinically measurable disease (lymphocytosis > 5×10^9/L and/or palpable and measurable nodes by physical exam and/or organomegally assessed by physical exam);
    - Subject must have relapsed/refractory CLL or previously untreated CLL (previously untreated chronic lymphocytic leukemia harboring 17p deletion patients will not be enrolled in Germany);
        - Refractory or relapsed CLL subjects must meet the following requirements:
            - Refractory or relapsed after receiving at least one prior line of therapy (subjects that have progressed after 1 cycle of treatment or have completed at least 2 cycles of treatment for a given line of therapy);
        - Previously untreated CLL subjects must meet the following requirements:
            - Received no prior chemotherapy or immunotherapy. Subjects with a history of emergency, loco-regional radiotherapy (e.g., for relief of compressive signs or symptoms) are eligible.
            - CLL diagnostic criteria above and must have > 5×10^9/L B-Lymphocytes in the peripheral blood.

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

Main Inclusion (Continued):

- Subjects must have 17p deletion, assessed by local laboratory (in bone marrow or peripheral blood) or assessed by central laboratory (peripheral blood). A local result obtained prior to study Screening may be used for eligibility. Additionally, a confirmatory sample (peripheral blood) will be sent to the central laboratory.

4. Subject has an Eastern Cooperative Oncology Group (ECOG) performance score of ≤ 2.
5. Subject must have adequate bone marrow function at Screening as follows:
   - Absolute Neutrophil Count (ANC) ≥ 1000/μL, or
   - For subjects with an ANC < 1000/μL at Screening and bone marrow heavily infiltrated with underlying disease (unless cytopenia is clearly due to marrow involvement of CLL), growth factor support may be administered 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 within 14 days of Screening
     - without evidence of mucosal bleeding
     - without known history of bleeding episode within 3 months of Screening
     - without history of bleeding disorder
   - Hemoglobin ≥ 8.0 g/dL.
6. Subject must have adequate coagulation, 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);
   - Calculated creatinine clearance ≥ 50 mL/min using 24-hour Creatinine Clearance or modified Cockcroft-Gault equation (using Ideal Body Mass [IBM] instead of Mass):

$$eCC_r = \frac{(140 - \text{Age}) \times \text{IBM (kg)} \times [0.85 \text{ if Female}]}{72 \times \text{Serum Creatinine (mg/dL)}}$$

Or, if serum creatinine is in μmol/L:

$$eCC_r = \frac{(140 - \text{Age}) \times \text{IBM (kg)} \times [1.23 \text{ if Male, } 1.04 \text{ if Female}]}{\text{Serum Creatinine (μmol/L)}}$$

Ideal Body Mass should be used:

$$\text{IBM (kg)} = [(\text{height cm} - 154) \times 0.9] + (50 \text{ if Male, } 45.5 \text{ if Female})$$

Note: For subjects that have BMI of > 30 kg/m^2 or < 19 kg/m^2, 24-hour measured urine creatinine clearance is required.

- AST and ALT ≤ 3.0 × the upper normal limit (ULN) of institution's normal range; Bilirubin ≤ 1.5 × ULN. Subjects with Gilbert's Syndrome may have a bilirubin > 1.5 × ULN, per correspondence between the investigator and AbbVie medical monitor.

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

Main Exclusion (Continued):

7. 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 life style of the subject; periodic abstinence is not acceptable;
   - Surgically sterile partner(s); acceptable sterility surgeries are: vasectomy, bilateral tubal ligation, bilateral oophorectomy or hysterectomy;
   - Intrauterine device (IUD);

   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.
8. Females of childbearing potential (i.e., not 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 a urine sample obtained on Week 1 Day 1 (tested locally), if it has been > 7 days since obtaining the serum pregnancy test results.
9. Male subjects must agree to refrain from sperm donation, from initial study drug administration until 90 days after the last dose of study drug.
10. For high risk subjects (as defined in Section 6.1.8.1) a pre-approval by the AbbVie medical monitor is required prior to enrollment.

Main Exclusion:

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

1. Subject has undergone an allogeneic stem cell transplant.
2. Subject has developed Richter's transformation confirmed by biopsy.
3. Subject has prolymphocytic leukemia.
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 previously received venetoclax.
6. Subject is known to be positive for HIV (due to potential drug-drug interactions between anti-retroviral medications and venetoclax, as well as anticipated venetoclax mechanism based lymphopenia that may potentially increase the risk of opportunistic infections).
7. Subject has received the following **within 30 days** prior to the first dose of study drug:
   - A biologic agent (i.e., monoclonal antibodies) for anti-neoplastic intent.

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

Main Exclusion (Continued):

8. Subject has received radiotherapy **within 14 days or** any of the following **within 5 half-lives as applicable** prior to the first dose of study drug, or has not recovered to less than CTC grade 2 clinically significant adverse effect(s)/toxicity(s) of the previous therapy:
   - Any anti-cancer therapy including chemotherapy,
   - Investigational therapy, including targeted small molecule agents.
9. Subject has received the following **within 7 days** prior to the first dose of study drug:
   - Steroid therapy for anti-neoplastic intent;
   - CYP3A inhibitors (such as fluconazole, ketoconazole, and clarithromycin);
   - Potent CYP3A inducers (e.g., rifampin, phenytoin, carbamazepine or St. John's Wort);
   - Coumarins (vitamin K antagonists) or warfarin or phenprocoumon (Germany); or requires the use of coumarins (vitamin K antagonists) or warfarin or phenprocoumon (due to potential drug-drug interactions that may potentially increase the exposure of coumarins [vitamin K antagonists] or warfarin or phenprocoumon and complications of this effect).
10. Subject has consumed the following **within 3 days** prior to the first dose of study drug.
    - Grapefruit or grapefruit products;
    - Seville oranges (including marmalade containing Seville oranges);
    - Star fruit.
11. Subject has known allergy to both xanthine oxidase inhibitors and rasburicase.
12. Subject has a cardiovascular disability status of New York Heart Association Class ≥ 2. Class 2 is defined as cardiac disease in which subjects are comfortable at rest but ordinary physical activity, results in fatigue, palpitations, dyspnea or anginal pain.
13. Subject exhibits evidence of other clinically significant uncontrolled condition(s) including, but not limited to:
    - Uncontrolled and/or active systemic infection (viral, bacterial, or fungal).
    - Chronic hepatitis B virus (HBV) or hepatitis C (HCV) requiring treatment. 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.
    - Febrile neutropenia.
14. Subject has a significant history of renal, pulmonary, neurologic, psychiatric, endocrinologic, metabolic, immunologic, cardiovascular, or hepatic disease that in the opinion of the investigator would adversely affect his/her participating in this study. For subjects who have required an intervention for any above diseases within the past 6 months correspondence with the investigator and the AbbVie medical monitor must occur.
15. A female subject is pregnant or breast-feeding.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued): **Main Exclusion (Continued):** 16. Subject has a history of active malignancies 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. Subject has malabsorption syndrome or other condition that precludes enteral route of administration.	
Investigational Product:	Venetoclax: 10 mg, 50 mg, and 100 mg tablet 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 will be employed to evaluate a step wise dose escalation.
Dose – Main Cohort:	Subjects will be admitted to the hospital and begin the lead-in period with an initial test dose of 20 mg venetoclax on Week 1 Day 1. If no significant findings occur within 24 hours, then a test dose of 50 mg will be administered on Week 1 Day 2 followed by 50 mg venetoclax QD for 5 days (Week 1 Day 3 – Day 7). If significant findings occur within 24 hours on Week 1 Day 1, the 20 mg dose will be maintained for 1 week prior to dose escalation to 50 mg on Week 2 Day 1 – 7. After a week at 50 mg, the following dose escalation will proceed with weekly dose escalations → 100 mg → 200 mg → 400 mg (or additional lead-in steps to designated 400 mg dose), as tolerated. A lower starting dose and/or modification to the lead-in regimen may be implemented for individual subject(s) at particularly high risk for TLS.
Dose – Safety Expansion Cohort:	Single daily doses QD starting with 20 mg; dose escalations will proceed weekly → 50 mg → 100 mg → 200 mg → 400 mg, as tolerated. A lower starting dose and/or modification to the lead-in regimen may be implemented for individual subject(s) at particularly high risk for TLS.
Mode of Administration:	Oral
Duration of 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. The anticipated median treatment duration is approximately 24 months or greater.	

Survival Assessments: Survival information will be collected every 3 months (±7 days) for up to 5 years after the last subject has been enrolled for subjects who have not withdrawn consent.

Richter's Transformation and Second Primary Malignancies Assessment: Information on Richter's Transformation and second primary malignancies will be collected every 3 months for up to 5 years after the last subject has been enrolled for subjects who have not withdrawn consent.

Survival – Extended Access: For subjects who continue to derive benefit from venetoclax treatment 2 years following the date of the last subject enrolled, AbbVie will provide venetoclax until the subject develops disease progression or until 5 years following the date of last subject enrolled (12 May 2020).

Criteria for Evaluation:

Efficacy:

Response will be assessed by the investigator, based on laboratory values, physical examinations, CT scans (or MRI if CT scan is medically contraindicated), and bone marrow examinations, using the 2008 Modified IWCLL NCI-WG Guidelines for Tumor Response.

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 Guidelines for Tumor Response. 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.

All measurable disease must be documented at screening by physical examination, laboratory testing and CT scan (or MRI if CT is medically contraindicated), and bone marrow.

During the study, subjects will be assessed at each visit by a physical examination and laboratory testing. Clinical disease assessments will take place at baseline, monthly for the first 9 months and then every 3 months until disease progression, death, discontinuation from the study, or study completion.

Additional radiographic studies will be performed as described below:

A CT scan must be performed to confirm the response no earlier than 8 weeks after a response is determined by clinical criteria (laboratory results and physical exam). For consistency, the same method of imaging should be performed for a subject throughout the study.

For determination of CR, both the CT scan and bone marrow are required to be negative.

A CT scan (or MRI if CT is medically contraindicated), will be also performed in all subjects at 36 weeks from the beginning of the study.

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.

Criteria for Evaluation (Continued):

MRD:

MRD for enumeration of CLL cells will be assessed using IWG-CLL recommended methods of flow cytometry and/or ASO-PCR. The ERIC panel based flow cytometry will be assessed by regional laboratories on available samples. Specimens (bone marrow aspirate and peripheral blood) for MRD analysis should be collected at the same time as the bone marrow aspirate and biopsy performed for tumor assessments to confirm the CR/CRi. If MRD negativity is achieved in the bone marrow no further MRD analyses are required. Otherwise, MRD should be assessed at 12-week intervals thereafter (in peripheral blood) until MRD negativity is achieved. Once MRD negativity is achieved and confirmed in peripheral blood (e.g., two MRD negative consecutive peripheral blood samples), a bone marrow aspirate specimen will again be collected for analysis of MRD levels to confirm the peripheral blood negativity.

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 and MRD assessment. If a bone marrow and MRD assessment was not performed at the time of the confirmatory CT scan, then they should be performed after the Week 36 Day 1 CT scan. If MRD negativity is achieved in the bone marrow no further MRD analyses are required. Otherwise, MRD should be assessed at 12-week intervals thereafter (in peripheral blood) until MRD negativity is achieved. Once MRD negativity is achieved and confirmed in peripheral blood (e.g., two MRD negative consecutive peripheral blood samples), a bone marrow aspirate specimen will again be collected for analysis of MRD levels to confirm the peripheral blood negativity.

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.

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. 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.

Safety:

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

Statistical Methods:

Main Cohort:

Efficacy:

The following efficacy analyses will be analyzed: ORR, CR rate, PR rate, duration of overall response, progression-free survival, event free survival, time to progression, time to first response, time to 50% reduction in ALC, overall survival and percent of subjects who move on to stem cell transplant. Additional efficacy analyses will include time to next anti-CLL treatment, rate of minimal residual disease (MRD) negativity status, and Health Economic and Patient Reported Outcome (PRO) measures.

Statistical Methods (Continued):

Safety Expansion Cohort:

Secondary Efficacy:

The following secondary efficacy analyses will be analyzed: ORR, CR rate, PR rate, duration of overall response, progression-free survival, event free survival, time to progression, time to first response, time to 50% reduction in ALC, overall survival, and percent of subjects who move on to stem cell transplant. Additional efficacy analyses will include time to next anti-CLL treatment, rate of minimal residual disease (MRD) negativity status, and Health Economic and Patient Reported Outcome (PRO) measures.

Pharmacokinetic/Pharmacodynamic:

An analysis will 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.

Safety:

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

1.3 List of Abbreviations and Definition of Terms

Abbreviations

AE	Adverse Event
ALL	Acute Lymphoblastic Leukemia
ALT	Alanine aminotransferase
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
ASCO	American Society of Clinical Oncology
ASO-PCR	Allele Specific Oligonucleotide Polymerase Chain Reaction
AST	Aspartate aminotransferase
aPTT	Activated Partial Thromboplastin Time
Bcl	B-Cell Lymphoma
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CLL	Chronic Lymphocytic Leukemia
cm	Centimeter
CR	Complete Remission
CRi	Complete Remission with Incomplete Marrow Recovery
CT	Computed Tomography
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
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
DOR	Duration of Overall Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eC_{Cr}	Estimated creatinine clearance rate using Cockcroft-Gault Formula
eCRF	Electronic Case Report Form

EFS	Event Free Survival
EMA	European Medicines Agency
ERIC	European Research Initiative in CLL
FCR	Fludarabine, cyclophosphamide, and rituximab
FDA	Food and Drug Administration
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
HBsAg	Hepatitis B Surface Antigen
HDPE	High Density Polyethylene
HIV	Human Immunodeficiency Virus
hr	Hour
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
IUO	Investigational Use Only
IV	Intravenous
IWCLL	International Workshop for Chronic Lymphocytic Leukemia
IxRS	Interactive Response System
kg	Kilogram
LDH	Lactate Dehydrogenase
LN	Lymph Node
LVEF	Left Ventricular Ejection Fraction
MCHC	Mean Corpuscular Hemoglobin Concentration
MCL	Mantle Cell Lymphoma
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
µg	Microgram
µM	Micromolar
mg	Milligram

mL	Milliliter
mm	Millimeter
MM	Multiple Myeloma
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
NHL	Non-Hodgkin's Lymphoma
nM	Nanomolar
nPR	Nodular Partial Remission
NPT	Non-protocol anti-lymphoma therapy
ORR	Overall Response Rate
OS	Overall Survival
PCR	Polymerase Chain Reaction
PD	Pharmacodynamic
PD	Progressive Disease
PEO	Performance Evaluation Only
PFS	Progression-free Survival
PG	Pharmacogenetic
PK	Pharmacokinetic
PR	Partial Remission
PT	Prothrombin Time
QD	Once Daily
qPCR	Quantitative Polymerase Chain Reaction
QTcF	QT interval measurement corrected by Fridericia's formula
RBC	Red Blood Cell
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
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
TLS	Tumor Lysis Syndrome
TTNT	Time to next anti-CLL treatment

TTP	Time to Tumor Progression
ULN	Upper Limit of Normal
US	Ultrasound
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
QT Interval	The interval between the beginning of the QRS complex to the end of the T wave in an ECG
T_{max}	Time to maximum observed plasma concentration
V/F	Apparent volume of distribution

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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] Bcl-2 overexpression is a major contributor to the pathogenesis of some types of lymphoid malignancies. Bcl-2 is also overexpressed in acute and chronic leukemias. Chronic lymphocytic leukemia (CLL) is a genetic disease where the microRNAs miR15a and miR16-1 that negatively regulate the transcription of Bcl-2 are deleted or down-regulated, resulting in uncontrolled expression of Bcl-2.[5,6]

Venetoclax in vitro/in vivo Activity and Preclinical Pharmacokinetic Profile

Venetoclax is a novel, orally available small molecule Bcl-2 family protein inhibitor that binds with > 500-fold higher affinity (K_i < 0.010 nM) to Bcl-2 and with lower affinity to other Bcl-2 family proteins Bcl-X_L (K_i – 48 nM) and Bcl-w (K_i – 245 nM).[7] Overexpression of antiapoptotic Bcl-2 family proteins is associated with increased resistance to chemotherapy, and antagonism of the action of these proteins might enhance response to such therapy and overcome resistance. Antiapoptotic Bcl-2 family members are associated with tumor initiation, disease progression, and drug resistance, and making them compelling targets for antitumor therapy.

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

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

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.

In vivo, venetoclax was metabolized by CYP3A4; it was not a potent inhibitor of CYP3A4, CYP1A2, CYP2B6, CYP2C19, or CYP2D6 (IC_{50} > 30 μM); it did not induce CYP3A4 or CYP1A2 at concentrations up to 10 μM. Venetoclax is a substrate for P-gp and BCRP. Studies in Oatp1a/b cluster KO mice indicated that venetoclax may be an OATP substrate. Active uptake of venetoclax or M27 metabolite was not observed in cells overexpressing OATP1B1, OATP1B3 or OCT1. Venetoclax is a P-gp, BCRP and OATP1B1 inhibitor in vitro.

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 Nonclinical Toxicology

Venetoclax has been assessed in repeated-dose general toxicology studies, and in genetic, developmental/reproductive, phototoxicity, and safety pharmacology studies.

The primary toxicities associated with repeat-dose administration of venetoclax were effects on the hematologic system (decreased lymphocytes and red blood cell [RBC] mass) in mice, rats and dogs, the male reproductive system (testicular germ cell depletion in dogs) and embryofetal toxicity in mice. Other noteworthy findings were epithelial single cell necrosis in multiple tissues and hair coat color change, both in dogs.

In mice, rats, and dogs, venetoclax produced robust decreases in lymphocytes in the peripheral blood (up to 75% in mice, 64% in rats, and 81% in dogs) and in lymphoid tissues. These findings are consistent with the expected pharmacologic effects of venetoclax (a selective Bcl-2 inhibitor).[8] In mice, total lymphocyte counts at 600 mg/kg/day after 4 weeks of dosing were minimally decreased 21% to 6% relative to concurrent controls at the end of the 4-week recovery period. In dogs, the recovery of peripheral blood decreases in total lymphocytes and lymphocyte subsets (CD4+ T-cells and CD8+ T-cells and [CD21+] mature B cells) was prolonged, requiring up to 18 weeks after a single dose or after completion of 2 weeks of dosing. B-cells were the most sensitive lymphocyte subtype based on the magnitude of decrease (> 90%) and/or the length of time required for recovery. Lymphocyte decreases in lymphoid tissues were reversible in mice and dogs. Venetoclax produced dose-related decreases in RBC mass due to decreased cellular hemoglobin in mice and dogs; these effects were adverse at the highest dosages in the 4-week mouse and dog studies and were reversible. In studies to select carcinogenicity dose levels, RBC mass decreases were also observed in rats and were generally more severe than in mice or dogs. Venetoclax produced adverse, non-dose related microscopic findings of testicular germ cell depletion in dogs at all doses tested; reversibility was not observed following a 4-week recovery period. There were no testicular effects in mice. Venetoclax resulted in increased post-implantation loss and decreased fetal body weights in the mouse embryo fetal development study at the highest dosage administered (150 mg/kg/day); the no-observed-adverse-effect-level (NOAEL)

was defined at the mid dose of 50 mg/kg/day. In mice and rabbits, venetoclax was not teratogenic, and there were no other effects on development or fertility.

Additional noteworthy effects of venetoclax included white hair coat discoloration in dogs (occurring after approximately 3 months of dosing in the 9-month study) and minimal to mild single cell necrosis in multiple epithelial tissues (e.g., gallbladder and exocrine pancreas) in dogs. None of these effects was considered to be adverse.

There was no evidence of in vitro or in vivo genetic toxicity of venetoclax, and there was no evidence of cutaneous phototoxicity of venetoclax in an in vivo study in Crl:SKH1-*hr* female hairless mice.

Other minor effects of venetoclax were observed in dogs. (1) At the high dosage of 150 mg/kg/day in the 4-week study had clinical signs of swelling of the skin on the ears, head (cranial area), and forepaws and/or hindpaws. Most but not all animals (8 of 10 dogs) were affected, and in 3 dogs the swelling reaction was observed after the first dose. The clinical signs were limited to the 150 mg/kg/dosage, were transient and sporadic in occurrence, and were absent during the recovery period. A mechanistic basis for the swelling reactions was not established, but the clinical signs were mild to moderate in severity and reversible, and there were no signs of anaphylaxis. (2) Dose-related, transient post dose emesis, increased salivation, and fecal alterations (unformed or watery feces) were observed at dosages of ≥ 5 mg/kg/day. These clinical signs were present throughout the dosing phase, but were not dose-limiting and were not observed in the recovery phase. In the 9-month dog study, non-adverse decreases in mean body weight and body weight gain, associated with decreases in food consumption, were observed at ≥ 2 mg/kg/day.

M27 is a major human metabolite of venetoclax. Although observed in mice and dogs, M27 is present at much lower levels (0.05- to 0.09-fold), as compared with steady-state levels in humans, and therefore is a disproportionate metabolite. By in silico analysis, M27 does not generate new alerts for mutagenicity, as compared with the venetoclax parent compound. M27 shows low in vitro potency (at least 58-fold less than parent) and

produced no evidence of in vitro genotoxicity in Ames and chromosome aberration assays. In a secondary pharmacology receptor panel screening study, M27 produced significant displacement of control-specific binding at the delta-opioid receptor (DOP K_i = 0.65 μM); however, when evaluated in a functional assay, agonist or antagonist activity was not observed at the DOP receptor up to a maximum concentration of 10 μM. No CNS or respiratory adverse events that could be attributed to off-target receptor-mediated pharmacologic effects of M27 have been observed in clinical trial subjects.

Venetoclax was tested in a battery of safety pharmacology assays, and produced no effects in the CNS/neurobehavioral or respiratory studies in mice at oral doses up to and including the highest dose of 600 mg/kg. No effects on QTc were observed up to a maximum plasma concentration of 46 μg/mL in dogs. In conscious dogs, venetoclax did not produce any cardiovascular effects up to and including the highest oral dose of 150 mg/kg (C_{max} = 16 μg/mL). In the anesthetized dog at higher plasma concentrations, venetoclax produced mild reductions in myocardial contractility (6% – 13%) and cardiac output (–11% to –19%) at plasma concentrations of ≥ 16 μg/mL and ≥ 32 μg/mL, respectively. These concentrations are greater than the plasma concentration of venetoclax in oncology subjects (2.8 μg/mL at the 600 mg dose).

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,[9] signs of tumor lysis, reduction in red cell mass, decreased spermatogenesis, skin swelling, and hair hypopigmentation. Although no effects of venetoclax on female reproductive tissues have been observed in general repeat-dose toxicology studies, embryo-fetal toxicity studies in animals have identified a fetal toxicity risk. 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.

A detailed discussion of the preclinical toxicology, metabolism, and pharmacology can be found in the Investigator's Brochure.[10]

Venetoclax Clinical Exposure

As of 28 November 2016, on the basis of data available in the AbbVie and Genentech/Roche clinical databases, a total of 2573 subjects have been exposed to at least 1 dose of venetoclax in the oncology development programs. Of these 2573, 1429 subjects had CLL/small lymphocytic leukemia (SLL), 637 subjects had NHL, 180 subjects had MM, and 327 had AML. An additional 114 subjects were healthy volunteers. A total of 749 oncology subjects received the drug as monotherapy, and 1922 received the drug in combination with other therapies.

Doses administered in venetoclax clinical studies have ranged from 20 mg to 1200 mg. 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. Data are available from DDI studies of venetoclax interaction with ketoconazole, with rifampin, and with warfarin. 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 nonclinical and clinical data available with venetoclax administration, important identified risks 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). Decreased spermatogenesis has been observed in

nonclinical studies with dogs and could present a risk to male infertility. 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 monitored.

Five dose limiting toxicities (DLTs) of tumor lysis syndrome (TLS) and 2 DLTs of fatalities in the setting of TLS were reported in the venetoclax clinical program for subjects with CLL/SLL (Study M12-175 and Study M13-365). The 5 DLTs of TLS occurred in Study M12-175 at either the starting dose of 100 or 200 mg venetoclax (3 subjects in Cohort 1) or the lower initial dose of 50 mg venetoclax implemented to minimize the risk of TLS (1 subject each in Cohorts 2 and 4). The sixth DLT of TLS occurred at the maximum designated cohort dose administered in the study (Cohort 8, 1200 mg), and the subject experienced sudden death. In Study M13-365, there was a single DLT of death due to grade 5 hyperkalemia in a setting of TLS at the 50 mg initial dose. (Additionally, single non-DLT adverse events of TLS were reported in a subject with MCL in Study M12-175 and a subject with CLL in Study M13-365). Events of laboratory TLS were also observed in 2 subjects during dosing in Study GP28331 at the step-up dose of 50 mg venetoclax. Additional DLTs included 2 cases of febrile neutropenia and 1 case of neutropenia in subjects with CLL and NHL, and 1 case each of histiocytosis hematophagic and thrombocytopenia in subjects with NHL (both considered related to rituximab rather than venetoclax).

Updated safety and efficacy data are described in detail in the Investigator Brochure.[10]

Chronic Lymphocytic Leukemia (CLL)

Chronic lymphocytic leukemia is a lymphoproliferative disorder characterized by a 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.[11] Chronic lymphocytic leukemia primarily affects elderly individuals; however, approximately one third of patients are less than 60 years of age at diagnosis.[12]

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.[13] 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.[11,14] The approximate 5-year survival rate for patients with CLL is 73%.[15] 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.[16]

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.

17p Deletion in Relapsed or Refractory CLL

17p deletion is a chromosomal aberration of prognostic relevance in CLL and accounts for up to 30% of all relapsed/refractory subjects with CLL due to clonal cell evolution or the selection pressure of chemotherapy and chemoimmunotherapy.[17-20]

At the time study was initiated, there were no treatments approved specifically to meet the need of the 17p deletion population and the median OS in relapsed CLL patients with 17p deletion is less than 24 months. Active treatments for the broader CLL population, such as fludarabine based regimens and alkylators, have been associated with poor response in the 17p patient population.[17] In a recent study conducted in subjects with relapsed CLL treated with FCR, PFS and OS were 5 months and 10.5 months, respectively, in subjects with 17p deletion, compared to 20.9 months and 46.5 months in subjects who did not have chromosome 17 abnormalities.[21] Overall response rates were also significantly lower in the patients with 17p deletion, with 35% of subjects achieving partial remission, no CR and 5% nodular PR (nPR), compared to 74% response rate, with 30% CR and 14% nPR in the CLL subjects without 17p deletion (Table 1).[21]

Table 1. Historical Data on Relapsed CLL with 17p Deletion

Drug/Regimen	CLL Population	Number of 17p Deleted Patients Enrolled	Response		
			ORR	CR	PFS
Ofatumumab[22]	double refractory	31	29%	NA	PFS 5.7 m
Alemtuzumab[#23]	relapsed/refractory	31	39%	NA	PFS 5.8 m
Alemtuzumab[#]+steroids[24]	relapsed*	22	77%	14%	PFS 6.5 m
Bendamustine+Rituximab[25]	relapsed/refractory	14	7.10%	7.10%	PFS 6.8 m
FCR[21]	relapsed	20	35%	5%	PFS 5 m

* In 17p deleted patients only.

\# The marketing authorization for Alemtuzumab has been withdrawn at the request of the marketing-authorization holder.

In the CLL population harboring 17p deletion, immunochemotherapy based regimens such as BR provide short durations of response with the median PFS of approximately 6.8 months and ORR of 7% (Table 1).[25] Although novel therapies, such as alemtuzumab based regimens and ofatumumab, show an improvement in ORR, the duration of response is still poor and the median PFS is approximately 6 months (Table 1).[22-24] Also alemtuzumab has limited use due to its toxicity profile.[24] Due to the limited effectiveness of available therapies, treatment guidelines recommend enrollment in clinical trials and in eligible patients who achieve a response allogeneic transplant, as preferred treatment

options for patients with 17p deletion.[26,27] Nonetheless, globally the access to allogeneic transplant and/or clinical trials is limited, and physicians often continue to use immunochemotherapy.

17p Deletion in Previously Untreated CLL

Deletions of the short arm of chromosome 17 (17p deletion) are found in 3% to 10% of CLL cases at diagnosis.[28]

Untreated CLL patients who harbor the 17p deletion have generally a short first remission if they respond to standard treatment. 17p deletion is prognostic marker for nonresponse to conventional chemotherapy and there is no standard treatment for patients with previously untreated CLL.[28]

Thus, alternative therapeutic approaches, which act independently of the p53 signaling pathway are needed.

Study Rationale

CLL patients with the 17p deletion have a poor prognosis characterized by suboptimal responses to first-line and subsequent therapies. There are currently no treatments approved and labeled specifically to meet the need of the 17p deletion population. Because treatment with the conventional therapy is poor, the treatment guidelines[26,27] recommend that CLL patients with 17p deletion (as well as TP53 mutations) should be treated within new clinical trials from the start. Those who achieve a response to initial therapy should be considered for an allogeneic transplant. For patients not eligible for an allogeneic transplant or clinical trial, until very recently suggested regimens included alemtuzumab, high-dose methylprednisolone (HDMP) or ofatumumab. None of these regimens have been shown to be superior to any other therapy in relapsed 17p deletion patients and median PFS with treatment with these agents was less than 7 months.

Venetoclax Mechanism of Action Compared with Other Therapeutic Agents

Many chemotherapeutics used in treating CLL, including fludarabine, cyclophosphamide, and bendamustine, act by inducing deoxyribonucleic acid (DNA) damage and triggering apoptosis. The p53 tumor suppressor is essential for relaying the DNA damage signal to the apoptotic machinery via upregulation of BH3-only proteins like Noxa and Puma.[29,30] When p53 is functionally inactivated, either through mutation or deletion, these signals are not effectively relayed and the efficacy of these agents is blunted.[23,31] However, because venetoclax bypasses these signaling events and inhibits Bcl-2 directly, it is expected to be equally effective in p53 wildtype and 17p del tumors.

Preliminary Clinical Data

Early results from the ongoing venetoclax first-in-human Study M12-175 (as of 03 February 2014) have demonstrated activity in 21 evaluable relapsed/refractory CLL subjects with 17p deletion who were treated with venetoclax. Fifteen (15) of the 21 subjects have > 50% reduction in absolute lymphocyte count and/or 50% reduction in lymph node measurements by CT scan, results consistent with at least a partial remission (71% ORR). Three subjects meet criteria for CR/CRi (complete remission with incomplete bone marrow recovery). These encouraging preliminary data indicate that venetoclax may be beneficial in this unique patient population.

3.1 Differences Statement

This is the first Phase 2 study for venetoclax monotherapy. Safety data and preliminary efficacy responses in the 17p deletion CLL population from Phase 1 support moving into Phase 2.

3.2 Benefits and Risks

The preliminary data of venetoclax monotherapy in subjects with CLL show a favorable benefit. The risk profile of the drug supports the continuous dosing of venetoclax in this indication. Dose titration and a prophylactic regimen of hydration and uric acid reducers, along with laboratory monitoring, provide adequate protection from the potential risk of

serious adverse events of TLS. In addition, safety will be reviewed on an ongoing basis by the Sponsor to evaluate accumulated safety data to assess any trends that would require modifications to the trial.

The encouraging preliminary data from the ongoing venetoclax first-in-human Study M12-175 indicate that venetoclax may be beneficial in subjects with relapsed CLL harboring 17p deletion.

Additionally, for previously untreated subjects with CLL harboring 17p deletion, venetoclax could provide an alternative treatment with the absence or reduction of the toxicities commonly associated with to the standard aggressive chemotherapy.

4.0 Study Objectives

Main Cohort

The primary objective of this cohort is to evaluate the efficacy of venetoclax monotherapy in subjects with relapsed or refractory chronic lymphocytic leukemia (CLL) harboring the 17p deletion. Efficacy will be measured by overall response rate (ORR).

The secondary objectives are to evaluate the complete remission rate (CR rate), partial remission rate (PR rate), duration of overall response (DOR), progression-free survival (PFS), event-free survival, time to progression (TTP), time to first response, time to 50% reduction in ALC, overall survival (OS) and percent of subjects who move on to stem cell transplant. The safety and tolerability of venetoclax in subjects with relapsed or refractory CLL harboring 17p deletion will also be evaluated.

Safety Expansion Cohort

The primary objective of the safety expansion cohort is to evaluate the safety of venetoclax in approximately 50 subjects with relapsed/refractory or previously untreated CLL harboring 17p deletion treated per the updated TLS prophylaxis and management measures.

The secondary objectives are to evaluate ORR, CR rate, PR rate, duration of overall response, progression-free survival, event-free survival, time to progression, time to first response, time to 50% reduction in ALC, overall survival, and percent of subjects who move on to stem cell transplant.

Exploratory objectives will be evaluated in both cohorts. Time to next anti-CLL treatment (TTNT) and minimal residual disease (MRD), assessed in the peripheral blood and/or bone marrow (BM), will be measured. Pharmacokinetics, pharmacogenetics and biomarkers will also be evaluated as exploratory objectives. Health Economic and Patient-Reported Outcome Measures will include the MDASI (measure of subject reported symptoms), 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) and EQ-5D-VAS.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is an open-label, single arm, multicenter, global study to determine the efficacy of venetoclax monotherapy in subjects with relapsed/refractory or previously untreated chronic lymphocytic leukemia harboring 17p deletion sponsored by AbbVie in collaboration with Genentech/Roche. Previously untreated chronic lymphocytic leukemia harboring 17p deletion patients will not be enrolled in Germany.

This study is designed to enroll in the main cohort approximately 100 subjects with relapsed or refractory chronic lymphocytic leukemia harboring 17p deletion, as confirmed by the central laboratory, and in the safety expansion cohort approximately 50 subjects with relapsed/refractory or previously untreated chronic lymphocytic leukemia harboring 17p deletion as confirmed by local or central laboratory, 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.

Subjects in this study will be enrolled at approximately 60 research sites.

After approximately 20 subjects have completed at least 12 weeks of study treatment in the main cohort, a safety analysis will be conducted by an Independent Data Monitoring Committee (IDMC). In the safety expansion cohort, interim analysis results will be reviewed by the IDMC after approximately 20 subjects have completed approximately 2 – 3 weeks of the lead-in period.

Main Cohort Dosing Schedule

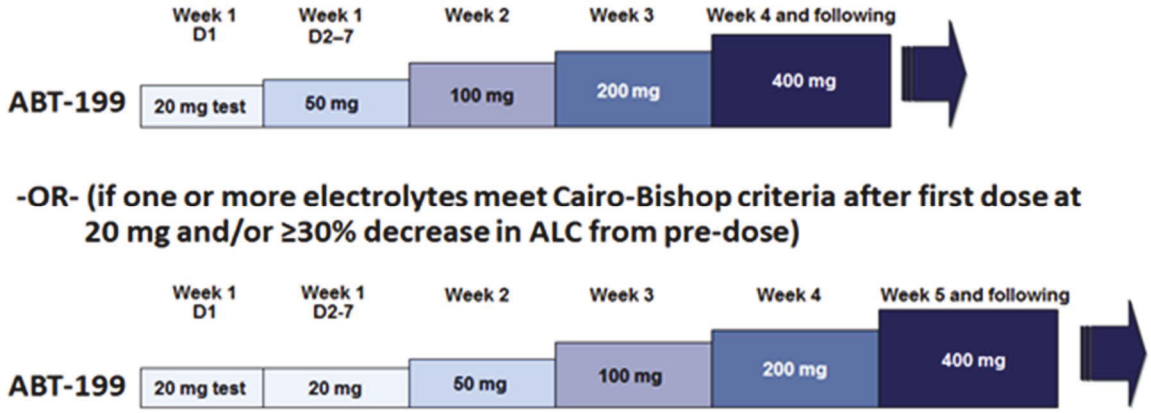
NOTE: Enrollment in the main cohort is complete, and all subjects have completed the lead-in period under Protocol Amendment 1.

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 (up to 5 weeks) will be employed to evaluate a step wise dose escalation. All subjects will be admitted to the hospital and begin the lead-in period with an initial test dose of 20 mg venetoclax on Week 1 Day 1. If no significant findings occur within 24 hours, then a test dose of 50 mg will be administered on Week 1 Day 2 followed by 50 mg venetoclax QD for 5 days (Week 1 Day 3 – Day 7). If significant findings occur within 24 hours of the initial test dose of 20 mg venetoclax on Week 1 Day 1, the 20 mg dose will be maintained for 1 week prior to dose escalation to 50 mg on Week 2 Day 1 – 7.

After a week at 50 mg, the following dose escalation will proceed with weekly dose escalations → 100 mg → 200 mg → 400 mg (or additional lead-in steps to designated 400 mg dose), as tolerated.

A lower starting dose and/or modification to the lead-in regimen may be implemented for individual subject(s) at particularly high risk for TLS (Figure 1).

Figure 1. Dosing Schematic – Main Cohort



Lead-in Period

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

1. *If one or more electrolyte changes (from the predose value) meeting Cairo-Bishop criteria occurs within 24 hours of the 20 mg dose and is confirmed on the next laboratory test (1 – 2 hours later),* ***no additional venetoclax doses will be administered until resolution****. (For Cairo Bishop criteria, see Appendix F, Cairo-Bishop and Howard Definitions of Tumor Lysis Syndrome. See Appendix D, Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome [TLS], for procedures to follow.) Upon laboratory abnormalities resolution, the subject will remain on the 20 mg dose through Week 1 (e.g., Week 1 Day 2 – Week 1 Day 7).*

and/or

2. *For subjects with a predose lymphocyte count ≥ 5000/mm^3, if a decrease (from the predose value) in lymphocyte count ≥ 30% occurs within 24 hours of the 20 mg dose on Day 1, the subject will remain on the 20 mg dose through Week 1 (e.g., Week 1 Day 2 – Week 1 Day 7).*

For subjects who meet the electrolyte and/or lymphocyte changes described in 1 and/or 2 above, escalation to 50 mg will occur on Week 2 Day 1 of the lead-in period. Subjects who had drug interruptions may escalate to 50 mg after they have been on a 20 mg dose for approximately a week (e.g., 5, 6 days).

If none of the electrolyte and/or lymphocyte changes described in 1 and/or 2 above occur within 24 hours from venetoclax 20 mg dose administration, the subject, while hospitalized, will dose escalate to 50 mg on Week 1 Day 2. After the first dose of 50 mg, if no laboratory abnormalities occur, the subject will remain on the 50 mg dose through Week 1 (e.g., Week 1 Day 2 – Week 1 Day 7). If abnormalities are observed, no additional venetoclax doses will be administered until resolution.

After the subject has received the 50 mg dose for approximately a week (6 – 7 days), the following dose escalation will proceed with weekly dose escalations → 100 mg → 200 mg → 400 mg (or additional lead-in steps to designated 400 mg dose), as tolerated.

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 6.1.8.1, Prophylaxis and Management of Tumor Lysis Syndrome, for additional details on TLS prophylaxis.

Safety Expansion Cohort Dosing Schedule

To mitigate the risk for TLS, a lead-in period of 5 weeks will be employed with a step wise dose escalation (Figure 2). 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 (Section 6.1.8.1, Prophylaxis and Management of Tumor Lysis Syndrome).

Subjects in the **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 laboratory TLS occur within 24 hours, the same dose will be continued through Week 1 Day 7 in the outpatient setting. Subjects with no laboratory abnormalities suggestive of TLS will escalate to a dose of 50 mg venetoclax on Week 2 Day 1 in the outpatient setting.
- If there is indication of laboratory or clinical TLS, the study drug dose will be held until resolution of all findings. TLS management will be implemented as appropriate.

Medium risk subjects with CrCl < 80 mL/min and/or higher tumor burden (i.e., ALC > 100×10^9/L or multiple bulky nodes) may be admitted to the hospital, at the investigator's 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 laboratory TLS occur within 24 hours, the same dose will be continued through Week 1 Day 7 in the outpatient setting. Subjects with no laboratory abnormalities suggestive of TLS will escalate to a dose of 50 mg venetoclax on Week 2 Day 1 in the outpatient setting. However, subjects may still be hospitalized prior to the first dose escalation at 50 mg if they continue to have CrCl < 80 mL/min and/or higher tumor burden (i.e., ALC > 100×10^9/L or multiple bulky nodes), at the investigator's discretion.
- If there is indication of laboratory or clinical TLS, the study drug dose will be held until resolution of all findings. TLS management will be implemented as appropriate.

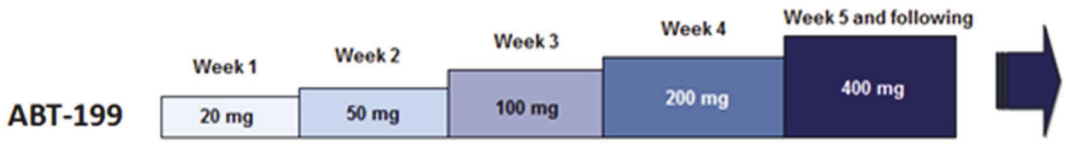
All **high risk subjects** will be admitted to the hospital and begin the lead-in period with an initial dose of 20 mg venetoclax on Week 1 Day 1.

- If no significant findings suggestive of clinical or laboratory TLS occur within 24 hours, the same dose will be continued through Week 1 Day 7 in the outpatient setting. Subjects will be hospitalized prior to the first dose escalation to 50 mg beginning on Week 2 Day 1. Each subject's risk status may be reassessed prior to subsequent dose escalations per the guidelines in Section 6.1.8.1, Prophylaxis and Management of Tumor Lysis Syndrome.
- If no significant findings occur within 24 hours of 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 laboratory or clinical TLS, the study drug dose will be held until resolution of all findings. TLS management will be implemented as appropriate.

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

If a high risk subject has clinical signs of progression during the first week of 20 mg dosing, correspondence between the investigator and the AbbVie medical monitor must occur.

Figure 2. Dosing Schematic – Safety Expansion Cohort



Lead-in Period

Every subject will receive a dose of 20 mg on Week 1, Day 1 of the lead-in period. If one or more electrolyte changes (from the 0 hour measurement prior to dosing) suggestive of TLS occur within 24 hours of the 20 mg dose, no additional venetoclax doses will be administered until resolution. If aggressive correction of electrolytes abnormalities is performed, the subsequent dose of venetoclax can only be given when electrolytes have been stable without any more treatment for at least 24 hours. See Appendix D, Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome (TLS), for additional laboratory assessments and management guidelines. Upon resolution of laboratory abnormalities, the subject will continue 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 at least one week (7 days).

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

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 additional laboratory assessments and management guidelines.

Refer to Section 6.1.8.1, Prophylaxis and Management of Tumor Lysis Syndrome, for additional details on TLS prophylaxis.

Main and Safety Expansion Cohorts

Dose Interruptions and Dose Reductions

If a subject has a venetoclax dose interruption or reduction, venetoclax may be reintroduced or escalated per correspondence between the Investigator and the AbbVie medical monitor.

Post-Treatment Follow-Up Visit(s)

For subjects who discontinue venetoclax (e.g., due to toxicity or stem cell/bone marrow transplant), post-treatment follow-up visits will be performed every 3 months until discontinuation from the study. Post-Treatment follow-up visits are not required for subjects who have discontinued due to disease progression or a subject's refusal of the Post-Treatment visits. This will be for a period of up to 5 years after the last subject has enrolled on the study.

Note: *Effective with protocol Amendment 6, subjects being followed in Post-Treatment as of 12 May 2017 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, etc.) will be collected via telephone calls and/or clinical visits at 3 month (± 7 days) intervals after the last study visit for a period of 5 years after the last subject has enrolled on the study for subjects who have not withdrawn consent.

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 post treatment cancer therapies, 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 not withdrawn consent.

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. Please see Section 5.4.1 for additional information.

Survival – Extended Access

For subjects who continue to derive benefit from venetoclax treatment 2 years following the date of the last subject enrolled, AbbVie will provide venetoclax for monotherapy use until the subject develops disease progression or until 5 years following the date of last subject enrolled (12 May 2020). In countries where venetoclax is commercially available, subjects have the option to discontinue receiving venetoclax via the study and switch to commercial supply at any time but may be contacted every 12 weeks (± 7 days) to collect the Survival information noted above, provided they have not withdrawn consent.

For subjects continuing into the Survival Extended Access portion of the trial, venetoclax will be dispensed at the Final Visit, and Survival visits will begin 12 weeks (± 7 days) following the 30-day Safety Follow-Up Visit. Survival visits will include collection of Survival information, AEs/SAEs and concomitant medication information, study drug administration, collection and dispensing of subject diaries, and MRD PCR sample collection for eligible subjects. All other procedures for disease assessments will be performed as standard of care.

5.2 Selection of Study Population

Subjects will undergo screening procedures within 28 days prior to initial study drug administration, with the exception of the CT scan and bone marrow biopsy and aspirate which must be completed within 35 days prior to study drug administration. Adult male and female subjects who meet the inclusion criteria and who do not meet any of the exclusion criteria will be eligible for enrollment into the study.

5.2.1 Inclusion Criteria

A subject will be eligible for participation in the safety expansion cohort 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 Modified IWCLL NCI-WG Guidelines.
    - Subject has an indication for treatment according to the 2008 Modified IWCLL NCI-WG Guidelines;
    - Subject has clinically measurable disease (lymphocytosis > 5×10^9/L and/or palpable and measurable nodes by physical exam and/or organomegally assessed by physical exam);
    - Subject must have relapsed/refractory CLL or previously untreated CLL;
        - Refractory or relapsed CLL subjects must meet the following requirements:
            - Refractory or relapsed after receiving at least one prior line of therapy (subjects that have progressed after 1 cycle of treatment or have completed at least 2 cycles of treatment for a given line of therapy);
        - Previously untreated CLL subjects must meet the following requirements (previously untreated chronic lymphocytic leukemia harboring 17p deletion patients will not be enrolled in Germany):
            - Received no prior chemotherapy or immunotherapy. Subjects with a history of emergency, loco-regional radiotherapy (e.g., for relief of compressive signs or symptoms) are eligible.
            - CLL diagnostic criteria above and must have > 5×10^9/L B-Lymphocytes in the peripheral blood.

- Subjects must have 17p deletion, assessed by local laboratory (in bone marrow or peripheral blood) or assessed by central laboratory (peripheral blood). A result obtained prior to study Screening may be used for eligibility. Additionally, a confirmatory sample (peripheral blood) will be sent to the central laboratory.

4. Subject has an Eastern Cooperative Oncology Group (ECOG) performance score of ≤ 2.

5. Subject must have adequate bone marrow function at Screening as follows:
   - Absolute Neutrophil Count (ANC) ≥ 1000/μL, or
     - For subjects with an ANC < 1000/μL at Screening and bone marrow heavily infiltrated with underlying disease (unless cytopenia is clearly due to marrow involvement of CLL), growth factor support may be administered 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 within 14 days of Screening,
     - without evidence of mucosal bleeding,
     - without known history of bleeding episode within 3 months of Screening, and
     - without history of bleeding disorder.
   - Hemoglobin ≥ 8.0 g/dL.

6. Subject must have adequate coagulation, 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);
   - Calculated creatinine clearance > 50 mL/min using 24-hour Creatinine Clearance or modified Cockcroft-Gault equation (using Ideal Body Mass [IBM] instead of Mass):

$$eCC_r = \frac{(140 - \text{Age}) \times \text{IBM (kg)} \times [0.85 \text{ if Female}]}{72 \times \text{Serum Creatinine (mg/dL)}}$$

Or, if serum creatinine is in µmol/L:

$$eCC_r = \frac{(140 - \text{Age}) \times \text{IBM (kg)} \times [1.23 \text{ if Male, } 1.04 \text{ if Female}]}{\text{Serum Creatinine (µmol/L)}}$$

Ideal Body Mass should be used:

IBM (kg) = [(height cm ‑154) × 0.9] + (50 if Male, 45.5 if Female)

Note: For subjects that have BMI of > 30 kg/m^2 or < 19 kg/m^2, 24-hour measured urine creatinine clearance is required.

- AST and ALT ≤ 3.0 × the upper normal limit (ULN) of institution's normal range; Bilirubin ≤ 1.5 × ULN. Subjects with Gilbert's Syndrome may have a bilirubin > 1.5 × ULN, per correspondence between the investigator and AbbVie medical monitor.

7. 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 life style of the subject; periodic abstinence is not acceptable;
   - Surgically sterile partner(s); acceptable sterility surgeries are: vasectomy, bilateral tubal ligation, bilateral oophorectomy or hysterectomy;
   - 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;

  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.

8. Females of childbearing potential (i.e., not 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 a urine sample obtained on Week 1 Day 1 (tested locally), if it has been > 7 days since obtaining the serum pregnancy test results.
9. Male subjects must agree to refrain from sperm donation, from initial study drug administration until 90 days after the last dose of study drug.
10. For high risk subjects (as defined in Section 6.1.8.1) a pre-approval by the AbbVie medical monitor is required prior to enrollment.

Rationale for Inclusion Criteria

(2 – 4) To select the subject population

(5, 6, 10) For the safety of the subjects

(7 – 9) The impact of venetoclax on pregnancy in humans is unknown

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

5.2.2 Exclusion Criteria

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

1. Subject has undergone an allogeneic stem cell transplant.
2. Subject has developed Richter's transformation confirmed by biopsy.
3. Subject has prolymphocytic leukemia.
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 previously received venetoclax.
6. Subject is known to be positive for HIV (due to potential drug-drug interactions between anti-retroviral medications and venetoclax, as well as anticipated venetoclax mechanism based lymphopenia that may potentially increase the risk of opportunistic infections).
7. Subject has received the following **within 30 days** prior to the first dose of study drug:
    - A biologic agent (i.e., monoclonal antibodies) for anti-neoplastic intent.
8. Subject has received radiotherapy **within 14 days or** any of the following within **5 half-lives as applicable** prior to the first dose of study drug, or has not recovered to less than CTC grade 2 clinically significant adverse effect(s)/toxicity(s) of the previous therapy:
    - Any anti-cancer therapy including chemotherapy, or radiotherapy;
    - Investigational therapy, including targeted small molecule agents.
9. Subject has received the following **within 7 days** prior to the first dose of study drug:
    - Steroid therapy for anti-neoplastic intent;

- CYP3A inhibitors (such as fluconazole, ketoconazole, and clarithromycin);
- Potent CYP3A inducers (e.g., rifampin, phenytoin, carbamazepine or St. John's Wort);
- Coumarins (vitamin K antagonists) or warfarin or phenprocoumon, or requires the use of coumarins (vitamin K antagonists) or warfarin (due to potential drug-drug interactions that may potentially increase the exposure of coumarins [vitamin K antagonists] or warfarin or phenprocoumon and complications of this effect).

10. Subject has consumed the following **within 3 days** prior to the first dose of study drug.
    - Grapefruit or grapefruit products;
    - Seville oranges (including marmalade containing Seville oranges);
    - Star fruit.
11. Subject has known allergy to both xanthine oxidase inhibitors and rasburicase.
12. Subject has a cardiovascular disability status of New York Heart Association Class ≥ 2. Class 2 is defined as cardiac disease in which subjects are comfortable at rest but ordinary physical activity, results in fatigue, palpitations, dyspnea or anginal pain.
13. Subject exhibits evidence of other clinically significant uncontrolled condition(s) including, but not limited to:
    - Uncontrolled and/or active systemic infection (viral, bacterial, or fungal).
    - Chronic hepatitis B virus (HBV) or hepatitis C (HCV) requiring treatment. 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.
    - Febrile neutropenia.
14. Subject has a significant history of renal, pulmonary, neurologic, psychiatric, endocrinologic, metabolic, immunologic, cardiovascular, or hepatic disease that in the opinion of the investigator would adversely affect his/her participating in this

study. For subjects who have required an intervention for any above diseases within the past 6 months, correspondence with the investigator and the AbbVie medical monitor must occur.

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

16. Subject has a history of active malignancies 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. Subject has malabsorption syndrome or other condition that precludes enteral route of administration.

Rationale for Exclusion Criteria

(1 – 3, 5, 16) To select the appropriate subject population

(4, 6 – 14, 17) For the safety of the subjects

(15) The impact of venetoclax on pregnancy in humans 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. Inhalational steroids for the treatment of asthma or COPD, topical steroids, replacement corticosteroid therapy for an inherited or acquired deficiency are allowable.

In addition, limited corticosteroid treatment (i.e., for approximately 21 days with rapid taper) is allowed while on study for significant active autoimmune cytopenias, e.g., autoimmune hemolytic anemia (AIHA) or immune thrombocytopenia (ITP). IVIG (intravenous immune globulin) is also allowable. Eltrombopag, a thrombopoiten receptor agonist, is another treatment option for ITP. However, it is cautionary as it is a BCRP and OATP1B1 inhibitor (refer to Appendix C).

For additional guidance regarding medications for management of neutropenia and management of lymphopenia, refer to Section 6.1.8.2 and Section 6.1.8.3.

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, cautionary and allowed medications are summarized in Table 2 and Table 3.

Table 2. Excluded and Cautionary Medications/Food Items

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**
  - Excluded 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 at least by 2-fold for moderate inhibitors and at least by 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

- **Coumarins (vitamin K antagonists) or warfarin or phenprocoumon***
- **P-gp substrates****
- **BCRP substrates**
- **OATP1B1/1B3 substrates**
- **BCRP inhibitors**

* Closely monitor international normalized ratio (INR).

** If a narrow therapeutic index P-gp substrate must be used, it should be taken at least 6 hours before venetoclax.

Table 3. 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 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 Pharmacokinetic, Pharmacodynamic, Pharmacogenetic, and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Table 4. Study Activities

Activity	Scr[a]	Within 72 Hours Prior to 1st Dose[b]	W1 D1[b]	W1 D2	W2 D1[b]	W2 D2	W3 D1[b]	W3 D2	W4 D1	W4 D2	W5 D1	W5 D2	W8 D1	W 12 D1	W 16 D1	W 20 D1	W 24 D1	W 28 D1	W 32 D1	Every 12 Wks Starting with Wk 36	8 Wks After 1st CR, CRi, or PR	FV	30-Day Safety Visit	Post-Treat[c]	Survival Follow-Up[t]
Informed Consent	X																								
Detection of 17p Deletion[d]	X																								
Medical History/ Oncology History Assessment	X		X																						
Adverse Event/ Concomitant Medication Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination[e]*	X		X		X		X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs*	X		X		X		X		X		X		X	X	X	X	X	X	X	X		X	X	X	
ECOG Performance Status*	X		X		X		X		X		X		X	X	X	X	X	X	X	X		X	X		

Table 4. Study Activities (Continued)

Activity	Scr[a]	Within 72 Hours Prior to 1st Dose[b]	W1 D1[b]	W1 D2	W2 D1[b]	W2 D2	W3 D1[b]	W3 D2	W4 D1	W4 D2	W5 D1	W5 D2	W8 D1	W 12 D1	W 16 D1	W 20 D1	W 24 D1	W 28 D1	W 32 D1	Every 12 Wks Starting with Wk 36	8 Wks After 1st CR, CRi, or PR	FV	30-Day Safety Visit	Post-Treat[c]	Survival Follow-Up[t]
Pregnancy Test[f]	X		X																						
Hematology/ Chemistry[g]	X	X	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X**	X**	X**	X**	X**	X**	X**	X**	X**	X**	X**	X**	
Coagulation Panel**	X													X			X					X	X	X	
Urinalysis**	X																X					X			
Viral Serologies	X																								
Viral Polymerase Chain Reaction	X																								
Quantitative Immuno-globulin**	X													X			X					X	X		
Lymphocyte Enumera-tion**	X										X			X			X			X		X			
ECG	X																					X			

Table 4. Study Activities (Continued)

Activity	Scr[a]	Within 72 Hours Prior to 1st Dose[b]	W1 D1[b]	W1 D2	W2 D1[b]	W2 D2	W3 D1[b]	W3 D2	W4 D1	W4 D2	W5 D1	W5 D2	W8 D1	W 12 D1	W 16 D1	W 20 D1	W 24 D1	W 28 D1	W 32 D1	Every 12 Wks Starting with Wk 36	8 Wks After 1st CR, CRi, or PR	FV	30-Day Safety Visit	Post-Treat[c]	Survival Follow-Up[t]
Echocardio-gram or a Multi Gated Acquisition Scan (MUGA)[i]	X																								
CT or MRI Scan[j]***	X																			X[k]	X[l]	X		X[m]	
Bone Marrow Aspirate and Biopsy	X[n]																			X[o]	X[o]	X			
Disease Assessments*	X[p]										X		X	X	X	X	X	X	X	X	X	X		X	
MRD Assessment																				X[q]	X[q]				X
Survival Assessment†																								X	X
Dispense/ Collect Venetoclax and Subject Calendars/ Diaries			X	X	X		X		X		X		X	X	X	X	X	X	X	X					X

Table 4. Study Activities (Continued)

Activity	Scr[a]	Within 72 Hours Prior to 1st Dose[b]	W1 D1[b]	W1 D2	W2 D1[b]	W2 D2	W3 D1[b]	W3 D2	W4 D1	W4 D2	W5 D1	W5 D2	W8 D1	W 12 D1	W 16 D1	W 20 D1	W 24 D1	W 28 D1	W 32 D1	Every 12 Wks Starting with Wk 36	8 Wks After 1st CR, CRi, or PR	FV	30-Day Safety Visit	Post-Treat[c]	Survival Follow-Up[t]
MDASI[r]			X								X			X			X			X		X			
EORTC QLQ-C30 and EORTC QLQ CLL16[r]			X								X			X			X			X		X		X	
EQ-5D-5L and EQ-5D-VAS[r]			X								X			X			X			X		X			
Subject TL Survey[s]					X																				

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

Study Windows:

* within 72 hours before or after scheduled visit starting with Week 8 Day 1;

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

*** within 7 days after scheduled visit.

† within ± 7 days of scheduled visit.

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

b. All subjects must receive tumor lysis prophylaxis prior to and during treatment. For details on tumor lysis prophylaxis and management, refer to Section 6.1.8.1, Prophylaxis and Management of Tumor Lysis Syndrome and Appendix D – Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome (TLS).

c. Assessments will be collected at 3 month intervals after the last study visit for a period of 5 years after the last subject has enrolled in the study.

Table 4. Study Activities (Continued)

d. Subjects must have 17p deletion as assessed by local or central laboratory to be considered for enrollment. A result obtained prior to study Screening may be used for eligibility. A confirmatory sample will be sent to central laboratory at Screening. Refer to Section 5.3.1.5, Collection and Handling of Biomarker Variables, for more details.

e. A complete physical examination will be performed at Screening. A symptom directed physical examination will be performed on Day 1 of Weeks 2 – 4 and the 30-day Safety Visit. All other physical examinations will be targeted. If during physical examination, signs or symptoms suggestive of Richter's Syndrome are observed, further assessments (e.g., lymph node biopsy, PET scan) should be considered to exclude or confirm the transformation. Refer to Section 5.3.1.1 Physical Examination, for more details.

f. For females of childbearing potential, a urine pregnancy test must be obtained and processed locally at the Week 1 Day 1, if it has been > 7 days since obtaining the serum pregnancy results at Screening.

g. Cholesterol and triglycerides are only required at Screening and Final Visit.

h. There is no 72 hour window for these samples. Refer to Section 6.1.8.1, Prophylaxis and Management of Tumor Lysis Syndrome and Appendix D – Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome (TLS).

i. 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.

j. 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 scan and/or bone marrow biopsy must be performed within 2 weeks to confirm or rule out PD as described in Section 5.3.3.2.

k. Imaging assessments are required for all subjects at Week 36 Day 1. Assessment to be performed on Week 36 Day 1 **only** (not every 12 weeks). The Week 36 scan may be performed within 4 weeks before or after the 36 week scheduled visit provided that it has been at least 8 weeks since the subject's last scan.

l. After a response is determined by clinical criteria, a CT scan will be performed no earlier than 8 weeks for confirmation of response. For determination of CR/CRi, both the CT scan and bone marrow are required to be negative. It is recommended that the CT scan is performed first, and if it does confirm a CR/CRi, then a BM biopsy should be obtained as soon as possible.

m. Post-treatment CT or MRI scans to be done only if collected by the site as part of standard of care.

n. A bone marrow aspirate and biopsy will be performed and assessed locally at Screening (within 35 days prior to the first dose of study drug). Bone marrow and aspirate for biomarker sample collection should be split from this sample. Refer to Table 6.

o. 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 not performed at the time of the confirmatory CT, then it should be performed after the Week 36 Day 1 CT scan.

Table 4. Study Activities (Continued)

p. At baseline, all measurable disease must be documented at screening by laboratory testing, physical examination and CT scans (or MRI if CT is medically contraindicated), and bone marrow examinations.

q. Specimens (bone marrow aspirate and peripheral blood) for MRD analysis should be collected at the same time as the bone marrow aspirate and biopsy performed for tumor assessments to confirm the CR/CRi. If MRD negativity is achieved in the bone marrow no further MRD analyses are required. Otherwise, MRD should be assessed at 12-week intervals thereafter (in peripheral blood) until MRD negativity is achieved. Once MRD negativity is achieved and confirmed in peripheral blood (e.g., two MRD negative consecutive peripheral blood samples), a bone marrow aspirate specimen will again be collected for analysis of MRD levels to confirm the peripheral blood negativity. 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 and MRD assessment. If a bone marrow and MRD assessment was not performed at the time of the confirmatory CT scan, then they should be performed after the Week 36 Day 1 CT scan. If MRD negativity is achieved in the bone marrow no further MRD analyses are required. Otherwise, MRD should be assessed at 12-week intervals thereafter (in peripheral blood) until MRD negativity is achieved. Once MRD negativity is achieved and confirmed in peripheral blood (e.g., two MRD negative consecutive peripheral blood samples), a bone marrow aspirate specimen will again be collected for analysis of MRD levels to confirm the peripheral blood negativity.

r. 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.

s. For subjects in the United States only: Subjects in the safety expansion cohort will be asked to complete a survey assessing the information they were provided for the Patient Information Card and the Tumor Lysis Syndrome Patient Information Brochure at Week 2 Day 1 or the next scheduled visit. For subjects participating in the main cohort, the survey will be given to the subject at the next scheduled study visit upon signing the Protocol Amendment 2 Informed Consent. This survey is optional.

t. For subjects continuing into the Survival Extended Access portion of the trial, Survival vists will include collection of Survival information, AEs/SAEs and concomitant medication information, study drug administration, collection and dispensing of subject diaries, and MRD PCR sample collection for eligible subjects. All other procedures for disease assessments will be perfomed as standard of care.

Table 5. Schedule of PK Blood Collection for Venetoclax (and Possible Metabolite[s])

Study Visit	Week 1 Day 1	Weeks 2, 3, 4, 5 Day 1	Weeks 8, 12, 16 Day 1	Week 24 Day 1 and Day 1 of Every 12 Weeks thereafter (e.g., Weeks 36, 48, 60, etc.)
Collection Times	8 hours post-dose	8 hours post-dose if escalation to a new dose level	0 hour (pre-dose)	0 hour (pre-dose)

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

2) 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 (with the exception of Week 1 Day 1 where no medication is given the 2 days prior to dosing).

Table 6. Schedule of Biomarkers and Pharmacogenetic Sample Collection

Sample Collections	Screening	Week 1 Day 1	Week 1 Day 2	Week 5 Day 1	Final Visit/ Time of Relapse[g,h]	Comments
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 FISH for Detection of 17p Deletion	X					4 mL Blood
Bone Marrow Aspirate for Bcl-2 Protein Analysis[c]	X				X	1 mL Bone Marrow Aspirate
Bone Marrow Aspirate for CD19 Cell Isolation[c]	X				X	6 mL Bone Marrow Aspirate
Tissue (Subjects with Richter's Transformation)[d]					X	Biopsy (FFPE Tissue of LN)
Tissue for IHC/FISH (Optional)	X[a,e]				X	FFPE Archival Tissue, or Biopsy
Pharmacogenetics (Optional)	X[a,f]					4 mL Blood

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

b. Obtain sample prior to dosing.

c. The aspirate (6 mL) samples should be split from samples obtained for 2008 Modified IWCLL NCI-WG Guidelines for Tumor Response assessment whenever possible. If additional bone marrow aspirates 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. Biopsies to be collected from all subjects whose CLL has undergone a Richter's transformation. Tumor tissue from accessible site of transformation should be submitted for biomarker testing.

e. Archive sample may be used at Screening if obtained within 35 days of starting study drug without intervening treatment and representative of subject's current disease state.

Table 6. Schedule of Biomarkers and Pharmacogenetic Sample Collection (Continued)

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

g. Subjects with PD who continue to receive treatment per the discretion of the investigator (per Section 5.4.1) will have biomarker samples collected at both time of relapse and their subsequent final visit at discontinuation of venetoclax.

h. No final visit biomarker specimens are required for subjects that transition to the survival extended assess portion of the study.

5.3.1.1 Study Procedures

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

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 and Oncologic 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 including:
  - Histology
  - Cytogenetics
  - Date of CLL diagnosis
  - Stage
  - Any surgical procedures
  - Treatments administered (including dates, type of modality, response to treatment and reason for treatment discontinuation)
- 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** performed should include the evaluation of head, eyes, ears, nose, and throat (HEENT); cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems.

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

Physical examinations 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.

At Screening, the subject should have a complete physical examination.

A targeted physical examination should be limited to systems of primary relevance-that is, cardiovascular, respiratory, those associated with symptoms, and those associated with disease assessment (lymph nodes, cervical, supraclavicular, axillary, inguinal nodes, liver, and spleen).

Targeted physical examinations 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.

A physical examination will be performed at:

- Screening (height will be measured only at Screening, subject should not wear shoes)
- 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 20 Day 1**
- Week 24 Day 1**
- Week 28 Day 1**
- Week 32 Day 1**
- Week 36 Day 1 and Day 1 of every 12 weeks thereafter (e.g., Weeks 48, 60, etc.)**
- No earlier than 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 Visits**, if applicable

Note: * indicates symptom directed physical examination and
** indicates targeted physical examination.

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

Vital Signs

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 20 Day 1
- Week 24 Day 1
- Week 28 Day 1
- Week 32 Day 1
- Week 36 Day 1 and Day 1 of every 12 weeks thereafter (e.g., Weeks 48, 60, 72, etc.)
- Final Visit
- 30-Day Safety Follow-Up Visit

- Post Treatment Visits, if applicable

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

The ECOG performance status[33] will be performed as follows:

- 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 20 Day 1
- Week 24 Day 1
- Week 28 Day 1
- Week 32 Day 1
- Week 36 Day 1 and Day 1 every 12 weeks thereafter (e.g., Weeks 48, 60, 72, etc.)
- Final Visit
- 30-Day Safety Follow-Up Visit

Note: ECOG performance status may be performed within 72 hours before or after the scheduled visit starting with Week 5 Day 1.

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

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

A central laboratory will be utilized to process and provide results for the clinical laboratory tests. The principal investigator or subinvestigator should review, initial, and date the Screening laboratory results after receipt from the central laboratory. For subsequent laboratory tests, the principal investigator or subinvestigator will review, initial, and date laboratory results used for subject management after receipt from the laboratory (i.e., local and/or central). The central laboratory values will be directly loaded to the clinical database from the central laboratory provider. Laboratory normal ranges will be provided to the AbbVie Clinical Team, as requested.

A laboratory test value that requires a subject to be discontinued from the study, requires a subject to receive treatment, meets protocol specific criteria (see Section 6.7 regarding toxicity management), and/or the Investigator considers clinically significant will be recorded as an adverse event.

Local Laboratory Tests

Sites must utilize local laboratories to provide results for immediate subject management. Duplicate samples should also be sent to the central laboratory for processing for all protocol required laboratory samples, with the exception of serial laboratory samples collected on the same day (i.e., 4, 8 and 12 hour post dose laboratory collections). Local laboratory results from samples that are also processed by the central laboratory should not be input into the eCRF with the exception of **calcium, inorganic phosphorus, potassium, uric acid, creatinine and LDH**, which should be entered through the lead-in period, and **ALC** (or % lymphocytes if ALC is not tested), **ANC** (or % neutrophils if ANC is not tested), **WBC, platelets and hemoglobin** which should be entered throughout the duration of the study.

If a duplicate sample is not able to be provided (e.g., subject in hospital), local laboratory values, as requested by AbbVie, will be entered by the site directly onto the appropriate eCRF and laboratory normal ranges for the laboratory that is used will be provided to the AbbVie Clinical Team.

Pregnancy Test

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

- Screening – Serum test
- Week 1 Day 1: Urine test performed locally, 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

Chemistry and hematology samples will be collected at the following time points.

- Screening
- Within 72 hours prior to first dose of venetoclax
- Weeks 1 – 5: Refer to Section 6.1.8.1 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 monitoring required during the lead-in period.
- Week 8 Day 1
- Week 12 Day 1
- Week 16 Day 1
- Week 20 Day 1
- Week 24 Day 1
- Week 28 Day 1
- Week 32 Day 1
- Week 36 Day 1 and Day 1 of every 12 weeks thereafter (e.g., Weeks 48, 60, 72, etc.)
- No earlier than 8 weeks (+1 week) after the CR, CRi or PR criteria for tumor response are first met
- Final Visit
- 30-Day Safety Follow-Up Visit
- Post Treatment Visits, if applicable
- 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 2.

Refer to Table 7 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.

Cholesterol and triglycerides are only required at Screening and Final Visit.

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

Coagulation Panel

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

- Screening
- Week 12 Day 1
- Week 24 Day 1
- Final Visit
- 30-Day Safety Follow-Up Visit
- Post Treatment Visits, if applicable

Note: Coagulation panel may be collected within 72 hours prior to the scheduled visit starting with Week 8 Day 1.

Urinalysis

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 starting with Week 8 Day 1.

Viral Polymerase Chain Reaction (PCR): Sample Collection

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

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

- Screening
- As needed for suspicion of viral infection

Note: If during Screening, a subject presents with a positive Hepatitis B core antibody, a Hepatitis B Viral DNA PCR test should be performed to rule out an active infection. Results will be reviewed by AbbVie.

Quantitative Immunoglobulin

A sample to identify serial immunoglobulin levels of IgA, IgG and IgM will be collected at the following time points:

- Screening
- Week 12 Day 1
- Week 24 Day 1
- Final Visit
- 30-Day Safety Follow-Up Visit

Note: Quantitative immunoglobulin may be collected within 72 hours prior to the scheduled visit starting with Week 8 Day 1.

Lymphocyte Enumeration

Lymphocyte enumeration to identify B and T-cell lymphocyte subpopulations will be performed at:

- Screening
- Week 5 Day 1
- Week 12 Day 1
- Week 24 Day 1
- Week 36 Day 1 and Day 1 of every 12 weeks thereafter (e.g., Weeks 48, 60, 72, etc.)
- Final Visit

The following B- and T-cell lymphocyte subpopulations will be assessed:

- T-cells (CD3)
- B-cells (CD19)
- B-cells (CD5 + CD19)
- Natural killer (CD16 + CD56)
- Helper T-cells (CD4)
- T-Suppressor or T-Cytotoxic cells (CD8)
- Other lymphocyte studies

Note: Lymphocyte enumeration samples may be collected within 72 hours prior to the scheduled visit starting with Week 12 Day 1.

Table 7. Clinical Laboratory Tests

Hematology	Chemistry	Urinalysis
Hematocrit Hemoglobin Red Blood Cell (RBC) count White Blood Cell (WBC) count Neutrophils Bands Lymphocytes Monocytes Basophils Eosinophils Platelet count (estimate not acceptable) Mean corpuscular hemoglobin (MCH) Mean corpuscular volume (MCV) Mean corpuscular hemoglobin concentration (MCHC) Reticulocyte count **Coagulation** Prothrombin time (PT) Activated partial thromboplastin time (aPTT)	Blood Urea Nitrogen (BUN) Creatinine[a] Total bilirubin Serum glutamic-pyruvic transaminase (SGPT/ALT) Serum glutamic-oxaloacetic transaminase (SGOT/AST) Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphorus Uric acid[b] Cholesterol (Screening and Final Visit) Total protein Glucose Triglycerides (Screening and Final Visit) Albumin Lactate dehydrogenase (LDH) Magnesium Chloride Bicarbonate	Specific gravity Ketones pH Protein Blood Glucose **Viral Analysis** Viral Polymerase Chain Reaction (PCR)[c] Viral Serologies **Quantitative Immunoglobulins** IgA, IgG, and IgM

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

b. 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.

c. 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.

Electrocardiogram

A 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, dose escalation, 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 reports that are abnormal and clinically significant will be faxed to the Oncology Safety Management Team via the contact information provided in Section 6.1.6 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 correspondence 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 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 (2008 Modified IWCLL NCI-WG Guidelines)

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

performed. Subjects will be evaluated against the 2008 Modified IWCLL NCI-WG Guidelines for Tumor Response[34] including CT imaging (or MRI).

Analysis of **clinical laboratory values and physical examination** will be performed at the following visits:

- Screening
- Week 5 Day 1
- Week 8 Day 1
- Week 12 Day 1
- Week 16 Day 1
- Week 20 Day 1
- Week 24 Day 1
- Week 28 Day 1
- Week 32 Day 1
- Week 36 Day 1 and Day 1 of every 12 weeks thereafter (e.g., Weeks 48, 60, 72, etc.)
- No earlier than 8 weeks after the CR ,CRi or PR criteria is first met (if applicable)
- Final Visit
- Post Treatment Visits, if applicable

Note: Disease Assessments may be performed within 72 hours prior to or after the scheduled visit starting with Week 8 Day 1.

Response criteria definitions are outlined in Section 5.3.3.1.

Computed Tomography (CT) Scans (or Magnetic Resonance Imaging [MRI])

A CT scan with contrast must be performed within 35 days prior to study drug administration for all subjects. CT scans (with contrast) should include neck, chest, abdomen, and pelvic sequences. A contrast-enhanced MRI of the neck, chest, abdomen

and pelvis with a non-contrast CT scan of the chest may be used for subjects in whom a contrast CT is medically contraindicated (i.e., subjects with an allergy to CT contrast agents or subjects with impaired renal clearance). Whichever method is used at Screening, it should be used consistently through the duration of the study.

When a response (PR or CR) is determined by clinical criteria (e.g., laboratory tests/physical exam) at any time during the study, a CT scan must be performed no earlier than 8 weeks later for confirmation per 2008 Modified IWCLL NCI-WG Guidelines for Tumor Response. If the CT scan confirms a CR, then a BM biopsy should be performed as soon as possible to confirm the CR. For determination of CR, both the CT scan and bone marrow are required to be negative.

A CT scan should also be performed at 36 weeks for all subjects. This scan may be performed within 4 weeks before or after the 36 week scheduled visit provided that it has been at least 8 weeks since the subject's last scan. For subjects whose response meets criteria for a PR at the time of the Week 36 CT scan, an additional CT scan should be performed (no earlier than 8 weeks following the Week 36 scan) if a subsequent clinical disease assessment indicates that a CR or CRi has been achieved.

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 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.

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 Guidelines for Tumor Response (refer to Table 8). 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.

Note: Computed Tomography (CT) Scans (or MRI) may be performed up to 7 days after the scheduled visit.

Bone Marrow Aspirate and Biopsy

A bone marrow aspirate and biopsy will be performed and assessed locally at Screening (within 35 days prior to the first dose of study drug). Bone marrow aspirate and biopsy for biomarker sample collection should be split from this sample. A portion of the baseline aspirate may be used to design primers for ASO-PCR based MRD assessment. The bone marrow aspirate and biopsy should be performed after all other eligibility criteria have been met, unless otherwise obtained through standard of care. Bone marrow aspirates and biopsies performed as standard of care throughout the study should also be captured on an eCRF.

Bone marrow aspirate and biopsy reports will be faxed to the AbbVie primary contact listed in Section 6.2 or designee.

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

Subjects who meet all criteria for CR/CRi with the exception of a node(s) that are enlarged around 1.5 – 2 cm may also have a bone marrow performed. If bone marrow was not performed at the time of the confirmatory CT, then it should be performed after the Week 36 Day 1 CT scan. Bone marrow for biomarker sample collection can be split from this sample, from the bone marrow used for eligibility criteria, or from any bone marrow performed as standard of care throughout the study.

Quantitative Minimal Residual Disease (MRD) Assessment

MRD[35] for enumeration of CLL cells using ERIC panel based flow cytometry will be assessed by regional laboratories from all available samples. Additionally, MRD may be assessed using a PCR based technique from all available samples. MRD negativity may

be defined as the presence of less than one CLL cell per 10,000 leukocytes (or below 10^4) in the peripheral blood and/or bone marrow.

Specimens (bone marrow aspirate and peripheral blood) for MRD analysis should be collected at the same time as the bone marrow aspirate and biopsy performed for tumor assessments to confirm the CR/CRi. If MRD negativity is achieved in the bone marrow no further MRD analyses are required. Otherwise, MRD should be assessed at 12-week intervals thereafter (in peripheral blood) until MRD negativity is achieved. Once MRD negativity is achieved and confirmed in peripheral blood (e.g., two MRD negative consecutive peripheral blood samples), a bone marrow aspirate specimen will again be collected for analysis of MRD levels to confirm the peripheral blood negativity.

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 and MRD assessment. If a bone marrow and MRD assessment was not performed at the time of the confirmatory CT scan, then they should be performed after the Week 36 Day 1 CT scan. If MRD negativity is achieved in the bone marrow no further MRD analyses are required. Otherwise, MRD should be assessed at 12-week intervals thereafter (in the peripheral blood) until MRD negativity is achieved. Once MRD negativity is achieved and confirmed in peripheral blood (e.g., two MRD negative consecutive peripheral blood samples), a bone marrow aspirate specimen will again be collected for analysis of MRD levels to confirm the peripheral blood negativity.

Subjects continuing into the Survival Extended Access portion of the study, and who continue to be eligible for MRD testing, will have blood specimens collected for MRD PCR collected at 12-week (± 7 days) intervals. If a subject undergoes a bone marrow biopsy as standard of care while on the survival extended access portion, a portion of the aspirate is requested to be collected for MRD-PCR.

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

Dispense/Collect Venetoclax and Subject Calendars/Diaries

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 20 Day 1
- Week 24 Day 1
- Week 28 Day 1
- Week 32 Day 1
- Week 36 Day 1 and Day 1 of every 12 weeks thereafter (e.g., Weeks 48, 60, 72, etc.)

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 (with the exception of Week 1 Day 1 where no medication is given the 2 days prior to dosing).

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 MDASI (measure of subject reported symptoms), 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.

The MDASI assessment will take place at:

- Week 1 Day 1
- Week 5 Day 1
- Week 12 Day 1
- Week 24 Day 1
- Week 36 Day 1 and Day 1 of every 12 weeks thereafter
- Final Visit

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

- Week 1 Day 1
- Week 5 Day 1
- Week 12 Day 1
- Week 24 Day 1
- Week 36 Day 1 and Day 1 of every 12 weeks thereafter (e.g., Weeks 48, 60, 72, etc.)
- Final Visit
- Post Treatment Visits, if applicable

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

- Week 1 Day 1
- Week 5 Day 1
- Week 12 Day 1
- Week 24 Day 1
- Week 36 Day 1 and Day 1 of every 12 weeks thereafter (e.g., Weeks 48, 60, 72, etc.)
- Final Visit

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.

TLS Survey

Subjects participating in the United States will be asked to complete an optional survey assessing the information they were provided for the Patient Information Card and the Tumor Lysis Syndrome Patient Information Brochure, at their next regularly scheduled visit following reconsent if the subject is in the main cohort, or at Week 2 Day 1 or the next scheduled visit if the subject is in the safety expansion cohort.

Post-Treatment Follow-Up Visit(s)

For subjects who discontinue venetoclax monotherapy (e.g., due to toxicity or stem cell/bone marrow transplant), the following assessments will be performed every 3 months (post treatment) until discontinuation from the study (e.g., disease progression or a subject's refusal of the Post-Treatment visits) for a period of 5 years after the last subject has enrolled on the study:

- Physical Examination
- Vital Signs

- Hematology and Chemistry
- Coagulation
- CT scan (or MRI) only if collected by the site as part of standard of care
- Disease Assessments
- The EORTC QLQ-C30 and EORTC QLQ CLL16 Assessment

Note: *Effective with protocol Amendment 6, subjects being followed in Post-Treatment as of 12 May 2017 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, etc.) will be collected via telephone calls and/or clinical visits at 3 month (± 7 days) intervals after the last study visit for a period of 5 years after the last subject has enrolled on the study for subjects who have not withdrawn consent.

Survival Assessment(s) – Extended Access

For subjects continuing into the Survival Extended Access portion of the trial, venetoclax will be dispensed at the Final Visit, and Survival visits will begin 12 weeks (±7 days) following the 30-day Safety Follow-Up Visit. Survival visits will continue every 12 weeks (±7 days) until disease progression; up to 5 years following last subject enrolled (12 May 2020); or until a subject chooses to switch to commercial supply. Survival visits will include:

- Collection of Survival information
- AE/SAE/Con Med assessment
- Study drug reconciliation and dispensing
- Collect/Dispense subject diaries
- MRD PCR sample collection for eligible subjects

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

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.

5.3.1.2 Confinement

Subjects will not be confined during this study, but all subjects at high risk for TLS 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, or medium risk subjects with low creatinine clearance and/or higher tumor burden (i.e., ALC > 100×10^9/L or multiple bulky nodes), may be hospitalized for prophylaxis and monitoring at each subsequent dose escalation, at the discretion of the investigator.

5.3.1.3 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. On days that pre-dose PK sampling is required, dosing will occur in the morning at the clinic to facilitate PK sampling.

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.

5.3.1.4 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.
- Within 30 minutes of blood collection, store samples at –20°C or colder until shipped to central laboratory on dry ice sufficient to last during 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.

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.

5.3.1.5 Collection and Handling of Biomarker Variables

5.3.1.5.1 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 pre-dose
- Week 5 Day 1 pre-dose
- Final Visit/Time of Relapse

Note: Subjects with PD who continue to receive treatment per the discretion of the investigator (per Section 5.4.1) will have biomarker samples collected at both time of relapse and their subsequent final visit at discontinuation of venetoclax.

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

Blood for CD19 Cell Isolation Bcl-2 Family Analysis

Approximately 8 mL of blood will be collected by venipuncture into one appropriately labeled 8.5 mL ACD vacutainer from all subjects at the following time points:

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

Note: Subjects with PD who continue to receive treatment per the discretion of the investigator (per Section 5.4.1) will have biomarker samples collected at both time of relapse and their subsequent final visit at discontinuation of venetoclax.

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 FISH for Detection of 17p Deletion

In order to determine subject eligibility, sites may use their local laboratory to test for 17p deletion in either bone marrow or peripheral blood or provide results previously obtained. For sites that are unable to test locally, the confirmatory sample (peripheral

blood) sent to the central laboratory, as described below, may be used to determine eligibility. The results will be provided to the site within 5 to 7 business days.

A confirmatory sample will be collected from all subjects and will be processed by the central laboratory. Approximately 4 mL of blood will be collected by venipuncture into an appropriately labeled Sodium Heparin vacutainer at the following time point:

- Screening

Central Laboratory 17p Deletion Testing Information

17p deletion status is defined using FISH cytogenetic testing, as recommended in ESMO guidelines.[26] The detection of 17p del, identified by loss of *TP53* locus, will be determined by FISH study using the Vysis CLL probe kit,[36] which is an IUO/PEO labeled test assessed by a central laboratory.

The kit uses FISH DNA probe technology to determine deletion status of probe targets for locus-specific identifier (LSI) including LSI- TP53 (containing tumor protein p53gene, located on the short arm of chromosome 17 (17p). LSI TP3 probe, approximately 172 Kilobases in length, is located at 17p13.1 and contains the complete TP53 gene. A normal/abnormal determination for LSI TP53 probe is made by comparing the number of nuclei observed (per 200 scoreable nuclei) with the abnormal signal pattern to the normal cut-off value, which is > 7% (defined as 14 nuclei observed per 200 nuclei scoreable).[36]

FISH for Detection of 17p Deletion samples will be processed and shipped directly to the testing laboratory from the site per the current laboratory manual.

Bone Marrow Aspirate 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 Guidelines 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

Note: Subjects with PD who continue to receive treatment per the discretion of the investigator (per Section 5.4.1) will have biomarker samples collected at both time of relapse and their subsequent final visit at discontinuation of venetoclax.

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 6 mL of bone marrow aspirate each will be collected and placed into a 6 mL ACD vacutainer. Bone marrow aspirate must be split for this analysis from samples obtained for 2008 Modified IWCLL NCI-WG Guidelines 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

Note: Subjects with PD who continue to receive treatment per the discretion of the investigator (per Section 5.4.1) will have biomarker samples collected at both time of relapse and their subsequent final visit at discontinuation of venetoclax.

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

Tissue from Subjects with Richter's Transformation

Formalin-fixed core needle biopsies will be obtained for all subjects in the study whose CLL has undergone Richter's transformation. Biopsies will be performed on readily accessible lymph node tissue at the following time point:

- Time of Relapse (when Richter's transformation is confirmed)

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.

5.3.1.5.2 Optional Collections

Tissue for IHC and FISH

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

Note: Subjects with PD who continue to receive treatment per the discretion of the investigator (per Section 5.4.1) will have biomarker samples collected at both time of relapse and their subsequent final visit at discontinuation of venetoclax.

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 Guidelines for Tumor Response whenever possible.

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 again after the subject has progressed on therapy.

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, inadequate sampling in screening, etc.

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 following times:

- Week 1 Day 1: 8 hour post dose

- Week 2 Day 1: 8 hour post dose (if escalation to a new dose level)
- Week 3 Day 1: 8 hour post dose (if escalation to a new dose level)
- Week 4 Day 1: 8 hour post dose (if escalation to a new dose level)
- Week 5 Day 1: 8 hour post dose (if escalation to a new dose level)
- Week 8 Day 1: 0 hour (pre-dose)
- Week 12 Day 1: 0 hour (pre-dose)
- Week 16 Day 1: 0 hour (pre-dose)
- Week 24 Day 1 and Day 1 of every 12 weeks thereafter: 0 hour (pre-dose)

A total of up to 9 blood samples (approximately 27 mL) will be collected per subject up to Week 24. After Week 24, additional blood samples will be collected from each subject pre-dose at Day 1 of every 12 weeks. The PK collection performed 8 hours post-dose after each dose escalation may be taken up to 1 hour prior or up to 20 minutes after to allow for processing, if necessary.

Refer to Table 5 for a schedule of the blood collection for venetoclax (and possible metabolite[s]) assay during the study.

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 (with the exception of Week 1 Days 1 and 2 where no medication is given the 2 days prior to dosing). In addition, on the scheduled venetoclax PK draws days, the subject's meal content will be captured on the day of venetoclax first dose and days where venetoclax dose escalation to a new dose level has occurred. Sites will ensure that all information is captured through source documents (e.g., 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. 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 screw-capped polypropylene tubes (cryovials) 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 one hour 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 (and possible metabolite[s]) will be determined under the supervision of the Drug Analysis Department at AbbVie.

5.3.3 Efficacy Variables

The primary objective of the main cohort is to evaluate the efficacy of venetoclax monotherapy in subjects with relapsed or refractory chronic lymphocytic leukemia (CLL) harboring the 17p deletion. Efficacy will be measured by overall response rate (ORR). The secondary objectives are to evaluate CR, PR, duration of overall response, determine

progression-free survival (PFS), event free survival, time to progression (TTP), time to first response, time to 50% reduction in ALC, overall survival (OS) and percent of subjects who move on to stem cell transplant.

For the safety expansion cohort in subjects with relapsed/refractory or previously untreated chronic lymphocytic leukemia (CLL) harboring the 17p deletion, efficacy will be considered a secondary endpoint. The secondary objectives are to evaluate ORR, CR, PR, duration of overall response, determine progression-free survival (PFS), event free survival, time to progression (TTP), time to first response, time to 50% reduction in ALC, overall survival (OS), and percent of subjects who move on to stem cell transplant.

Analyses of these endpoints are described in Section 8.0.

5.3.3.1 2008 Modified IWCLL NCI-WG Guidelines for Tumor Response

For disease assessments, response will be assessed by the investigator based on analysis of clinical laboratory tests (hematology laboratory values), complete physical examination, contrast-enhanced CT scan of involved anatomic regions, bone marrow aspirate and biopsy. If a contrast-enhanced CT is medically contraindicated (e.g., subjects with an allergy to CT contrast agents or subjects with impaired renal clearance), a contrast-enhanced MRI of all involved anatomical regions plus a non-contrast CT of the chest should be done. Subjects will be evaluated against the 2008 Modified IWCLL NCI-WG Guidelines for Tumor Response[34] with the addition of CT imaging (or MRI).

At Screening, all measurable disease must be documented by laboratory testing (hematology laboratory values), physical examination, CT scan, and bone marrow. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment with the exception of the CT scan and bone marrow biopsy and aspirate which must be completed within 5 weeks before the beginning of the treatment. All other tumor assessments after baseline should be performed within 7 days after the scheduled visit.

Beginning at Week 5 Day 1, disease response will be assessed by the investigator based on the analysis of clinical laboratory tests and a complete physical examination. When a response (PR or CR) is determined by clinical criteria (laboratory tests and physical exam) at any time during the study, a CT scan must be performed no earlier than 8 weeks later to confirm clinical response. If the CT scan confirms a CR, then a BM biopsy is required as soon as possible for confirmation of CR. For determination of CR, both the CT scan and bone marrow are required to be negative.

A CT scan should also be performed at 36 weeks for all subjects. This scan may be performed within 4 weeks before or after the 36 week scheduled visit provided that it has been at least 8 weeks since the subject's last scan. For subjects whose response meets criteria for a PR at the time of the Week 36 CT scan, an additional CT scan should be performed (no earlier than 8 weeks following the Week 36 scan) if a subsequent clinical disease assessment indicates that a CR or CRi has been achieved.

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 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 techniques 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 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. Evaluation for 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. Contrast-enhanced CT scans with anatomical coverage of the neck, chest, abdomen, and pelvis should be performed. CT scans for response assessment may be limited to areas of prior involvement only, if required by local regulatory authorities. Contrast-enhanced magnetic resonance imaging (MRI) scans with anatomical coverage of the neck, chest, abdomen, and pelvis plus a non-contrast CT scan of the chest may be used if CT is medically contraindicated (e.g., severe contrast allergy). Whichever scanning method was used at baseline must be used during follow-up. 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.

For accurate overall response evaluation, ultrasound (US) or PET scans 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 criteria and radiographic scans will be evaluated using the 2008 Modified IWCLL NCI-WG Guidelines for Tumor Response (refer to Table 8). 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.

Disease 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 (absence of 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) and CT scan (if abnormal prior to therapy or if physical exam is inconclusive at the time of evaluation)
- 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 as soon as possible after CR/CRi has been achieved by laboratory tests, physical exam and CT scan. 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 enlargement of the liver and/or spleen (if abnormal prior to therapy).

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

- Neutrophils > 1,500/μL or ≥ 50% improvement over baseline.
- Platelets > l00,000/μL or ≥ 50% improvement over baseline.
- Hemoglobin > 11.0 g/dL or ≥ 50% improvement over baseline without transfusions or exogenous growth factors.

Table 8. 2008 Modified IWCLL NCI-WG Guidelines 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,e]	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%[f]
Blood Lymphocytes	< 4000/µL	Decrease ≥ 50% from baseline	Increase ≥ 50% over nadir (≥ 5000/µL)[d]	Change of –49% to +49%
Hepatomegaly[g]	None	Decrease ≥ 50%	Increase ≥ 50%[h]	Change of –49% to +49%
Splenomegaly[g]	None	Decrease ≥ 50%	Increase ≥ 50%[h]	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[i]	> 100,000/µL or increase ≥ 50% over baseline[i]	Decrease of ≥ 50% from baseline secondary to CLL[e]	Change of –49% to +49%
Hemoglobin	> 11.0 g/dL[i]	> 11.0 g/dL or increase ≥ 50% over baseline[i]	Decrease of > 2 g/dL from baseline secondary to CLL[e]	Increase to ≤ 11.0 g/dL over baseline, or decrease < 2 g/dL
Neutrophils	> 1500/µL[i]	> 1500/µL or increase ≥ 50% over baseline[i]	Decrease ≥ 50% from baseline secondary to CLL[e]	N/A

Table 8. 2008 Modified IWCLL NCI-WG Guidelines 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,e]	Stable Disease (SD) All Criteria Must be Met
Other Considerations				
New Lesions	None	None	Appearance of new palpable lymph nodes (> 1.5 cm in longest diameter) or any new extra nodal lesion (> 5 mm) or transformation to a more aggressive histology, e.g., Richter Syndrome[d]	None
Non-Target Lesions	Nodes must be normal size as visually estimated; extra nodal and other assessable disease should be absent	No change/decreased	Unequivocal progression	No change or decrease or non-substantial increase
Target Extra Nodal Disease	Absence of any extra nodal disease by physical examination (palpable, visualized extra nodal) and CT scan	≥ 50% decrease in SPD	≥ 50% increase in the longest diameter of any extra nodal lesion	Not CR, CRi, PR, or PD

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

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

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

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

d. Increase in SPD of multiple nodes, or in greatest diameter of any previous site, or appearance of any new lymphadenopathy or organomegaly. Degree of change in LN or lymphocyte counts should be measured from nadir (lowest post-treatment) values. For lymphocyte only, an increase of ≥ 50% AND a value of ≥ 5000 μL are necessary to define PD.

Table 8. 2008 Modified IWCLL NCI-WG Guidelines for Tumor Response (Continued)

e. Worsening of cytopenias cannot define PD unless a bone marrow biopsy is performed to show unequivocal progression.
f. Sum products of up to 12 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.
g. If enlarged before therapy.
h. 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.
i. Without the need for exogenous growth factors or transfusions.

To be assigned a status of PR, the response must be confirmed no earlier than 8 weeks after the clinical criteria for response are first met.

5.3.3.2 Definition of Disease Progression

Disease progression according to 2008 Modified IWCLL NCI-WG Guidelines 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 and > 1.5 cm.
- 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 established 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 only if confirmed by a bone marrow assessment showing unequivocal progression.

5.3.3.3 Definition of Stable Disease

Patients who have not achieved a CR or a PR, or who have not exhibited PD, will be considered to have stable disease.

5.3.4 Safety Variables

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

5.3.5 Pharmacokinetic Variables

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 may 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 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. Serum samples may also be analyzed for predictive or drug-responsive markers. In the event that any serum samples are unused, remaining samples may 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.

Venetoclax inhibits the ability of cancer cells to evade cell death, or apoptosis, by blocking the activity of the anti-apoptotic protein Bcl-2. Nonclinical studies have demonstrated a pattern of response to venetoclax based on the levels of Bcl-2 family proteins. High levels of Bcl-2 and low levels of Mcl-1 and Bcl-X_L are generally predictive of response to this drug in vitro. Therefore, the proteins levels of relevant BCL-2 family members may be determined in tumor cells isolated from the bone marrow aspirate and examined for correlations with 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, bone marrow and/or tumor tissue samples and/or DNA/RNA extracted from serum from subjects participating in this study. Analysis of the nucleic acids can be used to identify and track the CLL cells for MRD. The analysis

may include but is not limited to members of the BCL-2 family, p53, Notch-1 and other genes/proteins that may be informative to venetoclax mechanism of action or CLL disease progression. Additionally, comprehensive genomic sequencing of CLL cells isolated from the blood or bone marrow aspirate may also be performed. 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

MDASI

The MDASI is a multi-symptom PRO measure for clinical and research use. The M.D. Anderson Symptom Inventory[37] contains 13 core symptom severity items (pain, fatigue, nausea, disturbed sleep, distess [emotional], shortness of breath, lack of appetite, drowsiness, dry mouth, sadness, vomiting, difficulty remembering, and numbness or tingling), 6 symptom interference items (general activity, mood, walking ability, normal work, relations with other people, and enjoyment of life), and 5 chronic lymphocytic leukemia specific items (abdominal pain, lymph node pain, night sweating, fevers/temperature fluctuation, and frequent infections).

Mean symptom, symptom interference, domain and total scores will be calculated for each observation as defined in the MDASI scoring manual and then 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.[38,39]

EORTC QLQ-C30 and EORTC QLQ CLL16

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).

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.[40]

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.[41]

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.[41]

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

Subjects with disease progression who continue to receive venetoclax will also be allowed to receive other agents approved to treat CLL in addition to venetoclax. This will be added at the discretion of the investigator, and AbbVie or its partners will not reimburse for treatment agents or for the procedures required to monitor subjects other than those required per protocol.

The investigator will inform AbbVie prior to discontinuing a subject from the study by contacting the Clinical Team Leader as identified in Section 6.2. All subjects will be included for analysis of safety data. Subjects who withdraw from the study will not be replaced.

In the event that a subject withdraws or is discontinued from the study, the reason(s) for the discontinuation from the study will be recorded. Final visit procedures as listed in Table 4 will be performed as soon as possible after discontinuation from the study.

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.

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 separate 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.

For subjects who discontinue venetoclax (e.g., due to toxicity or stem cell/bone marrow transplant), post-treatment follow-up visits will be performed every 3 months until discontinuation from the study. Post-Treatment follow-up visits are not required for subjects who have discontinued due to disease progression or a subject's refusal of the Post-Treatment visits. This will be for a period of up to 5 years after the last subject has enrolled on the study.

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 for subjects who have not withdrawn consent. Additionally, information regarding Richter's Transformation and second primary malignancies will also be collected during this period for subjects who have not withdrawn consent.

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 6.1.6 or Section 6.2.

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, in the judgment of the investigator and AbbVie, the continued exposure to the study drug represents a significant risk to subjects, the study will be stopped. The following procedures for discontinuation will be followed:

- If the sponsor has decided to prematurely discontinue the study, the sponsor will promptly notify in writing the investigator as well as regulatory authorities of the decision and give detailed reasons for the discontinuation.
- The investigator must promptly notify the IEC/IRB and give detailed reasons for the discontinuation.
- The investigator must promptly notify the enrolled subjects of the premature discontinuation and administer appropriate treatments such as replacement of the treatment regimen, if applicable, by other appropriate regimens.

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.

If the subject vomits after taking venetoclax, no additional dose should be taken that day and the next dose should be taken at the usual time the next day. Any dose of venetoclax can be given up to 8 hours after its usual time, in which case the following day's dose should be taken at the usual time. If a dose of venetoclax is missed by more than 8 hours, the dose should not be taken that day, and should not be made up. The next dose should be taken at the usual time the next day.

5.5.2 Identity of Investigational Product

The individual study drug information is presented in Table 9.

Table 9. Identity of Investigational Product

Study Drug	Trademark	Formulation	Route of Administration	Manufacturer
Venetoclax (ABT-199)	N/A	10 mg Tablet	Oral	AbbVie/Abbott
Venetoclax (ABT-199)	N/A	50 mg Tablet	Oral	AbbVie/Abbott
Venetoclax (ABT-199)	N/A	100 mg Tablet	Oral	AbbVie/Abbott

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 Drug

The investigational products supplied in this study are 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 a unique consecutive subject number at Screening. In the main cohort, subject numbers will consist of 5 digits (XXX01), with the first three digits denoting site number and the last 2 digits as the subject number, beginning with 01. In the safety expansion cohort, subject numbers will also consist of 5 digits (XXX50), with the first three digits denoting site number and the last 2 digits as the subject number, beginning with 50. 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 screening 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. On days that pre-dose PK sampling is required, dosing will occur in the morning to facilitate PK sampling. On all other dosing days 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, single arm study.

5.5.6 Treatment Compliance

The investigator or his/her designated and qualified representatives will administer/dispense study drug only to subjects enrolled in the study in accordance with

the protocol. The study drug must not be used for reasons other than that described in the protocol.

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

There are currently no treatments approved and labeled specifically to meet the need of the 17p deletion population and currently available treatments for the broader CLL population, such as FCR and BR, are not adequate for this patient population. Due to the

limited effectiveness of available therapies, treatment guidelines recommend enrollment in clinical trials as a preferred treatment option for patients with 17p deletion. Those patients who achieve a response to initial therapy should be considered for an allogeneic transplant. For relapsed/refractory patients not eligible for an allogeneic transplant, suggested regimens in cases where a clinical trial is not available include alemtuzumab; however, alemtuzumab has limited use due to its toxicity profile and its efficacy signals are more limited in subjects with bulky disease.

Untreated CLL patients who harbor the 17p deletion have generally a short first remission if they respond to conventional chemotherapy such as fludarabine, cyclophosphamide, and rituximab (FCR) and alemtuzumab, because 17p deletion is a prognostic marker for nonresponse to standard chemotherapy. Thus, novel treatment strategies, which act independently of the p53 signaling pathway are needed.

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 first-in-class, 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-X_L and Bcl-w. The mechanism of action of venetoclax is independent of the TP53 pathway. Briefly, venetoclax inhibits Bcl-2 allowing the release of BIM, which includes oligomerization of pro-apoptotic molecules such as BAK and BAX. This triggers rapid apoptosis, bypassing the TP53 pathway.

Preliminary data from the ongoing venetoclax first-in-human study, Study M12-175, had indicated a strong efficacy signal in oncology subjects. In the CLL Arm A, 56 subjects have been dosed with 54 evaluable. Best response reported for 54 evaluable subjects with CLL/SLL was 7 (13%) subjects with complete remission (CR) or CR with incomplete marrow recovery (CRi), 39 (72%) with partial remission (PR),4 (7%) with stable disease (SD), 0% with progressive disease (PD), and 4 (7%) subjects discontinued prior to Week 6. The response rate (CR + PR) was 85%.

Sixteen (28.6%) of 56 subjects with relapsed/refractory CLL had a 17p deletion, as evaluated by FISH. Subjects with the 17p deletion remained on study for a median of 159 days (range: 33 to 495 days). Best response in all 16 CLL subjects with a 17p deletion was 1 (6%) subject with CR/CRi, 13 (81%) with PR, 1 with SD (6%), 0% with PD, and 1 (6%) discontinued prior to Week 6; the response rate was 88%.

Updated safety and efficacy data are described in detail in the Investigator Brochure.[10]

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 who harbor 17p deletion will be selected to participate in the main cohort of this study. In addition, subjects in the main cohort of the study must have 17p deletion, assessed by central laboratory and determined by FISH using the Vysis CLL probe kit. Subjects must have relapsed or be refractory after receiving at least one prior treatment regimen. Subjects with relapsed/refractory or previously untreated CLL who harbor 17p deletion will be selected to participate in the safety expansion cohort of this study. Subjects in the Safety Expansion Cohort must have 17p deletion, assessed by local laboratory or by central laboratory. Pre-clinical and clinical findings support the possibility of efficacy in this patient population. As CLL subjects with 17p deletion who relapse have very limited treatment options, it is appropriate to enroll such subjects in a clinical trial of an investigational agent.

5.6.4 Selection of Doses in the Study

The dose of 400 mg was selected on the basis of preliminary 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. This 400 mg QD venetoclax dose has been deemed tolerable in Study M12-175.

To mitigate the risk for TLS, a step-wise lead-in period (up to 5 weeks) will be employed to escalate venetoclax dose to the treatment dose of 400 mg.

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.

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 6.2.2). For adverse events, please refer to Sections 6.1 through 6.1.8. For product complaints, please refer to Section 6.2.

6.1 Medical Complaints

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

All adverse events will be followed to a satisfactory conclusion.

6.1.1 Definitions

6.1.1.1 Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a 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 6.1.8 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.

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. Such events include known consequences of the underlying disease 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 for this protocol.

An Independent Data Monitoring Committee will monitor the incidence of these expected events during the study. An aggregate report of any clinically relevant imbalances that do not favor the test product will be submitted to health authorities.

Although exempted from expedited reporting to certain Health Authorities and ECs/IRBs as individual cases, if an event commonly associated with CLL or progression of CLL meets seriousness criteria, it must be reported to AbbVie within 24 hours of the site being made aware of the serious adverse event (as defined in Section 6.1.6). 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).[42] 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	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is **sufficient** evidence (information) to suggest a causal relationship.
No Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is **insufficient** evidence (information) to suggest a causal relationship.

For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered "associated." Events assessed as having no reasonable possibility of being related to study drug will be considered "not associated." In addition, when the investigator has not reported causality or deemed it not assessable, AbbVie will consider the event associated. If an investigator's opinion of no reasonable possibility of being related to study drug is given, an "Other" cause of event must be provided by the investigator for the serious adverse event.

6.1.4 Adverse Events Expected Due to Study Related Endpoints

6.1.4.1 Deaths

For this protocol, overall survival is an efficacy endpoint. Deaths that occur during the protocol specified adverse event reporting period (see Section 6.1.6) that are more likely related to disease progression will therefore be an expected adverse event and will not be subject to expedited reporting.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. The term "sudden death" should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without pre-existing heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should not be replaced by the established cause of death.

6.1.4.2 Lack of Efficacy or Worsening of Disease

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

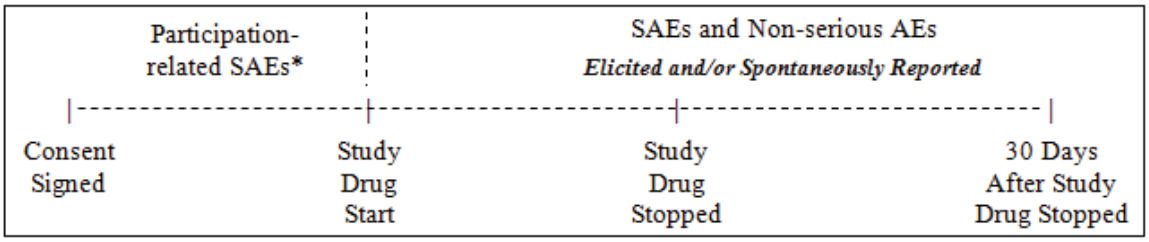
6.1.5 Adverse Event Collection Period

All adverse events (serious and nonserious) reported from the time of study drug administration until 30 days following discontinuation of study drug administration will be collected, whether elicited or spontaneously reported by the subject.

Serious adverse events occurring after the study-specific informed consent is signed, but prior to the first 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.

6.1.6 Adverse Event Reporting

In the event of a serious adverse event, whether related to study drug or not, the investigator will notify Clinical Pharmacovigilance within 24 hours of the site becoming aware of the serious adverse event by entering the serious adverse event by email.

In the event of a serious adverse event, whether related to 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 site awareness.

Email (preferred method):
PPDINDPharmacovigilance@abbvie.com
cc: SafetyManagement_Oncology@abbvie.com
Or FAX:
+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 Email: SafetyManagement_Oncology@abbvie.com

For any subject safety concerns, please contact the AbbVie medical monitor:

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

Phone:
Cell:
Fax:
Email: [redacted]

In emergency situations involving study subjects when the primary medical monitor is not available by phone, please contact the 24-hour **AbbVie Medical Escalation Hotline** where your call will be re-directed to a designated AbbVie medical monitor.

Phone: +1 (973) 784-6402

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

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 or 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.

6.1.7 Pregnancy

Pregnancy in a study subject must be reported to an AbbVie representative (Section 6.1.6 or Section 6.2) 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. Male subjects should be informed that contraceptive measures should be taken by their female partner. Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected. In the event of a pregnancy occurring in the partner of an enrolled subject, written informed consent for release of medical information from the partner must be obtained prior to the collection of any pregnancy-specific information and the pregnancy will be followed to outcome.

Pregnancy in a study subject is not considered an adverse event. 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.

6.1.8 Toxicity Management

6.1.8.1 Prophylaxis and Management of Tumor Lysis Syndrome

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 subjects with higher tumor burden are at increased risk of TLS. Reduced creatinine clearance could further increase the risk among subjects with higher tumor burden. Data analyses have resulted in development of three risk categories, listed below. The risk category for an individual subject 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.

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

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

For tumor lysis syndrome prophylaxis, subjects have been classified in 3 risk categories based on the risk for developing medically concerning TLS with venetoclax administration. The tumor burden assessed by the nodal disease and absolute lymphocyte count at screening has been used to define each category as described below:

Risk Categories for Developing TLS

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

First Dose of Venetoclax at 20 mg and at 50 mg

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

- An oral agent to reduce the uric acid level (e.g., allopurinol) to be initiated at least 72 hours prior to dosing. Treatment may need to be continued for approximately 5 weeks based on the ongoing risk of TLS development. Subjects allergic to allopurinol must use another uric acid reducer.
- Oral hydration consisting of fluid intake of 1.5 to 2 L per day starting at least 48 hours prior to the start of treatment for all subjects prior to first dose and at all subsequent dose escalations and continued for at least 24 hours after dosing and all of the chemistries laboratory values remain within ULN. Oral hydration is recommended beyond 24 hours post-dose for subjects who demonstrate any laboratory changes. Oral hydration should be maintained, as tolerated, even during the days the subjects receive IV hydration.
- Serum chemistry and hematology laboratory samples (low and medium risk subjects) must be drawn anytime within 72 hours prior to first dose at 20 mg and at 50 mg, and 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. The investigator's decision to proceed with venetoclax treatment initiation may be based on these laboratory values.

- For subjects demonstrating any clinically significant laboratory abnormalities in this baseline laboratory assessment, the first dose of venetoclax at 20 mg and at 50 mg must be delayed until resolution and management of the laboratory abnormalities should be initiated, per the protocol Appendix D (Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome [TLS]). If needed, the subject should receive additional treatment prior to the initiation of dosing.

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

Low Risk Category

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

- For subjects who are unable to maintain adequate oral hydration, IV hydration of 1.5 to 2 L is recommended in the outpatient setting on Day 1 of 20 mg and 50 mg dose to assure this full amount of hydration is achieved. In subjects for whom volume overload is considered a significant risk, hospitalization should be considered.
- Chemistry and hematology laboratory tests are to be collected within 72 hours prior to the first dose of venetoclax at 20 mg and at 50 mg. These laboratory values must be reviewed by the investigator. The investigator's decision to proceed with venetoclax treatment initiation may be based on these laboratory values.
- Chemistry laboratory tests must be performed by local laboratory 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. 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. Subjects must remain at the hospital or clinic until the 8 hour laboratory values have been reviewed by the investigator.

- 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.
- If any significant laboratory changes are observed within the first 24 hours after initiation of dosing, see 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 is performed, the subsequent dose of venetoclax can only be given when electrolytes have been stable without any more treatment for at least 24 hours.
  - Additional laboratory assessments may be performed per investigator discretion.
- Hematology laboratory tests must be performed 0 hour (pre-dose, within 4 hours before venetoclax administration), and 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.

Medium Risk Category

- Subjects in Medium Risk category who have creatinine clearance ≥ 80 mL/min will receive their initial doses of venetoclax at 20 and 50 mg as outpatients.
- Subjects in the Medium Risk category who have creatinine clearance of < 80 mL/min and/or higher tumor burden (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 in Medium Risk category (independently of their creatinine clearance and/or tumor burden) will receive IV hydration of 1.5 to 2 L in the outpatient setting on Day 1 of 20 mg and 50 mg dose. In subjects for whom volume overload is considered a significant risk, hospitalization should be considered.
- Chemistry and hematology laboratory tests are to be collected within 72 hours prior to the first dose of venetoclax at 20 mg and at 50 mg. These laboratory values must be reviewed by the investigator. The investigator's decision to proceed with venetoclax treatment initiation may be based on these laboratory values.
- Chemistry laboratory tests must be performed by local laboratory 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. 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. Subjects must remain at the hospital, or clinic, until the 8 hour laboratory values have been reviewed by the investigator.
- 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.
- If any significant laboratory changes are observed within the first 24 hours after initiation of dosing, see 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 is performed, the subsequent dose of venetoclax can only be given when electrolytes have been stable without any more treatment for at least 24 hours.
    - Additional laboratory assessments may be performed per investigator discretion.

- Hematology laboratory tests must be performed 0 hour (pre-dose, within 4 hours before venetoclax administration), and 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.

High Risk Category

Hospitalization and monitoring will begin the night before administration of the first dose of 20 mg and 50 mg of venetoclax and will continue until at least the 24 hour post-dose chemistry laboratory values are reviewed by the investigator.

- Chemistry and hematology laboratory tests to be collected upon admission the night before first dose of venetoclax. The investigator's decision to proceed with venetoclax treatment initiation will be based on these laboratory values.
- Nephrology (or other acute dialysis service) consultation should be considered upon admission per institutional standards at investigators' discretion to ensure emergency dialysis is available and the appropriate staff is aware and prepared to handle any necessary intervention for TLS. Telemetry should also be considered.
- IV hydration must be started the night before first dose of 20 mg and again the night before the first dose of 50 mg, with a target of approximately 1.5 – 2 L/day, or as clinically appropriate, and continue for at least 24 hours after dose.
- Rasburicase will be administered per regional standards or institutional dosing guidelines for subjects with elevated uric acid level at baseline (> ULN or > Cairo-Bishop threshold of 476 μmol/L) prior to the initial dose of venetoclax at 20 mg and 50 mg. 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.
- Prophylactic reductions for potassium, inorganic phosphorus and/or uric acid above of normal range prior to dosing are recommended.
- Chemistry laboratory tests must be performed by local laboratory 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. 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.

- Day 2 dose should not be administered until the 24 hours 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.
- If any significant laboratory changes are observed within the first 24 hours after initiation of dosing, see 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 is performed, the subsequent dose of venetoclax can only be given when electrolytes have been stable without any more treatment for at least 24 hours.
    - Additional laboratory assessments may be performed per investigator discretion.
- Hematology laboratory tests will be performed 0 hour (pre-dose, within 4 hours before venetoclax administration), and 24* hours post-dose after the first dose of venetoclax at 20 mg and 50 mg.
    - * All 24 hours laboratory assessments may be taken within 2 hour window, if necessary.
- The 24-hour post-dose laboratory results must be reviewed by the investigator prior to the subject leaving the hospital.

First Dose of Venetoclax at Dose Escalation 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 prior to each dose escalation and continued for at least 24 hours after the dose. IV hydration is encouraged at subsequent dose escalations for subjects who are unable to maintain such oral hydration. IV hydration will be in the outpatient setting on the day of dose escalation. In subjects for whom volume overload is considered a significant risk, hospitalization should be considered. Oral hydration should be maintained, as tolerated, even during the days the subjects receive IV hydration.
- Chemistry and Hematology laboratory tests for all subjects treated in the outpatient setting must be collected within 72 hours prior to the first dose of venetoclax of each dose escalation, and results must be reviewed by the investigator prior to each escalation. The investigator's decision to proceed with venetoclax treatment initiation may be based on these laboratory values.
- For subjects demonstrating any clinically significant laboratory abnormalities in this baseline laboratory assessment, the first dose of venetoclax at 100 mg, 200 mg and at 400 mg must be delayed until resolution and management of the laboratory abnormalities should be initiated, per the protocol Appendix D (Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome [TLS]). If needed, the subject should receive additional treatment prior to the initiation of dosing.

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

Low Risk Category

- Subjects in Low Risk category will receive the subsequent dose escalations (100, 200 and 400 mg) as outpatients.
- Chemistry and Hematology laboratory tests will be collected within 72 hours prior to the first dose of venetoclax of each dose escalation. The investigator's decision to proceed with venetoclax treatment initiation may be based on these laboratory values.
- Chemistry laboratory tests will be performed by local laboratory STAT at 0 hour (pre-dose, within 4 hours before venetoclax administration), 8 and

24 hours after dose administration. These laboratory values must be reviewed in real time by the investigator. 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. Subjects must remain at the hospital, or clinic, until the 8 hour laboratory values have been reviewed by the investigator.

- 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.
- If any significant laboratory changes are observed within the first 24 hours after initiation of dosing, see 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 is performed, the subsequent dose of venetoclax can only be given when electrolytes have been stable without any more treatment for at least 24 hours.
  - Additional laboratory assessments may be performed per investigator discretion.
- Hematology laboratory tests will be performed at 0 hour (pre-dose, within 4 hours before venetoclax administration), and 24* hours post-dose after each dose escalation.
  - * All 24 hours laboratory assessments may be taken within 2 hour window, if necessary.

Medium Risk Category

- Subjects in Medium Risk category may receive their subsequent dose escalations in the outpatient setting.
- Subjects with creatinine clearance < 80 mL/min and/or higher tumor burden (i.e., ALC > 100×10^9/L or multiple bulky nodes) may be hospitalized per investigator's discretion.

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

- Chemistry and Hematology laboratory tests will be collected within 72 hours prior to the first dose of venetoclax of each dose escalation. The investigator's decision to proceed with venetoclax treatment initiation may be based on these laboratory values.
- Chemistry laboratory tests will be performed by local laboratory at 0 hour (pre-dose, within 4 hours before venetoclax administration), 8 and 24 hours post dose administration. These laboratory values must be reviewed in real time by the investigator. 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. Subjects must remain at the hospital, or clinic, until the 8 hour laboratory values have been reviewed by the investigator.
- 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.
- If any significant laboratory changes are observed within the first 24 hours after initiation of dosing, see 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 is performed, the subsequent dose of venetoclax can only be given when electrolytes have been stable without any more treatment for at least 24 hours.
- Additional laboratory assessments may be performed per investigator discretion.

- Hematology laboratory tests will be performed at 0 hour (pre-dose, within 4 hours before venetoclax administration), and 24* hours post-dose after each dose escalation.
  - * All 24 hours laboratory assessments may be taken within 2 hour window, if necessary.

For subjects who are hospitalized during subsequent dose escalations:

- Nephrology (or acute dialysis service) consultation may be considered on admission (based on investigator discretion) for hospitalized subjects.
- 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.
- Chemistry and Hematology laboratory tests will be collected upon admission.
- Chemistry tests will be performed by local laboratory 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. 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 ventoclax treatment.
- If no significant findings suggestive of clinical or lab TLS occur within 24 hours, the same dose will be continued until Day 7 in the outpatient setting.
- If any significant laboratory changes are observed within the first 24 hours after initiation of dosing, see Appendix 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 is performed, the subsequent dose of venetoclax can only be given when electrolytes have been stable without any more treatment for at least 24 hours.
- Additional laboratory assessments may be performed per investigator discretion.

- Hematology laboratory tests will be performed at 0 hour (pre-dose, within 4 hours before venetoclax administration), and 24* hours post-dose after each dose escalation.
  - * All 24 hours laboratory assessments may be taken within 2 hour window, if necessary.
- The 24-hour post-dose laboratory results must be reviewed by the investigator prior to the subject leaving the hospital or receiving any additional doses of the study drug.

High Risk Category

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

Subjects 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:

1. Re-categorization to Medium Risk

   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 management guidelines for the medium-risk TLS category for subsequent dose escalations of venetoclax during the Lead-In Period.

2. Re-categorization to High Risk

   If the subject's ALC remains $\geq 25 \times 10^9$/L, the subject will remain in the high-risk TLS category and continue to follow management guidelines for high-risk TLS 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.

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 before the dose of venetoclax and continue for 24 hours after dose administration.

For subjects who are hospitalized during subsequent dose escalations:

- Nephrology (or acute dialysis service) consultation may be considered on admission (based on investigator discretion) for hospitalized subjects.
- 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.
- Chemistry and Hematology laboratory tests will be collected upon admission.
- Chemistry tests will be performed by local laboratory 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. 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.
- Day 2 dose should not be administered until the 24 hours 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.
- If any significant laboratory changes are observed within the first 24 hours after initiation of dosing, see 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 is performed, the subsequent dose of venetoclax can only be given when

electrolytes have been stable without any more treatment for at least 24 hours.

- Additional laboratory assessments may be performed per investigator discretion.
- Hematology laboratory tests will be performed 0 hour (pre-dose, within 4 hours before venetoclax administration), and 24* hours post-dose after each dose escalation.
  - * All 24 hours laboratory assessments may be taken within 2 hour window, if necessary.
- The 24-hour post-dose laboratory results must be reviewed by the investigator prior to the subject leaving the hospital or receiving any additional doses of the study drug.

For subjects who are not hospitalized:

- Intravenous hydration (1.5 to 2 L) will be given in the outpatient setting.
- Chemistry and Hematology laboratory tests will be collected within 72 hours prior to the first dose of venetoclax of each dose escalation. The investigator's decision to proceed with venetoclax treatment initiation may be based on these laboratory values.
- Chemistry tests will be collected and performed by local laboratory at 0 hour (pre-dose, within 4 hours before venetoclax administration), 8 and 24 hours post dose administration. These laboratory values must be reviewed in real time by the investigator. 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. Subjects must remain at the hospital, or clinic, until the 8 hour laboratory values have been reviewed by the investigator.
- 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.

- If any significant laboratory changes are observed within the first 24 hours after initiation of dosing, see 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 is performed, the subsequent dose of venetoclax can only be given when electrolytes have been stable without any more treatment for at least 24 hours.
- Additional laboratory assessments may be performed per investigator discretion.
- Hematology laboratory tests will be performed at 0 hour (pre-dose, within 4 hours before venetoclax administration), and 24* hours post-dose after each dose escalation.
  * All 24 hours laboratory assessments may be taken within 2 hour window, if necessary.

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

6.1.8.2 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.

Table 10. Dose Reduction Guidelines for Management of Neutropenia

Venetoclax Dose	Reduced Dose
400 mg	300 mg
300 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 20 mg will discontinue venetoclax, but may remain on study to assess for progression.

6.1.8.3 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, Table 2 and Appendix C for a description of excluded and cautionary medications.

6.1.8.4 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.

6.2 Product Complaint

6.2.1 Definition

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

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

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

6.2.2 Reporting

Product Complaints concerning the investigational product must be reported to the Sponsor within 24 hours of the study site's knowledge of the event via the Product Complaint form. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. Product Complaints associated with adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

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

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

7.0 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol. 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]
AbbVie
1 North Waukegan Road
North Chicago, IL 60064

Office: [redacted]
Cell:
Fax:
Email:

Medical Monitor:

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

Phone: [redacted]
Cell:
Fax:
Email:

Back-up Contact:

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

Office: [redacted]
Cell:
Fax:
Email:

Program Lead:

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

Contact Information:
Office: [redacted]
Fax:
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.

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

Efficacy analyses will be performed separately for each cohort (main and safety expansion). Safety analyses will be performed separately for each cohort, and will be pooled for assessment of venetoclax.

8.1.1 Statistical and Analytical Plans – Main Cohort

Efficacy and safety analyses will be performed on all subjects who receive at least one dose of venetoclax in the main cohort, unless otherwise specified.

For the primary efficacy analyses, statistical significance will be determined by a two-sided p value < 0.05 (one-sided < 0.025).

Detailed analysis descriptions for the main cohort will be provided in a statistical analysis plan.

8.1.1.1 Baseline Parameters

8.1.1.1.1 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.

8.1.1.1.2 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.

8.1.1.1.3 Medical Histories

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

8.1.1.2 Primary Efficacy

8.1.1.2.1 Primary Efficacy Analyses in Main Cohort

The primary efficacy endpoint will be overall response rate (ORR) – the proportion of subjects with an overall response (complete remission, plus complete remission with incomplete bone marrow recovery, plus nodular partial remission, plus partial remission) per the NCI-CWG guidelines as assessed by the Independent Review Committee (IRC) in the first 70 subjects enrolled treated in the main cohort.

The ORR for venetoclax will be tested to reject the null hypothesis of 40%. If the null hypothesis is rejected and the ORR is higher than 40%, then venetoclax has been shown to have an ORR significantly higher than 40%.

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

The assessment of ORR will be performed once 70 subjects in the main cohort have completed the scheduled 36-week disease assessment, have progressed prior to the 36-week disease assessment, discontinued study drug for any reason, or after all treated subjects have discontinued venetoclax, whichever is earlier. Among these 70 subjects, those who have not achieved a CR, CRi, nPR or confirmed PR prior to the cutoff date will be considered to be non-responders.

8.1.1.2.2 Secondary Efficacy Analyses in Main Cohort

Secondary efficacy endpoints will include CR rate, PR rate, duration of overall response, progression-free survival, event free survival, time to progression, time or response, time to 50% reduction in ALC, overall survival, and percent of subjects who move on to stem cell transplant.

CR rate will be defined as the proportion of subjects who achieved a CR or CRi per the NCI-CWG criteria (determined by the IRC in the main cohort). In addition, the 95% confidence interval based on the binomial distribution will be provided. Subjects who do not achieve a CR or CRi will be considered to be non-responders in the calculation of CR rate.

PR rate per the IRC assessment will be defined as the proportion of subjects who achieved a nPR or PR per the NCI-CWG criteria (determined by the IRC in the main cohort). In addition, the 95% confidence interval based on the binomial distribution will be provided. Subjects who do not achieve a nPR or PR will be considered to be non-responders in the calculation of PR rate.

Duration of overall response will be defined as the number of days from the date of first response (CR, CRi, nPR, or PR) (determined by the IRC in the main cohort) to the earliest recurrence or PD per the IRC assessment. 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 not be included in the analysis. Duration of overall response will be analyzed by Kaplan-Meier methodology. Median duration of response will be calculated and the corresponding 95% confidence interval will be presented.

Duration of 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 (determined by the IRC in the main cohort) or death. All disease progression will be included regardless whether the event occurred while the subject was taking the study drug or had previously discontinued the study drug. If the subject does not experience disease progression or death, then the data will be censored at the date of last disease assessment. Data for subjects who receive non-protocol, CLL therapy prior to disease progression will be censored at the last disease assessment prior to receiving non-protocol therapy. Data for subjects without any disease assessments performed after the baseline visit will be censored at the time of enrollment plus 1 day. PFS will be analyzed by Kaplan-Meier methodology. Median time PFS will be calculated and 95% confidence interval for median time PFS will be presented.

Event-free survival (EFS) is defined as the number of days from the date of first dose to the date of earliest disease progression, death, or start of a new anti-leukemic therapy. If the specified event (disease progression, death, start of a new anti-leukemic treatment) does not occur, patients will be censored at the date of last disease assessment. Data for subjects without any disease assessments performed after the baseline visit will be censored at the date of first dose plus 1 day. EFS will be analyzed by Kaplan-Meier methodology. EFS will be calculated and 95% confidence interval for median EFS will be presented.

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

Time to first response will be defined as the number of days from the date of first dose to the date of the first sign of response (CR, CRi, nPR, or PR) given the subject has had a CR, CRi, confirmed nPR or confirmed PR per the 2008 Modified IWCLL NCI-WG criteria. The first response can be an assessment by physical exam as long as the results are later confirmed per the NCI-WG criteria. For subjects who never experience a response, the subject's data will not be included in the analysis. Descriptive statistics (mean, standard deviation, median, and range) and the 95% confidence interval of the mean will be presented.

Time to 50% reduction in ALC will be defined as the number of days (hours if applicable) from the date of first dose to the date when the ALC has reduced to 50% of the baseline

value (as defined in Section 6.0). For subjects who never achieve a 50% reduction in ALC, the subject's data will not be included in the analysis. Descriptive statistics (mean, standard deviation, median, and range) and the 95% confidence interval of the mean 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. Median time survival will be estimated and 95% confidence interval for the median time survival will be presented.

The percent of subjects who move on to stem cell transplant will be summarized and the 95% confidence interval base on the binomial distribution will be provided.

8.1.1.2.3 Supplemental Efficacy in Main Cohort

A supplemental assessment of efficacy will occur when the last subject enrolled in the main cohort has completed the 36-week disease assessment. This assessment will be based on the IRC assessment for all treated subjects in the main cohort.

The following analyses will be provided ORR, CR Rate, PR Rate, DoR, PFS, EFS, TTP, time to response, time to 50% reduction in ALC and MRD response rate. The analysis will be performed as described above in Section 8.1.1.2. Confidence intervals will be presented for each analysis. No statistical tests will be performed on the supplemental assessment of efficacy.

8.1.1.2.4 Timing of Efficacy and Safety Analyses

The date once 70 subjects in the main cohort have completed the scheduled 36-week disease assessment, have progressed prior to the 36-week disease assessment, discontinued study drug for any reason, or after all enrolled subjects have discontinued venetoclax, whichever is earlier, will be defined as the data "cutoff" date for the primary efficacy analyses (ORR, CR rate, PR rate, duration of overall response, PFS, TTP, OS,

and additional exploratory efficacy analyses). Efficacy data (IRC assessment of first 70 subjects treated in the main cohort and investigators' assessment on all treated subjects in the main cohort) and safety data (all treated subjects in the main cohort) up to and including this date will be collected. Exact data cutoff date for all efficacy and safety analyses 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.

When all subjects treated into the main cohort have completed the scheduled 36-week disease assessment, have progressed prior to the 36-week disease assessment, or discontinued study drug for any reason, additional supplemental efficacy assessments based on the IRC review of response will be performed. 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 cohort, the cohort will be considered complete, and all remaining data will be collected and entered into the clinical database. A final efficacy assessment based on investigator assessment (ORR, CR rate, PR rate, duration of overall response, PFS, TTP, OS, and additional exploratory efficacy analyses) will be performed once all subjects from the main cohort have completed/discontinued. No statistical tests will be performed; only descriptive statistics and the 95% confidence interval will be presented.

Overall survival will be collected on all subjects for up to 5 years from the first subject enrolled in the cohort. After all survival data have been collected and entered into the clinical database, a final analysis will be performed on this dataset.

8.1.1.2.5 Pharmacokinetics

Plasma concentrations of venetoclax will be tabulated for each subject by visit.

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. The results from the population pharmacokinetic analysis may not be reported in the clinical study report. Additional analyses may be performed if useful in the interpretation of the data.

8.1.1.2.6 Interim Analyses

Independent Data Monitoring Committee (IDMC)

Safety data, after approximately 20 subjects had completed at least 12 weeks of study treatment in the main cohort, was reviewed by an Independent Data Monitoring Committee (IDMC). A separate charter had been created to provide detailed descriptions of the schedule of the analyses and the IDMC meetings. The IDMC membership, responsibilities and the description of the data coordinating center are documented in the charter. The IDMC received analysis data summary, which included enrollment data, subject baseline characteristics and safety data.

8.1.1.2.7 Additional Exploratory Efficacy Analyses

Time to next anti-CLL treatment (TTNT) 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 treated 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 by MRD-flow. Ninety-five percent (95%) confidence intervals based on the binomial distribution will be

provided. MRD data for this exploratory analysis was based on the MRD flow cytometry data and will not be collected for subjects who continue on in the survival extended access portion of the study. MRD-PCR specimens will be collected and analyzed for subjects who are eligible. This data will not be included in the clinical study report.

Health Economic and Patient Reported Outcome measures will include the MDASI (measure of subject reported symptoms), 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 all scales of the MDASI, 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.

A sensitivity analysis of overall response rate, CR rate, PR rate, duration of overall response, PFS and TTP based on the investigator assessment will be performed using the primary subjects analysis set (first 70 subjects treated) and all subjects treated in the main cohort.

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

8.1.1.3 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 using subjects who take at least one dose of study drug. The safety analysis sets will include all treated subjects in the main cohort, all treated subjects in the safety expansion cohort, all treated subjects with 17p deletion CLL, and all treated subjects in the study (combination of main cohort and safety expansion cohort).

8.1.1.3.1 Adverse Events

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

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

Treatment-emergent adverse events will be summarized by preferred terms within a System and Organ Class according to the most current Medical Dictionary for Regulatory Activities (MedDRA)[43] adverse event coding dictionary. In addition, the percentage of subjects experiencing an adverse event at an NCI CTCAE Version 4.0 toxicity grade, and relationship to study drug will be provided.

8.1.1.3.2 Serious Adverse Events

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

8.1.1.3.3 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.

8.1.1.3.4 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.

8.1.1.3.5 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, 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 1000/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.

8.1.2 Statistical and Analytical Plans for the Safety Expansion Cohort

Safety and efficacy analyses will be performed on all subjects who receive at least one dose of venetoclax in the safety expansion cohort. The analyses for the subjects in the safety expansion cohort will occur when the last subject enrolled in this cohort has been receiving 400 mg of venetoclax for 1 week.

Secondary efficacy analysis will be performed for subjects with central confirmation of 17p deletion and all subjects combined in the safety expansion cohort. All secondary efficacy endpoints will be summarized using the investigator assessment of response. CT scans will be collected by the IRC for archival purposes.

No statistical testing will be performed on the safety expansion cohort.

Detailed analysis descriptions for the safety expansion cohort will be provided in a statistical analysis plan.

8.1.2.1 Baseline Parameters

8.1.2.1.1 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.

8.1.2.1.2 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.

8.1.2.1.3 Medical Histories

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

8.1.3 Safety

The safety of venetoclax for subject enrolled in the safety expansion will be assessed by evaluation of 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.

8.1.3.1 Adverse Events

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

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

Treatment-emergent adverse events will be summarized by preferred terms within a System and Organ Class according to the most current Medical Dictionary for Regulatory Activities (MedDRA)[43] adverse event coding dictionary. In addition, the percentage of subjects experiencing an adverse event at an NCI CTCAE Version 4.0 toxicity grade, and relationship to study drug will be provided.

8.1.3.2 Serious Adverse Events

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

8.1.3.3 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.

8.1.3.4 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.

8.1.3.5 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, 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 1000/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.

8.1.3.6 Assessment of TLS

Analyses of the TLS measures implemented in Safety Expansion Cohort will be performed. Analyses will be performed by risk category and overall for the following analyses:

- TLS-associated adverse events
- TLS-associated adverse events leading to discontinuation, interruption or drug delay

- Laboratory changes (see Appendix F Cairo-Bishop and Howard Definitions of Tumor Lysis Syndrome)

8.1.4 Efficacy Endpoints

The secondary efficacy endpoint for the safety expansion cohort will be ORR, CR rate, PR rate, duration of overall response, event free survival, progression-free survival, time to response, time to 50% reduction in ALC, time to progression, overall survival, time to next anti-CLL treatment (TTNT), MRD negativity rate, and Health Economic and Patient Reported Outcome measures. Determination of disease progression will be based on investigator assessment.

ORR rate will be defined as the proportion of subjects who achieved a CR, CRi, nPR, or PR per the NCI-CWG guidelines. In addition, the 95% confidence interval based on the binomial distribution will be provided. Subjects who do not achieve a CR, CRi, nPR, or PR will be considered to be non-responders in the calculation of ORR rate.

CR rate will be defined as the proportion of subjects who achieved a CR or CRi per the NCI-CWG guidelines. In addition, the 95% confidence interval based on the binomial distribution will be provided. Subjects who do not achieve a CR or CRi will be considered to be non-responders in the calculation of CR rate.

PR rate will be defined as the proportion of subjects who achieved a nPR or PR per the NCI-CWG guidelines. In addition, the 95% confidence interval based on the binomial distribution will be provided. Subjects who do not achieve a nPR or PR will be considered to be non-responders in the calculation of PR rate.

Duration of overall 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 not be included in the analysis. Duration of overall response will be analyzed by Kaplan-Meier

methodology using data for all treated subjects who responded. Median duration of response will be calculated and the corresponding 95% confidence interval will be presented.

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

Event-free survival (EFS) is defined as the number of days from the date of first dose to the date of earliest disease progression, death, or start of a new anti-leukemic therapy. If the specified event (disease progression, death, start of a new anti-leukemic treatment) does not occur, patients will be censored at the date of last disease assessment. Data for subjects without any disease assessments performed after the baseline visit will be censored at the date of first dose plus 1 day. EFS will be analyzed by Kaplan-Meier methodology. EFS will be calculated and 95% confidence interval for median EFS will be presented.

Time to progression (TTP) will be defined as the number of days from the date of first dose to the date of earliest disease progression. All disease progression will be included regardless whether the event occurred while the subject was taking the study drug or had previously discontinued the study drug. If the subject does not experience disease progression, then the data will be censored at the date of last available disease assessment. Data for subjects who receive non-protocol, CLL therapy prior to disease

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

Time to first response will be defined as the number of days from the date of first dose to the date of the first sign of response (CR, CRi, nPR, or PR) given the subject has had a CR, CRi, confirmed nPR or confirmed PR per the 2008 Modified IWCLL NCI-WG criteria. The first response can be an assessment by physical exam as long as the results are later confirmed per the NCI-WG criteria. For subjects who never experience a response, the subject's data will not be included in the analysis. Descriptive statistics (mean, standard deviation, median, and range) and the 95% confidence interval of the mean will be presented.

Time to 50% reduction in ALC will be defined as the number of days (hours if applicable) from the date of first dose to the date when the ALC has reduced to 50% of the baseline value (as defined in Section 6.0). For subjects who never achieve a 50% reduction in ALC, the subject's data will not be included in the analysis. Descriptive statistics (mean, standard deviation, median, and range) and the 95% confidence interval of the mean 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 treated subjects. Median time survival will be estimated and 95% confidence interval for the median time survival will be presented.

The percent of subjects who move on to stem cell transplant will be summarized and the 95% confidence interval base on the binomial distribution will be provided.

8.1.4.1 Additional Exploratory Efficacy Analyses

Time to next anti-CLL treatment (TTNT) 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 treated 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. MRD data for this exploratory analysis was based on the MRD-Flow specimens and will not be collected for subjects who continue on in the survival extended access portion of the study. MRD-PCR specimens will be collected and analyzed for subjects who are eligible. This data will not be included in the final clinical study report.

Health Economic and Patient Reported Outcome measures will include the MDASI (measure of subject reported symptoms), 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 all scales of the MDASI, 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.

8.1.4.2 Timing of Safety Evaluations and Secondary Efficacy Endpoints

The date once all subjects in the safety expansion cohort have completed the dose escalation, or have discontinued venetoclax, whichever is earlier, will be defined as the

data "cutoff" date for the safety analyses. Safety Data up to and including this date will be collected. 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 this cohort.

Once the last enrolled subject discontinues/completes the cohort, the cohort will be considered complete, and all remaining data will be collected and entered into the clinical database. A final safety and efficacy assessment on the subjects treated in the safety expansion cohort will be performed once all subjects have completed/discontinued from the cohort. No statistical testing procedures will be performed and only descriptive statistics and the 95% confidence interval will be presented.

Overall survival will be collected on all subjects for up to 5 years from the first subject enrolled on the cohort. After all survival data have been collected and entered into the clinical database, a final analysis will be performed on this dataset.

8.1.4.3 Pharmacokinetics

Plasma concentrations of venetoclax will be tabulated for each subject by visit.

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. The results from the population pharmacokinetic analysis may not be reported in the clinical study report. Additional analyses may be performed if useful in the interpretation of the data.

8.1.4.4 Independent Data Monitoring Committee

Interim analysis results will be reviewed by the IDMC after approximately 20 subjects have completed approximately 2 – 3 weeks of the lead-in period in the safety expansion cohort.

8.2 Determination of Sample Size

Approximately 100 subjects will be enrolled in the main cohort to assess the safety and efficacy of venetoclax in subjects with relapsed or refractory chronic lymphocytic leukemia (CLL) harboring the 17p deletion. With this sample size, if a rare adverse event occurs at a rate of 2%, then the probability of observing at least 1 event in a trial with 100 subjects is 86%.

Assuming a peak enrollment rate of 0.11 subjects/site/month, it is anticipated that approximately 100 subjects will be enrolled during the 14 month enrollment phase. The primary assessment of the efficacy of venetoclax will occur around Month 19 at which time 70 subjects should have had their 36-week disease assessment. The final efficacy summary will occur around Month 38 (two years after last subject enrolled).

Overall response rates for CLL subjects with 17p deletion range from approximately 7% to 77% with the higher responses in alternative but also more toxic regimens such as alemtuzumab + steroids.[24] Conventional therapies such as FCR and BR, demonstrated ORRs of 35% and 7%, respectively. Therefore, a therapy providing significant benefit in overall response rate over a standard rate of 40% would be considered clinically meaningful.

Performing the efficacy analyses at 70 subjects provides at least 90% power (at 2-sided alpha of 5%) to reject the null hypothesis of 40% ORR in favor of an alternative hypothesis of 60% ORR. The power calculations for a range of different sample sizes are presented in Table 11.

Table 11. Sample Size Calculation

Subjects (N)	Power (%)
50	76
60	82
70	90
80	93
90	96

For the safety expansion cohort, an additional 50 subjects with relapsed/refractory or previously untreated chronic lymphocytic leukemia (CLL) harboring the 17p deletion will be enrolled to assess the modifications made to the initial dosing of venetoclax for the management of TLS. With this sample size, if a TLS event occurs at a rate of 2%, then the probability of observing at least 1 event in this cohort of 50 subjects is 64%.

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.

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.

Pharmacogenetic analysis and a portion of the pharmacodynamic analyses will only be performed if the subject has voluntarily signed and dated the 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 informed consent must be signed before pharmacogenetic and/or pharmacodynamic testing is performed. If the subject does not

consent to pharmacogenetic and/or the optional pharmacodynamic 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 Electronic Case Report Forms

Electronic case report forms (eCRF) must be completed for each subject enrolled in this study. These forms will be used to transmit information collected during the study to AbbVie and regulatory authorities, as applicable. The eCRF 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 (Medidata). The EDC system and the study specific electronic case report forms will be in compliance 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. 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 an audit trail that 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/her electronic signature and date to the 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 the investigative sites at the end of the site's participation in the study. Data from the EDC system will be archived on appropriate data media (CD-ROM, etc.) and provided to the investigator at that time as a durable record of the site's eCRF data. It will be possible for the investigator to make paper printouts from that media.

11.0 Data Quality Assurance

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 a central laboratory. The data from these analyses will be electronically transferred from the central laboratory to the study database.

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 and/or any research performed on the biomarker samples from this study will be experimental in nature. Hence, neither the investigator, the subject nor the subject's physician (if different than the investigator) will be informed of individual subject pharmacogenetic or biomarker results, should analyses be performed, nor will anyone not directly involved in this research. Correspondingly, genetic and biomarker 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 and exploratory research information from this study may also be used in scientific publications or presented at medical conventions. Pharmacogenetic and biomarker 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 Medicines Agency (EMA) Guidance on Investigator's Signature for Study Reports.

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

14.0 Investigator's Agreement

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

Protocol Title:	A Phase 2 Open-Label Study of the Efficacy of ABT-199 (GDC-0199) in Subjects with Relapsed/Refractory or Previously Untreated Chronic Lymphocytic Leukemia Harboring the 17p Deletion
Protocol Date:	28 February 2017

Signature of Principal Investigator _____ Date _____

Name of Principal Investigator (printed or typed) _____

15.0 Reference List

1. Willis S, Day CL, Hinds MG, et al. The Bcl-2-regulated apoptotic pathway. J Cell Sci. 2003;116(Pt 20):4053-6.
2. Cory S, Adams JM. The Bcl-2 family: regulators of the cellular life-or-death switch. Nature Reviews. Cancer. 2002;2:647-656.
3. Borner C. The Bcl-2 protein family: sensors and checkpoints for life-or-death decisions. Molecular Immunology. 2003;39:615-647.
4. Cory S, Huang DCS, Adam JM. The Bcl-2 family: roles in cell survival and oncogenesis. Oncogene. 2003;22:8590-8607.
5. Cimmino A, Calin GA, Fabbri M, et al. miR-15 and miR-16 induce apoptosis by targeting BCL2. Proc Natl Acad Sci USA. 2005;102(39):13944-9.
6. Calin GA, Cimmino A, Fabbri M, et al. MiR-15a and miR-16-1 cluster functions in human leukemia. Proc Natl Acad Sci. 2008;105(13):5166-71.
7. Souers AJ, Leverson JD, Boghaert ER, et al. ABT-199, a potent and selective BCL-2 inhibitor, achieves antitumor activity while sparing platelets. Nat Med. 2013;19(2):202-8.
8. Marsden VS, Strasser A. Control of apoptosis in the immune system: Bcl-2, BH3 only proteins and more. Annu Rev Immunol. 2003;21:71-104.
9. Wilson H, O'Connor A, Czuczman S, et al. Phase 1/2a study of navitoclax (ABT-263) in relapsed or refractory lymphoid malignancies. Haematologica. 2010;95(s2):116-7.
10. AbbVie. ABT-199 Investigator's Brochure Edition 8. 15 February 2017.
11. Jaglowski S, Jones JA. Choosing first-line therapy for chronic lymphocytic leukemia. Expert Rev Anticancer Ther. 2011;11(9):1379-90.
12. Zwiebel JA, Cheson BD. Chronic lymphocytic leukemia: staging and prognostic factors. Semin Oncol. 1998;25:42-59.

13. Ries LAG, Harkins D, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2003. Bethesda, MD: National Cancer Institute [based on November 2005 SEER data submission, posted to the SEER Web site, 2006].

14. Sant M, Allemani C, Tereanu C, et al. Incidence of hematologic malignancies in Europe by morphologic subtype: results of the HAEMACARE project. Blood. 2010;116(19):3724-35.

15. Jemal A, Clegg LX, Ward E, et al. Annual report to the nation on the status of cancer, 1975-2001, with a special feature regarding survival. Cancer. 2004;101(1):3-27.

16. Francis S, Karanth M, Pratt G, et al. The effect of immunoglobulin VH gene mutation status and other prognostic factors on the incidence of major infections in patients with chronic lymphocytic leukemia. Cancer. 2006;107(5):1023-33.

17. Döhner H, Stilgenbauer S, Benner A, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. N Engl J Med. 2000;343(26):1910-6.

18. Stilgenbauer S, Zenz T. Understanding and managing ultra high-risk chronic lymphocytic leukemia. Hematology Am Soc Hematol Educ Program. 2010;2010:481-8.

19. Geisler CH, Phillip P, Christensen BE, et al. In B-cell chronic lymphocytic leukemia chromosome 17 abnormalities and not trisomy 12 are the single most important cytogenetic abnormalities for the prognosis: a cytogenetic and immunophenotypic study of 480 unselected newly diagnosed patients. Leuk Res. 1997;21:1011-23.

20. Byrd JC, Gribben JG, Peterson BL, et al. Select high-risk genetic features predict earlier progression after chemoimmunotherapy with fludarabine and rituximab in chronic lymphocytic leukemia: justification for risk-adapted therapy. J Clin Oncol. 2006;24:437-43.

21. Badoux XC, Keating MJ, Wang X, et al. Fludarabine, cyclophosphamide, and rituximab chemoimmunotherapy is highly effective treatment for relapsed patients with CLL. Blood. 2011;117(11):3016-24.

22. Wierda WG, Kipps TJ, Mayer J. Ofatumumab as single-agent CD20 immunotherapy in fludarabine-refractory chronic lymphocytic leukemia. J Clin Oncol. 2010;28(10):1749-55.

23. Stilgenbauer S, Zenz T, Winkler D. German Chronic Lymphocytic Leukemia Study Group. Subcutaneous alemtuzumab in fludarabine-refractory chronic lymphocytic leukemia: clinical results and prognostic marker analyses from the CLL2H study of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol. 2009;27(24):3994-4001.

24. Pettitt AR, Jackson R, Carruthers S, et al. Alemtuzumab in combination with methylprednisolone is a highly effective induction regimen for patients with chronic lymphocytic leukemia and deletion of TP53: final results of the National Cancer Research Institute CLL206 trial. J Clin Oncol. 2012;30(14):1647-55.

25. Fischer K, Cramer P, Busch R, et al. Bendamustine combined with rituximab in patients with relapsed and/or refractory chronic lymphocytic leukemia: a multicenter Phase II trial of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol. 2011;29:3559-66.

26. Eichorst B, Dreyling M, Robak T, et al. Chronic lymphocytic leukemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2011;22 (Suppl 6):vi504.

27. National Comprehensive Cancer Network. Available from: www.nccn.org/professionals/physician_gls/f_guidelines.asp.

28. Schnaiter A, Stilgenbauer S. 17p deletion in chronic lymphocytic leukemia: risk stratification and therapeutic approach. Hematol Oncol Clin North Am. 2013;27(2):289-301.

29. Zhu HJ, Liu L, Fan L, et al. The BH3-only protein Puma plays an essential role in p53-mediated apoptosis of chronic lymphocytic leukemia cells. Leuk Lymphoma. 2013;54(12):2712-9.

30. Mackus WJ, Kater AP, Grummels A, et al. Chronic lymphocytic leukemia cells display p53-dependent drug-induced Puma upregulation. Leukemia. 2005;19(3):427-34.

31. Badoux XC, Keating M, O'Brien S, et al. Patients with relapsed CLL and 17p deletion by FISH have very poor survival outcomes. In: Abstracts of the American Society of Hematology 51st Annual Meeting, December 5-8, 2009; New Orleans, Louisiana, USA. Blood. 2009;114(22):3-1587. Abstract 1248.

32. Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol. 2006;24(19):3187-205.

33. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5(6):649-55.

34. Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute–Working Group 1996 guidelines. Blood. 2008;111(12):5446-56.

35. Böttcher S, Ritgen M, Fischer K, et al. Minimal residual disease quantification is an independent predictor of progression-free and overall survival in chronic lymphocytic leukemia: a multivariate analysis from the randomized GCLLSG CLL8 trial. J Clin Oncol. 2012;30(9):980-8.

36. Vysis CLL CDx FISH Kit List No. 07N67-020.

37. MDASI; Cleeland et al., 2000.

38. MDASI-CLL: http://www3.mdanderson.org/depts/symptomresearch.

39. http://www.mdanderson.org/education-and-research/departments-programs-and-labs/departments-and-divisions/symptom-research/symptom-assessment-tools/m-d-anderson-symptom-inventory.html.

40. EORTC QLQ-C30 and EORTC QLQ CLL16: http://groups.eortc.be/qol.

41. EQ-5D-5L and EQ-5D-VAS: http://www.euroqol.org.

42. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE), v4.0, NCI, NIH, DHHS. 28 May 2009. Available from: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Accessed on: 09 September 2010.

43. Coding Guidelines for MedDRA Term Selection, AbbVie Global Pharmaceutical Research and Development (GPRD), Global Pharmacovigilance and Clinical Project Team, current version on file at AbbVie.

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]		Statistics
		Clinical
		Clinical
		Global Drug Supply Management
		Clinical
		Biomarkers
		Pharmacokinetics
		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, azithromycin, 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) should be contacted/consulted (per institutional standards to ensure emergency dialysis is available) on admission for any subject hospitalized prophylactically or in response to laboratory changes.
- IV fluids (e.g., D5 1/2 normal saline) should be initiated at a rate of at least 1 mL/kg/hr rounded to the nearest 10 mL (target 150 to 200 mL/hr; not < 50 mL/hr). Modification of fluid rate should also be considered for individuals with specific medical needs.
- Monitor for symptoms or signs of TLS (e.g., fever, chills, tachycardia, nausea, vomiting, diarrhea, diaphoresis, hypotension, muscle aches, weakness, paresthesias, mental status changes, confusion and seizures). If any clinical features are observed, recheck potassium, phosphorus, uric acid, calcium and creatinine within 1 hour STAT.
- Vital signs should be taken at time of all blood draws or any intervention.
- The management recommendations below focus on the minimum initial responses required. If a diagnosis of TLS is established, ongoing intensive monitoring and multi-disciplinary management will be per institutional protocols.

In addition to the recommendations in the table below, for subjects receiving the first dose of venetoclax:

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

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

Abnormality	Management Recommendations
Hyperkalemia (Including Rapidly Rising Potassium) (continued)	
Potassium ≥ 6.0 mmol/L (6.0 mEq/L) and/or symptomatic (e.g., muscle cramps, weakness, paresthesias, nausea, vomiting, diarrhea)	• 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 IV push. o If sodium bicarbonate is used, rasburicase should not be used as this may exacerbate calcium phosphate precipitation. • Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. Do not administer in same IV line as sodium bicarbonate. • Recheck potassium, phosphorus, uric acid, calcium and creatinine every hour STAT.
Hyperuricemia	
Uric acid ≥ 8.0 mg/dL (476 µmol/L)	• Consider rasburicase (dose based on local guidelines and/or institutional standards). o If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hr STAT.
Uric acid ≥ 10 mg/dL (595 µmol/L) OR Uric acid ≥ 8.0 mg/dL (476 µmol/L) with 25% increase and creatinine increase ≥ 0.3 mg/dL (≥ 0.027 mmol/L) from pre-dose level	• Administer rasburicase (dose based on local guidelines and/or institutional standards). o When rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Notify nephrology (or other acute dialysis service). • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. o If uric acid < 8.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hrs., later, if no other evidence of tumor lysis.

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

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)
Second primary cancers, all types
Fatigue
Unexplained weight loss
Pyrexia
Bruising
Minor hemorrhages
Pain, all types
Malignant neoplasm progression, including death

Population-Related Comorbidities

Hypertension
Rheumatoid arthritis/osteoarthritis
Hyperlipidemia
Peptic ulcer
Inflammatory bowel disease
Coronary artery disease

Peripheral vascular disease
Cardiomyopathy
Valvular disease
Atrial fibrillation
Diabetes mellitus
Chronic obstructive pulmonary disease
Cerebrovascular accident
Transient ischemia attack

Appendix F. Cairo-Bishop and Howard Definitions of Tumor Lysis Syndrome

Table 12. Cairo-Bishop Clinical Tumor Lysis Syndrome Definition and Grading

	Grade					
Complication	**0**	**1**	**2**	**3**	**4**	**5**
Creatinine*,†	≤ 1.5 × ULN	1.5 × ULN	1.5 – 3.0 × ULN	> 3.0 – 6.0 × ULN	> 6.0 × ULN	Death
Cardiac Arrhythmia*	None	Intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with device (e.g., defibrillator)	Life-threatening (e.g., arrhythmia associated with CHF, hypotension, syncope, shock)	Death
Seizure*	None	–	One brief, generalized seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL	Seizure in which consciousness is altered; poorly controlled seizure disorder; with breakthrough generalized seizures despite medical intervention	Seizure of any kind which are prolonged, repetitive or difficult to control (e.g., status epilepticus, intractable epilepsy)	Death

ULN = upper limit of normal; CHF = congestive heart failure; ADL = activities of daily living

* Not directly or probably attributable to therapeutic agent.

† If no institutional ULN is specified, age/sex ULN creatinine may be defined as follows: Cairo-Bishop Clinical Tumor Lysis Syndrome Definition and Grading.

Note: Laboratory tumor lysis syndrome and at least one clinical complication.

Table 13. Cairo-Bishop Definition of Laboratory Tumor Lysis Syndrome

This definition comprises ≥ 2 of the following metabolic abnormalities occurring within 7 days from first dose at initial dosing or at dose escalation.

Element	Value	Change from Baseline
Uric Acid	≥ 476 µmol/L or 8 mg/dL	25% increase
Potassium	≥ 6.0 mmol/L or 6 mEq/L	25% increase
Inorganic Phosphorus	≥ 1.45 mmol/L	25% increase
Calcium	≤ 1.75 mmol/L	25% decrease

Table 14. Howard Definition of Laboratory Tumor Lysis Syndrome

This definition comprises ≥ 2 of the following metabolic abnormalities.

Element	Value
Uric Acid	≥ 476 µmol/L or 8 mg/dL
Potassium	≥ 6.0 mmol/L or 6 mEq/L
Inorganic Phosphorus	≥ 1.45 mmol/L
Calcium	≤ 1.75 mmol/L

Appendix G. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes:

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

Sponsor/Emergency Contact:	[redacted]	Phone: [redacted] Cell: Fax:
	AbbVie 1 North Waukegan Road North Chicago, IL 60064	

Has been changed to read:

Sponsor/Emergency Contact:	[redacted]	Phone: [redacted] Cell: Fax:
	AbbVie 1 North Waukegan Road North Chicago, IL 60064	

Section 1.2 Synopsis
Subsection Exploratory objectives (both main and safety expansion cohorts):
Add: new last paragraph

Note: All study objectives, with the exception of Safety and MRD analyses, will cease to be evaluated beyond 2 years after last subject first dose.

Section 1.2 Synopsis
Subsection Survival Assessments:
Previously read:

Survival information will be collected every 3 months for up to 5 years after the last subject has been enrolled for subjects who have not withdrawn consent.

Has been changed to read:

Survival information will be collected every 3 months (± 7 days) for up to 5 years after the last subject has been enrolled for subjects who have not withdrawn consent.

Section 1.2 Synopsis
Subsection Survival – Extended Access:
Add: new subsection title and text

Survival – Extended Access: For subjects who continue to derive benefit from venetoclax treatment 2 years following the date of the last subject enrolled, AbbVie will provide venetoclax until the subject develops disease progression or until 5 years following the date of last subject enrolled (12 May 2020).

Section 3.0 Introduction
Subsection Venetoclax Clinical Exposure
First paragraph previously read:

As of 28 November 2015, on the basis of data available 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, 102 had AML. An additional 66 subjects were healthy volunteers. A total of 564 oncology subjects received the drug as monotherapy, 933 received the drug in combination with other therapies, and 1 subject received venetoclax as a single dose in a DDI study and did not re-enroll into a subsequent monotherapy study. Additionally, 98 subjects were exposed to at least 1 dose of venetoclax in the AbbVie immunology study, Study M13-093, as of 28 November 2015.

Has been changed to read:

As of 28 November 2016, on the basis of data available in the AbbVie and Genentech/Roche clinical databases, a total of 2573 subjects have been exposed to at least

1 dose of venetoclax in the oncology development programs. Of these 2573, 1429 subjects had CLL/small lymphocytic leukemia (SLL), 637 subjects had NHL, 180 subjects had MM, and 327 had AML. An additional 114 subjects were healthy volunteers. A total of 749 oncology subjects received the drug as monotherapy, and 1922 received the drug in combination with other therapies.

Section 5.1 Overall Study Design and Plan: Description
Subsection Main and Safety Expansion Cohorts
Heading "Post-Treatment Follow-Up Visit(s)"
Add: new last paragraph

Note: *Effective with protocol Amendment 6, subjects being followed in Post-Treatment as of 12 May 2017 will switch to being assessed per the Survival Assessments below. No new subjects will enter the Post-Treatment period.*

Section 5.1 Overall Study Design and Plan: Description
Subsection Main and Safety Expansion Cohorts
Heading "Survival Assessment(s)" previously read:

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 for subjects who have not withdrawn consent.

Has been changed to read:

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 (±7 days) intervals after the last study visit for a period of 5 years after the last subject has enrolled on the study for subjects who have not withdrawn consent.

Section 5.1 Overall Study Design and Plan: Description
Subsection Main and Safety Expansion Cohorts
Heading "Option to Continue Venetoclax Treatment" previously read:
Heading title and text previously read:

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). For subjects that continue to derive benefit after 2 years of treatment following the date of the last subject enrolled, AbbVie will work with the investigator to evaluate options for continuation of venetoclax. In countries where venetoclax is not commercially available, the Study M13-982 will be extended to provide subjects with the opportunity to continue on venetoclax until alternative options become available.

Has been changed to read:

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. Please see Section 5.4.1 for additional information.

Survival – Extended Access

For subjects who continue to derive benefit from venetoclax treatment 2 years following the date of the last subject enrolled, AbbVie will provide venetoclax for monotherapy use until the subject develops disease progression or until 5 years following the date of last subject enrolled (12 May 2020). In countries where venetoclax is commercially available, subjects have the option to discontinue receiving venetoclax via the study and switch to commercial supply at any time but may be contacted every 12 weeks (± 7 days) to collect the Survival information noted above, provided they have not withdrawn consent.

For subjects continuing into the Survival Extended Access portion of the trial, venetoclax will be dispensed at the Final Visit, and Survival visits will begin 12 weeks (± 7 days) following the 30-day Safety Follow-Up Visit. Survival visits will include collection of Survival information, AEs/SAEs and concomitant medication information, study drug administration, collection and dispensing of subject diaries, and MRD PCR sample collection for eligible subjects. All other procedures for disease assessments will be performed as standard of care.

Table 2. Excluded and Cautionary Medications/Food Items
Previously read:

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**
  o 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 at least by 2-fold for moderate inhibitors and at least by 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**
  o 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 • **Coumarins (vitamin K antagonists) or warfarin or phenprocoumon*** • **Weak CYP3A inducers** • **Weak CYP3A inhibitors** • **P-gp substrates** • **BCRP substrates** • **OATP1B1/1B3 substrates** • **P-gp inhibitors** • **BCRP inhibitors** • **OATP1B1/B3 inhibitors**

* Closely monitor international normalized ratio (INR).

Has been changed to read:

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** o Excluded 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 at least by 2-fold for moderate inhibitors and at least by 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** o 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 • **Coumarins (vitamin K antagonists) or warfarin or phenprocoumon*** • **P-gp substrates**** • **BCRP substrates** • **OATP1B1/1B3 substrates** • **BCRP inhibitors**

* Closely monitor international normalized ratio (INR).

** If a narrow therapeutic index P-gp substrate must be used, it should be taken at least 6 hours before venetoclax.

Table 4. Study Activities
Previously read:

Activity	Scr[a]	Within 72 Hours Prior to 1st Dose[b]	W1 D1[b]	W1 D2	W2 D1[b]	W2 D2	W3 D1[b]	W3 D2	W4 D1	W4 D2	W5 D1	W5 D2	W8 D1	W 12 D1	W 16 D1	W 20 D1	W 24 D1	W 28 D1	W 32 D1	Every 12 Wks Starting with Wk 36	8 Wks After 1st CR, CRi, or PR	FV	30-Day Safety Visit	Post-Treat[c]
Informed Consent	X																							
Detection of 17p Deletion[d]	X																							
Medical History/ Oncology History Assessment	X		X																					
Adverse Event/ Concomitant Medication Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Examination[e]*	X		X		X		X		X		X		X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs*	X		X		X		X		X		X		X	X	X	X	X	X	X	X		X	X	X
ECOG Performance Status*	X		X		X		X		X		X		X	X	X	X	X	X	X	X		X	X	

Activity	Scr[a]	Within 72 Hours Prior to 1st Dose[b]	W1 D1[b]	W1 D2	W2 D1[b]	W2 D2	W3 D1[b]	W3 D2	W4 D1	W4 D2	W5 D1	W5 D2	W8 D1	W 12 D1	W 16 D1	W 20 D1	W 24 D1	W 28 D1	W 32 D1	Every 12 Wks Starting with Wk 36	8 Wks After 1st CR, CRi, or PR	FV	30-Day Safety Visit	Post-Treat[c]
Pregnancy Test[f]	X		X																					
Hematology/ Chemistry[g]	X	X	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X**	X**	X**	X**	X**	X**	X**	X**	X**	X**	X**	X**
Coagulation Panel**	X													X			X					X	X	X
Urinalysis**	X																X					X		
Viral Serologies	X																							
Viral Polymerase Chain Reaction	X																							
Quantitative Immuno-globulin**	X													X			X					X	X	
Lymphocyte Enumera-tion**	X										X			X			X			X		X		
ECG	X																					X		

Activity	Scr[a]	Within 72 Hours Prior to 1st Dose[b]	W1 D1[b]	W1 D2	W2 D1[b]	W2 D2	W3 D1[b]	W3 D2	W4 D1	W4 D2	W5 D1	W5 D2	W8 D1	W 12 D1	W 16 D1	W 20 D1	W 24 D1	W 28 D1	W 32 D1	Every 12 Wks Starting with Wk 36	8 Wks After 1st CR, CRi, or PR	FV	30-Day Safety Visit	Post-Treat[c]
Echocardio-gram or a Multi Gated Acquisition Scan (MUGA)[i]	X																							
CT or MRI Scan[j]***	X																			X[k]	X[l]	X		X[m]
Bone Marrow Aspirate and Biopsy	X[n]																			X[o]	X[o]	X		
Disease Assessments*	X[p]										X		X	X	X	X	X	X	X	X	X	X		X
MRD Assessment																				X[q]	X[q]			
Survival Assessment																								X

Activity	Scr[a]	Within 72 Hours Prior to 1st Dose[b]	W1 D1[b]	W1 D2	W2 D1[b]	W2 D2	W3 D1[b]	W3 D2	W4 D1	W4 D2	W5 D1	W5 D2	W8 D1	W 12 D1	W 16 D1	W 20 D1	W 24 D1	W 28 D1	W 32 D1	Every 12 Wks Starting with Wk 36	8 Wks After 1st CR, CRi, or PR	FV	30-Day Safety Visit	Post-Treat[c]
Dispense/ Collect Venetoclax and Subject Calendars/ Diaries			X	X	X		X		X		X		X	X	X	X	X	X	X	X				
MDASI[r]			X								X			X			X			X		X		
EORTC QLQ-C30 and EORTC QLQ CLL16[r]			X								X			X			X			X		X		X
EQ-5D-5L and EQ-5D-VAS[r]			X								X			X			X			X		X		
Subject TL Survey[s]					X																			

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

Study Windows:

* within 72 hours before or after scheduled visit starting with Week 8 Day 1;

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

*** within 7 days after scheduled visit.

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

b. All subjects must receive tumor lysis prophylaxis prior to and during treatment. For details on tumor lysis prophylaxis and management, refer to Section 6.8.1, Prophylaxis and Management of Tumor Lysis Syndrome and Appendix D – Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome (TLS).
c. Assessments will be collected at 3 month intervals after the last study visit for a period of 5 years after the last subject has enrolled in the study.
d. Subjects must have 17p deletion as assessed by local or central laboratory to be considered for enrollment. A result obtained prior to study Screening may be used for eligibility. A confirmatory sample will be sent to central laboratory at Screening. Refer to Section 5.3.1.5, Collection and Handling of Biomarker Variables, for more details.
e. A complete physical examination will be performed at Screening. A symptom directed physical examination will be performed on Day 1 of Weeks 2 – 4 and the 30-day Safety Visit. All other physical examinations will be targeted. If during physical examination, signs or symptoms suggestive of Richter's Syndrome are observed, further assessments (e.g., lymph node biopsy, PET scan) should be considered to exclude or confirm the transformation. Refer to Section 5.3.1.1 Physical Examination, for more details.
f. For females of childbearing potential, a urine pregnancy test must be obtained and processed locally at the Week 1 Day 1, if it has been > 7 days since obtaining the serum pregnancy results at Screening.
g. Cholesterol and triglycerides are only required at Screening and Final Visit.
h. There is no 72 hour window for these samples. Refer to Section 6.8.1, Prophylaxis and Management of Tumor Lysis Syndrome and Appendix D – Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome (TLS).
i. 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.
j. 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 scan and/or bone marrow biopsy must be performed within 2 weeks to confirm or rule out PD as described in Section 5.3.3.2.
k. Imaging assessments are required for all subjects at Week 36 Day 1. Assessment to be performed on Week 36 Day 1 **only** (not every 12 weeks). The Week 36 scan may be performed within 4 weeks before or after the 36 week scheduled visit provided that it has been at least 8 weeks since the subject's last scan.
l. After a response is determined by clinical criteria, a CT scan will be performed no earlier than 8 weeks for confirmation of response. For determination of CR/CRi, both the CT scan and bone marrow are required to be negative. It is recommended that the CT scan is performed first, and if it does confirm a CR/CRi, then a BM biopsy should be obtained as soon as possible.
m. Post-treatment CT or MRI scans to be done only if collected by the site as part of standard of care.
n. A bone marrow aspirate and biopsy will be performed and assessed locally at Screening (within 35 days prior to the first dose of study drug). Bone marrow and aspirate for biomarker sample collection should be split from this sample. Refer to Table 6.

o. 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 not performed at the time of the confirmatory CT, then it should be performed after the Week 36 Day 1 CT scan.

p. At baseline, all measurable disease must be documented at screening by laboratory testing, physical examination and CT scans (or MRI if CT is medically contraindicated), and bone marrow examinations.

q. Specimens (bone marrow aspirate and peripheral blood) for MRD analysis should be collected at the same time as the bone marrow aspirate and biopsy performed for tumor assessments to confirm the CR/CRi. If MRD negativity is achieved in the bone marrow no further MRD analyses are required. Otherwise, MRD should be assessed at 12-week intervals thereafter (in peripheral blood) until MRD negativity is achieved. Once MRD negativity is achieved and confirmed in peripheral blood (e.g., two MRD negative consecutive peripheral blood samples), a bone marrow aspirate specimen will again be collected for analysis of MRD levels to confirm the peripheral blood negativity. 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 and MRD assessment. If a bone marrow and MRD assessment was not performed at the time of the confirmatory CT scan, then they should be performed after the Week 36 Day 1 CT scan. If MRD negativity is achieved in the bone marrow no further MRD analyses are required. Otherwise, MRD should be assessed at 12-week intervals thereafter (in peripheral blood) until MRD negativity is achieved. Once MRD negativity is achieved and confirmed in peripheral blood (e.g., two MRD negative consecutive peripheral blood samples), a bone marrow aspirate specimen will again be collected for analysis of MRD levels to confirm the peripheral blood negativity.

r. 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.

s. For subjects in the United States only: Subjects in the safety expansion cohort will be asked to complete a survey assessing the information they were provided for the Patient Information Card and the Tumor Lysis Syndrome Patient Information Brochure at Week 2 Day 1 or the next scheduled visit. For subjects participating in the main cohort, the survey will be given to the subject at the next scheduled study visit upon signing the Protocol Amendment 2 Informed Consent. This survey is optional.

Has been changed to read:

Activity	Scr[a]	Within 72 Hours Prior to 1st Dose[b]	W1 D1[b]	W1 D2	W2 D1[b]	W2 D2	W3 D1[b]	W3 D2	W4 D1	W4 D2	W5 D1	W5 D2	W8 D1	W 12 D1	W 16 D1	W 20 D1	W 24 D1	W 28 D1	W 32 D1	Every 12 Wks Starting with Wk 36	8 Wks After 1st CR, CRi, or PR	FV	30-Day Safety Visit	Post-Treat[c]	Survival Follow-Up[t]
Informed Consent	X																								
Detection of 17p Deletion[d]	X																								
Medical History/ Oncology History Assessment	X		X																						
Adverse Event/ Concomitant Medication Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Physical Examination[e]*	X		X		X		X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs*	X		X		X		X		X		X		X	X	X	X	X	X	X	X		X	X	X	
ECOG Performance Status*	X		X		X		X		X		X		X	X	X	X	X	X	X	X		X	X		

Activity	Scr[a]	Within 72 Hours Prior to 1st Dose[b]	W1 D1[b]	W1 D2	W2 D1[b]	W2 D2	W3 D1[b]	W3 D2	W4 D1	W4 D2	W5 D1	W5 D2	W8 D1	W 12 D1	W 16 D1	W 20 D1	W 24 D1	W 28 D1	W 32 D1	Every 12 Wks Starting with Wk 36	8 Wks After 1st CR, CRi, or PR	FV	30-Day Safety Visit	Post-Treat[c]	Survival Follow-Up[t]
Pregnancy Test[f]	X		X																						
Hematology/ Chemistry[g]	X	X	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X**	X**	X**	X**	X**	X**	X**	X**	X**	X**	X**	X**	
Coagulation Panel**	X													X			X					X	X	X	
Urinalysis**	X																X					X			
Viral Serologies	X																								
Viral Polymerase Chain Reaction	X																								
Quantitative Immuno-globulin**	X													X			X					X	X		
Lymphocyte Enumera-tion**	X										X			X			X			X		X			
ECG	X																					X			

Activity	Scr[a]	Within 72 Hours Prior to 1st Dose[b]	W1 D1[b]	W1 D2	W2 D1[b]	W2 D2	W3 D1[b]	W3 D2	W4 D1	W4 D2	W5 D1	W5 D2	W8 D1	W 12 D1	W 16 D1	W 20 D1	W 24 D1	W 28 D1	W 32 D1	Every 12 Wks Starting with Wk 36	8 Wks After 1st CR, CRi, or PR	FV	30-Day Safety Visit	Post-Treat[c]	Survival Follow-Up[t]
Echocardio-gram or a Multi Gated Acquisition Scan (MUGA)[i]	X																								
CT or MRI Scan[j]***	X																			X[k]	X[l]	X		X[m]	
Bone Marrow Aspirate and Biopsy	X[n]																			X[o]	X[o]	X			
Disease Assessments*	X[p]										X		X	X	X	X	X	X	X	X	X	X		X	
MRD Assessment																				X[q]	X[q]				X
Survival Assessment†																								X	X
Dispense/ Collect Venetoclax and Subject Calendars/ Diaries			X	X	X		X		X		X		X	X	X	X	X	X	X	X					X

Activity	Scr[a]	Within 72 Hours Prior to 1st Dose[b]	W1 D1[b]	W1 D2	W2 D1[b]	W2 D2	W3 D1[b]	W3 D2	W4 D1	W4 D2	W5 D1	W5 D2	W8 D1	W 12 D1	W 16 D1	W 20 D1	W 24 D1	W 28 D1	W 32 D1	Every 12 Wks Starting with Wk 36	8 Wks After 1st CR, CRi, or PR	FV	30-Day Safety Visit	Post-Treat[c]	Survival Follow-Up[t]
MDASI[r]			X								X			X			X			X		X			
EORTC QLQ-C30 and EORTC QLQ CLL16[r]			X								X			X			X			X		X		X	
EQ-5D-5L and EQ-5D-VAS[r]			X								X			X			X			X		X			
Subject TL Survey[s]					X																				

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

Study Windows:

* within 72 hours before or after scheduled visit starting with Week 8 Day 1;

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

*** within 7 days after scheduled visit.

† within ± 7 days of scheduled visit.

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

b. All subjects must receive tumor lysis prophylaxis prior to and during treatment. For details on tumor lysis prophylaxis and management, refer to Section 6.1.8.1, Prophylaxis and Management of Tumor Lysis Syndrome and Appendix D – Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome (TLS).

c. Assessments will be collected at 3 month intervals after the last study visit for a period of 5 years after the last subject has enrolled in the study.

d. Subjects must have 17p deletion as assessed by local or central laboratory to be considered for enrollment. A result obtained prior to study Screening may be used for eligibility. A confirmatory sample will be sent to central laboratory at Screening. Refer to Section 5.3.1.5, Collection and Handling of Biomarker Variables, for more details.

e. A complete physical examination will be performed at Screening. A symptom directed physical examination will be performed on Day 1 of Weeks 2 – 4 and the 30-day Safety Visit. All other physical examinations will be targeted. If during physical examination, signs or symptoms suggestive of Richter's Syndrome are observed, further assessments (e.g., lymph node biopsy, PET scan) should be considered to exclude or confirm the transformation. Refer to Section 5.3.1.1 Physical Examination, for more details.

f. For females of childbearing potential, a urine pregnancy test must be obtained and processed locally at the Week 1 Day 1, if it has been > 7 days since obtaining the serum pregnancy results at Screening.

g. Cholesterol and triglycerides are only required at Screening and Final Visit.

h. There is no 72 hour window for these samples. Refer to Section 6.1.8.1, Prophylaxis and Management of Tumor Lysis Syndrome and Appendix D – Recommendations for Initial Management of Electrolyte Abnormalities and Prevention of Tumor Lysis Syndrome (TLS).

i. 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.

j. 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 scan and/or bone marrow biopsy must be performed within 2 weeks to confirm or rule out PD as described in Section 5.3.3.2.

k. Imaging assessments are required for all subjects at Week 36 Day 1. Assessment to be performed on Week 36 Day 1 **only** (not every 12 weeks). The Week 36 scan may be performed within 4 weeks before or after the 36 week scheduled visit provided that it has been at least 8 weeks since the subject's last scan.

l. After a response is determined by clinical criteria, a CT scan will be performed no earlier than 8 weeks for confirmation of response. For determination of CR/CRi, both the CT scan and bone marrow are required to be negative. It is recommended that the CT scan is performed first, and if it does confirm a CR/CRi, then a BM biopsy should be obtained as soon as possible.

m. Post-treatment CT or MRI scans to be done only if collected by the site as part of standard of care.

n. A bone marrow aspirate and biopsy will be performed and assessed locally at Screening (within 35 days prior to the first dose of study drug). Bone marrow and aspirate for biomarker sample collection should be split from this sample. Refer to Table 6.

o. 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 not performed at the time of the confirmatory CT, then it should be performed after the Week 36 Day 1 CT scan.

p. At baseline, all measurable disease must be documented at screening by laboratory testing, physical examination and CT scans (or MRI if CT is medically contraindicated), and bone marrow examinations.

q. Specimens (bone marrow aspirate and peripheral blood) for MRD analysis should be collected at the same time as the bone marrow aspirate and biopsy performed for tumor assessments to confirm the CR/CRi. If MRD negativity is achieved in the bone marrow no further MRD analyses are required. Otherwise, MRD should be assessed at 12-week intervals thereafter (in peripheral blood) until MRD negativity is achieved. Once MRD negativity is achieved and confirmed in peripheral blood (e.g., two MRD negative consecutive peripheral blood samples), a bone marrow aspirate specimen will again be collected for analysis of MRD levels to confirm the peripheral blood negativity. 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 and MRD assessment. If a bone marrow and MRD assessment was not performed at the time of the confirmatory CT scan, then they should be performed after the Week 36 Day 1 CT scan. If MRD negativity is achieved in the bone marrow no further MRD analyses are required. Otherwise, MRD should be assessed at 12-week intervals thereafter (in peripheral blood) until MRD negativity is achieved. Once MRD negativity is achieved and confirmed in peripheral blood (e.g., two MRD negative consecutive peripheral blood samples), a bone marrow aspirate specimen will again be collected for analysis of MRD levels to confirm the peripheral blood negativity.

r. 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.

s. For subjects in the United States only: Subjects in the safety expansion cohort will be asked to complete a survey assessing the information they were provided for the Patient Information Card and the Tumor Lysis Syndrome Patient Information Brochure at Week 2 Day 1 or the next scheduled visit. For subjects participating in the main cohort, the survey will be given to the subject at the next scheduled study visit upon signing the Protocol Amendment 2 Informed Consent. This survey is optional.

t. For subjects continuing into the Survival Extended Access portion of the trial, Survival vists will include collection of Survival information, AEs/SAEs and concomitant medication information, study drug administration, collection and dispensing of subject diaries, and MRD PCR sample collection for eligible subjects. All other procedures for disease assessments will be perfomed as standard of care.

Table 6. Schedule of Biomarkers and Pharmacogenetic Sample Collection
Header row, column "Final Visit/Time of Relapse[g]" previously read:

Final Visit/Time of Relapse[g]

Has been changed to read:

Final Visit/Time of Relapse[g,h]

Table 6. Schedule of Biomarkers and Pharmacogenetic Sample Collection
Add: table note "h."

No final visit biomarker specimens are required for subjects that transition to the survival extended assess portion of the study.

Section 5.3.1.1 Study Procedures
Subsection Quantitative Minimal Residual Disease (MRD) Assessment
Add: new fourth paragraph

Subjects continuing into the Survival Extended Access portion of the study, and who continue to be eligible for MRD testing, will have blood specimens collected for MRD PCR collected at 12-week (± 7 days) intervals. If a subject undergoes a bone marrow biopsy as standard of care while on the survival extended access portion, a portion of the aspirate is requested to be collected for MRD-PCR.

Section 5.3.1.1 Study Procedures
Subsection Post-Treatment Follow-Up Visit(s)
Add: new last paragraph

Note: *Effective with protocol Amendment 6, subjects being followed in Post-Treatment as of 12 May 2017 will switch to being assessed per the Survival Assessments below. No new subjects will enter the Post-Treatment period.*

Section 5.3.1.1 Study Procedures
Subsection Survival Assessment(s)
Previously read:

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 for subjects who have not withdrawn consent.

Has been changed to read:

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 (± 7 days) intervals after the last study visit for a period of 5 years after the last subject has enrolled on the study for subjects who have not withdrawn consent.

Section 5.3.1.1 Study Procedures
Subsection Survival Assessment(s) – Extended Access
Add: new subsection title and text

Survival Assessment(s) – Extended Access

For subjects continuing into the Survival Extended Access portion of the trial, venetoclax will be dispensed at the Final Visit, and Survival visits will begin 12 weeks (± 7 days) following the 30-day Safety Follow-Up Visit. Survival visits will continue every 12 weeks (±7 days) until disease progression; up to 5 years following last subject enrolled (12 May 2020); or until a subject chooses to switch to commercial supply. Survival visits will include:

- Collection of Survival information
- AE/SAE/Con Med assessment
- Study drug reconciliation and dispensing
- Collect/Dispense subject diaries
- MRD PCR sample collection for eligible subjects

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

Section 5.4.1 Discontinuation of Individual Subjects
Add: new third paragraph

Subjects with disease progression who continue to receive venetoclax will also be allowed to receive other agents approved to treat CLL in addition to venetoclax. This will be added at the discretion of the investigator, and AbbVie or its partners will not reimburse for treatment agents or for the procedures required to monitor subjects other than those required per protocol.

Section 6.0 Complaints
Add: new section title and text

6.0 Complaints

A Complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device after it is released for distribution.

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 6.2.2). For adverse events, please refer to Sections 6.1 through 6.1.7. For product complaints, please refer to Section 6.2.

Section 6.0 through 6.8.4
Section number and title previously read:

6.0 Adverse Events

6.1 Definitions

6.1.1 Adverse Event

6.1.2 Serious Adverse Events

6.2 Adverse Event Severity

6.3 Adverse Events Expected Due to Study Related Endpoints

6.3.1 Deaths

6.3.2 Lack of Efficacy or Worsening of Disease

6.4 Relationship to Study Drug

6.5 Adverse Event Collection Period

6.6 Adverse Event Reporting

6.7 Pregnancy

6.8 Toxicity Management

6.8.1 Prophylaxis and Management of Tumor Lysis Syndrome

6.8.2 Management of Neutropenia

6.8.3 Management of Lymphopenia

6.8.4 Management of Decrease in Spermatogenesis

Has been changed to read:

6.0 Complaints

6.1 Medical Complaints

6.1.1 Definitions

6.1.1.1 Adverse Event

6.1.1.2 Serious Adverse Events

6.1.2 Adverse Event Severity

6.1.3 Relationship to Study Drug

6.1.4 Adverse Events Expected Due to Study Related Endpoints

6.1.4.1 Deaths

Section 6.1.3 Relationship to Study Drug
Add: new section title and text

6.1.3 Relationship to Study Drug

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

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

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

AbbVie will consider the event associated. If an investigator's opinion of no reasonable possibility of being related to study drug is given, an "Other" cause of event must be provided by the investigator for the serious adverse event.

Section 6.4 Relationship to Study Drug
Delete: section title and text

6.4 Relationship to Study Drug

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

Reasonable Possibility	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 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.

Section 6.6 Adverse Event Reporting
Third paragraph
Delete: "Safety Phone:"

Safety Phone: (847) 935-2609

Section 6.6 Adverse Event Reporting
Fourth paragraph previously read:

For any subject safety concerns, please contact the AbbVie medical monitor:

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

Phone:
Cell:
Fax:
Email: [redacted]

Has been changed to read:

For any subject safety concerns, please contact the AbbVie medical monitor:

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

Phone:
Cell:
Fax:
Email: [redacted]

Section 6.2 Product Complaint
Add: new section and text, renumber subsequent sections

6.2 Product Complaint

6.2.1 Definition

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

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

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

6.2.2 Reporting

Product Complaints concerning the investigational product must be reported to the Sponsor within 24 hours of the study site's knowledge of the event via the Product Complaint form. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. Product Complaints associated with adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

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

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

Section 7.0 Protocol Deviations
"Medical Monitor:" previously read:

Medical Monitor:

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

Phone:
Cell:
Fax:
Email: [redacted]

Has been changed to read:

Medical Monitor:

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

Phone:
Cell:
Fax:
Email: [redacted]

Section 7.0 Protocol Deviations
"Associate Director:" previously read:

Associate Director:

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

Contact Information:
Office:
Fax:
Email: [redacted]

Has been changed to read:

Program Lead:

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

Contact Information:
Office:
Fax:
Email: [redacted]

Section 8.1.1.2.7 Additional Exploratory Efficacy Analyses
Second paragraph previously read:

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.

Has been changed to read:

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 by MRD-flow. Ninety-five percent (95%) confidence intervals based on the binomial distribution will be provided. MRD data for this exploratory analysis was based on the MRD flow cytometry data and will not be collected for subjects who continue on in the survival extended access portion of the study. MRD-PCR specimens will be collected and analyzed for subjects who are eligible. This data will not be included in the clinical study report.

Section 8.1.4.1 Additional Exploratory Efficacy Analyses
Second paragraph previously read:

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.

Has been changed to read:

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. MRD data for this exploratory analysis was based on the MRD-Flow specimens and will not be collected for subjects who continue on in the survival extended access portion of the study. MRD-PCR specimens will be collected and analyzed for subjects who are eligible. This data will not be included in the final clinical study report.

Section 15.0 Reference List
Reference 10 previously read:

AbbVie. ABT-199 Investigator's Brochure Edition 7. 15 February 2016.

Has been changed to read:

AbbVie. ABT-199 Investigator's Brochure Edition 8. 15 February 2017.

Appendix B. List of Protocol Signatories

Previously read:

Name	Title	Functional Area
[redacted]		Statistics
		Clinical
		Clinical
		Global Drug Supply Management
		Clinical
		Biomarkers
		Pharmacokinetics
		Bioanalysis

Has been changed to read:

Name	Title	Functional Area
[redacted]		Statistics
		Clinical
		Clinical
		Global Drug Supply Management
		Clinical
		Biomarkers
		Pharmacokinetics
		Bioanalysis

Appendix C. Sample List of Excluded and Cautionary Medications
Previously read:

Excluded During Ramp-Up Phase and Cautionary Afterwards: (Additional Guidance Noted):
Strong CYP3A inducers ——^— avasimibe, carbamazepine (Tegretol®), phenytoin (Dilantin®), rifampin (Rifadin®), St. John's wort **Moderate CYP3A inducers^** – bosentan, efavirenz, etravirine, modafinil, nafcillin **Strong CYP3A inhibitors†** – Boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, mibefradil, lopinavir/ritonavir, nefazodone, nelfinavir, ritonavir, posaconazole, saquinavir, telaprevir, telithromycin, voriconazole **Moderate CYP3A inhibitors††** – Amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib*, darunavir/ritonavir, diltiazem, dronedarone, erythromycin, fluconazole, fosamprenavir, imatinib*, verapamil
Cautionary
Coumarins (vitamin K antagonists): Warfarin (Coumadin)** phenprocoumon (Marcumar)** **Weak CYP3A inducers** Amprenavir, aprepitant, armodafinil, clobazamechinacea, pioglitazone, prednisone, rufinamide, vemurafenib* **Weak CYP3A inhibitors** Alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide*, cilostazol, cimetidine, cyclosporine*, fluoxetine, fluvoxamine, ginkgo, goldenseal, isoniazid, nilotinib*, oral contraceptives, pazopanib*, ranitidine, ranolazine, tipranavir/ritonavir, ticagrelor, zileuton **P-gp substrates** Aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus*, fexofenadine, lapatinib*, loperamide, maraviroc, nilotinib*, ranolazine, saxagliptin, sirolimus*, sitagliptin, talinolol, tolvaptan, topotecan* **BCRP substrates** Methotrexate*, mitoxantrone*, irrinotecan*, lapatinib*, rosuvastatin, sulfasalazine, topotecan* **OATP1B1/1B3 substrates** Atrasentan, atorvastatin, ezetimibe, fluvastatin, glyburide, rosuvastatin, simvastatin acid, pitavastatin, pravastatin, repaglinide, telmisartan, valsartan, olmesartan **P-gp inhibitors** Amiodarone, azithromycin, captopril, carvedilol, felodipine, quercetin, ronalzine, quinidine, ronalzine, ticagrelor **BCRP inhibitors** Geftinib*, cyclosporine* **OATP1B1/B3 inhibitors** Gemfibrozil, eltrombopag, cyclosporine*, tipranavir

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.

Has been changed to read:

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, azithromycin, 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.