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Protocol for Study M16-788

Previously Untreated Chronic Lymphocytic Leukemia (CLL): Debulking Regimens Prior to Initiating Venetoclax Combination Therapy in Frontline CLL Excluding 17p Deletion

VERSION:	5.0	DATE:	19 December 2019
SPONSOR:	AbbVie Inc.*	NUMBER OF SITES:	25 – 35
ABBVIE INVESTIGATIONAL PRODUCT:	Venetoclax	EUDRACT:	Not applicable

FULL TITLE: A Phase 3b Study in Previously Untreated Chronic Lymphocytic Leukemia (CLL) Subjects, Excluding Those with the 17p Deletion, to Evaluate Debulking Regimens Prior to Initiating Venetoclax Combination Therapy

Incorporating Versions 1.0, 2.0, and 3.0

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1 SYNOPSIS

Title: A Phase 3b Study in Previously Untreated Chronic Lymphocytic Leukemia (CLL) Subjects, Excluding Those with the 17p Deletion, to Evaluate Debulking Regimens Prior to Initiating Venetoclax Combination Therapy	
Background and Rationale:	Most patients with newly diagnosed chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) are likely to present with a medium to high tumor burden. Therefore, the ability to start patients with newly diagnosed CLL/SLL on venetoclax is complicated by the risk of tumor lysis syndrome (TLS). As such, this trial explores the possibility of safely debulking patients with obinutuzumab or with obinutuzumab and bendamustine prior to the initiation of venetoclax therapy.
Objective(s) and Endpoint(s):	Primary Objectives: • To evaluate the anti-tumor effects of both induction therapies of obinutuzumab (Group A) or obinutuzumab in combination with bendamustine (Group B) prior to initiation of venetoclax and obinutuzumab therapy with the goal of initiating venetoclax in all subjects with low-tumor burden as defined by peripheral lymphocyte counts of $< 25 \times 10^9$/L and all lymph nodes < 5 cm per computed tomography (CT) scans. • To evaluate the efficacy of this regimen as defined by the rate of complete remission (CR) and complete remission with incomplete marrow recovery (CRi) following the debulking regimens and subsequent venetoclax and obinutuzumab therapy per 2008 Modified IWCLL NCI-WG criteria. Secondary Objectives: • To evaluate Overall Response Rate (ORR), Duration of Overall Response (DoR), Progression-Free Survival (PFS), Time to Progression (TTP), Overall Survival (OS), and the level of Minimal Residual Disease (MRD) defined as rate of subjects who achieve Undetectable Minimal Residual Disease (UMRD; $< 10^{-4}$) in the peripheral blood. • To evaluate safety and tolerability of the debulking regimens, venetoclax ramp-up, and the venetoclax and obinutuzumab combination. Primary Endpoints: • Percent of subjects achieving low tumor burden status after 2, 4 and 6 cycles of therapy with obinutuzumab or obinutuzumab and bendamustine. • The rate of complete remission (CR) and CRi: Defined as the proportion of subjects who achieved a CR or CRi (per the 2008 Modified International Workshop on Chronic Lymphocytic Leukemia National Cancer Institute–sponsored Working Group [IWCLL NCI-WG] criteria).

	Secondary Endpoints: • Overall Response Rate (ORR): Defined as the proportion of subjects with an overall response (complete remission, complete remission with incomplete marrow recovery, nodular partial remission [nPR] or partial remission [PR]) (per the 2008 Modified IWCLL NCI-WG criteria). • Duration of Response (DoR): Defined as the number of days from the date of first response (CR, CRi, nPR, or PR) (per the 2008 Modified IWCLL NCI-WG criteria) to the date of disease progression or death, whichever occurs first. All disease progression will be included regardless whether the event occurred during or after the subject was taking any study drug (either venetoclax, obinutuzumab, or bendamustine). • Progression-Free Survival (PFS): Defined as the number of days from the date of first dose of any study drug (either venetoclax, obinutuzumab, or bendamustine) to the date of disease progression or death, whichever occurs first. All disease progression will be included regardless whether the event occurred during or after the subject was taking any study drug. • Time to Progression (TTP): Defined as the number of days from the date of first dose of any study drug (either venetoclax, obinutuzumab, or bendamustine) to date of disease progression. All disease progression will be included regardless of whether the event occurred during or after the subject was taking any study drug. • Overall Survival (OS): Defined as number of days from the date of first dose of any study drug (either venetoclax, obinutuzumab, or bendamustine) to the date of death. • Undetectable Minimal Residual Disease (UMRD) Rate: The level of MRD will be assessed in the peripheral blood of all subjects at 5 months after last dose of obinutuzumab, and at the end of treatment (including early study termination) to determine the rate of UMRD. Undetectable Minimal Residual Disease will be defined as less than one CLL cell per 10,000 leukocytes ($< 10^{-4}$). Rate of UMRD status will be defined as the proportion of subjects who have UMRD. Safety Evaluations and Potential Endpoints: • Adverse Event (AE) monitoring • Serious Adverse Event (SAE) monitoring • Vital sign measurements • Physical examinations • Laboratory assessments • Incidence and reasons for any premature discontinuation, dose reductions, or interruptions of obinutuzumab, bendamustine, and/or venetoclax

Investigator(s):	Multi-center
Study Site(s):	25 – 35 sites in the United States
Study Population and Number of Subjects to be Enrolled:	Approximately 120 previously untreated subjects with CLL/SLL excluding those with the 17p deletion
Investigational Plan:	Multi-cohort, open-label study in previously untreated CLL/SLL patients, excluding those with the 17p deletion, to evaluate a debulking strategy that would enable all patients to receive subsequent venetoclax as outpatients with lower risk of tumor lysis.
Key Eligibility Criteria:	• Diagnosis of previously untreated CLL/SLL according to 2008 Modified IWCLL NCI-WG criteria • Eastern Cooperative Oncology Group (ECOG) performance score of 0 – 1 • CLL/SLL requires treatment according to the IWCLL criteria • Medium tumor burden (any lymph node [LN] 5 to < 10 cm OR absolute lymphocyte count [ALC] ≥ 25 × 10^9/L) OR High tumor burden (any LN ≥ 10 cm OR ALC ≥ 25 × 10^9/L AND LN ≥ 5 cm) • No presence of 17p deletion at Screening • No Richter's syndrome (transformation of CLL/SLL to aggressive non-Hodgkin's lymphoma or Hodgkin's lymphoma) • No prolymphocytic leukemia
Study Drug and Duration of Treatment:	Debulking: • Up to six 28-day cycles • Obinutuzumab (100 mg on Day 1 of Cycle 1, 900 mg on Day 2 of Cycle 1, and 1000 mg on Days 8 and 15 of Cycle 1 and Day 1 of Cycle 2; for Cycles 3 – 6 (1000 mg on Day 1) only as needed for subjects to achieve low tumor burden) intravenously • In subjects with > 10 cm nodes or nodal mass, or with del(11q) and > 5 cm nodes, additionally bendamustine (90 mg/m^2) on Days 1 and 2 (or 2 and 3 at investigator's discretion during Cycle 1) of each cycle intravenously for Cycles 1 and 2, for subsequent cycles (up to Cycle 6) as needed based on debulking achieved. For subjects receiving obinutuzumab plus bendamustine during the debulking period, use of growth factor support in treating or preventing neutropenia is allowed and encouraged. For those subjects categorized as having high risk of TLS, use of prophylactic rasburicase as well as laboratory monitoring on Cycle 1 Day 2 are recommended. Venetoclax plus obinutuzumab regimen: • To be initiated when lymphocyte count is < 25 × 10^9/L and all lymph nodes are < 5 cm at restaging evaluation with CT scan. If a subject does not achieve low tumor burden status after 6 cycles, the subject may proceed to venetoclax therapy per the discretion of the treating provider after discussion with the study physician.

	• Venetoclax will be administered for a total of up to 53 weeks, including a 5-week ramp-up schedule, at a dose of 400 mg after ramp-up • Obinutuzumab (1000 mg) will be administered intravenously on Day 1 of one 5-week (venetoclax ramp-up) and four 4-week cycles
Date of Protocol Synopsis:	19 December 2019

2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted

Chronic lymphocytic leukemia (CLL) is the most common of the chronic leukemias, comprising 30% of all adult leukemias.[1] The World Health Organization classification of hematopoietic neoplasias describes CLL as leukemic, lymphocytic lymphoma, being only distinguishable from small lymphocytic lymphoma (SLL) by its leukemic appearance.[2] Patients' median age at first diagnosis is 71 years.[3] Chronic lymphocytic leukemia is a clonal disease of unknown etiology, characterized by the accumulation of mature B cells in blood, lymph nodes, spleen, liver, and bone marrow. Morphologically, CLL cells are relatively mature looking but immunologically incompetent. About 95% of CLL is of B-cell origin (B-CLL) with a characteristic phenotype (CD19+, CD5+, CD23+ and FMC7–; weak expression of surface immunoglobulin (sIg) and membrane CD79b). The most common chromosomal abnormalities of leukemia cells in CLL are deletion 13q14 (incidence 51%), deletion 11q22-q23 (17 – 20%), trisomy 12 (15%), and deletion 17p13 (5%) and 6q21 (6%).[4] Response rates to initial chemoimmunotherapy treatment tend to be high, but residual disease often remains and patients tend to relapse or progress, eventually becoming resistant to chemotherapy, (i.e., fludarabine, alkylator).

Bendamustine is an alkylating agent, which also has properties of a purine and amino acid antagonist. Bendamustine is mainly metabolized in the liver via cytochrome P450; renal elimination accounts for about 20% of its excretion. Bendamustine was developed in the 1960s and is approved by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for treatment of CLL.[5,6]

Obinutuzumab is a humanized and glycoengineered type II anti-CD20 monoclonal antibody that recognizes the CD20 antigen present on normal and malignant B cells. It was developed for the treatment of hematological malignancies by F. Hoffmann-La Roche LTD and was approved by the FDA in November 2013[7] and by the EMA in July 2014[8] for the use in combination with chlorambucil in patients with previously untreated CLL. The combination of bendamustine and obinutuzumab has recently shown high overall response rates in frontline CLL patients, with an overall response rate (ORR) of 90%.[9]

The B-cell lymphoma-2 (Bcl-2) family proteins are important regulators of the intrinsic apoptosis pathway. Bcl-2 overexpression is a major contributor to the pathogenesis of some types of lymphoid malignancies, including in chronic leukemias. Chronic lymphocytic leukemia is a genetic disease where the microRNAs miR15a and miR16-1 that negatively regulate the transcription of Bcl-2 are deleted or downregulated, resulting in uncontrolled expression of Bcl-2.[10-13] The Bcl2-antagonist venetoclax has very promising efficacy and a favorable toxicity profile in del(17p) CLL and is currently being studied in frontline CLL patients in combination with obinutuzumab.[14] Preliminary data in the first 12 treated patients reported 100% ORR and 90% peripheral blood Undetectable Minimal Residual Disease (UMRD). However, due to the fast and overwhelming activity of venetoclax, tumor lysis syndrome (TLS) has occurred in patients with high tumor burden. TLS can be managed and prevented with certain measures of precaution, especially during dose-escalation.

As most patients with frontline CLL/SLL are likely to present with medium to high tumor cell burden, the ability to start patients with newly diagnosed CLL/SLL on venetoclax is complicated by the risk of TLS. As

such, this trial explores the role of obinutuzumab, or obinutuzumab in combination with bendamustine, in safely debulking patients prior to the initiation of venetoclax therapy.

Clinical Hypothesis

Obinutuzumab or obinutuzumab and bendamustine may safely be used to achieve low tumor burden status prior to initiation of venetoclax in subjects with previously untreated CLL/SLL.

2.2 Benefits and Risks to Patients

Clinical data show efficacy of venetoclax therapy in the treatment of CLL/SLL. Clinical safety data indicate that the adverse effects of venetoclax, when administered with appropriate measures, are manageable and as expected from a treatment targeting hematologic cells. Due to the medium to high tumor burden of subjects with newly diagnosed CLL/SLL, treatment with venetoclax is associated with a higher risk of TLS. Successful debulking before treatment initiation with venetoclax may significantly reduce the risk of TLS.

For further details, please see findings from completed studies, including safety data in the current venetoclax Investigator's Brochure.[14]

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Objectives

Primary

1. To evaluate the anti-tumor effects of both induction therapies of obinutuzumab (Group A), or obinutuzumab in combination with bendamustine (Group B), prior to initiation of venetoclax and obinutuzumab therapy, with the goal of initiating venetoclax in all subjects with low-tumor burden as defined by peripheral lymphocyte counts of $< 25 \times 10^9$/L and all lymph nodes < 5 cm per computed tomography (CT) scans.
2. To evaluate the efficacy of this regimen as defined by the rate of complete remission (CR) and complete remission with incomplete marrow recovery (CRi) following the debulking regimens and subsequent venetoclax and obinutuzumab therapy per 2008 Modified International Workshop on Chronic Lymphocytic Leukemia National Cancer Institute-sponsored Working Group [IWCLL NCI-WG] criteria.[15]

Secondary

3. To evaluate Overall Response Rate (ORR), Duration of Overall Response (DoR), Progression-Free Survival (PFS), Time to Progression (TTP), Overall Survival (OS), and the level of Minimal Residual Disease (MRD) defined as rate of subjects who achieve Undetectable Minimal Residual Disease (UMRD; $< 10^{-4}$) in the peripheral blood.
4. To evaluate safety and tolerability of the debulking regimens, venetoclax ramp-up, and the venetoclax and obinutuzumab combination.

3.2 Primary Endpoints

The primary endpoints are:

- Percent of subjects achieving low tumor burden status after 2, 4 and 6 cycles of therapy with obinutuzumab or obinutuzumab and bendamustine.
- The rate of complete remission (CR) and complete remission with incomplete marrow recovery (CRi): Defined as the proportion of subjects who achieved CR or CRi (per the 2008 Modified IWCLL NCI-WG criteria).[15]

3.3 Secondary Endpoints

Key Secondary Endpoints

- Overall Response Rate (ORR): Defined as the proportion of subjects with an overall response (complete remission, complete remission with incomplete marrow recovery, nodular partial remission [nPR] or partial remission [PR]) (per the 2008 Modified IWCLL NCI-WG criteria).
- Duration of Response (DoR): Defined as the number of days from the date of first response (CR, CRi, nPR, or PR) (per the 2008 Modified IWCLL NCI-WG criteria) to the date of disease progression or death, whichever occurs first. All disease progression will be included regardless whether the event occurred during or after the subject was taking any study drug (either venetoclax, obinutuzumab, or bendamustine).
- Progression-Free Survival (PFS): Defined as the number of days from the date of first dose of any study drug (either venetoclax, obinutuzumab, or bendamustine) to the date of disease progression or death, whichever occurs first. All disease progression will be included regardless whether the event occurred during or after the subject was taking any study drug.
- Time to Progression (TTP): Defined as the number of days from the date of first dose of any study drug (either venetoclax, obinutuzumab, or bendamustine) to date of disease progression. All disease progression will be included regardless of whether the event occurred during or after the subject was taking any study drug.
- Overall Survival (OS): Defined as number of days from the date of first dose of any study drug (either venetoclax, obinutuzumab, or bendamustine) to the date of death.
- Undetectable Minimal Residual Disease (UMRD) Rate: The level of MRD will be assessed in the peripheral blood of all subjects at 5 months after last dose of obinutuzumab, and at the end of treatment (including early study termination) to determine the rate of UMRD. Undetectable Minimal Residual Disease will be defined as less than one CLL cell per 10,000 leukocytes ($< 10^{-4}$). Rate of UMRD status will be defined as the proportion of subjects who have UMRD.

3.4 Safety Evaluations and Potential Endpoints

The following safety evaluations will be performed during the study: Serious Adverse Event (SAE) and Adverse Event (AE) monitoring, vital signs, physical examinations, and laboratory assessments. Certain

types of events require immediate reporting to the Sponsor, as outlined in Section 6.1. Safety will be monitored on an ongoing basis and summarized periodically in aggregate safety reports and end of study. All AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03.[16]

The safety evaluations for this study are as follows:

- All SAEs during and after treatment with obinutuzumab, bendamustine, and/or venetoclax up to 2 years or until another anti-cancer therapy has been started.
- Incidence, nature and severity of all AEs during and after treatment with obinutuzumab, bendamustine, and/or venetoclax up to 2 years or until another anti-cancer therapy has been started.
- Incidence and nature of all Grade 3 – 4 AEs during and after treatment with obinutuzumab, bendamustine, and/or venetoclax up to 2 years or until another anti-cancer therapy has been started.
- Grade 5 AEs or AEs leading to death while receiving obinutuzumab, bendamustine, and/or venetoclax and up to 30 days after receiving last dose of study drug.
- Incidence and reasons for any premature discontinuation, dose reductions, or interruptions of obinutuzumab, bendamustine, and/or venetoclax.

For venetoclax:

- Single laboratory abnormalities that meet the following criteria: calcium < 1.75 mmol/L (< 7 mg/dL), phosphorus > 1.5 mmol/L (> 4.5 mg/dL), potassium > 6 mmol/L (> 6 mEq/L), and uric acid > 476 µmol/L (> 8 mg/dL) will be collected through up to 53 weeks of treatment.
- Incidence and prevalence of cytopenias from initiation of venetoclax through up to 53 weeks of treatment will be collected.

For obinutuzumab:

- Grade 1 or 2 AEs (related and unrelated) up to 28 days after the last dose of obinutuzumab or until another anti-cancer therapy has been started.
- Grade 3 or 4 AEs other than infections (related and unrelated) for up to 6 months after the last dose of obinutuzumab or until another anti-cancer therapy has been started.
- Grade 3 to 4 infections (related and unrelated) for up to 2 years after the last dose of obinutuzumab or until another anti-cancer therapy has been started.
- Unrelated SAEs for up to 12 months after the last dose of obinutuzumab or until another anti-cancer therapy has been started.
- Study drug-related SAEs will be collected from the last study drug administration up to 2 years or until another anti-cancer therapy has been started.

- All events of second malignancies will be collected from the last study drug administration indefinitely (or until another anti-cancer therapy has been started) even after study closure, but not after study termination.

3.5 Biomarker Research

Peripheral blood will be collected at specified time points (Appendix D) throughout the study to evaluate known and/or novel disease-related or drug-related biomarkers. Types of biomarkers may include nucleic acids, proteins, lipids, and/or metabolites. The planned analyses include identification and tracking of CLL cells for determination of minimal or measurable residual disease in the peripheral blood. Additional analyses (e.g., UMRD [$< 10^{-4}$] in bone marrow and/or other known or novel biomarkers) may be conducted but may not be included in the clinical study report. Furthermore, biomarker analyses which are exploratory in nature may be performed in non-Good Laboratory Practice/Good Clinical Practice (GLP/GCP) laboratories. Further details regarding the biomarker research rationale and collection time points are located in the Operations Manual, Section 3.17 and Table 2. The samples may be retained for no longer than 20 years after study completion or per local requirements.

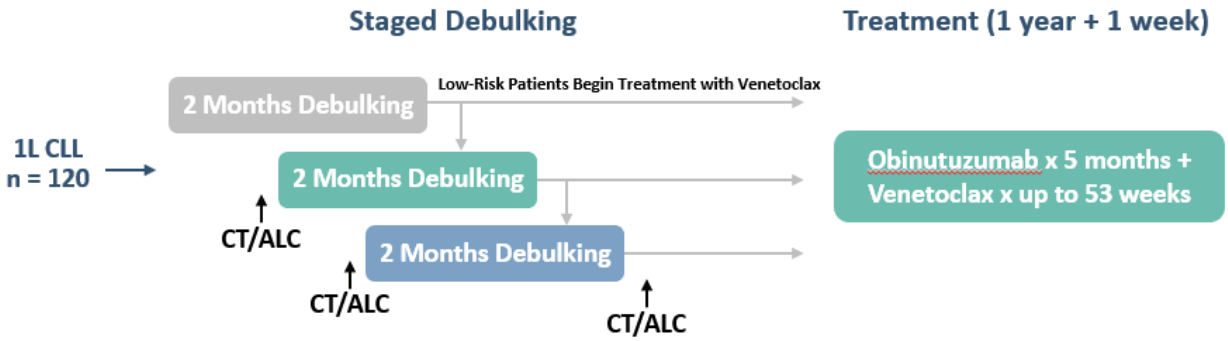
4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a multi-cohort, open-label study in previously untreated CLL/SLL patients, excluding those with the 17p deletion, to evaluate a debulking strategy that would enable all patients to receive subsequent venetoclax as outpatients, with lower risk of tumor lysis.

The schematic of the study is shown in Figure 1. Further details regarding study procedures are located in the Operations Manual.

Figure 1. Study Schematic



Abbreviations: 1L = first line; ALC = absolute lymphocyte count; CLL = chronic lymphocytic leukemia; CT = computed tomography

Debulking

Prior studies have identified that obinutuzumab is expected to abrogate lymphocytosis after one cycle;[17] however the impact on lymph nodes has not been established. Subjects will receive induction therapy with either obinutuzumab (Group A) or obinutuzumab in combination with bendamustine (Group B) upon initiating the debulking period. Group assignment will not change if bendamustine is subsequently added or removed from a subject's debulking regimen during the debulking period.

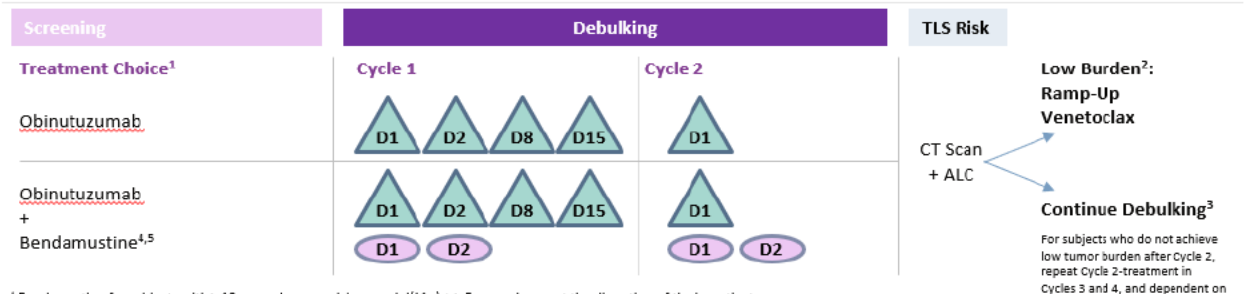
Subjects with > 10 cm nodes or nodal mass, or the presence of del(11q) and > 5 cm nodes, should receive obinutuzumab-bendamustine to ensure optimal cytoreduction prior to venetoclax initiation. This regimen may also be selected for cytoreduction in other subjects at the discretion of the investigator.

For subjects receiving obinutuzumab-bendamustine during the debulking period, use of growth factor support in treating or preventing neutropenia is allowed and encouraged. For those subjects categorized as having high risk of TLS, use of prophylactic rasburicase as well as laboratory monitoring on Cycle 1 Day 2 are recommended.

Subjects will receive induction therapy with restaging evaluation, including CT scans, at 2 months. If subjects are not determined to meet low tumor burden criteria, reassessment will occur at 4 months, and 6 months, if needed. If tumor burden does not decrease after at least two cycles of obinutuzumab, and there are no signs of disease progression, subjects receiving induction therapy with obinutuzumab may have bendamustine added, at the start of Cycle 3 or Cycle 5, for the remaining cycles of debulking. If a subject's disease progresses, does not respond to, or the subject is otherwise intolerant to debulking with bendamustine-obinutuzumab, the subject will discontinue the study after discussion with the AbbVie therapeutic area Medical Director (TA MD). Following a maximum of six cycles of debulking, if a subject has not met low tumor burden criteria, it will be up to principal investigator (PI) discretion (after consultation with the AbbVie TA MD) whether to initiate venetoclax or discontinue the subject from the study. Any subjects receiving obinutuzumab in combination with bendamustine should discontinue bendamustine upon achieving low tumor burden status and initiating venetoclax.

The schematic of the debulking period is shown in Figure 2. Further details regarding debulking procedures are located in the Operations Manual.

Figure 2. Debulking Period Schematic



[1] Bendamustine for subjects with > 10 cm nodes or nodal mass, del(11q) + > 5 cm nodes, or at the discretion of the investigator.
[2] Low tumor burden is defined as nodes < 5 cm and ALC < 25 × 10^9/L
[3] TLS Risk (CT scan and ALC) are assessed every 2 cycles for a maximum of 6 cycles
[4] Bendamustine may be administered on days 1/2 or days 2/3 of each cycle by physician preference
[5] For subjects receiving obinutuzumab - bendamustine during the debulking period, use of growth factor support in treating or preventing neutropenia is allowed and encouraged

Abbreviations: ALC = absolute lymphocyte count; CT = computed tomography; D = Day; TLS = tumor lysis syndrome

Venetoclax Plus Obinutuzumab Regimen

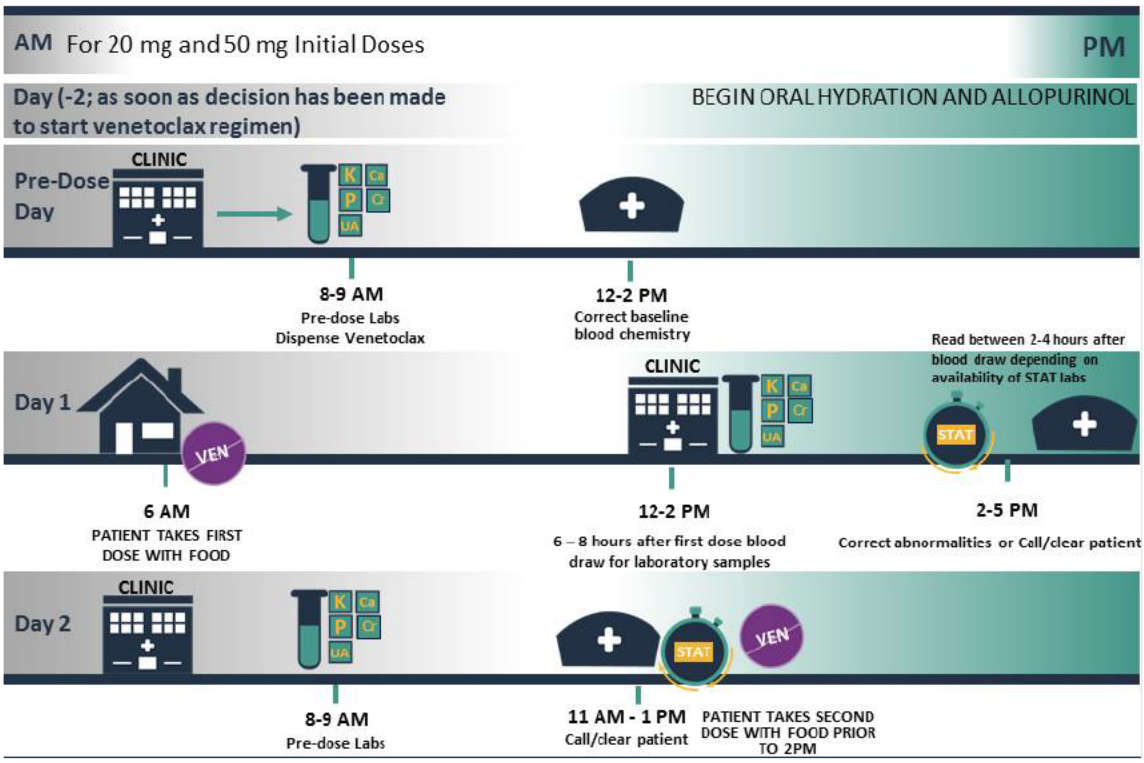
Venetoclax will be initiated when lymphocyte count is < 25 × 10^9/L and all lymph nodes are < 5 cm at restaging evaluation with CT scan. If the subject has not achieved low tumor burden status after six cycles of debulking, the subject may proceed to venetoclax after discussion with the study physician.

For both debulking groups, subjects will receive obinutuzumab in combination with venetoclax for 5 months to maximize synergy. Venetoclax therapy will continue for a total treatment period of up to 53 weeks.

Based upon pre-dose laboratory assessments (prior to venetoclax Day 1), venetoclax administration will begin with therapy initiated in the home early enough to enable clinic monitoring of laboratory values at 6 – 8 hours post dosing to assess for emergence of tumor lysis (Appendix E). At the first dose of 20 mg and 50 mg venetoclax, laboratory analytes will be assessed pre-dose on Day 0 (prior to venetoclax Day 1), 6 – 8 hours post-dose on Day 1, and the following morning prior to dosing to assess emergence of tumor lysis. At all subsequent dose levels laboratory analytes will only be assessed prior to the first dose of venetoclax at the new dose level. Venetoclax (400 mg) will be continued for a total duration of up to 53 weeks, including a 5-week ramp-up schedule.

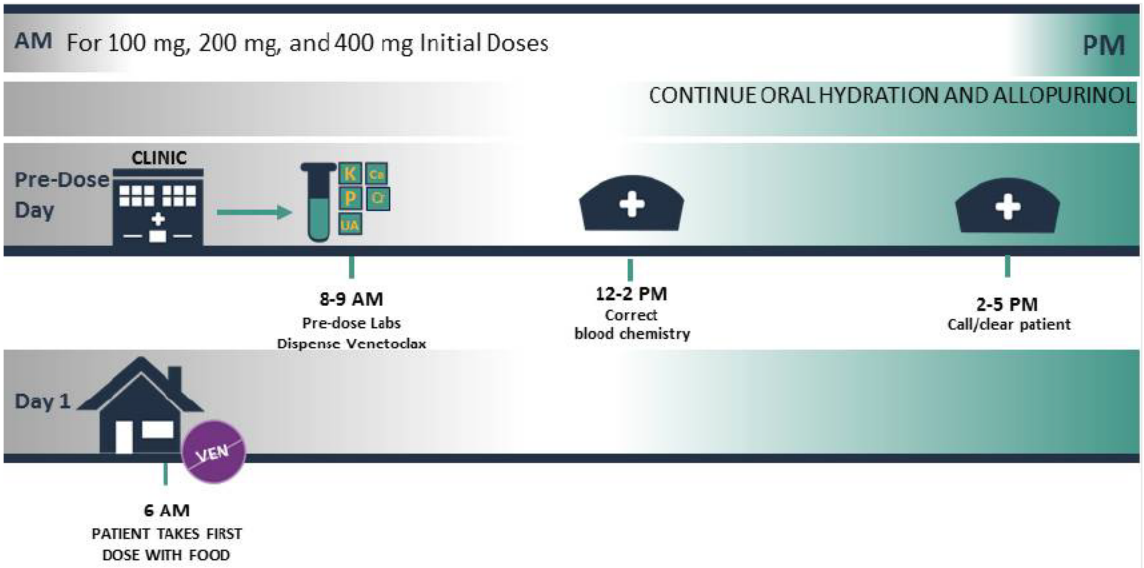
The schematic of the Venetoclax Outpatient Dosing Regimen is shown in Figure 3 and Figure 4. Further details regarding study procedures are located in the Operations Manual.

Figure 3. Venetoclax Outpatient Dosing Schema (20 mg and 50 mg Initial Doses)



Abbreviations: Ca = calcium; Cr = creatinine; K = potassium; P = phosphorus; STAT lab = A free-standing lab capable of performing an abbreviated battery of tests; UA = uric acid; VEN = take dose of venetoclax

Figure 4. Venetoclax Outpatient Dosing Schema (100 mg, 200 mg, and 400 mg Initial Doses)



Abbreviations: Ca = calcium; Cr = creatinine; K = potassium; P = phosphorus; UA = uric acid; VEN = take dose of venetoclax

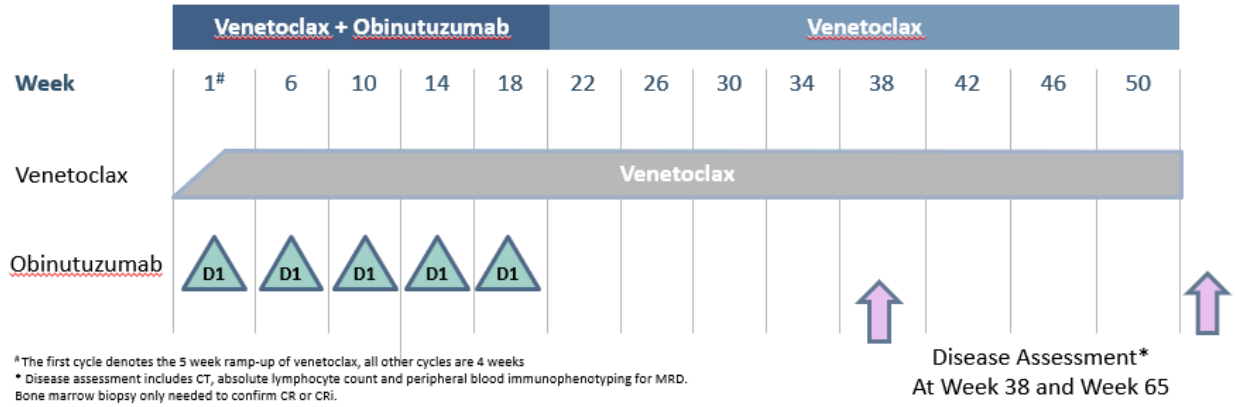
A Disease Assessment for response will be performed at Screening, 5 months after the last dose of obinutuzumab, and at 3 months from the end of treatment.

In the case of a CR or CRi, a confirmatory bone marrow aspirate and biopsy will be required. A portion of the aspirate will be split from this sample and stored for possible future analysis which may include MRD assessment.

Disease response will be assessed by the investigator, based on laboratory results, physical examinations, using the 2008 modified IWCLL Guidelines For Tumor Response with the addition of CT imaging (or magnetic resonance imaging [MRI]) when available. All measurable disease must be documented at Screening by physical examination, laboratory testing, and CT scan (or MRI if CT is medically contraindicated).

The schematic of the venetoclax plus obinutuzumab period is shown in Figure 5. Further details regarding study procedures are located in the Operations Manual.

Figure 5. Venetoclax Plus Obinutuzumab Period Schematic



[#] The first cycle denotes the 5 week ramp-up of venetoclax, all other cycles are 4 weeks
* Disease assessment includes CT, absolute lymphocyte count and peripheral blood immunophenotyping for MRD. Bone marrow biopsy only needed to confirm CR or CRi.

Abbreviations: CR = complete remission; CRi = complete remission with incomplete marrow recovery; CT = computed tomography; D = day; MRD = minimal residual disease

Previously untreated subjects with CLL/SLL excluding those with the 17p deletion will be enrolled in this study. See Section 5 for information regarding eligibility criteria.

At the time the 20th subject completes the venetoclax ramp-up, an internal safety committee will review data from all subjects who have been enrolled and received study drug in order to determine the relative safety of the debulking and ramp-up regimen, as well as to assess feasibility of modification to monitoring. An interim safety and efficacy analysis will be conducted after 50 subjects have completed the Week 38 disease assessment. This analysis will include review by an advisory steering committee as well as the Data Monitoring Committee (DMC).

4.2 Discussion of Study Design

Choice of Control Group

This is a single-arm study without control group.

Appropriateness of Efficacy and Safety Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. All efficacy measurements in this study are standard for assessing disease activity in subjects with CLL/SLL. All clinical and laboratory procedures in this study are standard and generally accepted.

Suitability of Subject Population

Previously untreated subjects with CLL/SLL excluding those with the 17p deletion are expected to respond well to the debulking regimen followed by venetoclax treatment. Subjects with 17p deletion were excluded due to their expected poor response to the proposed debulking regimen.

Selection of Doses in the Study

After a weekly ramp-up schedule over 5 weeks, venetoclax will be administered at a daily dose of 400 mg. Bendamustine will be administered intravenously at a dose of 90 mg/m^2 during debulking on

Days 1 and 2 of Cycles 1 and 2 (Days 2 and 3 at the investigator's discretion during Cycle 1), for subsequent cycles (up to Cycle 6) as needed based on debulking achieved. During debulking, obinutuzumab will be administered intravenously at a dose of 100 mg on Day 1 of Cycle 1, 900 mg on Day 2 of Cycle 1, and 1000 mg on Days 8 and 15 of Cycle 1. In subsequent debulking cycles, obinutuzumab will be administered intravenously at a dose of 1000 mg on Day 1 of each cycle.

During the venetoclax/obinutuzumab regimen, obinutuzumab will be administered intravenously at a dose of 1000 mg on Day 1 of Cycles 1 through 5. The dose selection in this study is based on prior clinical experience with the study drugs.

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

Subjects must meet all of the following criteria in order to be included in the study. Anything other than a positive response to the questions below will result in exclusion from study participation.

Consent

- 1. Subjects, or their legally authorized representative, 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.

Demographic and Laboratory Assessments

- 2. Adult **male or female**, at least 18 years old.
- 3. **Laboratory values** meeting the following criteria within the screening period prior to the first dose of obinutuzumab or obinutuzumab plus bendamustine:
  - Creatinine clearance (CrCl) ≥ 30 mL/min unless bendamustine will be used, in which case CrCl must be ≥ 40 mL/min
  - Adequate marrow function independent of growth factor or transfusion support within 2 weeks of Screening as follows, unless cytopenia is due to marrow involvement of CLL/SLL:
    - Absolute neutrophil count (ANC) ≥ 1.0×10^9/L
    - Platelet counts ≥ 25×10^9/L without any of the following:
      - Transfusion support within 14 days of screening
      - Evidence of mucosal bleeding
      - Known history of major bleeding episode within 3 months of screening
    - Total hemoglobin ≥ 8 g/dL (without transfusion support, unless anemia is due to marrow involvement of CLL/SLL)
  - Adequate liver function as indicated by a total bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) ≤ 3 times the institutional upper limit of normal (ULN),

unless bendamustine will be used, in which case bilirubin ≤ 1.5 × ULN, and AST and ALT ≤ 2.5 × ULN, unless directly attributable to the subject's CLL/SLL.

- No positive test results for, or suspicion of, active infection, including hepatitis B virus (HBV) infection (defined as positive hepatitis B surface antibody [HBsAg] serology), based on site standard practices prior to anti-CD20 antibody infusion and obinutuzumab prescribing information.[7] Testing should be conducted prior to initiation of obinutuzumab per site standard of care and obinutuzumab prescribing information.
  - For subjects who show evidence of hepatitis B infection (HBsAg positive [regardless of antibody status] or HBsAg negative but anti-HBc positive), consult physicians with expertise in managing hepatitis B regarding monitoring and consideration for HBV antiviral therapy. Subjects may be included if HBV deoxyribonucleic acid (DNA) is undetectable, provided that they are willing to undergo monthly DNA testing, during and for several months following treatment with obinutuzumab. Subjects who have protective titers of hepatitis B surface antibody (HBsAb) after vaccination or prior but cured hepatitis B are eligible.
- No positive test result for hepatitis C (hepatitis C virus [HCV] antibody serology testing), based on site standard practices prior to anti-CD20 antibody infusion and obinutuzumab prescribing information.[7] Testing should be conducted prior to initiation of obinutuzumab per site standard of care and obinutuzumab prescribing information.
  - Subjects who are positive for HCV antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV ribonucleic acid (RNA).
- No known infection with human immunodeficiency virus (HIV) or Human T-Cell Leukemia Virus 1 (HTLV-1).

- 4. No serious medical condition or abnormality in a clinical laboratory test that, in the investigator's judgment, precludes the subject's safe participation in, and completion of, the study.
- 5. Are willing and able to comply with procedures required in this protocol.

Disease Activity

- 6. Diagnosis of previously untreated CLL/SLL according to IWCLL criteria.[15] Subjects must not have received systemic therapy for CLL/SLL prior to the time of study enrollment.
- 7. Subject meets the following disease activity criteria:
  - Eastern Cooperative Oncology Group (ECOG) performance score of 0 – 1.
  - CLL/SLL requires treatment according to the IWCLL criteria (Appendix G).
  - Medium tumor burden (any lymph node [LN] 5 to < 10 cm OR absolute lymphocyte count [ALC] ≥ 25 × 10^9/L) OR High tumor burden (any LN ≥ 10 cm OR ALC ≥ 25 × 10^9/L AND LN ≥ 5 cm).
- 8. No presence of 17p deletion at Screening (or within 2 years if an historical test result is used).
- 9. No Richter's syndrome (transformation of CLL/SLL to aggressive non-Hodgkin's lymphoma or Hodgkin's lymphoma).

- 10. No prolymphocytic leukemia.
- 11. No known central nervous system involvement.
- 12. No uncontrolled autoimmune hemolytic anemia or immune thrombocytopenia within 2 weeks of study entry.

Subject History

- 13. No history of confirmed progressive multifocal leukoencephalopathy (PML).
- 14. No history of prior malignancy, except for conditions as listed below if subjects have recovered from the acute side effects incurred as a result of previous therapy:
  - Malignancies surgically treated, or treated with radiation, with curative intent and with no known active disease present for ≥ 3 years before randomization.
  - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
  - Adequately treated cervical carcinoma in situ without evidence of disease.
  - Surgically/adequately treated low grade, early stage, localized prostate cancer without evidence of disease.
- 15. No history of an **allergic reaction** or significant sensitivity to constituents of the study drug (and its excipients) and/or other products in the same class.
- 16. No history of severe **allergic reaction** or anaphylactic reactions to humanized or murine monoclonal antibodies or known sensitivity or allergy to murine products.
- 17. No history of clinically significant (per Investigator's judgment) **drug or alcohol abuse** within the last 6 months.
- 18. No conditions that could **interfere with drug absorption** including but not limited to short bowel syndrome.
- 19. No history of clinically significant medical conditions or any other reason that in the opinion of the Investigator would **interfere with the subject's participation** in this study or would make the subject an unsuitable candidate to receive study drug.
- 20. No history of clinically relevant or **significant electrocardiogram (ECG) abnormalities**, including ECG with QT interval corrected for heart rate (QTc) using Fridericia's formula (QTcF) > 450 msec (males) or > 470 msec (females).

Contraception

- 21. A **negative serum pregnancy test** for all female subjects (except post-menopausal) at the Screening Visit and a **negative urine pregnancy test** for all female subjects (except post-menopausal) at baseline prior to the first dose of study drug.

- 22. **If female**, subject must be either **postmenopausal**, OR permanently **surgically sterile** OR for women of childbearing potential practicing at least 1 protocol-specified highly effective **method of birth control**, that is effective from Study Day 1 through at least 30 days after the last dose of venetoclax or 18 months after the last dose of obinutuzumab or 3 months after the last dose of bendamustine, whichever is longer.
- 23. **If male**, and subject is **sexually active with female partner(s) of childbearing potential**, he must agree, from Study Day 1 through at least 18 months after the last dose of obinutuzumab or 3 months after the last dose of bendamustine, whichever is longer, to practice the protocol-specified contraception.
- 24. **Female** who is not **pregnant, breastfeeding, or considering becoming pregnant** during the study or for at least 30 days after the last dose of venetoclax or 18 months after the last dose of obinutuzumab or 3 months after the last dose of bendamustine, whichever is longer.
- 25. **Male** who is not considering **fathering a child or donating sperm** during the study or for at least 18 months after the last dose of obinutuzumab or 3 months after the last dose of bendamustine, whichever is longer.

Concomitant Medications

- 26. Subject must not have been treated with **any investigational drug** within 30 days or 5 half-lives of the drug (whichever is longer) prior to the first dose of study drug or is currently enrolled in another clinical study.
- 27. Subject must not have received **any live vaccine** within 4 weeks prior to the first dose of study drug, or expected need of live vaccination during study participation including at least 4 weeks after the last dose of study drug.

5.2 Contraception Recommendations

Contraception Requirements for Females

Subjects must follow the following contraceptive guidelines as specified:

- Females, Non-Childbearing Potential

  Females do not need to use birth control during or following study drug treatment if considered of non-childbearing potential due to meeting any of the following criteria:

  - Postmenopausal, age > 55 years with no menses for 12 or more months without an alternative medical cause.
  - Postmenopausal, age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND a follicle-stimulating hormone (FSH) level > 40 IU/L.
  - Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy).

- Females, of Childbearing Potential
  - Females of childbearing potential must avoid pregnancy throughout the study including at least 30 days after the last dose of venetoclax or 18 months after the last dose of obinutuzumab or 3 months after the last dose of bendamustine, whichever is longer.
  - Females must commit to one of the following methods of birth control:
    - Combined (estrogen and progestogen containing) hormonal birth control (oral, intravaginal, transdermal) associated with inhibition of ovulation initiated at least 1 month prior to study Cycle 1 Day 1. Also, barrier method must be used during this study from initial study drug administration to 30 days after the last dose of venetoclax as drug-drug interaction with venetoclax upon the hormonal contraception is unknown.
    - Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 1 month prior to study Cycle 1 Day 1. Also, barrier method must be used during this study from initial study drug administration to 30 days after the last dose of venetoclax as drug-drug interaction with venetoclax upon the hormonal contraception is unknown.
    - Bilateral tubal occlusion/ligation at least 1 month before study Cycle 1 Day 1.
    - Bilateral tubal occlusion via hysteroscopy (i.e., Essure), provided a hysterosalpingogram confirms success of the procedure at least 1 month before study Cycle 1 Day 1.
    - Intrauterine device (IUD).
    - Intrauterine hormone-releasing system (IUS).
    - Vasectomized sexual partner(s) (the vasectomized partner(s) provided the vasectomized partner has received medical assessment of the surgical success and is the sole sexual partner of the trial participant).
    - True abstinence: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

Contraception Requirements for Males

Male subjects who are sexually active with a female partner of childbearing potential must agree to use condoms, even if the male subject has undergone a successful vasectomy, from Study Day 1 through at least 18 months after the last dose of obinutuzumab or 3 months after the last dose of bendamustine, whichever is longer, and his female partner(s) must use at least one of the contraceptive measures (as defined above for female study subjects of childbearing potential).

5.3 Prohibited Medications and Therapy

During treatment with venetoclax:

- Steroid therapy for anti-neoplastic intent will not be allowed either during, or within 7 days prior to, the first dose of venetoclax with the exception of inhaled steroids for the treatment of

asthma or Chronic Obstructive Pulmonary Disease (COPD), topical steroids, replacement corticosteroid therapy for an inherited or acquired deficiency.

- **Anticancer therapies including chemotherapy, radiotherapy, or other investigational therapy, including targeted small molecule agents** are excluded 5 half-lives prior to first dose and throughout venetoclax administration.
- **Biologic agents (e.g., monoclonal antibodies) for anti-neoplastic intent** are excluded 30 days prior to first dose and throughout venetoclax administration.

Excluded during initiation and dose-titration (ramp-up) of venetoclax and cautionary at 400 mg steady daily dose (See Appendix H):

- Exclude **strong cytochrome P450 3A (CYP3A) inhibitors** (Appendix H) during initiation and the dose-titration (ramp-up) phase. If subject requires use of these medications after the dose titration phase at steady daily doses, use with caution and reduce the venetoclax dose by at least 75% during co-administration. Resume the venetoclax dose that was used prior to initiating the CYP3A inhibitor 2 to 3 days after discontinuation of the inhibitor.
- Do not consume grapefruit, grapefruit products, Seville oranges (often used in marmalades), or star fruit.
- Avoid concomitant use of venetoclax with **moderate CYP3A inhibitors**. Consider alternative treatments. If a moderate CYP3A inhibitor must be used, reduce the venetoclax dose by at least 50%. Monitor these subjects more closely for signs of toxicities. Resume the venetoclax dose that was used prior to initiating the CYP3A inhibitor 2 to 3 days after discontinuation of the inhibitor.
- Avoid concomitant use of venetoclax with **strong or moderate CYP3A inducers**. Consider alternative treatments with less CYP3A induction.
- Avoid concomitant use of venetoclax with **P-glycoprotein (P-gp) inhibitors**. If a moderate P-gp inhibitor must be used, reduce the venetoclax dose by at least 50%. Monitor these subjects more closely for signs of toxicities.

For subjects being treated with bendamustine (See Appendix H):

- **Inhibitors of CYP1A2** (e.g., fluvoxamine, ciprofloxacin) have potential to increase plasma concentrations of bendamustine and decrease plasma concentrations of active metabolites. Inducers of CYP1A2 (e.g., omeprazole, smoking) have potential to decrease plasma concentrations of bendamustine and increase plasma concentrations of its active metabolites. Caution should be used, or alternative treatments considered if concomitant treatment with CYP1A2 inhibitors or inducers is needed.
- Due to the risk of toxic skin reactions (e.g., Stevens-Johnson syndrome/toxic epidermal necrolysis), concomitant administration of bendamustine and **allopurinol** should be avoided. If allopurinol is indispensable, it should be stopped > 24 hours before and reinitiated ≥ 24 hours after administration of bendamustine.

5.4 Prior and Concomitant Therapy

Any medication or vaccine (including over the counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded through the post-treatment visit for venetoclax (Week 157).

Please refer to Appendix H. Any questions regarding concomitant or prior therapy should be raised to the AbbVie emergency contact (see title page). Information regarding potential drug interactions with obinutuzumab, bendamustine, or venetoclax can be located in the respective Investigator's Brochures.

Subjects must be able to safely discontinue any prohibited medications 5 half-lives or 4 weeks prior to initial study drug administration, whichever is shorter. Subjects must be consented for the study prior to discontinuing any prohibited medications for the purpose of meeting study eligibility.

5.5 Withdrawal of Subjects and Discontinuation of Study and/or Study Treatment

A subject may voluntarily withdraw or be withdrawn from the study and/or study drug treatment at any time for reasons including, but not limited to, the following:

- Clinically significant abnormal laboratory results or AEs, which rule out continuation of the study drug, as determined by the Investigator or the AbbVie TA MD.
- The Investigator believes it is in the best interest of the subject.
- The subject requests withdrawal from the study.
- The subjects' response to therapy is unsatisfactory, as evidenced by progression of disease while on study drug.
- The subject requires other cancer treatment (e.g., radiotherapy, alternate anti-neoplastic agent).
- Eligibility criteria violation was noted after the subject started study drug and continuation of the study drug would place the subject at risk.
- Introduction of prohibited medications or dosages and continuation of the study drug would place the subject at risk.
- The subject becomes pregnant while on study drug.
- Subject is significantly non-compliant with study procedures which would put the subject at risk for continued participation in the trial.

For subjects to be considered lost to follow-up, reasonable attempts must be made to obtain information on the final status of the subject. At a minimum, 2 telephone calls must be made and 1 certified letter must be sent and documented in the subject's source documentation.

AbbVie may terminate this study prematurely, either in its entirety or at any site. The Investigator may also stop the study at his/her site if he/she has safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will promptly notify the Investigator.

In the event AbbVie is notified in writing that a subject withdraws consent to participate in the clinical study and no longer consents to the biomarker research, no new biomarker data will be collected for the withdrawn subject or added to the existing data or database(s). Data generated from biomarker research collected before subject withdrawal of consent is received will remain part of the study results.

5.6 Follow-Up for Subject Withdrawal from Study and/or Study Treatment

To minimize missing data for efficacy and safety assessments, subjects who prematurely discontinue study drug treatment should continue to be followed up, unless subjects have decided to discontinue the study participation entirely (e.g., withdrawal of informed consent). Subjects should be advised on the continued scientific importance of their data even if they discontinue treatment with study drug early.

If a subject prematurely discontinues study participation (e.g., withdrawal of informed consent) and/or study treatment, the procedures outlined for the early termination visit should be completed as soon as possible, preferably within 2 weeks of early termination, but before initiation of another treatment algorithm, if applicable. In addition, if subject is willing, a 30-day follow-up phone call after the last dose of study drug may be completed to ensure all treatment-emergent AEs/SAEs have been resolved. If the subject refuses, this should be noted in the subject's source documentation.

Subjects prematurely discontinuing study treatment will be followed for disease progression and survival. Post-treatment follow-up calls will be performed every 3 months until discontinuation from the study. Survival information (e.g., the date and cause of death, post-treatment cancer therapies, date of progression) will be collected. This period will continue for 2 years following discontinuation of venetoclax.

All attempts must be made to determine the date of the last study drug dose and the primary reason for discontinuation of study drug or study participation. The information will be recorded on the appropriate electronic Case Report Form (eCRF) page. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the Investigator feels are necessary to treat the subject's condition. Following discontinuation of study drug, the subject will be treated in accordance with the Investigator's best clinical judgment, irrespective of whether or not the subject decides to continue participation in the study.

5.7 Study Drug

Venetoclax will be initiated when lymphocyte count is $< 25 \times 10^9$/L and all lymph nodes are < 5 cm at restaging evaluation with CT scan. If the subject has not achieved low tumor burden status after 6 cycles of debulking, the subject may proceed to venetoclax per the discretion of the treating physician after discussion with the study physician. The venetoclax dose will be administered according to a weekly ramp-up schedule over 5 weeks to the recommended daily dose of 400 mg. Subjects will be

instructed to take venetoclax tablets with a meal and water at approximately the same time each day. Venetoclax tablets should be swallowed whole and not chewed, crushed, or broken prior to swallowing. If a subject misses a dose of venetoclax within 8 hours of the time it is usually taken, the subject should take the missed dose as soon as possible and resume the normal daily dosing schedule. If a subject misses a dose by more than 8 hours, the subject should not take the missed dose and should resume the usual dosing schedule the next day.

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

Subjects will be instructed to return all drug containers (even if empty) to the study site personnel at each study visit. The study site personnel will document compliance.

Obinutuzumab (100 mg on Day 1 of Cycle 1, 900 mg on Day 2 of Cycle 1, and 1000 mg on Days 8 and 15 of Cycle 1 and Day 1 of Cycle 2; for Cycles 3 – 6 (1000 mg on Day 1) only as needed for subjects to achieve low tumor burden) will be administered via intravenous infusion during the debulking regimen. After debulking, obinutuzumab (1000 mg) will be administered via intravenous infusion on Day 1 of one 5-week and four 4-week cycles during the obinutuzumab/venetoclax combination part of the regimen.

Bendamustine (90 mg/m^2) will be administered in subjects with nodes or nodal mass > 10 cm, or with del(11q) and > 5 cm nodes, or at the discretion of the investigator as above, via intravenous infusion over 10 minutes on Days 1 and 2 (or Days 2 and 3 at the discretion of the investigator during Cycle 1) of each 28-day cycle for up to 6 cycles during the debulking regimen.

Bendamustine and obinutuzumab will be packaged in vials and venetoclax will be packaged in blister cards and bottles with quantities sufficient to accommodate study design. Each kit will be labeled per local requirements and this label must remain affixed to the kit. Upon receipt, study drug should be stored as specified on the label and kept in a secure location. Each kit will contain a unique kit number. This kit number is assigned to a subject via interactive response technology (IRT) and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit. All blank spaces on the label will be completed by the site staff prior to dispensing to subjects. Study drug will only be used for the conduct of this study.

Instructions for drug preparation will be provided by AbbVie.

AbbVie will not supply drugs other than obinutuzumab, bendamustine and venetoclax.

5.8 Drug Assignment

All subjects will be assigned a unique identification number by the IRT at the Screening visit. For subjects who rescreen, the screening number assigned by the IRT at the initial screening visit should be used.

Subjects with 1) > 10 cm lymph nodes or nodal mass or 2) with del(11q) and > 5 cm nodes, or 3) for whom aggressive debulking would be beneficial in the opinion of the investigator, should be assigned to the obinutuzumab plus bendamustine debulking regimen to ensure adequate cytoreduction. All other subjects should be assigned to the obinutuzumab debulking regimen. For all subjects, but particularly

for those receiving obinutuzumab plus bendamustine during the debulking period, use of growth factor support in treating or preventing neutropenia is allowed and encouraged.

5.9 Protocol Deviations

The Investigator is responsible for complying with all protocol requirements, written instructions and applicable laws regarding protocol deviations. Protocol deviations are prohibited except when necessary to eliminate an immediate hazard to study subjects. If a protocol deviation occurs (or is identified), the Investigator is responsible for notifying Independent Ethics Committee (IEC)/Independent Review Board (IRB), regulatory authorities (as applicable) and AbbVie.

6 SAFETY CONSIDERATIONS

6.1 Complaints and Adverse Events

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. Complaints associated with any component of this investigational product must be reported to AbbVie.

Product Complaint

A product complaint is any complaint related to the biologic or drug component of the product or to the medical device component(s).

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 (e.g., printing illegible), missing components/product, device not working properly, or packaging issues.

Product complaints concerning the investigational product and/or device must be reported to AbbVie within 24 hours of the study site's knowledge of the event. Product complaints occurring during the study will be followed up to a satisfactory conclusion.

Medical Complaints/Adverse Events and Serious Adverse Events

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

The investigators will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. All adverse events will be followed to a satisfactory conclusion; improvements in grade should not be captured as a separate event.

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and/or 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.

If an adverse event, whether associated with study drug or not, meets any of the following criteria, it is to be reported to AbbVie clinical pharmacovigilance as a serious adverse event within 24 hours of the site being made aware of the serious adverse event (refer to Section 4.5 of the Operations Manual for reporting details and contact information):

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.

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

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with global and local guidelines.

Adverse events will be monitored throughout the study to identify any of special interest that may indicate a trend or risk to subjects.

Adverse Events of Special Interest

The following adverse events of special interest (AESI) will be monitored during the study:

- Tumor lysis syndrome;
- Second primary malignancies;
- Serious infections.

These AESIs are to be entered into the electronic data capture (EDC) system immediately (i.e., no more than 24 hours after the site becoming aware of the event), also if they do not meet seriousness criteria. Adverse events of lab or clinical TLS need to be reported as adverse events of special interest.

Adverse Event Severity and Relationship to Study Drug

The investigators will rate the severity of each adverse event according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03. If a reported AE increases in severity, the initial AE should be given an outcome date and a new AE must be reported on a different onset date than the end date of the previous AE to reflect the change in severity. The dates on the AEs cannot overlap. For all reported SAEs that increase in severity, the supplemental eCRFs also need to be updated to reflect any changes due to the increase in severity.

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.

Pregnancy

While not an adverse event, pregnancy in a study subject must be reported to AbbVie within 24 hours of the site becoming aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (see Section 5.5). If a pregnancy occurs in a study subject or in the partner of a study subject, information regarding the pregnancy and the outcome will be collected.

In the event of pregnancy occurring in a subject's partner during the study, written informed consent from the partner must be obtained prior to collection of any such information. A separate consent will be provided by AbbVie for this purpose. Pregnancies in study subject's partners will be collected from the date of the first dose through 90 days after the last dose of venetoclax or 18 months after the last dose of obinutuzumab, whichever is longer.

The medical outcome for either mother or infant, meeting any serious criteria including an elective or spontaneous abortion, stillbirth, or congenital anomaly is considered a serious adverse event and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

6.2 Toxicity Management

The management of specific AEs and laboratory parameters is described in the Operations Manual. This includes AEs of TLS, febrile infections, and any grade 3/4 AEs non-hematologic AEs, and Grade 3 neutropenia with infection or fever, or Grade 4 hematologic toxicities (except lymphopenia). For allowed study drug interruption, the following rules apply:

1. Allow study drug interruption up to 14 consecutive days for AEs and emergency surgery. Elective surgery will not be allowed during the debulking period, or within 4 weeks of completion of the venetoclax ramp up period. If study drug administration is interrupted for more than 3 days (i.e., AE), the site will contact the AbbVie study team or AbbVie Therapeutic Area Medical Director (TA MD) to adjust the subject's visit schedule, procedures and/or dosing on a case by case basis. For subjects who have had a dosing interruption greater than 1 week during the first 5 weeks of dose titration or greater than 2 weeks when at the daily dose of 400 mg, TLS risk should be reassessed to determine if restarting at a reduced dose is necessary (e.g., all or some levels of the dose titration).
2. If the subject must undergo emergency surgery, the study drug should be interrupted at the time of the surgery and the AbbVie study team must be notified, but does not need to be consulted. After emergency surgery, consult with AbbVie study team before reintroduction of

study drug, once the physician has examined the surgical site and determined that it has healed and there is no sign of infection.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

Complete and specific details of the statistical analysis will be described and fully documented in the Statistical Analysis Plan (SAP). All statistical analyses will be performed using SAS version 9.4 or newer (SAS Institute Inc., Cary, North Carolina, USA).

7.2 Determination of Sample Size

Given that this is a hypothesis generating study, no formal statistical comparisons will be performed. The planned study will enroll total sample size of 120 subjects.

7.3 Definition for Analysis Populations

The Full Analysis Set (FAS) includes all enrolled subjects who received at least 1 dose of any study drug. The FAS will be used for all safety, efficacy and baseline analyses.

7.4 Statistical Analyses for Efficacy

Analysis of the primary endpoint will be conducted on the FAS. Only descriptive statistical analyses will be performed on both induction therapies of obinutuzumab (Group A) or obinutuzumab plus bendamustine (Group B) at 2, 4, and 6 cycles of therapy.

Point estimates and 95% confidence interval of complete remission rate (defined as % of CR + CRi) will be calculated based on the 2008 Modified IWCLL NCI-WG criteria. Details of the analysis methods for all efficacy endpoints will be provided in the SAP.

7.5 Statistical Analyses for Safety

Details pertaining to the safety analyses can be found in the SAP.

7.6 Study Interim Analysis

After 20 subjects have completed the ramp-up regimen with venetoclax, an exploratory analysis will be performed to assess the overall safety profile among all subjects who have been enrolled and received study drug, with an emphasis on the risk of TLS. As it is expected that all 20 subjects will be in the low-risk group for tumor lysis, further subgroup analyses will be performed to better understand risk stratification in these subjects. These results may identify new subsets of risk based on 1) disease-related factors such as lymphadenopathy and absolute lymphocyte count and 2) individual subject-

related factors such as renal function, performance status and co-morbidities. In addition, safety and efficacy data for the debulking regimens will be reviewed by an advisory committee of experts in treating CLL/SLL and the use of venetoclax. Based on that feedback the study team may choose to modify the safety monitoring plan and treatment regimens by amendment to the protocol.

An additional interim analysis for efficacy and similar safety measures will be performed once 50 subjects have completed the Week 38 disease assessment. This data will also be reviewed by the steering committee and, in the case of the safety data, by the DMC.

7.7 Data Monitoring Committee

A DMC comprised of persons independent of the study team and with relevant expertise in their field will review data from all subjects who have been enrolled and received study drug at the time the first 20 subjects complete the venetoclax ramp-up, in order to determine relative safety of the debulking and ramp up regimen, as well as to assess feasibility of modification to monitoring. The primary responsibility of the DMC will be to protect the safety of the subjects participating in this study.

A separate DMC charter will be prepared outside of the protocol and will describe the roles and responsibilities of the DMC members, frequency of data reviews, relevant safety data to be assessed and expectations for blinded communications.

8 ETHICS

8.1 Institutional Review Board (IRB)

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IRB for review and approval. Approval of both the protocol and the informed consent form(s) must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form(s) will be IRB approved.

8.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, Operations Manual, International Council for Harmonisation (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 Investigator are specified in Appendix B.

8.3 Subject Confidentiality

To protect subjects' confidentiality, all subjects and their associated samples will be assigned numerical study identifiers or "codes." No identifiable information will be provided to AbbVie.

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be attributable, legible, contemporaneous, original, accurate, and complete to ensure accurate interpretation of data. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, ICH Good Clinical Practice (GCP), and applicable local regulatory requirement(s).

10 DATA QUALITY ASSURANCE

AbbVie will ensure that the clinical trial is conducted with a quality management system that will define quality tolerance limits in order to ensure human subject protection and reliability of study results. Data will be generated, documented and reported in compliance with the protocol, ICH GCP and applicable regulatory requirements.

11 COMPLETION OF THE STUDY

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.

Subjects will be followed for disease progression and survival. Post-treatment follow-up calls will be performed every 3 months until discontinuation from the study. Survival information (e.g., the date and cause of death, post-treatment cancer therapies, date of progression) will be collected. This period will continue for 2 years following discontinuation of venetoclax.

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APPENDIX A. STUDY SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALC	Absolute Lymphocyte Count
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ANC	Absolute Neutrophil Count
Bcl-2	B-cell lymphoma-2
CLL	Chronic Lymphocytic Leukemia
COPD	Chronic Obstructive Pulmonary Disease
CR	Complete Remission
CrCl	Creatinine Clearance
CRi	Complete Remission with Incomplete Marrow Recovery
CT	Computed Tomography
CYP3A	Cytochrome P450 3A
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DoR	Duration of Overall Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicines Agency
FAS	Full Analysis Set
FDA	Food and Drug Administration
FISH	Fluorescence in-situ hybridization
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBsAb	Hepatitis B surface Antibody
HBsAg	Hepatitis B surface Antigen

HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HTLV-1	Human T-Cell Leukemia Virus 1
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgHV	Immunoglobulin variable region heavy chain
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IWCLL	International Workshop for Chronic Lymphocytic Leukemia
LDH	Lactate dehydrogenase
LN	Lymph Node
MRD	Minimal Residual Disease
MRI	Magnetic Resonance Imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCI-WG	National Cancer Institute – Working Group
nPR	Nodular Partial Remission
ORR	Overall Response Rate
OS	Overall Survival
PCR	Polymerase Chain Reaction
PD	Progressive Disease
PFS	Progression-Free Survival
P-gp	P-glycoprotein
PI	Principal Investigator
PML	Progressive Multifocal Leukoencephalopathy
PR	Partial Remission
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

SD	Stable Disease
sIg	Surface Immunoglobulin
SLL	Small Lymphocytic Lymphoma
SUSAR	Suspected Unexpected Serious Adverse Reactions
TA MD	Therapeutic Area Medical Director
TLS	Tumor Lysis Syndrome
TTP	Time To Progression
ULN	Upper Limit of Normal
UMRD	Undetectable MRD

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M16-788: Debulking Regimens Prior to Initiating Venetoclax Combination Therapy in Frontline CLL Excluding 17p Deletion

Protocol Date: 19 December 2019

Clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation (ICH) Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement, the investigator is agreeing to the following:

1. Conducting the study in accordance with ICH GCP, the applicable regulatory requirements, current protocol and operations manual, and making changes to a protocol only after notifying AbbVie and the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC), except when necessary to protect the subject from immediate harm.
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., IEC or IRB) review and approval of the protocol and its amendments.
4. Reporting complaints that occur in the course of the investigation(s) to AbbVie.
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 protocol and all of its 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. Providing direct access to source data documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s).

Signature of Principal Investigator	Date

Name of Principal Investigator (printed or typed)	

APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]	Study Project Manager	Clinical Program Development
[redacted]	Assistant Medical Director	Global Medical Affairs
[redacted]	Hematology Lead	Medical Affairs
[redacted]	Director Statistics	Statistics
[redacted]	Principal Medical Writer	Medical Writing

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APPENDIX D. ACTIVITY SCHEDULE

The following table shows the required activities the subject encounters during debulking. The individual activities are described in detail in the **Operations Manual**.

Study Activities Table 1 – Debulking

Study Activities Table 1 – Debulking	Screening	Cycle 1 Day 1	Cycle 1 Day 2*	Cycle 1 Day 8	Cycle 1 Day 15	Cycle 2 Day 1**	Cycle 2 Day 2***	Cycle 2 Day 28	Cycle 3 Day 1**	Cycle 3 Day 2***	Cycle 4 Day 1**	Cycle 4 Day 2***	Cycle 4 Day 28	Cycle 5 Day 1**	Cycle 5 Day 2***	Cycle 6 Day 1**	Cycle 6 Day 2***	Cycle 6 Day 28
INTERVIEWS & QUESTIONNAIRES																		
Subject Information and Informed Consent	✓																	
Eligibility criteria	✓	✓																
Medical/oncology history	✓	✓																
Adverse event assessment	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓		✓	✓	✓	✓	
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓		✓	✓	✓	✓	
ECOG performance status	✓																	
LABS & EXAMS																		
Vital signs	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓		✓	✓	✓	✓	
Physical exam	✓																	
Height	✓																	
Weight	✓	✓				✓			✓		✓			✓		✓		
TLS risk assessment	✓							✓					✓					✓
Disease assessment	✓																	

Study Activities Table 1 – Debulking	Screening	Cycle 1 Day 1	Cycle 1 Day 2*	Cycle 1 Day 8	Cycle 1 Day 15	Cycle 2 Day 1**	Cycle 2 Day 2***	Cycle 2 Day 28	Cycle 3 Day 1**	Cycle 3 Day 2***	Cycle 4 Day 1**	Cycle 4 Day 2***	Cycle 4 Day 28	Cycle 5 Day 1**	Cycle 5 Day 2***	Cycle 6 Day 1**	Cycle 6 Day 2***	Cycle 6 Day 28
CT or MRI scan	✓							✓					✓					✓
FISH for 17p deletion	✓																	
IgHV mutation status	✓																	
Beta-2 microglobulin level	✓																	
LDH level	✓																	
Hematology/chemistry	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓		✓	✓	✓	✓
Peripheral blood for MRD (collected pre-dose, either at Screening or Cycle 1 Day 1)	✓	✓																
Serum pregnancy test	✓																	
Urine pregnancy test		✓																
Bone marrow aspirate (not required, but results will be recorded if available)	✓																	
℞ TREATMENT																		
Administer bendamustine (during Cycle 1: on Day 1 and Day 2, or on Day 2 and Day 3)		✓	✓			✓	✓		✓	✓	✓	✓		✓	✓	✓	✓	
Administer obinutuzumab		✓	✓	✓	✓	✓			✓		✓			✓		✓		

Abbreviations: CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; FISH = Fluorescence in-situ hybridization; IgHV = Immunoglobulin variable region heavy chain; LDH = lactate dehydrogenase; MRD = minimal residual disease; MRI = magnetic resonance imaging; TLS = tumor lysis syndrome

* **Cycle 1 Day 2 procedures, with the exception of obinutuzumab administration, are to be completed on Cycle 1 Day 3 for all subjects receiving bendamustine on a Cycle 1 Day 2 – Cycle 1 Day 3 dosing schedule.**

** Day 1 of each Cycle may be performed within +/– 3 days of the expected visit date provided that the planned 28-day interval between cycles is maintained.

*** Visit required only for subjects receiving bendamustine.

The following tables show the required activities during the venetoclax/obinutuzumab regimen and follow-up subject encounters. The individual activities are described in detail in the **Operations Manual**.

Study Activities Table 2 – VENETOCLAX/OBINUTUZUMAB REGIMEN THROUGH WEEK 18

	PRE-DOSE On or After Day 28 of Previous Cycle	Week 1 Day 1*	Week 1 Day 2	Week 1 Day 7	Week 2 Day 1	Week 2 Day 2	Week 2 Day 7	Week 3 Day 1**	Week 3 Day 7	Week 4 Day 1**	Week 4 Day 7	Week 5 Day 1**	Week 6 Day 1*	Week 10 Day 1*	Week 14 Day 1*	Week 18 Day 1*
INTERVIEWS & QUESTIONNAIRES																
Adverse event assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
ECOG Performance Status	✓															
LABS & EXAMS																
Hematology/chemistry	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
TLS chemistries	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓				
Vital signs	✓	✓			✓			✓		✓		✓	✓	✓	✓	✓
Physical exam	✓															
TREATMENT																
TLS prophylaxis	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓				
Dispense venetoclax	20 mg			50 mg			100 mg		200 mg		400 mg		400 mg	400 mg	400 mg	400 mg
Administer obinutuzumab		✓											✓	✓	✓	✓
Dispense subject diary	✓															
Review/collect subject diary (Collect diary at Week 6 Day 1, review at all previous visits)		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			

Abbreviations: ECOG = Eastern Cooperative Oncology Group; TLS = tumor lysis syndrome

* The Week 1 Day 1 visit may be performed within +3 days/– 0 days; thereafter Day 1 of each subsequent Cycle may be performed within +/– 3 days of the expected visit date provided that the planned 28-day interval between cycles is maintained.

** The Week 3 Day 1, Week 4 Day 1, and Week 5 Day 1 (+/– 3 days) visits are optional if the investigator wants to recheck lab values.

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Study Activities Table 3 – VENETOCLAX/OBINUTUZUMAB REGIMEN – WEEK 26 THROUGH 2-YEAR POST TREATMENT FOLLOW-UP

	Week 26 Day 1*	Week 34 Day 1*	Week 38 Day 1*	Week 42 Day 1*	Week 50 Day 1*	Week 54 Day 1*	Week 65 Day 1* OR EARLY TERMINATION	FOLLOW-UP Week 77	FOLLOW-UP Week 89	FOLLOW-UP Week 101	FOLLOW-UP Week 113	FOLLOW-UP Week 125	FOLLOW-UP Week 137	FOLLOW-UP Week 149	FOLLOW-UP Week 157
INTERVIEWS & QUESTIONNAIRES															
Adverse event assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
ECOG Performance Status			✓				✓								
LABS & EXAMS															
Hematology/chemistry	✓	✓	✓	✓	✓	✓	✓								
Peripheral blood for MRD			✓				✓								
Vital signs	✓	✓	✓	✓	✓	✓	✓								
Physical exam															
Disease assessment			✓				✓								
CT or MRI scan			✓				✓								
Bone marrow aspirate and biopsy (if sample is collected for confirmation of CR or CRi, part of sample should be used for MRD assessment)			✓**				✓**								
TREATMENT															
Dispense venetoclax	400 mg	400 mg		400 mg	400 mg (4 wks only)										

Abbreviations: CR = complete remission; CRi = complete remission with incomplete marrow recovery; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; MRD = minimal residual disease; MRI = magnetic resonance imaging

* Day 1 of each Cycle may be performed within +/– 3 days of the expected visit date provided that the planned 28-day interval between cycles is maintained.

** If needed to confirm CR or CRi.

APPENDIX E. DEFINITIONS OF LABORATORY AND CLINICAL TUMOR LYSIS SYNDROME

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

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

‡ Acute kidney injury is defined as an increase in the creatinine level of at least 0.3 mg per deciliter (26.5 µmol per liter) or a period of oliguria lasting 6 hours or more. By definition, if acute kidney injury is present, the subject has clinical tumor lysis syndrome. Data about acute kidney injury from Levin et al.[18]

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

Source: Howard et al., 2011[19]

APPENDIX F. 2008 MODIFIED IWCLL NCI-WG CRITERIA FOR TUMOR RESPONSE

Parameter	Complete Remission (CR) All Criteria Must Be Met[a,b]	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[c]	Stable Disease (SD) All Criteria Must Be Met
Group A				
Lymphadenopathy	None > 1.5 cm	Decrease ≥ 50%[d] from baseline	Increase ≥ 50%[e] from baseline or any new LN > 1.5 cm	Change of –49% to +49%[f] from baseline
Blood Lymphocytes	< 4000/µL	Decrease ≥ 50% from baseline	Increase ≥ 50% over baseline (≥ 5000/µL)	Change of –49% to +49% from baseline
Hepatomegaly[g]	None	Decrease ≥ 50% from baseline	Increase ≥ 50%[h] from baseline	Change of –49% to +49% from baseline
Splenomegaly[g]	None	Decrease ≥ 50% from baseline	Increase ≥ 50%[h] from baseline	Change of –49% to +49% from baseline
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	Change of –49% to +49% from baseline
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	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	N/A

Parameter	Complete Remission (CR) All Criteria Must Be Met[a,b]	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[c]	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 (regardless of size) or transformation to a more aggressive histology, e.g., Richter Syndrome[e]	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, nPR, PR, or PD

Abbreviations: CLL = chronic lymphocytic leukemia; CR = complete remission; CRi = complete remission with incomplete marrow recovery; CT = computed tomography; LN = lymph nodes; N/A = Not applicable; nPR = nodular partial remission; PD = progressive disease; PR = partial remission; SD = stable disease; SPD = sum of the products of diameters

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

b. Complete Remission plus the presence of persistent lymphoid nodules on bone marrow biopsy is nodular partial remission (nPR).

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

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

e. 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.

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

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.

APPENDIX G. INTERNATIONAL WORKSHOP ON CLL RECOMMENDATIONS REGARDING INDICATIONS FOR TREATMENT IN CLL

	General Practice	Clinical Trial
Treat with Rai stage 0	NGI[a]	RQ
Treat with Binet stage A	NGI[a]	RQ
Treat with Binet stage B or Rai stage I or Rai stage II	Possible[a]	Possible[a]
Treat with Binet stage C or Rai stage III or Rai stage IV[b]	Yes	Yes
Treatment of active/progressive disease	Yes	Yes
Treatment without active/progressive disease	No	RQ

Abbreviations: NGI = not generally indicated; RQ = early therapy of CLL is generally not recommended outside of clinical trials. However we recognize the need to conduct clinical trials testing the early use of novel agents.

a. Treatment is indicated, if the disease is active as defined.

b. Anemia and/or thrombocytopenia due to CLL-unrelated causes should be excluded.

Note: General practice is defined as the use of accepted treatment options for a CLL patient not enrolled on a clinical trial.

"Active disease" should be clearly documented to initiate therapy. At least one of the following criteria should be met:

1. Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia and/or thrombocytopenia. Cut-off levels of Hb < 10 g/dl or platelet counts of < 100,000/µl are generally regarded as indication for treatment. However, it should be pointed out that in some patients platelet counts of < 100,000/µl may remain stable over a long-period of time; this situation does not automatically require therapeutic intervention.
2. Massive (i.e., ≥ 6 cm below the left costal margin) or progressive or symptomatic splenomegaly.
3. Massive nodes (i.e., ≥ 10 cm in longest diameter) or progressive or symptomatic lymphadenopathy.
4. Progressive lymphocytosis with an increase of ≥ 50% over a 2-month period, or lymphocyte doubling time (LDT) of less than 6 months. LDT can be obtained by linear regression extrapolation of absolute lymphocyte counts (ALC) obtained at intervals of two weeks over an observation period of 2 - 3 months; patients with initial blood lymphocyte counts of < 30,000/µl may require a longer observation period to determine the LDT. Factors contributing to lymphocytosis other than CLL (e.g., infections, steroid administration) should be excluded.
5. Autoimmune complications including anemia or thrombocytopenia poorly responsive to corticosteroids.

6. Symptomatic or functional extranodal involvement (e.g., skin, kidney, lung, spine).
7. Disease-related symptoms as defined by any of the following:

   a) Unintentional weight loss ≥ 10% within the previous 6 months.

   b) Significant fatigue (i.e., ECOG PS 2 or worse; cannot work or unable to perform usual activities).

   c) Fevers ≥ 100.5° F or 38.0° C for 2 or more weeks without evidence of infection.

   d) Night sweats for 1 month without evidence of infection.

Source: Hallek et al., 2018[20]

APPENDIX H. SAMPLE LIST OF EXCLUDED AND CAUTIONARY MEDICATIONS

Excluded During Initiation and Dose-Titration (Ramp-Up) of Venetoclax and Cautionary at 400 mg Steady Daily Dose of Venetoclax:
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,# dronedarone, erythromycin, fluconazole, fluvoxamine, fosamprenavir, imatinib,* isavuconazole, tofisopam, verapamil
P-gp inhibitors†† – Amiodarone, azithromycin, captopril, carvedilol, felodipine, propafenone, quercetin, ronalzine, ticagrelor
Cautionary During Initiation and Dose-Titration (Ramp-Up) and Cautionary at 400 mg Steady Daily Dose of Venetoclax:
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
BCRP inhibitors
Geftinib,* curcumin

Excluded During Treatment with Bendamustine
Inhibitors of CYP1A2 – fluvoxamine, ciprofloxacin
Inducers of CYP1A2 – omeprazole, smoking
Allopurinol

Note that this is not an exhaustive list. For an updated list, see the following link:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm

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

* These are anticancer agents and are excluded for 5 half-lives prior to first dose and throughout venetoclax administration; contact AbbVie TA MD before use.

** Closely monitor international normalized ratio (INR).

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

† If subject requires use of these medications after the dose titration phase, use with caution and reduce the venetoclax dose by at least 75% during co-administration. After discontinuation of the CYP3A inhibitor, wait for 2 - 3 days before venetoclax dose is increased back to the dose that was used prior to initiating the CYP3A inhibitor.

†† If subject requires use of these medications, use with caution and reduce the venetoclax dose by at least 50%. After discontinuation of CYP3A inhibitor or P-gp inhibitor, wait for 2 - 3 days before venetoclax dose is increased back to the dose that was used prior to initiating the CYP3A inhibitor or P-gp inhibitor.

Moderate CYP3A inhibitor per venetoclax FDA USPI.

APPENDIX I. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	07 December 2017
Version 2.0	13 July 2018
Version 3.0	25 October 2018
Version 4.0	18 July 2019

The purpose of this Version is to correct minor inconsistencies within the protocol in addition to the following:

Section 3.1, Objectives, and Section 3.3: Secondary Endpoints: Changed the term "MRD negativity" to "Undetectable MRD (< 10^{-4})" or "UMRD;" updated text throughout to indicate this change in terminology.

Rationale: To update the terminology used to define minimal residual disease status of < 10^{-4}

Section 4.1: Overall Study Design and Plan: Clarified in Figure 1 and in text that venetoclax therapy would continue for a total treatment period of up to 53 weeks; clarified that in addition to bone marrow aspirate, biopsy is required to confirm CR or CRi; updated Figure 5 to correct inconsistencies; clarified that interim analysis will occur after 50 subjects have completed the Week 38 disease assessment;

Rationale: Clarifications.

Section 5.5: Withdrawal of Subjects and Discontinuation of Study and/or Study Treatment: Clarified that subjects may be withdrawn from the study and/or study drug treatment; specified two additional reasons for withdrawal from the study and/or study drug treatment, including that subject's response to therapy is unsatisfactory, as evidenced by progression of disease while on study drug, or requiring other cancer treatment.

Rationale: Clarifications and to ensure consistency with other AbbVie protocols in this therapeutic area.

Section 5.6: Follow-Up for Subject Withdrawal from Study and/or Study Treatment: Clarified that subjects who discontinue study participation and/or study treatment should have an early termination visit before initiation of another treatment, if applicable; clarified post-treatment follow-up for subjects who prematurely discontinue study treatment.

Rationale: Clarifications.

Section 7.6, Study Interim Analysis: Clarified that interim analysis will occur after 50 subjects have completed the Week 38 disease assessment.

Rationale: Clarification.

Appendix D, Activity Schedule: Specified that MRD assessment will use peripheral blood; removed term "Treatment Completion Visit" from Week 65 Day 1 visit; clarified that Week 38 and Week 65 bone marrow aspirate and biopsy will be collected only if needed to confirm CR or CRi.

Rationale: Clarifications.