



Protocol for Study M20-353

Previously Untreated CLL and SLL: Safety and Efficacy of Venetoclax in Combination with Obinutuzumab or Ibrutinib in Japanese Subjects

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1 SYNOPSIS

Title: A Phase 2 Study of the Safety and Efficacy of Venetoclax in Combination with Obinutuzumab or Ibrutinib in Japanese Subjects with Previously Untreated Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)	
Background and Rationale:	Chronic lymphocytic leukemia (CLL) is a clonal disease of unknown etiology, characterized by the accumulation of mature B cells in blood, lymph nodes, spleen, liver, and bone marrow (BM). The disease has a characteristic immunophenotype, which includes co-expression of CD5 (T-cell antigen) and the B-cell surface antigens CD19, CD20, and CD23, and low levels of surface immunoglobulin, CD20 and CD79b compared with normal B cells. The clonality of the disease is confirmed by the presence of a single immunoglobulin light chain. Small lymphocytic lymphoma (SLL) is defined as a tumor of the same cells as CLL without infiltration into peripheral blood or bone marrow. SLL is considered to be the same disease concept as CLL, and the treatment for SLL follows the treatment for CLL. CLL generally follows an indolent course. Treatment is usually associated with a high rate of initial responses followed inevitably by relapse. Subsequent treatments can induce remissions, but at a progressively lower rate with responses of shorter duration. Although the median survival of patients with CLL is around 10 years, the disease has an extremely variable clinical course and the prognosis depends on disease stage and a range of prognostic biomarkers. Despite recent advances in treatment, CLL remains an incurable disease. The objective of the treatment of slowly progressing CLL is to control the disease, improve symptoms, and prolong survival. At the same time, the aim is to maintain and improve the quality of life by minimizing toxicity with a tolerable treatment regimen even in elderly patients. Deep remissions and clinically significant progression-free survival (PFS) can be achieved with chemo immunotherapy combinations, such as fludarabine-based regimens, but these intensive regimens cannot or should not be used for the majority of newly diagnosed patients with CLL/SLL who are older and/or have comorbidities. Novel agents (such as ibrutinib) have resulted in improvements in long-term clinical outcomes, but the majority of patients continue treatment for a long period. Venetoclax + obinutuzumab combination therapy (V+G) was approved in the US and the European Union based on the results of CLL14 study, which demonstrated statistically significant prolongation of PFS and high complete remission (CR) rate during a fixed treatment period of 12 months. Also, a high CR rate and prolongation of PFS are expected with a fixed treatment period of 15 months for venetoclax + ibrutinib combination therapy (V+I) based on preliminary data from the overseas Phase 2 CAPTIVATE study. Therefore, there is an unmet medical need in Japan for the development of new treatments in CLL/SLL that are not only better tolerated by all patients, including patients who are older and/or have

	comorbidities that comprise the majority of CLL/SLL patients, but that also produce deeper and more durable responses in fixed treatment duration.
Objective(s) and Endpoint(s):	Objectives <u>Primary Objective</u> The primary objective is to evaluate the efficacy of venetoclax in combination with obinutuzumab (V+G, Cohort 1) or with ibrutinib (V+I, Cohort 2) in Japanese subjects with previously untreated CLL/SLL. <u>Secondary Objective</u> The secondary objectives are to evaluate the safety of the V+G and V+I combinations, and to further characterize their efficacy. For the V+G combination only, the tolerability will also be evaluated in Japanese subjects. Endpoints <u>Primary Endpoint</u> The primary efficacy endpoint is the CR/complete remission with an incomplete marrow recovery (CRi) rate, as assessed by an Independent Review Committee (IRC) per modified 2008 International Workshop on Chronic Lymphocytic Leukemia (iwCLL) criteria for tumor response. <u>Secondary Endpoints</u> The secondary endpoints are the following: 1. CR/CRi rate as assessed by investigator per 2008 iwCLL. 2. Overall response rate (ORR), defined as the proportion of subjects with a best overall response of CR, CRi, partial remission (PR) or nodular partial remission (nPR) per 2008 iwCLL criteria as assessed by an IRC. 3. ORR, defined as the proportion of subjects with a best overall response of CR, CRi, PR or nPR per 2008 iwCLL criteria as assessed by investigator. 4. PFS, defined as the time from the date of first dose of any study drug until the date of disease progression or death due to any cause, whichever occurs first, as determined by an IRC according to iwCLL criteria. 5. PFS, defined as the time from the date of first dose of any study drug until the date of disease progression or death due to any cause, whichever occurs first, as determined by the investigator according to iwCLL criteria. 6. Duration of response (DOR), defined as the time from the first occurrence of overall response (CR, CRi, PR or nPR) until disease progression or death due to any cause, whichever occurs first, as determined by an IRC according to iwCLL criteria. 7. Duration of response (DOR), defined as the time from the first occurrence of overall response (CR, CRi, PR or nPR) until disease progression or death due to any cause, whichever

	occurs first, as determined by the investigator according to iwCLL criteria. 8. Overall survival (OS), defined as the time from the date of the first dose of any study drug until death due to any cause. 9. Time to progression (TTP), defined as the time from the date of first dose of any study drug until the date of disease progression, as determined by an IRC according to iwCLL criteria. Time to progression (TTP), defined as the time from the date of first dose of any study drug until the date of disease progression, as determined by the investigator according to iwCLL criteria.
Investigator(s):	Multicenter.
Study Site(s):	Approximately 20 sites in Japan.
Study Population and Number of Subjects to be Enrolled:	Approximately 20 adult Japanese subjects with previously untreated CLL/SLL (10 subjects per cohort).
Investigational Plan:	This is a Phase 2, open-label, multicenter, non-comparator, two-cohorts study of previously untreated CLL/SLL subjects. Subjects will be assigned to one of two treatment groups via 1:1 variable alternating assignment. The study will explore safety and efficacy of two treatment arms: • Venetoclax + obinutuzumab (V+G; Cohort 1) • Venetoclax + ibrutinib (V+I; Cohort 2)
Key Eligibility Criteria:	• Adult male or female, at least ≥ 65 years old; or 20 to 64 years old and have at least 1 of the following: • Cumulative Illness Rating Scale (CIRS) score > 6 • Creatinine clearance (CrCl) estimated < 70 mL/min using Cockcroft-Gault equation • Subject must have measurable nodal disease (by computed tomography [CT]), defined as at least one lymph node > 1.5 cm in longest diameter. • Subjects with diagnosed CLL/SLL that requires treatment according to the iwCLL criteria. • No transformation of CLL to aggressive non-Hodgkin lymphoma (NHL; Richter's transformation or pro-lymphocytic leukemia). • No previous treatment history for CLL/SLL.
Study Drug and Duration of Treatment:	Venetoclax will be provided by AbbVie as ■ mg, ■ mg, and ■ mg tablets that will be used to dose daily treatments starting at ■ mg up to ■ mg. The venetoclax dose will be administered according to a weekly ramp-up schedule over 5 weeks to the recommended daily dose of ■ mg. Obinutuzumab (Cohort 1) will be provided by AbbVie as ■ mg single-dose vials that will be used in ■, ■, and ■ mg

	intravenous (IV) treatments. Obinutuzumab will be administered via IV infusion on Day 1 of six 4-week cycles. Ibrutinib (Cohort 2) will be provided by AbbVie as [REDACTED] mg capsules that will be used to dose daily treatments of [REDACTED] mg.
Date of Protocol Synopsis:	19 March 2024

2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted?

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Chronic lymphocytic leukemia (CLL) is the most common leukemia in Western countries, representing approximately 30% of all adult leukemias. The incidence is higher in males than females¹ and increases with age, with the median age at diagnosis being 72 years.² There is a large difference in proportion of malignant lymphoma between the United States (US) and Japan was seen in CLL/small lymphocytic lymphoma (SLL) (Japan, 3.2%; US, 24.1%).³ In Western countries, the incidence rate is 5.1/100,000. In Japan, the rate is 0.5/100,000 and the estimated total number of CLL patients was reported to be approximately 2,000 in the 2014 patient survey (Statistics and Information Division, Minister's Secretariat, Ministry of Health, Labour and Welfare), indicating that CLL is a rare disease with a small number of patients.⁴

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. The disease has a characteristic immunophenotype, which includes co-expression of CD5 (T-cell antigen) and the B-cell surface antigens CD19, CD20, and CD23, and low levels of surface immunoglobulin, CD20 and CD79b compared with normal B cells.⁵ The clonality of the disease is confirmed by the presence of a single immunoglobulin light chain. Small lymphocytic lymphoma is defined as a tumor of the same cells as CLL without infiltration into peripheral blood or bone marrow.⁶⁻⁸ SLL is considered to be the same disease concept as CLL, and the treatment for SLL follows the treatment for CLL.⁴ Throughout this protocol, use of the term "CLL" refers to CLL and SLL.

Chronic lymphocytic leukemia generally follows an indolent course. Treatment is usually associated with a high rate of initial responses followed inevitably by relapse. Subsequent treatments can induce remissions, but at a progressively lower rate with responses of shorter duration. Although the median survival of patients with CLL is around 10 years, the disease has an extremely variable clinical course and the prognosis depends on disease stage and a range of prognostic biomarkers. Two clinical staging systems have been developed by Rai⁹ and Binet.¹⁰ They are both widely used and are an accepted prognostic tool, and it was estimated that the median overall survival (OS) is approximately 6.5 years in patients who are high risk or stage C per Rai or Binet respectively.⁶ There are also a number of biomarkers that can help predict patient prognosis with CLL. In particular, patients with del(17p) or TP53 mutation have the poorest prognosis. Approximately 5% to 10% of patients with early stage CLL have del(17p) and/or TP53 mutation and this rate increases with subsequent treatment lines up to 40% in advanced refractory CLL.¹¹⁻¹³

According to the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) guideline, treatment will be started when the disease is judged to be active disease.⁷ Starting treatments are considered based on the patient's condition (physical fitness) and the presence of the 17p deletion/TP53 mutation, which is a poor prognostic factor. Despite recent advances in treatment, CLL remains an incurable disease. The objective of the treatment of slowly progressing CLL is to control the disease, improve

symptoms, and prolong survival. At the same time, the aim is to maintain and improve the quality of life by minimizing toxicity with a tolerable treatment regimen even in elderly patients.

The Japanese Society of Hematology guidelines for Hematopoietic Malignancy 2018 (hereinafter, "JSH Guidelines") mainly recommends ibrutinib monotherapy and fludarabine + cyclophosphamide ± rituximab (FCR) for previously untreated fit patients. In particular, FCR is recommended for patients without 17p deletion/TP53 mutation, and ibrutinib is recommended for patients with 17p deletion and elderly patients. For unfit patients, JSH guidelines recommends ibrutinib monotherapy regardless of the status of the 17p deletion/TP53 mutation. In addition, reduced FC ± R therapy and bendamustine ± rituximab therapy are also recommended.

Combination therapy with acalabrutinib ± obinutuzumab, ibrutinib monotherapy and venetoclax + obinutuzumab (V+G) are recommended as preferred regimens for fit and unfit patients, including patients with 17p deletion, according to the National Comprehensive Cancer Network (NCCN) guidelines.

Rationale for the Combination of Venetoclax with Obinutuzumab

Obinutuzumab (Gazyva™ also known as GA101 and RO5072759) is a novel, humanized, type II glycoengineered monoclonal antibody directed against the CD20 antigen, which is found on most malignant and benign cells of B cell origin. Obinutuzumab was derived by humanization of the parental B Ly1 mouse antibody and subsequent glycoengineering, leading to the following characteristics: high affinity binding to the CD20 antigen, low complement-dependent cytotoxicity activity, high direct cell death induction, high antibody-dependent cellular cytotoxicity, and antibody-dependent cellular phagocytosis. Currently, in Japan, obinutuzumab is only approved for CD20 positive follicular lymphoma. However, in 2013, the US Food and Drug Administration (FDA) approved obinutuzumab for the treatment of patients with previously untreated CLL. In addition, in 2019, the US FDA granted AbbVie approval for supplemental new drug application for a new indication of V+G in previously untreated patients with CLL or SLL based on data from the pivotal Phase 3 study BO25323/CLL14 and supportive data from the Phase 1b study GP28331.

Rationale for the Combination of Venetoclax with Ibrutinib

Venetoclax is an oral, potent and selective inhibitor of B-cell lymphoma-2 (BCL-2). Overexpression of BCL-2 contributes to the pathogenesis of CLL/SLL, and BCL-2 is frequently overexpressed in CLL/SLL, indicating that CLL/SLL cell survival generally depends on BCL-2. By directly inhibiting BCL-2, venetoclax releases pro-apoptotic proteins and then induces rapid apoptosis in cancer cells. In 2019, the US FDA granted venetoclax breakthrough therapy designation for the treatment of adult patients with CLL in combination with obinutuzumab. In Japan, venetoclax was approved for relapsed/refractory CLL/SLL in 2019. Ibrutinib is an oral, once-daily Bruton's tyrosine kinase inhibitor. Currently, in Japan, ibrutinib is approved for CLL/SLL and relapsed/refractory mantle cell lymphoma. Ibrutinib and venetoclax have complementary mechanisms of action targeting distinct B-cell pathways involved in the propagation of CLL cells. Ibrutinib arrests CLL cell proliferation. Venetoclax is pro-apoptotic and induces early cell death. Ibrutinib also affects the adhesion and migration of CLL cells resulting in rapid efflux of CLL cells from tissue compartments, especially lymph node and spleen, into the peripheral blood. Venetoclax treatment results in effective clearance of the blood and bone marrow, but residual disease can be observed in lymph nodes. Together, the two drugs are expected to provide complementary and

effective clearance of disease from all compartments. Venetoclax + ibrutinib combination has been evaluated in the overseas Phase 3 study (GLOW; 54179060CLL3011).

Unmet Medical Need

Deep remissions and clinically significant progression-free survival (PFS) can be achieved with chemo immunotherapy combinations, such as fludarabine-based regimens, but these intensive regimens cannot or should not be used for the majority of newly diagnosed patients with CLL/SLL who are older and/or have comorbidities. Novel agents (such as ibrutinib) have resulted in improvements in long-term clinical outcomes, but the majority of patients continue treatment for a long period. V+G was approved in the US and the European Union based on the results of CLL14 study, which demonstrated statistically significant prolongation of PFS and high complete remission (CR) rate during a fixed treatment period of 12 months. Also, a high CR rate and prolongation of PFS are expected with a fixed treatment period of 15 months for V+I based on preliminary data from the overseas Phase 2 CAPTIVATE study.

Therefore, there is an unmet medical need in Japan for the development of new treatments in CLL/SLL that are not only better tolerated by all patients, including patients who are older and/or have comorbidities that comprise the majority of CLL/SLL patients, but that also produce deeper and more durable responses in fixed treatment duration.

2.2 Benefits and Risks to Subjects

In the overseas Phase 3 study CLL14, 432 patients were randomized, and a pre-planned interim analysis at 110 events (65% of total planned PFS events), with all patients having been off study treatment for at least 12 months, was reviewed by the Independent Data Monitoring Committee (IDMC) and confirmed that the study had met its primary efficacy endpoint by crossing the pre-specified boundary. Therefore, the IDMC recommended that the study team be unblinded. This interim analysis is considered the primary analysis and is presented below. At clinical cutoff date [CCOD] 17 August 2018, and with a median follow-up of 28.8 months, the investigator-assessed PFS was higher in patients in the V+G arm than in patients in the obinutuzumab and chlorambucil (GClb) arm (hazard ratio [HR] = 0.35; 95% confidence interval [CI]: 0.23 ~ 0.53; $p < 0.0001$). A total of 30 events occurred in the V+G arm (14 patients with progressive disease [PD] and 16 deaths) versus 77 events in the GClb arm (69 patients with PD and 8 deaths). Median PFS was not reached in either study arm, and the 2-year estimate for PFS was 64.10% (95% CI: 57.39 to 70.81) in the GClb arm compared with 88.15% (95% CI: 83.69 to 92.60) in the V+G arm. These results were supported by sensitivity analyses related to the censoring mechanism for PFS. Unstratified and subgroup analyses supported the robustness of the results. Also, as of the 17 August 2018 data cutoff, the results of analysis of PFS based on independent review committee (IRC) assessment were similar to the results of analysis based on investigator assessment, with a high concordance rate of 98.1%. PFS based on IRC assessment was also significantly longer in the V+G group than in the GClb group (HR = 0.33; 95% CI: 0.22 ~ 0.51, $p < 0.0001$). There were 29 events (progressive disease in 14 patients, death in 15 patients) in the V+G group and 79 events (progressive disease [PD]: 71 patients, death: 8 patients) in the GClb group. The estimated median PFS was not reached in either group. The estimated 2-year PFS was 63.70% (95% CI: 56.99 ~ 70.42) in the GClb group and 88.59% (95% CI: 84.20 ~ 92.98) in the V+G group. Improvement of PFS observed with V+G was statistically significant and clinically meaningful. All key secondary hierarchically tested efficacy endpoints showed consistent, statistically significant benefit apart from OS, which was expected as the data was considered too immature to be evaluable for OS at the time of the CCOD. At the end of

treatment (EOT) assessment, there was a statistically significant difference ($p < 0.0001$) in the proportion of patients with a complete response of CR/complete remission with an incomplete marrow recovery (CRi) per investigator assessment between the V+G arm (107 of 216, 49.5%) and the GClb arm (50 of 216, 23.1%). Thus, patients treated with V+G achieved a higher rate of CR/CRi in comparison to the GClb arm at EOT, and the difference was clinically meaningful. In addition, the results of sub-analysis in subjects with TP 53 deletion and/or mutation (24 in V+G [14.0%], 22 in GClb [13.7%]) showed that the investigator-assessed PFS estimate at 2 years was 32.7% in the GClb group and 73.9% in the V+G group, HR = 0.31, 95% CI: 0.13 ~ 0.76.¹⁴

In the overseas Phase 2 study (CAPTIVATE), 159 patients were enrolled in the study in a fixed duration cohort (FD cohort). The CR rate assessed by the investigator, the primary endpoint, had showed significantly outstanding results as of the data cutoff date of 15 December 2020; CR/CRi rate per investigator assessment in subjects without del17p, 55.9% (76/136) (95% CI: 47.5, 64.2), significantly higher than the study assumption of 37% (1-side $p < 0.0001$) as well as the 40% rate with the historical comparator of FCR in CLL10 which excluded patients with del17p.¹⁵ Twenty-four month PFS was 96.2%. Complete remission/CRi was observed in 55.3% (88 /159) of subjects including patients with del17p and 24 months estimated PFS was 94.8%. Outcomes of primary and secondary endpoints in the FD cohort are similar in subjects without del17p and all subjects (including del17p). The majority ($\geq 90\%$, 32/34 patients) of subjects with baseline tumor lysis syndrome (TLS) high risk reduced to low or medium risk (based on tumor bulk reductions) with the 3-cycle ibrutinib lead in prior to venetoclax ramp-up. Additionally, an overseas Phase 3 study (GLOW) is ongoing to evaluate efficacy of V+I combination.

In conclusion, based on the overseas Phase 2 and Phase 3 studies mentioned above, it is anticipated that the combination therapy of V+G and V+I exhibit different mechanisms of actions, and combination therapy of venetoclax with either of these drugs could improve tumor response and delay progression of disease or completely avoid the occurrence of resistance. Safety profiles of both drugs seem to be compatible, especially in light of a chemotherapy-free setting.

For further details, please see findings from completed studies, including safety data in the current venetoclax and obinutuzumab Investigator's Brochures^{16,17} and ibrutinib package insert.¹⁸

Considering the coronavirus-2019 (COVID-19) pandemic and based on the information to date, the benefit and risk to subjects participating in this study have been re-evaluated. Subjects receiving venetoclax, ibrutinib, or obinutuzumab may be at an increased risk for COVID-19 infection or experience serious illness if infected. Management of these adverse events (AEs) will be made on a case-by-case basis with consideration of benefit/risk. However, based on the population, the disease being studied, and the anticipation that COVID-19 related risks are unknown between study subjects and the broader population of subjects receiving treatment for CLL/SLL, no known change to the benefit/risk balance for subjects in this study is expected.

3 OBJECTIVES AND ENDPOINTS

3.1 Objectives, Hypotheses, and Estimands

Primary

The primary objective is to evaluate the efficacy of venetoclax in combination with obinutuzumab (V+G, Cohort 1) or with ibrutinib (V+I, Cohort 2) in Japanese subjects with previously untreated CLL/SLL.

The corresponding estimands of interest for evaluating the primary objective are:

1. The CR/CRi rate for subjects treated with V+G (Cohort 1) based on objective assessment by an IRC.
2. The CR/CRi rate for subjects treated with V+I (Cohort 2) based on objective assessment by an IRC.

For each of these regimens, efficacy will be considered "established" if the lower bound of the corresponding 95% CI for CR/CRi rate is greater than the threshold of 10%.

Secondary

The secondary objectives are to evaluate the safety of the V+G and V+I combinations, and to further characterize their efficacy. For the V+G combination only, the tolerability will also be evaluated in Japanese subjects.

The hypothesis corresponding to the secondary objectives is that the V+G and V+I combinations are reasonably safe and effective for Japanese subjects.

See Section 3.3 for additional details on secondary endpoints, and the Statistical Analysis Plan (SAP) for additional details on corresponding estimands.

3.2 Primary Endpoint

The primary efficacy endpoint is the CR/CRi rate, as assessed by an IRC per modified 2008 International Workshop on Chronic Lymphocytic Leukemia Working Group (iwCLL) criteria for tumor response (refer to [Appendix D](#)).

3.3 Secondary Endpoint(s)

Secondary Endpoint(s)

The secondary endpoints are the following:

1. CR/CRi rate as assessed by investigator per 2008 iwCLL.

2. Overall response rate (ORR), defined as the proportion of subjects with a best overall response of CR, CRi, partial remission (PR) or nodular partial remission (nPR) per 2008 iwCLL criteria as assessed by an IRC.
3. ORR, defined as the proportion of subjects with a best overall response of CR, CRi, PR or nPR per 2008 iwCLL criteria as assessed by investigator.
4. PFS, defined as the time from the date of first dose of any study drug until the date of disease progression or death due to any cause, whichever occurs first, as determined by an IRC according to iwCLL criteria.
5. PFS, defined as the time from the date of first dose of any study drug until the date of disease progression or death due to any cause, whichever occurs first, as determined by the investigator according to iwCLL criteria.
6. Duration of response (DOR), defined as the time from the first occurrence of overall response (CR, CRi, PR or nPR) until disease progression or death due to any cause, whichever occurs first, as determined by an IRC according to iwCLL criteria.
7. DOR, defined as the time from the first occurrence of overall response (CR, CRi, PR or nPR) until disease progression or death due to any cause, whichever occurs first, as determined by the investigator according to iwCLL criteria.
8. OS, defined as the time from the date of the first dose of any study drug until death due to any cause.
9. Time to progression (TTP), defined as the time from the date of first dose of any study drug until the date of disease progression, as determined by an IRC according to iwCLL criteria.
10. TTP, defined as the time from the date of first dose of any study drug until the date of disease progression, as determined by the investigator according to iwCLL criteria.

3.4 Safety Endpoints

Safety evaluations include AE monitoring, physical examinations, vital sign measurements, and clinical laboratory testing (hematology and chemistry) as measures of safety and tolerability for the entire study duration.

3.5 Pharmacokinetic Endpoints

Blood samples to assess plasma concentration of venetoclax and ibrutinib and serum concentration of obinutuzumab will be obtained at specified time points as indicated in [Appendix L](#).

3.6 Biomarker Research Endpoints

Biomarker values are exploratory endpoints in this study and may include but are not limited to: determination of undetectable minimal residual disease (uMRD) status at pre-specified study endpoints, evaluation of the relationship between baseline prognostic factors (e.g., immunoglobulin variable region heavy chain [IgHV], *TP53*, del(17p), and other somatic mutations) with clinical outcome parameters.

Undetectable minimal residual disease is defined as less than one CLL cells detected among 10,000 leukocytes.

Prespecified biomarker endpoints include:

- uMRD rates 3 months after EOT
- Overall uMRD rate

Biospecimens (whole blood) will be collected at specified time points ([Appendix L](#)) throughout the study, to evaluate known and/or novel disease-related or drug-related biomarkers in circulation. Some of these samples may be optional. Types of biomarkers may include nucleic acids, proteins, lipids, and/or metabolites, either free or in association with particular cell types. Further details regarding the biomarker research rationale and collection time points are located in the Operations Manual, Section 3.16 and [Appendix N](#).

Provision of mandatory biospecimens for biomarker research is required but they will not be collected from sites where local regulations do not allow for the collection, use, and storage of samples as described in the protocol.

Non-prespecified biomarker assessments may be used to assess and generate prognostic, predictive, pharmacodynamic, or surrogate biomarker signatures. These assessments may be explored in the context of CLL or related conditions and/or venetoclax or drugs of similar classes. Additionally, they may include, but are not limited to evaluation of minimal residual disease (MRD) kinetics (i.e., on therapy and after therapy completion) and potential biomarker signatures associated with relapse. The results from some of the biomarker analyses are exploratory in nature and may or may not be included with the clinical study report.

The samples may also be used to develop new therapies, research methods, or technologies. In addition, samples from this study may be stored for future use. Samples may then be used to validate putative biomarker signatures obtained from a prospective study, leading to the development of diagnostic tests. 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 Phase 2, open-label, multicenter, non-comparator, two-cohorts study of previously untreated CLL/SLL subjects. Subjects will be assigned to one of two treatment groups via 1:1 variable alternating assignment. The study will explore safety and efficacy of two treatment arms:

- Venetoclax + obinutuzumab (V+G; Cohort 1)
- Venetoclax + ibrutinib (V+I; Cohort 2)

The study will enroll 20 subjects (10 subjects per cohort) across 20 sites in Japan.

The study will consist of Screening, Treatment, and Follow-up periods. The schematic of the study is shown in [Figure 1](#). Further details regarding study procedures are located in the Operations Manual ([Appendix N](#)).

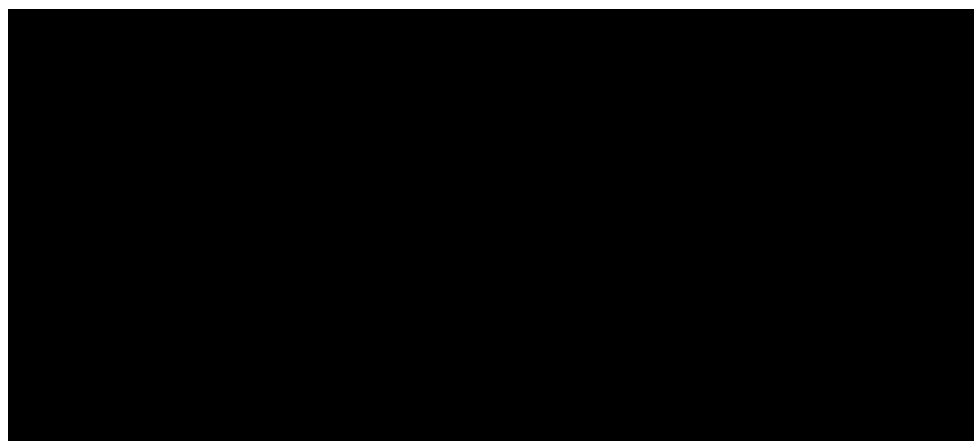
Efficacy will be examined as follows:

- Cohort 1 (V+G) Cycle 4 Day 1, Cycle 7 Day 1, and Cycle 9 Day 1, and EOT and follow-up visits.
- Cohort 2 (V+I) - Cycle 4 Day 1, Cycle 9 Day 1, and Cycle 15 Day 1, and EOT and follow-up visits.

In Cohort 1, dose-limiting toxicities (DLTs) will be evaluated in the first 6 subjects, from Cycle 1 Day 22 for a minimum of 5 weeks and at least 1 week of venetoclax dosing at [REDACTED] mg, in order to confirm the initial safety and tolerability in Japanese subjects. After the completion of the DLT evaluation period in the first 6 subjects, the Sponsor will review all available safety data to evaluate the tolerability of venetoclax in combination with obinutuzumab in Japanese subjects. If there are 0 or 1 DLTs in the first 6 subjects, enrollment will proceed. If DLTs are observed in 2 or more of the first 6 subjects, further enrollment in Japan will be interrupted and additionally, a detailed safety assessment will be conducted. The Sponsor will provide the Independent Safety Monitor (ISM) with results of the safety evaluation and the Sponsor's conclusion on tolerability. The ISM will perform a review of the data and provide an opinion back to the Sponsor.

See Section 5 for information regarding eligibility criteria.

Figure 1. Study Schematic



Note: A cycle will be defined as 28 days in both cohorts.

Cohort 1 (V+G)

Subjects assigned to Cohort 1 (V+G) will receive obinutuzumab [REDACTED] mg or [REDACTED] mg, depending on splitting rules, intravenously (IV) on Cycle 1 Day 1 (if [REDACTED] mg administered on Day 1, then [REDACTED] mg will be administered on Day 2) and then [REDACTED] mg on [REDACTED] of Cycle 1. For all subsequent cycles (up through the end of Cycle 6) subjects will receive obinutuzumab [REDACTED] mg on Day 1. Venetoclax will be administered with a 5-step dose ramp-up beginning with a [REDACTED] mg dose (Cycle 1 [REDACTED]) to reach

the final dose of [REDACTED] mg (Cycle 2 [REDACTED]) (Table 1) to reduce the risk of TLS. Venetoclax will be continued at [REDACTED] mg daily thereafter through Cycle 12.

Table 1. Venetoclax Dose Ramp-Up Levels (Cohort 1)

Daily Venetoclax Dose (mg)					
Week 1	Week 2	Week 3	Week 4	Week 5	Subsequent Cycles
Cycle 1	Cycle 2	Cycle 2	Cycle 2	Cycle 2	Cycles 3 through Cycle 12 [REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Cohort 2 (V+I)

Subjects assigned to Cohort 2 (V+I) will receive ibrutinib [REDACTED] mg orally (PO) once a day (QD) for 15 cycles, starting with 3 cycles of ibrutinib monotherapy. Venetoclax will be administered with a 5-step dose ramp-up beginning at Cycle 4 (Table 2). The combination of V+I will be given for 12 cycles (through Cycle 15).

Table 2. Venetoclax Dose Ramp-Up Levels (Cohort 2)

Daily Venetoclax Dose (mg)					
Week 1	Week 2	Week 3	Week 4	Week 5	Subsequent Cycles
Cycle 4	Cycle 4	Cycle 4	Cycle 4	Cycle 5	Cycle 5 [REDACTED] and Cycles 6 through Cycle 15
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

4.2 Discussion of Study Design

Choice of Control Group

Not applicable.

Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. All efficacy and safety-related 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.

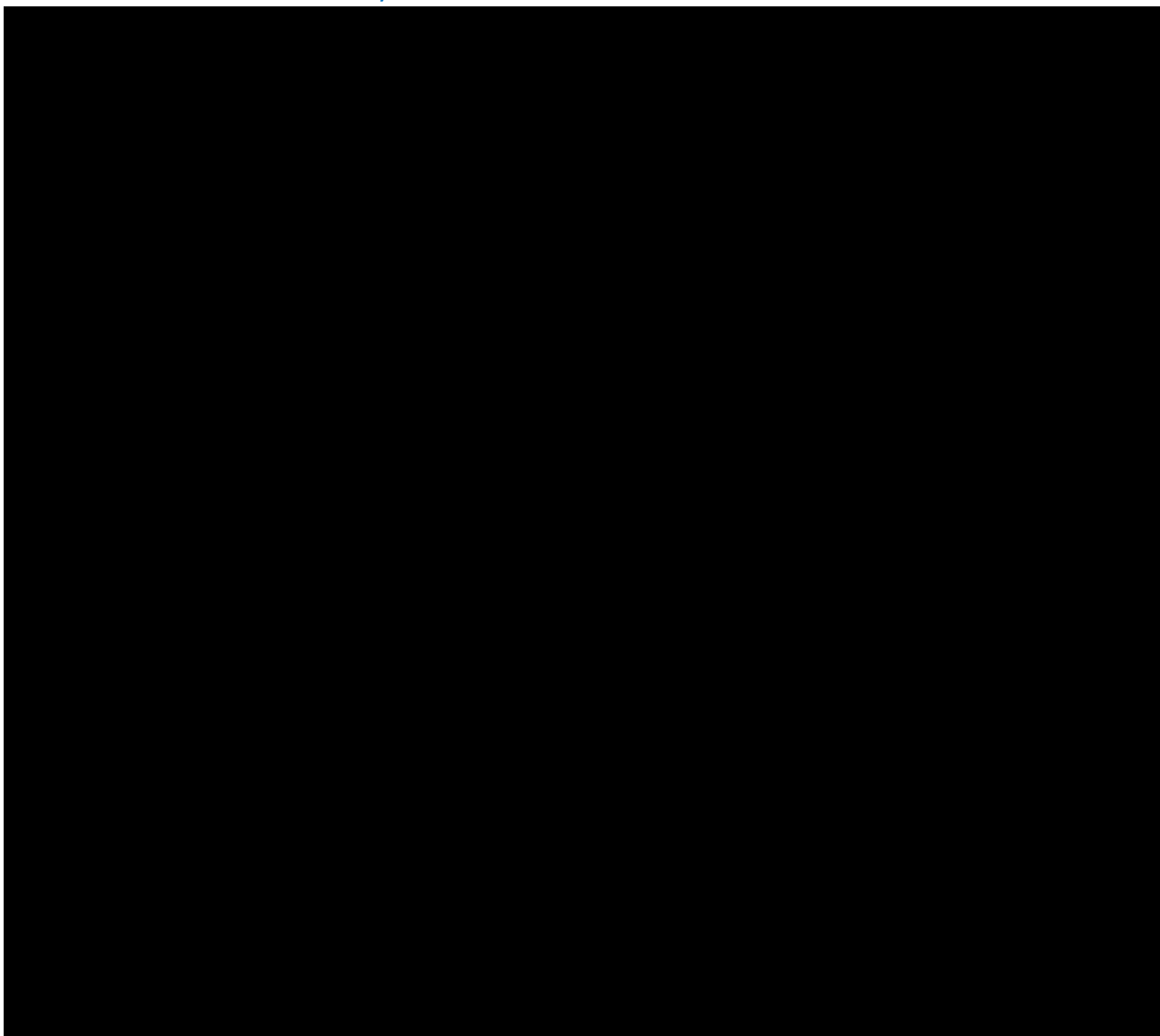
Suitability of Subject Population

Previously untreated CLL/SLL patients will be enrolled in this study. The patients aged 64 or younger, are required to meet the criteria of Cumulative Illness Rating Scale (CIRS) > 6 and/or creatinine clearance (CrCl) < 70 mL/min. The patients aged 65 years or older were allowed to be enrolled without setting

criteria for CIRS score or CrCl. In addition, patients with 17p deletion/TP53 mutation can be enrolled in both cohorts. The populations are selected to align with the patient populations of two Phase 3 studies, CLL14 and GLOW because this study is a bridging study to these two Phase 3 studies.

Regarding patients with 17p deletion/TP53 mutation, efficacy and safety of V+G has been confirmed in this population. In addition, V+G is recommended as a preferred regimen of the first line therapy for patients with 17p deletion/TP53 mutation in the NCCN Guidelines Version 4 2021. Efficacy and safety of V+I in this population has been confirmed in the CAPTIVATE study, a Phase 2 study of V+I in subjects with treatment-naïve CLL/SLL.

Selection of Doses in the Study



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 **individuals**, at least ≥ 65 years old
OR
 20 to 64 years old and have at least 1 of the following:
 - CIRS score > 6
 - CrCl estimated < 70 mL/min using Cockcroft-Gault equation ([Appendix E](#))
- ✓ 3. **Laboratory values** meeting the following criteria within the screening period prior to the first dose of study drug:
 - 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:
 - Absolute neutrophil count (ANC) $> 1.0 \times 10^9/L$
 - Platelet counts $> 50 \times 10^9/L$

In cases of thrombocytopenia clearly due to marrow involvement of CLL (per the discretion of the investigator), platelet count should be $> 10 \times 10^9/L$

- Total hemoglobin > 9 g/dL (without transfusion support, unless anemia is due to marrow involvement of CLL)
- Alanine transaminase (ALT), aspartate transaminase (AST), and total bilirubin $\leq 2.0 \times$ upper limit of normal (ULN), unless directly attributable to the subject's CLL;
- International normalized ratio (INR) or prothrombin time (PT) $\leq 1.5 \times$ ULN;
- Activated partial thromboplastin time $\leq 1.5 \times$ ULN (unless abnormalities are unrelated to coagulopathy or bleeding disorder);
- Creatinine clearance ≥ 30 mL/min (using Cockcroft-Gault equation [[Appendix E](#)]);
 - A 24-hour urine collection may be undertaken to determine CrCl
- **For CLL subjects only:** Historical data that confirms an absolute lymphocyte count (ALC) $\geq 5,000$ cells/ μ L at the time of diagnosis is required if screening ALC < 5,000 cells/ μ L.
- ✓ 4. Subject must have Eastern Cooperative Oncology Group (ECOG) Performance Status ≤ 2 .
- ✓ 5. Are willing and able to comply with procedures required in this protocol.
- ✓ 6. No individual organ/system impairment score of 4 as assessed by the CIRS definition limiting the ability to receive the treatment regimen of this trial with the exception of eyes, ears, nose, and throat organ system (note that symptoms related to CLL should not be included in the patient's screening CIRS score) ([Appendix F](#)).

Disease/Condition Activity

- ✓ 7. Subject must have measurable nodal disease (by computed tomography [CT]), defined as at least one lymph node > 1.5 cm in longest diameter.
- ✓ 8. Subjects with diagnosed CLL/SLL according to the iwCLL criteria. Subjects with active CLL/SLL that requires treatment according to the iwCLL criteria.
- ✓ 9. No transformation of CLL to aggressive NHL (Richter's transformation or pro-lymphocytic leukemia).
- ✓ 10. No previous treatment history for CLL/SLL.
- ✓ 11. No known history of confirmed progressive multifocal leukoencephalopathy.
- ✓ 12. No uncontrolled autoimmune hemolytic anemia or immune thrombocytopenia (Coombs positivity in the absence of hemolysis is not an exclusion).
- ✓ 13. No infections requiring IV treatment (Grade 3 or 4) within 2 months prior to enrollment.
- ✓ 14. No known central nervous system involvement.

Subject History

- ✓ 15. No history of renal, neurologic, psychiatric, endocrinologic, metabolic, immunologic, or hepatic condition that in the opinion of the investigator would adversely affect a subject's participation in the study.

- ✓ 16. No history of **any malignancy**, other than CLL/SLL, except for conditions as listed below if patients have recovered from the acute side effects incurred as a result of previous therapy:
 - Malignancies surgically treated with curative intent and with no known active disease present for ≥3 years before subject enrollment.
 - 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.
- ✓ 17. No history of clinically significant (per investigator's judgment) **drug or alcohol abuse** within the last 12 months.
- ✓ 18. No prior exposure to venetoclax, obinutuzumab or ibrutinib.
- ✓ 19. No known allergy to either xanthine oxidase inhibitors or rasburicase for subjects at risk for TLS.
- ✓ 20. 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 (e.g., trehalose).
- ✓ 21. No history of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies or known sensitivity or allergy to murine products.
- ✓ 22. No history of clinically significant medical conditions or any other reason that the investigator determines would **interfere with the subject's participation** in this study or would make the subject an unsuitable candidate to receive study drug.
- ✓ 23. No serious medical condition or abnormality in clinical laboratory tests that, in the investigator's judgment, precludes the patient's safe participation in and completion of the study.
- ✓ 24. No history of clinically significant medical conditions other than the indication being studied or any other reason that the investigator determines would interfere with the subject's participation in this study, would make the subject an unsuitable candidate to receive study drug, or would put the subject at risk by participating in the protocol.
- ✓ 25. No active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection.
 - History of HCV may enroll if their HCV RNA level is undetectable after antiviral therapy.
 - History of HBV infection (without active infection at Screening) may enroll if there is no evidence of active HBV infection. Subjects with hepatitis B surface antigen (HBsAg) negative and anti-HBs antibody positive or anti-HBc antibody positive may participate if HBV DNA quantitative is < 20 IU/ml. Refer to the latest Japan Society of Hepatology guideline.¹⁹
- ✓ 26. No known infection with human immunodeficiency virus (HIV).
- ✓ 27. Subjects must not have major surgery within 4 weeks of first dose of study treatment.
- ✓ 28. No known bleeding disorders (e.g., von Willebrand's disease or hemophilia).
- ✓ 29. Subjects must not have currently active, significant Child-Pugh Class B or C hepatic impairment according to the Child-Pugh classification (see [Appendix K](#)).

- ✓ 30. No history of stroke or intracranial hemorrhage within 6 months prior to enrollment.
- ✓ 31. No active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class 3 or 4 congestive heart failure as defined by the New York Heart Association (NYHA) Functional Classification; or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to enrollment.
- ✓ 32. No known active SARS-CoV-2 infection. If a subject has signs/symptoms suggestive of SARS-CoV-2 infection, the subject must have a negative molecular (e.g., polymerase chain reaction [PCR]) test result. Note: SARS-CoV-2 diagnostic tests should be applied following local requirements/recommendations.
 - Subjects who do not meet SARS-CoV-2 infection eligibility criteria must be screen failed and, may only rescreen after they meet the following SARS-CoV-2 infection viral clearance criteria:
 - At least 14 days have passed since first PCR test result in asymptomatic patients or 14 days since recovery, defined as resolution of fever without use of antipyretics and improvement in symptoms.

Contraception

- ✓ 33. Female who is not pregnant or breastfeeding and is not considering becoming pregnant or donating eggs (oocytes). Females must follow this eligibility criterion during the study or for at least 18 months after the last dose of obinutuzumab, 3 months after the last dose of ibrutinib, or 1 month after the last dose of venetoclax, **whichever is longer**.
- ✓ 34. For all females of child-bearing potential; a **negative serum pregnancy test** at the Screening Visit and a negative urine pregnancy test at baseline prior to the first dose of study drug.
- ✓ 35. Male and female subjects of reproductive potential who agree to use both a highly effective method of birth control (e.g., implants, injectables, combined oral contraceptives, some intrauterine devices [IUDs], complete abstinence, or sterilized partner) and a barrier method (e.g., condoms, cervical ring, sponge, etc.) during the period of therapy and for at least 18 months after the last dose of obinutuzumab, 3 months after the last dose of ibrutinib, or 1 month after the last dose of venetoclax, whichever is longer.
- ✓ 36. **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, 3 months after the last dose of ibrutinib, or 1 month after the last dose of venetoclax, whichever is longer, to practice the protocol-specified contraception.
- ✓ 37. If male, subject must not be considering fathering a child or donating sperm during the study or for at least 18 months after the last dose of obinutuzumab, 3 months after the last dose of ibrutinib, or 1 month after the last dose of venetoclax, whichever is longer.

Concomitant Medications

- ✓ 38. No chronic use of corticosteroids more than 20 mg/day of prednisone or its equivalent within 7 days of initiation of study treatment.

- ✓ 39. Subject must not have received (or known need to receive in the future) any of the following agents:
 - Strong and moderate CYP3A inhibitors and inducers within 7 days prior to the first dose of study drug administration.
 - Consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges), or star fruit within 3 days prior to the first dose of study drug and throughout venetoclax and/or ibrutinib administration.
 - Anticoagulation with warfarin or equivalent vitamin K antagonists (e.g., phenprocoumon).
- ✓ 40. 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 or was previously enrolled in this study.
- ✓ 41. Subject must not have received any live attenuated vaccine within 28 days prior to the first dose of study drug or expected need of live vaccination during study participation including at least 28 days after the last dose of study drug

5.2 Contraception Recommendations

Contraception Requirements for Females

Subjects must follow the following contraceptive guidelines as specified:

1. Females of 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 female, age > 55 years with no menses for 12 or more months without an alternative medical cause.
- Postmenopausal female, age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND a follicle-stimulating hormone level ≥ 30 IU/L.
- Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy).

2. Females, of Childbearing Potential

- Females of childbearing potential must avoid pregnancy while taking study drug(s) and for at least 18 months after the last dose of obinutuzumab, or at least 3 months after the last dose of ibrutinib or 1 month after the last dose of venetoclax, whichever is longer.
- Females must commit to one of the following methods of birth control:
 - Combined (estrogen and progestogen containing) hormonal birth control (oral) associated with inhibition of ovulation initiated at least 30 days prior to study baseline Day 1.
 - Progestogen-only hormonal birth control (oral) associated with inhibition of ovulation initiated at least 30 days prior to study baseline Day 1.

- Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure).
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- Vasectomized partner (provided the partner has received medical confirmation of the surgical success of the vasectomy and is the sole sexual partner of the trial subject).
- Practice true abstinence, defined as: 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).
- If required per local guidelines, male condom with or without spermicide should be used in addition to one of the birth control methods listed above (excluding true abstinence).

Contraception recommendations related to use of concomitant therapies prescribed should be based on the local label.

Contraception Requirements for Males

Male subjects who are sexually active with a female partner of childbearing potential, must agree **to use male 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, 3 months after the last dose of ibrutinib, or 1 month after the last dose of venetoclax, whichever is longer:

- His female partner(s) must also use at least 1 of the following methods of birth control:
 - Combined (estrogen and progestogen containing) hormonal birth control (oral) associated with inhibition of ovulation initiated at least 30 days prior to study baseline Day 1
 - Progestogen-only hormonal birth control (oral) associated with inhibition of ovulation initiated at least 30 days prior to study baseline Day 1
 - Bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure)
 - IUD
 - IUS
 - Vasectomized partner (provided the partner has received medical confirmation of the surgical success of the vasectomy and is the sole sexual partner of the trial subject).
 - Abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the patient, which is defined as: Refraining from heterosexual intercourse (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

5.3 Prohibited Medications and Therapy

Any non-study protocol-related chemotherapy and anticancer immunotherapy for other malignancy that is identified during study treatment, experimental therapy, or radiotherapy are prohibited while the subject is receiving study treatment.

A sample list of excluded and cautionary medications is provided in [Appendix G](#).

The following medications and foods are **prohibited** throughout the study:

- Any systemic CLL/SLL therapies other than the assigned treatment therapies. Patients who require the use of any of the excluded therapies listed below will be discontinued from study treatment.
 - Radiotherapy
 - Immunotherapy
 - Hormone therapy (other than contraceptives, hormone-replacement therapy, or megestrol acetate)
 - Any therapies intended for the treatment of lymphoma/leukemia whether approved or experimental (outside of this study)
- Strong and moderate CYP3A inhibitors

Note: not allowed within 7 days prior to the administration of the first dose of study drug and during the venetoclax dose ramp-up. These medications are cautionary once patients are receiving [REDACTED] mg per day of venetoclax (require venetoclax and ibrutinib dose reductions).
- Strong and moderate CYP3A inducers

Note: not allowed within 7 days prior to the administration of the first dose of study drug and during the venetoclax dose ramp-up. These medications are cautionary once patients are receiving [REDACTED] mg per day of venetoclax (avoid).
- Warfarin and other vitamin K antagonists (e.g., phenprocoumon) (only in Cohort 2).
- Corticosteroids at dosages equivalent to prednisone for > 14 days are prohibited until disease progression has occurred.
- Immunization with live attenuated vaccines.

Note: The safety of immunization with live virus vaccines following obinutuzumab therapy has not been studied. Thus, vaccination with live virus vaccines is not recommended during obinutuzumab treatment and until B cell recovery.
- Grapefruit or grapefruit products, Seville oranges (including marmalade containing Seville oranges, St. John's Wort), and starfruit (within 3 days before the first dose of study drug and throughout the trial).

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 from 28 days prior to study drug administration or receives during the study must be recorded through 30 days following last dose of study drug.

The following medications are **cautionary** throughout the study:

- Strong and moderate CYP3A inhibitors once patients are receiving [REDACTED] mg per day of venetoclax (require venetoclax and ibrutinib dose reductions)
- Strong and moderate CYP3A inducers once patients are receiving [REDACTED] mg per day of venetoclax (avoid)
- P-gp substrates (Note: If a narrow therapeutic index P-gp substrate must be used, it should be taken at least 6 hours before venetoclax and/or ibrutinib.)
- BCRP substrates
- OATP1B1/1B3 substrates
- P-gp inhibitors
- BCRP inhibitors
- Antiplatelet agents and anticoagulants (only Cohort 2)

Concomitant use of venetoclax with strong CYP3A inhibitors at initiation (7 days prior to first dose) and during the ramp-up period is contraindicated. Avoid concomitant use of systemic strong or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition when on ibrutinib treatment and during steady daily dosing of venetoclax. If moderate or strong CYP3A inhibitors must be used, refer to [Table 3](#) for dose adjustments of venetoclax and ibrutinib. Resume the venetoclax dose that was used prior to initiating the CYP3A inhibitor 2 to 3 days after discontinuation of the inhibitor.

After discontinuation of a CYP3A inhibitor, resume previous dose of ibrutinib.

Table 3. Management of Potential Ibrutinib and Venetoclax Interactions with CYP3A Inhibitor Use

Inhibitors	Venetoclax		Ibrutinib
	Initiation and Ramp-up Phase	Steady Daily Dose (After Ramp-up Phase)	At any time
Strong CYP3A Inhibitor	Contraindicated (from 7 days prior to first dose)	Avoid inhibitor use, consider alternate. If must be used, reduce the venetoclax dose by at least 75%.	Avoid inhibitor use, consider alternative agent. If must be used, withhold ibrutinib for duration of inhibitor use, or reduce ibrutinib to ■ mg.
Moderate CYP3A Inhibitor	Avoid inhibitor use, consider alternative agent. If must be used, reduce the venetoclax dose by at least 50%.		Avoid inhibitor use, consider alternate agent. If must be used, reduce ibrutinib to ■ mg.

CYP3A = cytochrome P450 3A

Note: 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 strong CYP3A inducers (e.g., carbamazepine, rifampin, phenytoin, and St. John's Wort). Consider alternative agents with less CYP3A induction.

Moderate and strong CYP3A inhibitors and inducers should only be used when no appropriate therapeutic alternative exists. Consider alternative agents with less CYP3A inhibition/induction.

Please refer to [Appendix G](#) for a sample list of excluded and cautionary medications. Any questions regarding concomitant or prior therapy should be raised to the AbbVie emergency contact. Information regarding potential drug interactions with venetoclax, obinutuzumab, or ibrutinib can be located in the venetoclax and obinutuzumab Investigator's Brochures^{16,17} and in the ibrutinib package insert.¹⁸

Subjects must be consented for the study prior to discontinuing any prohibited medications for the purpose of meeting study eligibility.

Subjects should receive supportive care during study participation, including fluids and electrolyte replacement, and antibiotics when appropriate. Use of neutrophil growth factors (filgrastim and pegfilgrastim) is permitted per the American Society of Clinical Oncology guidelines or per the institution's guidelines.²⁰ Transfusions may be given in accordance with institutional policy. Use of antimicrobial prophylaxis (e.g., *Pneumocystis jirovecii* pneumonia prophylaxis with sulfamethoxazole and trimethoprim or equivalent), per the institution's guidelines, is recommended.

Short courses (< 14 days) of corticosteroids for non-cancer related medical reasons (e.g., joint inflammation, asthma exacerbation, and infusion-related reaction [IRRs]) are permitted at doses not exceeding 100 mg/day of prednisone or its equivalent. Treatment for autoimmune cytopenias is permitted for < 14 days at doses that do not exceed 100 mg/day of prednisone or its equivalent.

Antiplatelet Agents and Anticoagulants (Only Cohort 2) :

Warfarin or other vitamin K antagonists should not be administered concomitantly with ibrutinib. Supplements such as fish oil and vitamin E preparations should be avoided during treatment with

ibrutinib. Use ibrutinib with caution in subjects requiring anticoagulants or medications that inhibit platelet function. Ibrutinib should be held at least 3 to 7 days pre-and post-surgery depending upon the type of surgery and the risk of bleeding (see Section 6.2). Subjects with congenital bleeding diathesis have not been studied.

Subjects requiring the initiation of therapeutic anticoagulation therapy (other than warfarin or a vitamin K antagonist) during the course of the study should be discussed with the medical monitor. If therapeutic anticoagulation is clinically indicated, treatment with ibrutinib should be held and not be restarted until the subject is clinically stable and has no signs of bleeding. Subjects should be observed closely for signs and symptoms of bleeding, and the risks and benefits of continuing ibrutinib treatment should be considered. No dose reduction is required when study drug is restarted.

COVID 19 Pandemic Related Vaccination Guidance

Given the ongoing COVID-19 pandemic, selected non-live vaccines (e.g., mRNA, non-replicating viral vector, protein subunit) to prevent SARS-CoV-2 infection may be administered during screening or the treatment period, as long as components of the vaccine are not contraindicated.

The decision to receive a locally available vaccine should be based on local guidance and an individual discussion between the treating physician and the subject.

The potential impact of venetoclax, ibrutinib, and/or obinutuzumab on SARS-CoV-2 vaccination is unknown. Therefore, venetoclax, ibrutinib, and/or obinutuzumab should be administered as follows:

- The first dose of venetoclax, ibrutinib, and/or obinutuzumab, when possible, is preferred to be given at least $\pm$ 7 days from the SARS-CoV-2 vaccine administration.

Note: The above guidance applies to all SARS-CoV-2 vaccine doses given as part of the complete vaccination course.

These recommendations may be subject to change based on the evolving knowledge around the use of SARS-CoV-2 vaccines in patients with CLL/SLL and as more data are collected in real-world scenarios and clinical trials.

Any SARS-CoV-2 vaccine information must be documented on the COVID-19 vaccine electronic case report form (eCRF). Refer to the Operations Manual for instructions on reporting any AEs associated with the COVID-19 vaccine.

5.5 Withdrawal of Subjects and Discontinuation of Study

A subject may voluntarily withdraw or be withdrawn from the study 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 Sponsor.
- The subject experiences disease progression or relapse.
- The subject experiences unacceptable toxicity.

- The investigator believes it is in the best interest of the subject.
- The subject requests withdrawal from the study or refuses further study treatment.
- 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.
- The investigator determines the subject is significantly noncompliant with study procedures.

For subjects to be considered lost to follow-up, reasonable attempts must be made to obtain information on the subject's final status. 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 their site if they have safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will promptly notify the investigator.

COVID 19 Pandemic Related Acceptable Protocol Modification

During the COVID-19 pandemic, it has been necessary to employ mitigation strategies to enable the investigator to ensure subject safety and continuity of care. Acceptable mitigation strategies are identified and included in the Operations Manual in [Appendix N](#).

The investigator should contact the sponsor medical contact before discontinuing a subject from the study for a reason other than described in the protocol to ensure all acceptable mitigation steps have been explored.

Interruption/Discontinuation of Study Drug Due to COVID 19 Infection

During the study drug dosing period, a subject with confirmed (viral test positive) or suspected COVID-19 infection can only be dosed with study drug if the following COVID-19 viral clearance criteria are met:

- At least 10 days since first positive test result have passed in asymptomatic patients or at least 10 days since recovery, defined as resolution of fever without use of antipyretics and improvement in symptoms.

Delays in study drug dosing due to the above COVID-19 testing guidance for subjects must be discussed with the AbbVie medical contact, along with the possibility of premature discontinuation from the study drug dosing period. Follow subsequent protocol Section [5.6](#) for subjects who discontinued study drug.

5.6 Follow-Up After Subject Discontinuation of Study Drug or from Study

To minimize missing data for efficacy and safety assessments, subjects who prematurely discontinue study drug treatment should continue to be followed for all regularly scheduled visits, unless subjects have decided to discontinue the study participation entirely (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 (withdrawal of informed consent), the procedures outlined for the final visit should be completed as soon as possible, preferably within 2 weeks. 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/serious adverse events (SAEs) have been resolved.

If a subject withdraws from study follow-up or withdraws permission for the collection of their personal data, the study staff may still use available public records to obtain information about survival status only, as appropriate per local regulations.

In the event a subject withdraws consent from the clinical study, biomarker research will continue unless the subject explicitly requests analysis to be stopped. When AbbVie is informed the subject has withdrawn and no longer wishes biomarker samples research to continue, samples will not be analyzed and no new biomarker analysis data will be collected for the withdrawn subject or added to the existing data or database(s) and the samples will be destroyed. A subject may withdraw consent for optional biomarker research at any time and remain in the clinical study. Data generated from clinical study, before subject withdrawal of consent, will remain part of the study results.

5.7 Study Drug

Study drugs refer to drugs that are used (or can be used) in this study to assess the safety and the efficacy of the Investigational Product. Investigators will assess the relationship of adverse events to the use of study drugs (See [Table 4](#)) for the list of study drugs.

Venetoclax will be dispensed beginning on Cycle 1 Day 22 (Cohort 1) or Cycle 4 Day 1 (Cohort 2) according to a weekly ramp-up schedule over 5 weeks to the recommended daily dose of [REDACTED] mg. Due to the risk of TLS, the dose of venetoclax will be increased weekly (i.e., progressing as [REDACTED] mg, [REDACTED] mg, [REDACTED] mg, [REDACTED] mg, and [REDACTED] mg) until the final dose of [REDACTED] mg is reached (ramp-up phase). Thereafter the venetoclax dose will be [REDACTED] mg QD.

Subjects will be instructed to take venetoclax tablets at approximately the same time each day with water within 30 minutes after the completion of a meal, preferably breakfast. 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.

Obinutuzumab will be provided as a single-dose, sterile liquid formulation in a 50-mL glass vial containing [REDACTED] mg/[REDACTED] mL of obinutuzumab. Obinutuzumab will be administered via intravenous infusion, through a dedicated line in an environment in which full resuscitation facilities are immediately available and under the close supervision of an experienced physician, on Day 1 of six 4-week cycles during the V+G part of the regimen (Cohort 1). The first dose of obinutuzumab will be administered at [REDACTED] mg on Cycle 1 Day 1 and [REDACTED] mg on Cycle 1 Day 2 (or Cycle 1 Day 1 if the [REDACTED]-mg infusion was completed without modifications of the infusion rate or interruptions, provided that appropriate time, conditions, and medical supervision are available throughout the infusion); thereafter, obinutuzumab will be administered at [REDACTED] mg on Cycle 1 [REDACTED]. For Cycles 2–6, obinutuzumab will be administered at [REDACTED] mg on Day 1.

Ibrutinib [REDACTED] mg will be administered PO, QD starting on Day 1 and should be taken around the same time each day. Subjects will be trained to self-administer ibrutinib (refer to Operations Manual Section 6.1).

AbbVie will provide study drug for venetoclax, ibrutinib, and obinutuzumab. AbbVie-provided study drugs should not be substituted or alternately sourced unless otherwise directed by AbbVie.

Venetoclax will be packaged in bottles, obinutuzumab will be packaged in vials, and ibrutinib will be packaged in 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. Site staff will complete all blank spaces on the label before dispensing to subjects. Study drug will only be used for the conduct of this study.

In Japan, safety information will be reported on the following "drugs used in the clinical study" (Table 4) in accordance with local guidelines.

Table 4. Study Drug Information

Investigational Product	Mode of Administration	Dosage Form	Strength
Venetoclax	Oral	Film-coated tablet	[REDACTED] mg
Obinutuzumab	Intravenous	IV vial	[REDACTED] mg
Ibrutinib	Oral	Hard capsule	[REDACTED] mg

IV = intravenous

5.8 Randomization/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.

5.9 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol except when necessary to eliminate an immediate hazard to study subjects. The investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. If a protocol deviation occurs (or is identified, including those that may be due to the COVID-19 pandemic), 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 damage or 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.

Reporting will be done via electronic data capture (EDC). The date the product complaint details are entered into EDC and the form is saved represents the date reported to AbbVie. A back-up paper form will be provided for reporting complaints related to unassigned product or in the event of an EDC system issue. If a back-up paper form is used, the date the form is emailed to RD_PQC_QA@abbvie.com represents the date reported to AbbVie.

All follow-up information is to be reported to the sponsor (or an authorized representative) and documented in source as required by the sponsor. Product complaints associated with AEs will be reported in the study summary. All other complaints will be monitored on an ongoing basis. 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.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from "special situations" such as accidental or intentional overdose, medication error, occupational or accidental exposure, off-label use, drug abuse, drug misuse, or drug withdrawal, all which must be reported whether associated with an adverse event or not. Any worsening of a pre-existing condition or illness is considered an adverse event. Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, meets protocol-specific criteria (see Section 6.2 regarding toxicity management), and/or if the investigator considers them to be adverse events.

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.

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 4.2 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

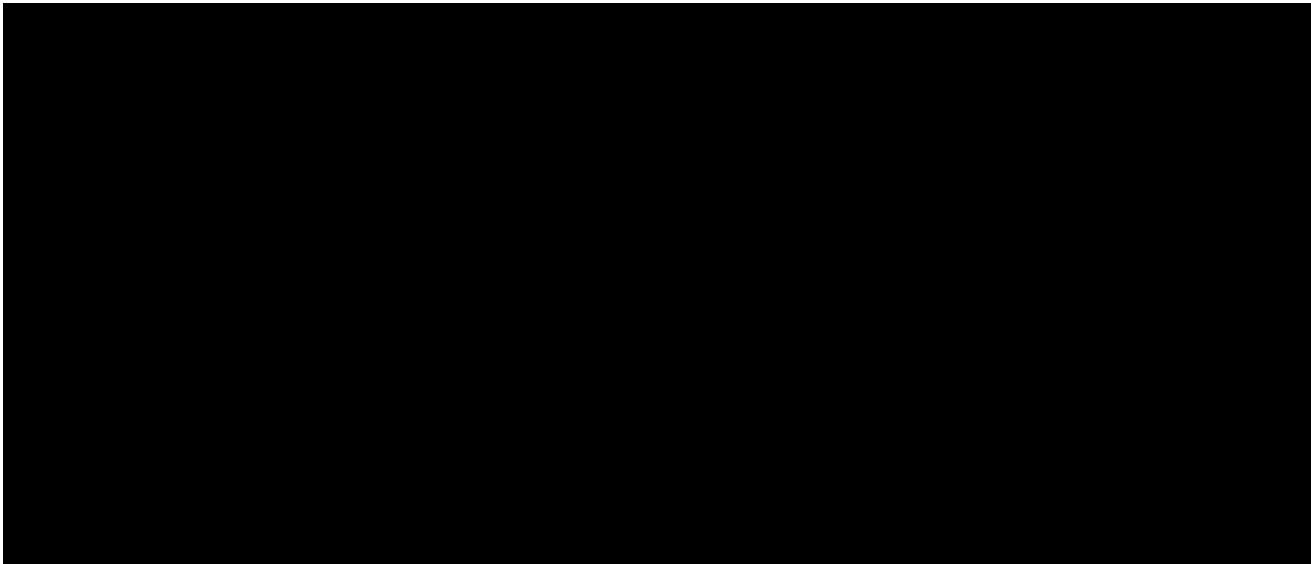
An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained 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 along with any suspected transmission of an infectious agent via a medicinal product if no other serious criterion is applicable. 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. After 30 days following the last dose of study drug or completion of study treatment, only spontaneously reported SAEs will be collected (nonserious AEs will not be collected). In addition, study procedure-related serious and nonserious adverse events will be collected from the time the subject signs the study-specific informed consent.

Adverse Events of Special Interest



Adverse Event Severity and Relationship to Study Drug

The investigator will rate the severity of each AE according to the NCI CTCAE Version 4.03.

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

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age appropriate instrumental activities of daily living.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

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 AE, pregnancy in a study subject must be reported to AbbVie within 24 hours after the site becomes aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (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. AbbVie will provide a separate consent form for this purpose. Pregnancy in a subject's partners will be collected from the date of the first dose through 90 days following the last dose of study drug.

The pregnancy outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a SAE and must be reported to AbbVie within 24 hours after the site becomes aware of the event.

6.2 Toxicity Management, Dose Modifications, and Interruptions

The evaluation of potential treatment-induced toxicity in patients with advanced CLL may be quite difficult, requiring careful consideration of both the manifestations of the underlying disease, as well as adverse reactions to the therapy under study. Some of the conventional criteria for toxicity are not applicable especially under circumstances of progressive bone marrow failure from the CLL itself. Dose modifications for hematological toxicity in patients with CLL must consider the increased frequency of hematological compromise at the initiation of therapy. Therefore, the standard criteria used for solid tumors are difficult to be applied directly; many patients would be considered to have Grade 2 to 4 hematological toxicity at presentation.

As a consequence, **dose modification decisions** for patients with cytopenia (below the lower limit of the normal range) at baseline will be based on iwCLL grading scale for hematological toxicity in CLL studies (see [Appendix I](#)). For patients with a normal neutrophil count, platelet count, and/or hemoglobin value at baseline, the NCI CTCAE Version 4.03 will be used.

Subjects who interrupt all study drug treatments for more than 28 days must be discontinued from study drug treatments.

Cohort 1 (V+G)

Management of Specific Adverse Events

Guidelines for management of specific AEs are outlined in [Table 5](#). Additional guidelines are provided in the subsections below.

Table 5. Guidelines for Management of Specific Adverse Events Cohort 1 (V+G)

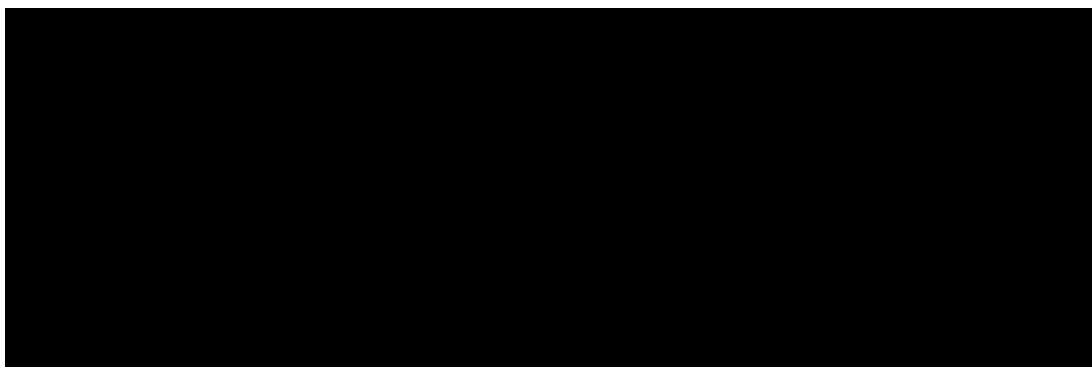
Event	Dose Delay or Dose Modification
Hematologic Toxicity	
Grade 3 or 4 (NCI CTCAE or iwCLL grading scale) neutropenia with or without fever and infection	• Withhold venetoclax (and obinutuzumab if neutropenia occurs during Cycles 1-6) for at least 7 days. • Administer G-CSF or growth factors for neutropenia as indicated • When counts recover to ANC $\geq 1 \times 10^9/L$ and/or platelets are $\geq 75 \times 10^9/L$, resume venetoclax at one dose level reduction. • Reinitiate Obinutuzumab.

Event	Dose Delay or Dose Modification
Severe thrombocytopenia (Platelets < 25000/ μ L) and/or symptomatic bleeding	- Withhold venetoclax (and obinutuzumab if event occurs during Cycle 1-6) for severe thrombocytopenia (platelet < 25,000/μL) or presence of symptomatic bleeding until resolution of bleeding. Platelets may be transfused at the discretion of the investigator. When platelet level rises to > 50,000/μL without transfusional support for 5 consecutive days, restart venetoclax at previous dose and obinutuzumab. - For a second episode of severe thrombocytopenia and/or symptomatic bleeding, withhold venetoclax (and obinutuzumab if event occurs during Cycles 1-6) When platelet level rises to > 50,000/μL without transfusional support for 5 consecutive days, restart venetoclax at one dose level reduction and obinutuzumab. - For subsequent episodes of severe thrombocytopenia, withhold venetoclax (and obinutuzumab if event occurs during Cycles 1-6) When platelet level rises to > 50,000/μL without transfusional support for 5 consecutive days, restart venetoclax at one dose level reduction and obinutuzumab. - For recurrent severe thrombocytopenia in spite of dose reduction and/or symptomatic bleeding, consult the AbbVie TA MD regarding continuation on the protocol.
Non-Hematologic Toxicity	
Grade 4 IRR	Discontinue obinutuzumab permanently. Subjects may continue venetoclax
Grade 3 IRR on first dose; the same grade 3 IRR on 2 subsequent occasions	- First episode: To be managed at investigator's discretion. - After 2 subsequent episodes of the same Grade 3 event: Discontinue obinutuzumab permanently. Patients may continue venetoclax
Grade 1-2 IRR, first and subsequent episodes	To be managed at investigator's discretion
Grade 3 or 4 TLS, first episode and subsequent episodes (see Howard Criteria in Appendix H)	See Appendix J

Event	Dose Delay or Dose Modification
Grade 3 or 4 non-hematologic events not specifically described above	- Delay venetoclax (and obinutuzumab if event occurs during Cycle 1-6) for a maximum of 28 days First episode: If improvement to Grade ≤ 1 or baseline, resume previous doses of venetoclax and obinutuzumab. For subsequent episodes: If improvement to Grade ≤ 1 or baseline, restart venetoclax at one dose level reduction - Certain treatment emergent non-hematologic adverse events (e.g., venous thromboembolic events) may be managed and become clinically stable following medical intervention but may not improve to Grade ≤ 1 according to the NCI CTCAE definitions. In such cases, if a patient is clinically stable, resumption of study drug may be possible after consultation with the AbbVie TA MD.
Grade 2 non-hematologic toxicity	- Delay treatment with venetoclax (and obinutuzumab if event occurs during Cycle 1-6) until resolution to Grade ≤ 1 (or baseline status) for a maximum of 28 days - After resolution, resume full dose venetoclax and obinutuzumab.
Grade 1 non-hematologic toxicity	No dose reduction or delay

ANC = Absolute neutrophil count; G-CSF = granulocyte colony stimulating factors; IRR = Infusion-related reaction; iwCLL = International Workshop on Chronic Lymphocytic Leukemia; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; TA MD = Therapeutic Area Medical Director; TLS = tumor lysis syndrome

Table 6. Dose Modification for Toxicity During Venetoclax Treatment (Cohort 1 and Cohort 2)



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

Gradual dose increase of venetoclax following resolution of toxicity leading to a dose reduction may be considered if the patient is stable for 2 weeks on the lower dose; however, if the toxicity recurs, the patient may continue treatment on the lower dose (Table 6).

Dose reduction of obinutuzumab is not permitted.

Patients who discontinue venetoclax for toxicity should also discontinue obinutuzumab, although they are to continue evaluation per protocol.

Patients who interrupt all study treatments secondary to treatment-related AEs events for longer than 28 days should discontinue all study drugs although they are to continue being followed for disease progression as described in [Appendix L](#).

Prophylaxis for Infusion Related Reactions

The rate of infusion of obinutuzumab may need to be slowed for those patients that experience infusion reactions, and medications to treat IRRs (including epinephrine for subcutaneous injections, corticosteroids, and diphenhydramine for IV injection) and resuscitation equipment should be available for immediate use during dosing.

All obinutuzumab infusions should be administered 30-60 minutes after premedication with oral antiphlogistic analgesic (e.g., acetaminophen [e.g., 650 1000 mg]) and an antihistamine such as diphenhydramine (50 100 mg).

For the first dose of obinutuzumab, premedication with corticosteroids (100 mg IV prednisolone or equivalent) is mandatory for all patients and must be administered at least 1 hour prior to the [REDACTED] mg dose on Cycle 1, Day 1 and the [REDACTED] mg dose on Cycle 1, Day 2. An equivalent dose of dexamethasone (20 mg) or methylprednisolone (80 mg) is permitted, but hydrocortisone should not be used. The required corticosteroid premedication may be modified by the investigator, in consultation with the sponsor, on the basis of observed safety from this study and review of data from other ongoing studies with obinutuzumab.

For subsequent infusions, corticosteroid premedication should be given to patients who experienced a Grade 3 IRR with the previous infusion, to patients with lymphocyte counts $> 25 \times 10^9 /L$, or at the investigator's discretion.

For patients who do not experience Grade ≥ 3 infusion-related symptoms with their previous infusion, corticosteroid premedication for subsequent infusions may be omitted at the investigator's discretion.

For patients with a high lymphocyte count or bulky lymphadenopathy, the infusion may be given extremely slowly over a longer period of time or the dose may be split and given over more than 1 day.

If a hypersensitivity or IRR develops, the infusion should be temporarily interrupted or slowed down and concomitant medication may be administered if deemed appropriate by the investigator. Investigators should consider administering the following medications/interventions in response to an IRR:

- Patients may be treated with antiphlogistic analgesic (e.g., acetaminophen/paracetamol) and an antihistamine if the patient had not received them in the 4 hours prior to the start of the IRR.
- Patients may receive additional IV hydration.
- In the event of bronchospasm, urticaria, or dyspnea, patients may require antihistamines, oxygen, additional corticosteroids (e.g., 100 mg of IV prednisolone or equivalent; please note hydrocortisone should not be used to manage an IRR), and/or bronchodilators.
- In the event of hypotension, patients may require vasopressors.

Upon resolution of symptoms, the infusion will resume at half of the previous rate (the rate being used at the time that the hypersensitivity or IRR occurred), and infusion rate escalation may resume at the increments and intervals described above.

Life Threatening Infusion Related Reactions and Anaphylaxis

In the event of a life-threatening IRR (which may include pulmonary or cardiac events) or IgE-mediated anaphylactic reaction, obinutuzumab should be discontinued and no additional obinutuzumab should be administered. Patients who experience any of these reactions should receive aggressive symptomatic treatment and will be discontinued from study treatment.

Cohort 2 (V+I)

Ibrutinib Dose Modification

Treatment with ibrutinib should be temporarily stopped for any Grade 2 cardiac failure, or unmanageable, potentially ibrutinib-related toxicity that is Grade ≥ 3 in severity. Recommendations for Grade 2 or higher cardiac failure and Grade 3 or higher cardiac arrhythmias are provided in [Table 8](#). Ibrutinib may be temporarily stopped for a maximum of 28 consecutive days. Ibrutinib should be discontinued permanently in the event of a toxicity lasting more than 28 days, unless continued treatment is approved by the sponsor.

The dose of ibrutinib must be modified according to the dose modification guidance in [Table 7](#) and [Table 8](#) if any of the following potentially drug-related toxicities occur:

- Absolute neutrophil count (ANC) < 500 cells/ μL for more than 7 days. See Section [5.4](#) for instructions regarding the use of growth factor support.
- Platelets $< 50,000$ cells/ μL in the presence of clinically significant bleeding.
- Platelets $< 25,000$ cells/ μL .
- Grade 3 nausea or Grade 3 or 4 vomiting or Grade 3 or 4 diarrhea, if persistent despite optimal anti-emetic or anti-diarrheal therapy.
- Any other Grade 4 or unmanageable Grade 3 toxicity (see [Table 8](#) for recommendations for cardiac failure and cardiac arrhythmias).
- Grade ≥ 2 cardiac failure (see [Table 8](#)).

Dose changes must be recorded in the Dose Administration eCRF.

Table 7. Ibrutinib Dose Modifications for Events not Specified in Table 8

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Recommended dose modifications for events of cardiac failure or cardiac arrhythmias are described below in [Table 8](#).

Table 8. Ibrutinib Dose Modifications for Cardiac Failure or Cardiac Arrhythmias

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Cerebrovascular Accidents

Although causality has not been established, cases of cerebrovascular accident, transient ischemic attack, and ischemic stroke including fatalities have been reported with the use of ibrutinib in the post-marketing setting, with and without concomitant atrial fibrillation and/or hypertension. Regular monitoring and appropriate treatment of conditions that can contribute to the occurrence of these events is recommended.

For dose modification during concomitant treatment with CYP3A inhibitors refer to [Table 3](#).

During cycles with venetoclax combination dosing, the decision to dose modify a study drug due to a toxicity will be based on the investigator attribution of relatedness to a given drug. For example, if an AE occurs and is considered related to venetoclax but not ibrutinib, the dose of venetoclax should be modified while ibrutinib should remain the same. If the AE is considered potentially related to both drugs, adjusting the dose of venetoclax before ibrutinib is the recommended first action, taking into consideration the possibility of higher systemic exposure of venetoclax when administered in combination with ibrutinib. For cases where the investigator is uncertain of what action to take, the study monitor may be contacted for further discussion. If ibrutinib is discontinued for toxicity, then treatment with venetoclax may be continued.

Ibrutinib Dose Modification for Subjects with Hepatic Impairment

Ibrutinib is metabolized in the liver. Therefore, subjects with clinically significant hepatic impairment at the time of screening (Child-Pugh Class B or C) are excluded from study participation. For subjects who develop mild liver impairment while on study (Child-Pugh Class A), the recommended dose reduction for ibrutinib is to a level of [REDACTED] mg daily. For subjects who develop moderate liver impairment while on study (Child-Pugh Class B), the recommended dose reduction is to a level of [REDACTED] mg daily. For subjects who develop severe hepatic impairment (Child-Pugh Class C), ibrutinib must be held until resolved to moderate impairment (Child-Pugh Class B) or better. Monitor subjects for signs of toxicity and follow dose modification guidance as needed (see [Appendix K](#) for Child-Pugh classification).

Ibrutinib Dose Modification for Subjects Who Require Surgical Intervention or an Invasive Procedure

The following guidance should be applied during the perioperative period for subjects who require surgical intervention or an invasive procedure while receiving ibrutinib:

- For major surgical procedures, including any surgery or invasive procedure requiring sutures or staples for closure, ibrutinib should be held at least 7 days prior to the intervention and at least 7 days after the procedure, and restarted at the discretion of the investigator, when the surgical site is reasonably healed without serosanguineous drainage or the need for drainage tubes.
- For minor procedures (such as a central line placement, needle biopsy, thoracentesis, or paracentesis), ibrutinib should be held for at least 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure. For bone marrow biopsies that are performed while the subject is on study medication, it is not necessary to hold the study medications.
- For emergency procedures, all study treatments should be held after the procedure until the surgical site is reasonably healed, for at least 7 days after the urgent surgical procedure.

Venetoclax Dose Modification: Cohort 2 (V+I)

See [Table 9](#) for dose modifications for toxicities related to venetoclax. For subjects who have had a dosing interruption greater than 1 week during the first 5 weeks of ramp-up phase or greater than 2 weeks when at the daily dose of [REDACTED] mg, reassess for risk of TLS to determine if re-initiation with a reduced dose is necessary (e.g., all or some levels of the dose ramp-up schedule). During the ramp-up phase, continue the reduced dose for 1 week before increasing the dose. Consider discontinuing venetoclax for subjects who require dose reductions to less than [REDACTED] mg for more than 2 weeks.

Table 9. Recommended Dose Modifications for Venetoclax-Related Toxicities: Cohort 2 (V+I)

Event	Occurrence	Action
Tumor Lysis Syndrome		
Blood chemistry changes or symptoms suggestive of TLS (see Howard Criteria in Appendix H)	Any	See Appendix J .
Non-Hematologic Toxicities		
Grade 3 or 4 non-hematologic toxicities	1 st occurrence	Withhold venetoclax Once the toxicity has resolved to Grade 1 or baseline level, venetoclax therapy may be resumed at the same dose. No dose modification is required.
	2 nd and subsequent occurrences	Withhold venetoclax Follow dose reduction guidelines in Table 6 when resuming treatment with venetoclax after resolution. A larger dose reduction may occur at the discretion of the investigator.
Hematologic Toxicities		
ANC < 1000/ μ L with infection or fever; ANC < 500/ μ L Platelet < 25,000/ μ L Hb < 8 g/dL	1 st occurrence	Withhold venetoclax. To reduce the infection risks associated with neutropenia, G-CSF may be administered with venetoclax if clinically indicated. Once the toxicity has resolved to study entry criteria or better, venetoclax may be resumed at the same dose.
	2 nd and subsequent occurrences	Withhold venetoclax. Consider using G-CSF as clinically indicated. Follow dose reduction guidelines in Table 6 when resuming treatment with venetoclax after resolution. Additional dose reductions may occur at the discretion of the investigator.

ANC = absolute neutrophil count; G-CSF = granulocyte-colony stimulating factor; Hb = hemoglobin; TLS = tumor lysis syndrome

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

Use of strong CYP3A inhibitors is contraindicated during venetoclax initiation and dose ramp-up. For dose modification during concomitant treatment with CYP3A inhibitors refer to [Table 3](#).

During cycles with V+I combination dosing, the decision to dose-modify a study drug due to a toxicity will be based on the investigator attribution of relatedness to a given drug. For example, if an AE occurs and is considered related to venetoclax but not ibrutinib, the dose of venetoclax should be modified while ibrutinib should remain the same. If the AE is considered potentially related to both drugs, adjusting the dose of venetoclax before ibrutinib is the recommended first action, taking into consideration the possibility of higher systemic exposure of venetoclax when administered in

combination with ibrutinib. For cases where the investigator is uncertain of what action to take, the study monitor may be contacted for further discussion.

If venetoclax is discontinued for toxicity, then treatment with ibrutinib may be continued.

Infections (Cohort 1 and Cohort 2)

If clinically indicated, anti-infective prophylaxis for viral, fungal, bacterial, or *Pneumocystis* infections is permitted. Although there is a potential for drug-drug interactions, there is likely to be limited potential clinical effects, therefore trimethoprim sulfamethoxazole can be considered for *Pneumocystis* prophylaxis with close clinical monitoring. The AbbVie Therapeutic Area Medical Director (TA MD) should also be consulted regarding any consideration of the use of azoles as anti-fungal prophylaxis or therapy, because of the potential for drug-drug interactions.

Tumor Lysis Syndrome (Cohort 1 and Cohort 2)

Prophylaxis and Management of Tumor Lysis Syndrome for Patients Being Treated with Obinutuzumab in Cohort 1

- Prophylaxis of hyperuricemia and dehydration are similar to the recommendations for venetoclax dosing described in [Table 11](#).
- Patients with a high tumor burden ($ALC \geq 25 \times 10^9/L$ or bulky lymphadenopathy) must receive prophylaxis for TLS prior to the initiation of treatment. These patients must be well-hydrated. It is desirable to maintain a fluid intake of approximately 3 L/day, 1–2 days before the first dose of obinutuzumab. All such patients with a high tumor burden must be treated with allopurinol or a suitable alternative treatment starting 12–24 hours prior to the first infusion. Patients should continue to receive prophylaxis with allopurinol and adequate hydration prior to each subsequent infusion, if deemed appropriate by the investigator.
- If any laboratory abnormalities that are consistent with TLS are observed, patients should undergo further management and monitoring as per the Recommendations for Initial Management of Electrolyte Imbalances and Prevention of TLS (see Protocol [Appendix J](#)).
- Hematology and chemistry samples will be obtained prior to obinutuzumab dosing and 24 hours after the initiation of each obinutuzumab infusion during Cycle 1. If the first infusion of obinutuzumab is given as a split dose on Cycle 1 Day 1 and Cycle 1 Day 2, hematology and chemistry samples will be collected: prior to dosing on both Day 1 and Day 2, and 24 hours after the initiation of the obinutuzumab infusion on Cycle 1 Day 2.; see Operations Manual Section 2 for details. Discharge of patient is dependent upon review of the 24-hour laboratory values by the investigator or designee.

Prophylaxis and Management of Tumor Lysis Syndrome for Patients Being Treated with Venetoclax in Cohort 1 and Cohort 2

Tumor lysis syndrome is a risk for patients with CLL who are treated with high cell-killing agents. Clinical data from patients with CLL treated to date with venetoclax suggest that patients with baseline lymph nodes ≥ 5 cm diameter are at a greater risk for TLS than those with baseline lymph nodes < 5 cm. In addition, the data showed that CrCl of ≤ 80 mL/min at screening was a secondary risk factor for TLS. A

detailed description of risk factors for developing TLS following treatment with venetoclax is available in the venetoclax Investigator's Brochure.¹⁶

Venetoclax may cause a rapid reduction in tumor burden and thus poses a risk for TLS in the initial 5-week ramp-up phase. Changes in electrolytes consistent with TLS that require prompt management may occur as early as 6 to 8 hours following the first dose of venetoclax and at each dose increase. The risk of TLS is a continuum based on multiple factors, including tumor burden and comorbidities (Table 11, Table 12). Subjects with high tumor burden are at a greater risk of TLS when initiating venetoclax. Reduced renal function further increases the risk. The risk may decrease as tumor burden decreases with treatment.

Based on the data review performed by the Sponsors, the following three risk categories for developing TLS after treatment with venetoclax were defined (see Table 10). These risk groups were developed using assessments of nodal disease burden obtained from imaging tests performed at screening in several other studies of venetoclax in CLL. Therefore, assigning a patient's TLS risk MUST be made based on an imaging test performed at screening and prior to initial venetoclax dosing. Assessments of TLS risk categorization and monitoring/prophylaxis guidance is being continuously assessed throughout the venetoclax program, and future updates to these guidelines are possible.

Table 10. Risk Categories for Developing Tumor Lysis Syndrome

TLS Risk Category	Definition
Low	All measurable lymph nodes with the largest diameter < 5 cm and < 25×10^9 /L ALC. Lymph node size will be determined by radiologic assessment.
Medium	Any measurable lymph node with the largest diameter ≥ 5 cm and < 10 cm OR $\geq 25 \times 10^9$ /L ALC. Lymph node size will be determined by radiologic assessment.
High	Any measurable lymph node with the largest diameter ≥ 10 cm or the presence of both $\geq 25 \times 10^9$ /L ALC AND any measurable lymph node with the largest diameter ≥ 5 cm but < 10 cm OR Any lymph node size or ALC AND CrCl ≤ 50 mL/min. Lymph node size will be determined by radiologic assessment.

ALC = absolute lymphocyte count; CrCl = creatinine clearance; CT = computed tomography; MR = magnetic resonance imaging; TLS = tumor lysis syndrome

Note: TLS Risk Assessment MUST be made based on measurement of nodal disease burden based on radiologic assessments (CT scan or MRI) performed during the screening period.

All patients enrolling in the study will be assessed at screening and prior to initial venetoclax dosing and categorized in a risk category as described above. Investigators may reassess patient's TLS risk after they start treatment and may assign them to a lower risk group. For example, patients classified as TLS high-risk at screening because of an ALC of $\geq 25 \times 10^9$ AND a measurable lymph node with the largest diameter ≥ 5 cm but < 10 cm by radiologic assessment may have a re-evaluation of their TLS risk category based on their most recent ALC after initiating study treatment. If the patient's ALC decreases to < 25×10^9 /L, the patient may be categorized as TLS medium-risk and may follow the management guidelines for the TLS medium-risk category at subsequent visits and during the venetoclax ramp-up period. Re-assessment of the patient's TLS risk category can occur continuously during the venetoclax

dose ramp-up period. If a patient is re-assigned to a lower risk group, the investigator may follow the prophylaxis guidance for the lower risk group to which they are assigned.

However, patients who are classified as high-risk because they have a lymph node with largest diameter ≥ 10 cm MAY NOT have their TLS risk re-assessed and should follow the prophylaxis plan for high-risk patients throughout the venetoclax ramp-up period.

Clinical chemistry, including TLS elements such as albumin, creatinine, potassium, calcium, inorganic phosphorus, lactate dehydrogenase (LDH), and uric acid, should be reviewed pre-dose and real time at the post dose timepoints defined in [Table 11](#) and [Table 12](#) below.

Patients who develop signs or symptoms of TLS regardless of the risk group to which they were assigned may have additional monitoring at subsequent visits at the investigator's discretion.

Any patient who, at any dose, develops clinically significant electrolyte abnormalities must have his or her subsequent venetoclax dose withheld until the electrolyte abnormalities resolve. Patients who develop electrolyte abnormalities should undergo aggressive management and further monitoring per [Appendix J](#), Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome. Any time during the ramp-up period, if venetoclax was withheld for 7 days or less, the patient may resume venetoclax at the same dose level or at one lower dose level as determined by the investigator based on a risk assessment (including tumor burden status). The dose must be resumed at one lower dose-level if interruption lasted more than 7 days, with the exception of the initial dose level of 100 mg (100 mg, 200 mg, 300 mg, 400 mg, 500 mg, 600 mg, 700 mg, 800 mg, 900 mg). All patients must receive the intended dose for at least 7 days before increasing to the next ramp-up dose.

This section describes the management of patients throughout dosing given their risk factors for developing TLS identified upon study entry.

Additional details for prevention of TLS can be found in [Appendix J](#).

Table 11. Summary of Tumor Lysis Syndrome Prophylaxis for Venetoclax and Monitoring Measures – COHORT 1

TLS Risk Category	Day 1 of Dose Level	Prophylaxis Medication	Hospitalization	Hydration ^a	Laboratory Assessments ^{b,e}
Low	██████ ██████ ██████ mg	Oral uric acid reducer (such as allopurinol 300 mg/day) beginning at least 72 hours prior to dose and continued until the end of the ramp-up period with venetoclax is completed.	No	Oral hydration of 1.5-2 L/day at least 48 hours prior to dose and continuing until the end of the ramp-up period with venetoclax.	Hematology, clinical chemistry and vital signs will be taken predose and 8 and 24 hours after dosing. Predose is defined as up to 4 hours before venetoclax administration, and results must be reviewed prior to dosing; if it is not possible to review result from a sample taken up to 4 hours predose, then it is acceptable to take a predose hematology and clinical chemistry sample within 24 hours prior to dosing. The results of these samples must be reviewed prior to dosing. If laboratory values from this sample have demonstrated no clinically significant abnormalities, the hematology and clinical chemistry samples drawn on the day of venetoclax administration prior to dosing are not required to be reviewed prior to dose administration. However, these predose (0-4 hours prior to dosing) laboratory samples should still be drawn, and these will serve as baseline for later laboratory values when assessing for laboratory evidence of TLS at the 8 and 24 hours after dosing timepoints. The 8-hour clinical chemistry results must be reviewed before the patients leaves the outpatient clinic that day. The investigator or subinvestigator must review the 24-hour laboratory results prior to dosing on the next day.

TLS Risk Category	Day 1 of Dose Level	Prophylaxis Medication	Hospitalization	Hydration ^a	Laboratory Assessments ^{b,e}
Medium	█████ ████ mg	Oral uric acid reducer (such as allopurinol 300 mg/day) beginning at least 72 hours prior to dose and continued until the end of the ramp-up period with venetoclax is completed.	No ^{c,d}	Oral hydration of 1.5-2 L/day at least 48 hours prior to dose and continuing until the end of the ramp-up period with venetoclax. In addition to oral hydration, IV hydration (1.5-2L) will be given in the outpatient setting during clinical stay.	Hematology, clinical chemistry and vital signs will be taken predose and 8 and 24 hours after dosing. Predose is defined as up to 4 hours before venetoclax administration, and results must be reviewed prior to dosing; if it is not possible to review result from a sample taken up to 4 hours predose, then it is acceptable to take a predose hematology and clinical chemistry sample within 24 hours prior to dosing. The results of these samples must be reviewed prior to dosing. If laboratory values from this sample have demonstrated no clinically significant abnormalities, the hematology and clinical chemistry samples drawn on the day of venetoclax administration prior to dosing are not required to be reviewed prior to dose administration. However, these predose (0-4 hours prior to dosing) laboratory samples should still be drawn, and these will serve as baseline for later laboratory values when assessing for laboratory evidence of TLS at the 8 and 24 hours after dosing timepoints. The 8-hour clinical chemistry results must be reviewed before the patients leaves the outpatient clinic that day. The investigator or subinvestigator must review the 24-hour laboratory results prior to dosing on the next day.
	█████ ████ mg	Continue oral uric-acid reducer as above		Oral hydration of 1.5-2 L/day at least 48 hours prior to dose and continuing until the end of the ramp-up period with venetoclax.	

TLS Risk Category	Day 1 of Dose Level	Prophylaxis Medication	Hospitalization	Hydration ^a	Laboratory Assessments ^{b,e}
High	██████ ████ mg	Oral uric acid reducer (such as allopurinol 300 mg/day) beginning at least 72 hours prior to dose and continued until the end of the ramp-up period with venetoclax is completed. Rasburicase^f must be administered per regional standards/institutional guidelines as prophylaxis prior to the first dose of venetoclax for high-risk patients with high uric acid levels at pre-dose (above the local laboratory ULN or the threshold of 8 mg/dL [475.8 µmol/L]). For patients with a contraindication to rasburicase (i.e., glucose 6 phosphate dehydrogenase deficiency), the TLS risk mitigation plan must be reviewed with the AbbVie TA MD. Uric acid levels following treatment with rasburicase must be analyzed using specific guidelines described in Section 6.2	Yes ^d	Oral hydration of 1.5-2 L/day at least 48 hours prior to dose and continuing until the end of the ramp-up period with venetoclax. Upon hospital admission, IV hydration should be started with a target of approximately 2-3L per day or as clinically appropriate.	Hematology, clinical chemistry and vital signs will be taken predose and 8, 12 and 24 hours after dosing. Predose is defined as up to 4 hours before venetoclax administration, and results must be reviewed prior to dosing; if it is not possible to review result from a sample taken up to 4 hours predose, then it is acceptable to take a predose hematology and clinical chemistry sample within 24 hours prior to dosing. The results of these samples must be reviewed prior to dosing. If laboratory values from this sample have demonstrated no clinically significant abnormalities, the hematology and clinical chemistry samples drawn on the day of venetoclax administration prior to dosing are not required to be reviewed prior to dose administration. However, these predose (0-4 hours prior to dosing) laboratory samples should still be drawn, and these will serve as baseline for later laboratory values when assessing for laboratory evidence of TLS at the 8, 12 and 24 hours after dosing timepoints. The investigator or subinvestigator must review the 24-hour laboratory results prior to dosing on the next day.

TLS Risk Category	Day 1 of Dose Level	Prophylaxis Medication	Hospitalization	Hydration ^a	Laboratory Assessments ^{b,e}
High, cont.	██████ ██████ mg	Continue oral uric acid reducer as above	No ^{c,d}	Oral hydration of 1.5-2 L/day at least 48 hours prior to dose and continuing until the end of the ramp-up period with venetoclax. In addition to oral hydration, IV hydration (1.5-2L) will be given in the outpatient setting during clinical stay.	- Patients who are not hospitalized at these timepoints will have hematology, clinical chemistry, and vital signs taken predose and 8 and 24 hours after dosing. - Predose is defined as up to 4 hours before venetoclax administration, and results must be reviewed prior to dosing; if it is not possible to review result from a sample taken up to 4 hours predose, then it is acceptable to take a predose hematology and clinical chemistry sample within 24 hours prior to dosing. The results of these samples must be reviewed prior to dosing. If laboratory values from this sample have demonstrated no clinically significant abnormalities, the hematology and clinical chemistry samples drawn on the day of venetoclax administration prior to dosing are not required to be reviewed prior to dose administration. However, these predose (0-4 hours prior to dosing) laboratory samples should still be drawn, and these will serve as baseline for later laboratory values when assessing for laboratory evidence of TLS. - The 8-hour clinical chemistry results must be reviewed before the patients leaves the outpatient clinic that day. - The investigator or subinvestigator must review the 24-hour laboratory results prior to dosing on the next day.

CrCl = creatinine clearance; IV = Intravenous(Iy); TA MD = Therapeutic Area Medical Director; TLS = tumor lysis syndrome; ULN = upper limit of normal

- a. For patients unable to maintain oral hydration at 1.5-2 L/day starting at least 48 hours prior to the start of treatment, IV hydration in the outpatient setting on the day of dosing during the clinic stay is recommended (unless being hospitalized) in order to assure that this full amount of hydration is achieved. For patients for whom volume overload is considered a significant risk, hospitalization should be considered.
- b. For laboratory samples drawn on days of study treatment, "predose" laboratory samples should be drawn within 0-4 hours before the dose. Other laboratory samples occurring on the same day should be obtained within a $\pm$ 15-minute window of any exact scheduled time. Any laboratory tests occurring at time intervals greater than or equal to 24 hours after dose should be obtained within a $\pm$ 2-hour window of the scheduled time.
- c. Patients with CrCl < 80 mL/min and/or who have a higher tumor burden (defined per the discretion of the investigator) may be handled as TLS high-risk patients. Currently, limited clinical experience has been gained with venetoclax in patients with CrCl 30-50 mL/min. Therefore, these patients should receive additional consideration by the investigator with regard to their management, including the decision on whether to administer IV hydration and to hospitalize the patient to facilitate monitoring and expedite response to electrolyte changes at initial dosing as well as at each first dose during the ramp-up period.
- d. Nephrology (or acute dialysis service) consultation should be considered on admission (per institutional standards or based on investigator discretion) for hospitalized patients to ensure emergency dialysis is available and the appropriate staff is aware and prepared to handle any necessary intervention for TLS. Telemetry should also be considered.
- e. Any patient who, at any dose, develops clinically significant electrolyte abnormalities must have subsequent venetoclax dose withheld until the electrolyte abnormalities resolve. Patients who develop electrolyte abnormalities should undergo aggressive management and further monitoring per [Appendix J](#). Any time during the ramp-up period, if venetoclax was withheld for 7 days or less, the patient may resume venetoclax at the same dose level or at one lower dose level as determined by the investigator based on a risk assessment (including tumor burden status). The dose must be resumed at one lower dose level if dose was withheld more than 7 days, with the exception of initial dose level of [REDACTED].
- f. At room temperature, rasburicase causes enzymatic degradation of the uric acid in blood, plasma, and serum samples, which could potentially result in spuriously low plasma uric acid assay readings. The following special sample handling procedure must be followed to avoid ex vivo uric acid degradation:
 - Uric acid must be analyzed in plasma/serum.
 - Blood must be collected into prechilled tubes containing heparin anticoagulant for plasma sample.
 - Immediately immerse plasma/serum samples for uric acid measurement in an ice water bath.
 - Plasma/serum samples must be prepared by centrifugation in a precooled centrifuge (4°C).
 - The plasma/serum must be maintained in an ice water bath and analyzed for uric acid within 4 hours of collection.

Table 12. Summary of Tumor Lysis Syndrome Prophylaxis for Venetoclax and Monitoring Measures – COHORT 2

Tumor Burden		Prophylaxis		Blood Chemistry Monitoring ^{c,d}
		Hydration ^a	Anti-Hyperuricemics	Setting and Frequency of Assessments
Low	All LN < 5 cm AND ALC < 25 × 10 ⁹ /L	Oral (1.5-2 L)/daily	Allopurinol ^b	Outpatient - Predose, 6 to 8 hours, 24 hours at first dose of ■ mg and ■ mg - Predose at subsequent ramp-up doses
Medium	Any LN 5 cm to < 10 cm OR ALC ≥ 25 × 10 ⁹ /L	Oral (1.5-2 L)/daily and consider additional intravenous	Allopurinol ^b	Outpatient - Predose, 6 to 8 hours and 24 hours at first dose of ■ mg and ■ mg - Predose at subsequent ramp-up doses - Consider hospitalization for subjects with CrCl < 80mL/min at first dose of ■ mg and ■ mg; see below for monitoring in hospital
High	Any LN ≥ 10 cm OR ALC ≥ 25 × 10 ⁹ /L AND any LN ≥ 5 cm Any LN size or ALC AND CrCl ≤ 50 mL/min	Oral (1.5-2 L)/daily and intravenous (150-200 mL/hr as tolerated)	Allopurinol ^b ; consider rasburicase if baseline uric acid is elevated	In hospital at first dose of ■ mg and ■ mg - Predose, 4, 8, 12 and 24 hours Outpatient at subsequent ramp-up doses - Predose, 6 to 8, and 24 hours

ALC = absolute lymphocyte count; CrCl = Creatinine clearance; LN = lymph node; TLS = tumor lysis syndrome

- Start oral hydration 2 days prior to the initiation of venetoclax continuing through the ramp-up period. Administer intravenous hydration for any subject who cannot tolerate oral hydration.
- Start allopurinol or xanthine oxidase inhibitor 2 to 3 days prior to initiation of venetoclax continuing through the ramp-up period.
- Evaluate blood chemistries (potassium, uric acid, phosphorus, calcium, and creatinine); review in real time.
- For subjects at risk of TLS, monitor blood chemistries at 6 to 8 hours and at 24 hours with each subsequent ramp-up dose.

Subjects with baseline CrCl $\leq$ 50 mL/min or with high risk for TLS as defined by at least one lesion $\geq$ 10 cm, or at least one lesion $\geq$ 5 cm plus circulating lymphocytes $>$ 25,000 cells/ μ L, should be hospitalized during the first 24 to 48 hours of treatment with ■ mg and ■ mg of venetoclax for TLS monitoring and intravenous hydration. Hospitalization should be considered for subjects who are at low or medium risk of TLS if they do not have immediate access to a facility capable of correcting TLS promptly or are otherwise considered at risk for TLS.

See [Appendix J](#) for recommendations for initial management of electrolyte abnormalities and prevention of TLS.

6.3 Dose-Limiting Toxicity

In Cohort 1, DLTs will be evaluated in the first 6 subjects during the DLT evaluation period (from Cycle 1 Day 22 for a minimum of 5 weeks and at least 1 week of venetoclax dosing at ■ mg), in order to confirm the initial safety and tolerability in Japanese subjects. After the completion of the DLT evaluation period in the first 6 subjects, the Sponsor will review all available safety data to evaluate the tolerability of venetoclax in combination with obinutuzumab in Japanese subjects. If there are zero or 1 DLTs in the first 6 subjects, enrollment will proceed. The Sponsor will provide the ISM with results of the safety evaluation and the Sponsor's conclusion on tolerability. The ISM will perform a review of the data and provide an opinion back to the Sponsor.

Subjects who miss $\geq$ 20% of the planned doses of venetoclax or obinutuzumab for reasons other than toxicity (e.g., non-compliance, withdrawal of consent, disease progression) during the DLT evaluation period, or subjects who do not complete the DLT assessment period for any reason other than a DLT, will be considered non-evaluable for DLT assessment and will need to be replaced.

Dose Limiting Toxicity Criteria

Any of the following AEs that are attributed as having a reasonable possibility of being related to the administration of venetoclax and/or obinutuzumab and which cannot be attributed by the investigator to a clearly identifiable cause such as tumor progression, concurrent illness, or concomitant medication, will be considered a DLT:

- Grade 4 neutropenia (that was not present at screening) not responsive to granulocyte colony stimulating factors (G-CSF) lasting more than 14 days
- Grade 3 or Grade 4 febrile neutropenia with fever lasting longer than 4 days
- Grade 4 thrombocytopenia resulting in bleeding, or thrombocytopenia that does not improve to Grade $\leq$ 2 (or to $\geq$ 80% of the baseline value, whichever is lower) within 4 weeks
- Clinical TLS (defined per Howard criteria)
- Grade 4 IRR to obinutuzumab despite appropriate premedication and administration rate (defined as an infusion-related toxicity occurring during or within 24 hours after completing an infusion of obinutuzumab). Note that a Grade 3 obinutuzumab IRR that is reversible with treatment and does not require a dose delay of 24 hours is not considered a DLT.

- All other Grades 3, 4, or 5 AEs persisting for more than 2 weeks with or without treatment will be considered a DLT with the following **exceptions**:
 - Grade 3 neutropenia without fever that does not resolve within 4 weeks
 - Grade 3 thrombocytopenia that does not result in bleeding and does not resolve within 4 weeks
 - Grades 3 or 4 lymphopenia and/or leukopenia
 - Grade 3 anemia in patients with heavy bone marrow infiltrate by CLL that does not resolve within 4 weeks
 - Grade 3 Laboratory TLS that resolves within 72 hours
 - Grade 3 or 4 hyperuricemia or hypocalcemia or Grade 3 hyperkalemia, if transient (lasting < 72 hours) and without manifestations of clinical TLS
 - Grade 3 hyperphosphatemia with hospitalization primarily for monitoring/prophylaxis
 - Grade 3 or 4 liver function tests (elevated AST, elevated ALT, or elevated alkaline phosphatase) attributable to obinutuzumab and without clinical symptoms that improve to Grade 2 within 7 days
 - Grade 3 or 4 elevations in bilirubin associated with hemolysis not resolving with 14 days
 - Grade 3 nausea, vomiting and/or diarrhea unless unresponsive to treatment

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

The statistical methods provided in this protocol will be focused on primary and key secondary analyses. The primary analysis will be performed when all subjects have completed two tumor response assessments or discontinued. Complete and specific details of the statistical analysis will be described in the SAP.

7.2 Definition for Analysis Populations

For Cohort 1, the Full Analysis Set (FAS) includes all subjects who received at least 1 dose of venetoclax and/or obinutuzumab. For Cohort 2, the FAS includes all subjects who received at least 1 dose of venetoclax and/or ibrutinib. The FAS will be used for all efficacy (except the endpoints assessed by IRC), safety, pharmacokinetic (PK), and baseline analyses. All analyses will be performed independently for each of the two enrolled cohorts.

The IRC assessed endpoints will be analyzed using per-protocol (PP) population for the primary and secondary efficacy endpoints data assessed by IRC. The PP population includes FAS subjects who have evaluable disease at baseline, i.e., excludes FAS subjects who have been determined as having non-evaluable disease at baseline, as determined by IRC: e.g., a subject with no disease at baseline and/or

malignancies other than CLL/SLL at baseline identified. The details and the timing of the statistical analysis will be described in the SAP.

7.3 Handling Potential Intercurrent Events for the Primary and Key Secondary Endpoints

The estimand for the primary efficacy endpoint CR/CRi rate (defined in Section 3.1) will be analyzed considering the following potential intercurrent events (ICEs):

Intercurrent event 1: Premature discontinuation of any or all study drugs due to any cause.

The disease assessments after ICE1 will be used for the derivation of the primary efficacy endpoint ("treatment policy" strategy, i.e., ignore the ICE).

Further discussion of the planned analysis and handling of intercurrent events can be found in the SAP.

7.4 Statistical Analyses for Efficacy

Summary and Analysis of the Primary Endpoint

Analysis of the primary endpoint will be performed on the PP population. The primary efficacy endpoint will be CR/CRi rate, as assessed by IRC per modified 2008 iwCLL criteria for tumor response.

Complete remission/CRi rate is defined as the proportion of subjects with a best response of CR or CRi. The estimated CR/CRi rate and corresponding 95% Clopper-Pearson exact CI will be provided.

V+G (Cohort 1) and V+I (Cohort 2) will be considered effective for Japanese patients with previously untreated CLL/SLL if the lower bound of the corresponding 95% CI for CR/CRi rate is greater than the threshold of 10%. The evaluation of effectiveness with respect to CR/CRi rate will be performed independently for each cohort.

Summary and Analysis of Secondary Endpoints

All IRC assessed secondary endpoints will use PP population. Analysis of the secondary endpoints will be performed on the FAS (except the analyses assessed by IRC). Secondary efficacy endpoints will include the following evaluations:

- CR/CRi rate as assessed by investigator
- ORR as assessed by IRC
- ORR as assessed by investigator
- PFS as assessed by IRC
- PFS as assessed by investigator
- DOR as assessed by IRC
- DOR as assessed by investigator
- OS

- TTP as assessed by IRC
- TTP as assessed by investigator

For the response rates (ORR), point estimates and corresponding 95% Clopper-Pearson exact CIs will be provided.

Time to event endpoints (PFS, DOR, OS, and TTP) will be analyzed using Kaplan-Meier methodology.

7.5 Statistical Analyses for Safety

The safety analysis will be performed on the FAS. The safety of V+G or V+I will be assessed by evaluation of study drug exposure, AEs, SAEs, deaths, and changes in laboratory determinations, physical examination, and vital sign parameters.

Details pertaining to safety analyses will be provided in the SAP.

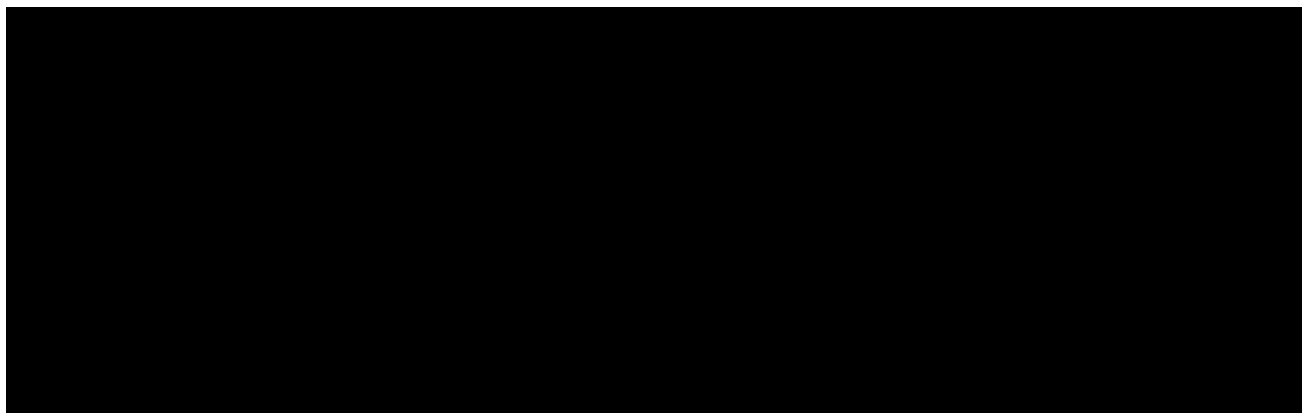
7.6 Interim Analysis

Not applicable for this study.

7.7 Overall Type I Error Control

Not applicable for this study.

7.8 Sample Size Determination



8 ETHICS

8.1 Independent Ethics Committee/Institutional Review Board (IEC/IRB)

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IEC/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 IEC/IRB before the changes are implemented to the study. In addition, all changes to the consent form(s) will be IEC/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). During the COVID-19 pandemic, remote data review/verification may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

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 the last follow-up contact with the subject, whichever is later.

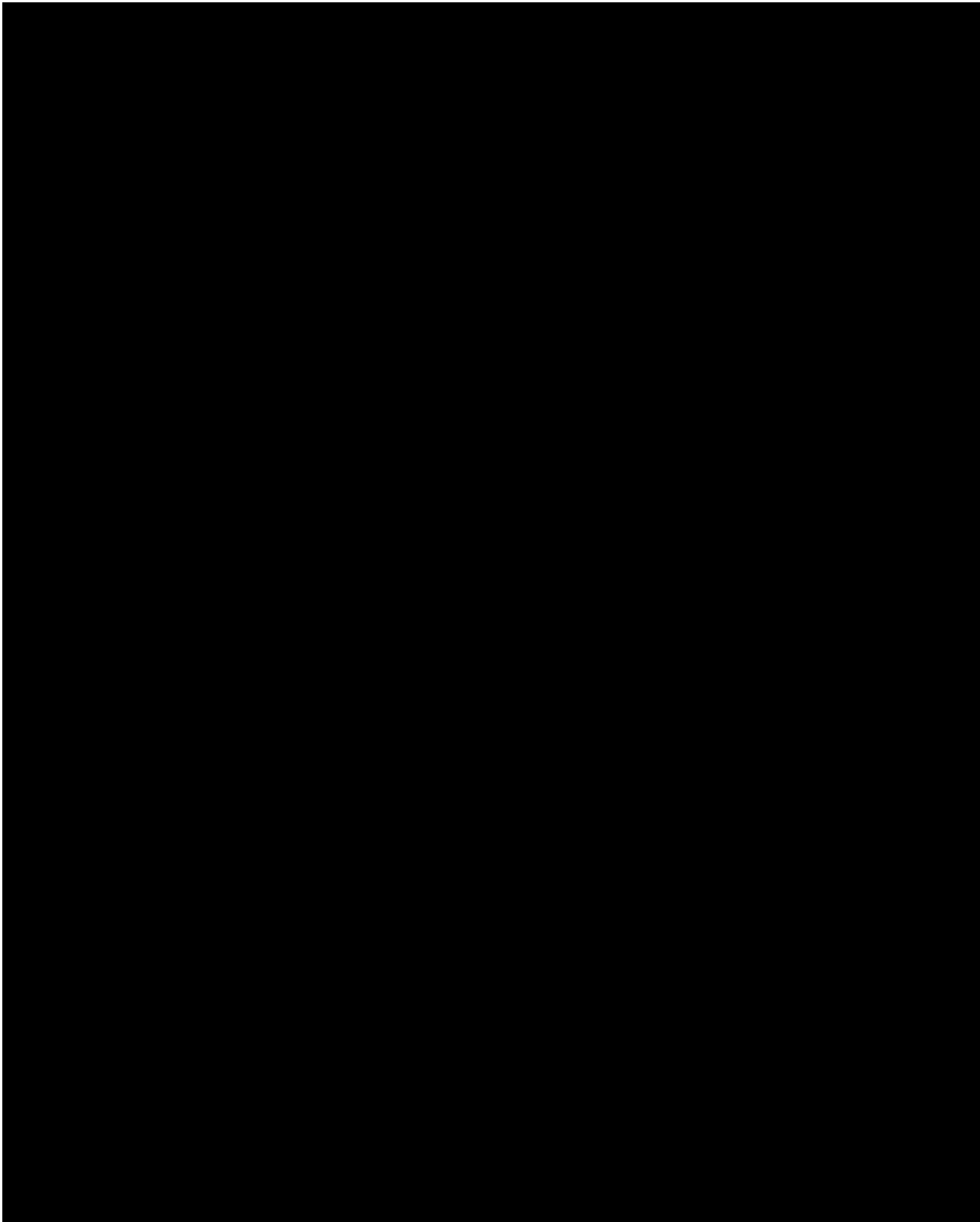
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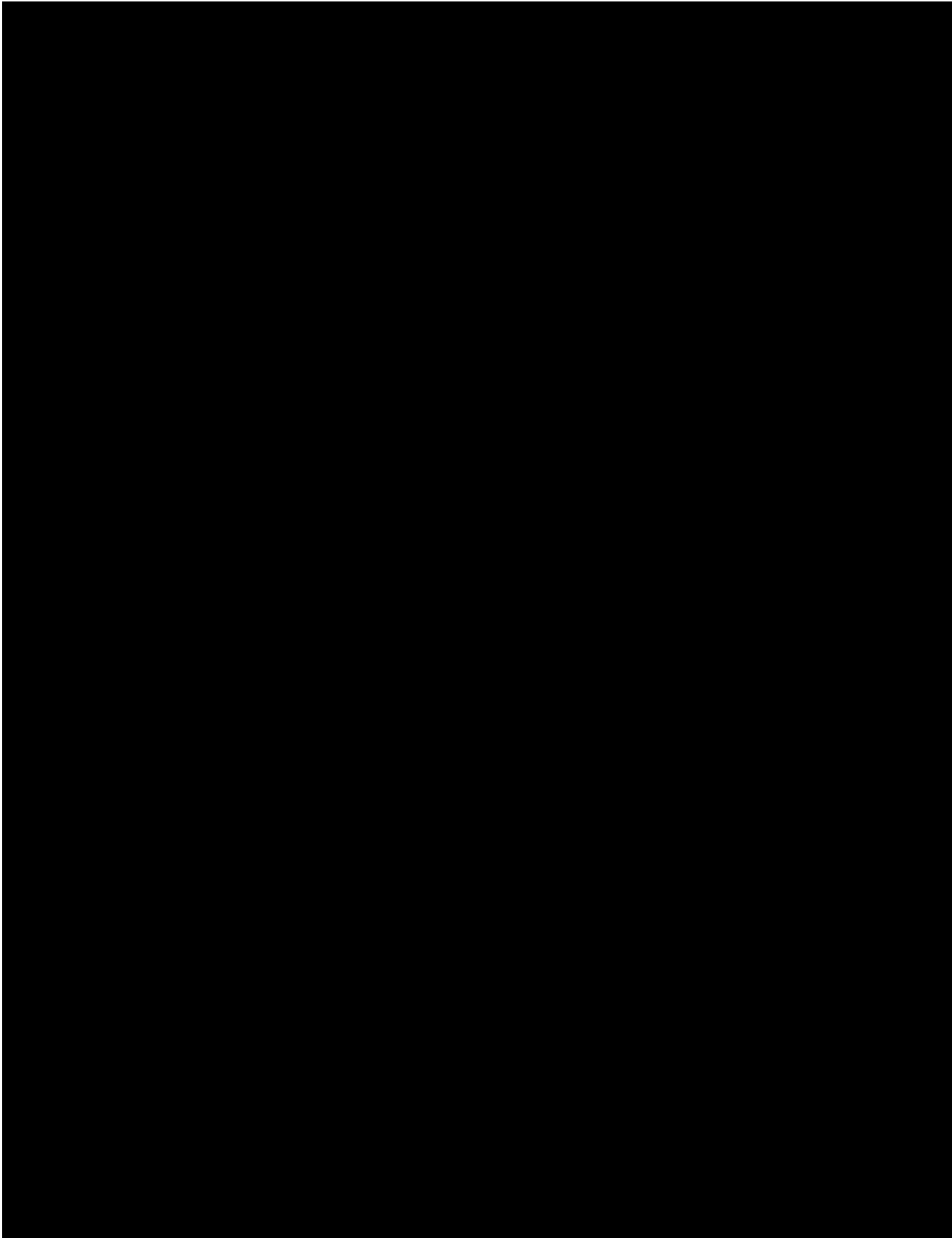
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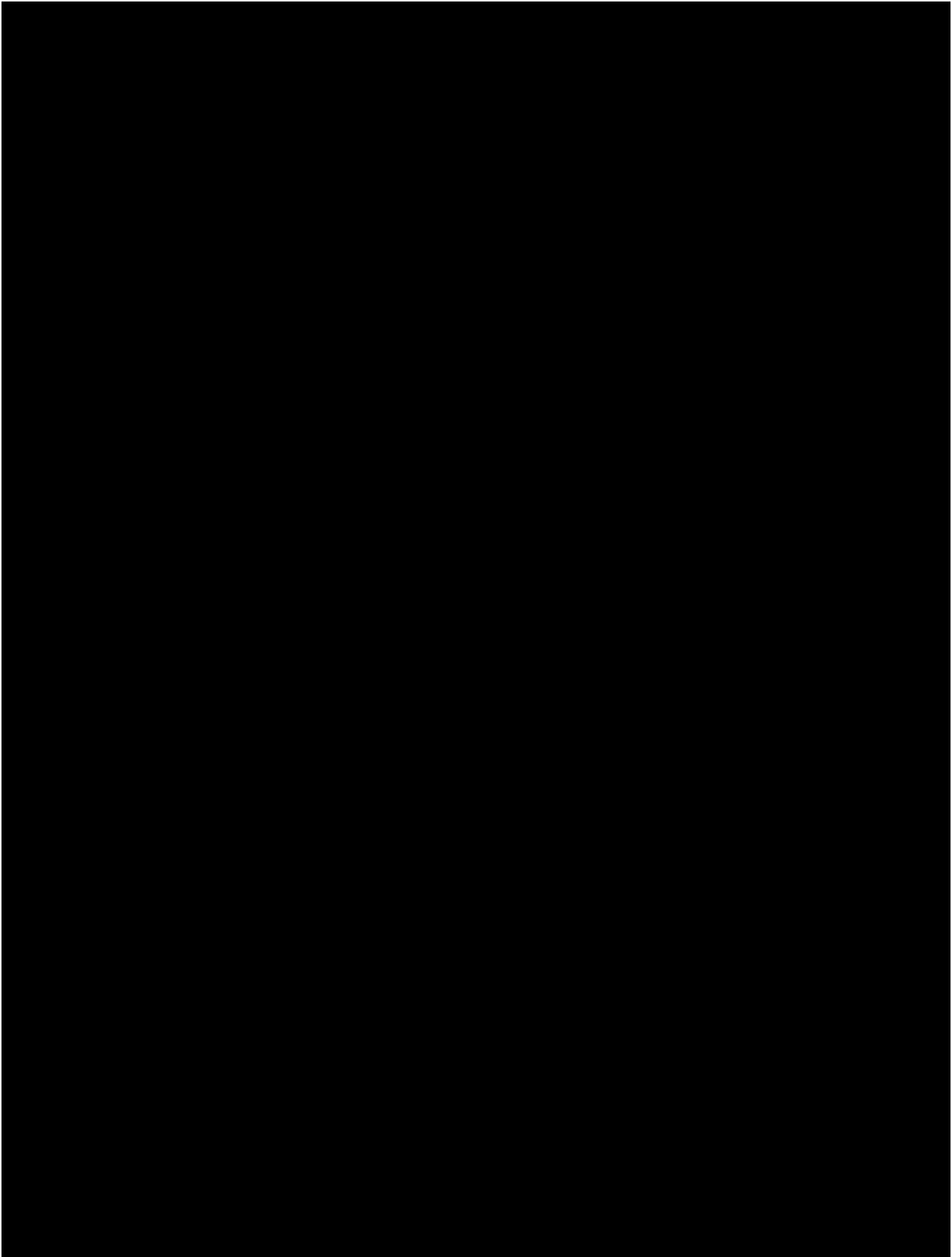
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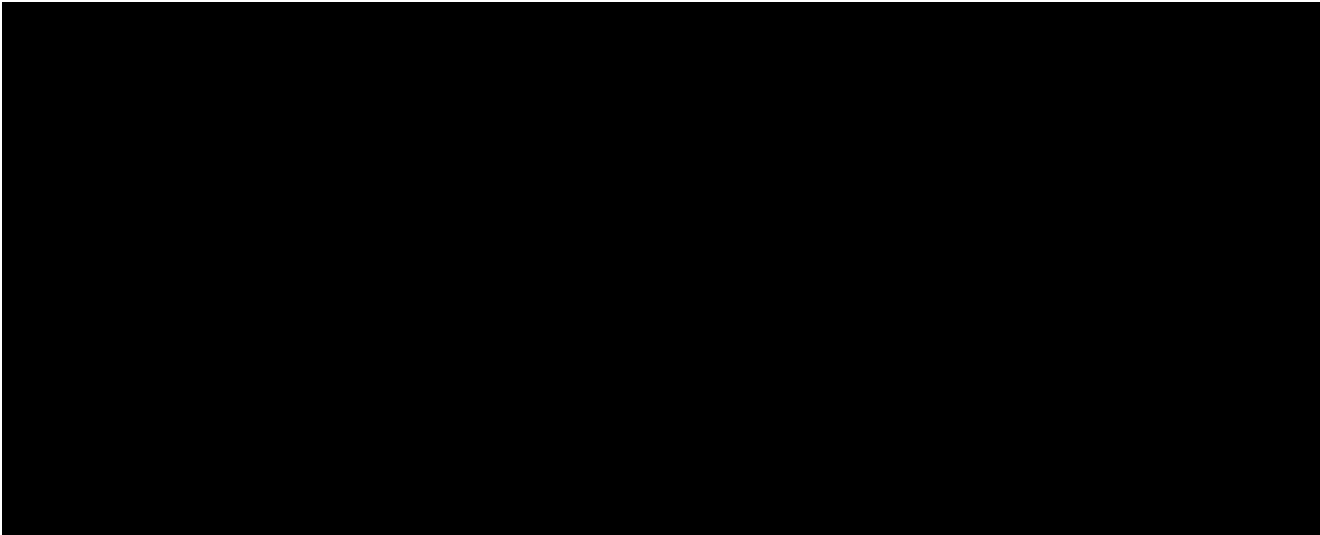
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APPENDIX A. STUDY-SPECIFIC ABBREVIATIONS AND TERMS









APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M20-353: A Phase 2 Study of the Safety and Efficacy of Venetoclax in Combination with Obinutuzumab or Ibrutinib in Japanese Subjects with Previously Untreated Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)

Protocol Date: 19 March 2024

Clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practices (GCP) and local laws and 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 to AbbVie, the ethics committees/institutional review boards (as required) and other appropriate individuals (e.g., coordinating investigator, institution director):
 - All changes in the research activity and all unanticipated problems involving risks to human subjects or others.
 - Any departure from relevant clinical trial law or regulation, GCP, or the trial protocol that has the potential to affect the following:
 - Rights, safety, physical or mental integrity of the subjects in the clinical trial
 - Scientific value of the clinical trial, reliability or robustness of data generated
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]	[REDACTED]r	Japan TA Oncology
[REDACTED]	[REDACTED]	Japan TA Oncology
[REDACTED]	[REDACTED]	Statistical Sciences

APPENDIX D. 2008 MODIFIED IWCLL GUIDELINES FOR TUMOR RESPONSE

Parameter	Complete Remission (CR) All Criteria Must be Met ^a	Partial Remission (PR) At Least 2 Criteria from Group A AND at Least 1 Criterion from Group B Must be Met	Progressive Disease (PD) ^j At Least 1 Criterion from Group A OR 1 Criterion from Group B Must be Met ^{b,c}	Stable Disease (SD)
Group A				
Lymphadenopathy ^d	None > 1.5 cm	Decrease ≥ 50% ^f	Increase ≥ 50% ^e or any new LN > 1.5 cm	Change of –49% to +49% ^f
Blood Lymphocytes	< 4000/μL	Decrease ≥ 50% from baseline	Increase ≥ 50% over baseline (≥ 5000/μL) ^e	Change of –49% to +49%
Hepatomegaly ^g	None	Decrease ≥ 50%	Increase ≥ 50% ^h	Change of –49% to +49%
Splenomegaly ^g	None	Decrease ≥ 50%	Increase ≥ 50% ^h	Change of –49% to +49%
Marrow	Normocellular, < 30% lymphocytes, no B-lymphoid nodules; hypocellular marrow defines CRi	50% reduction in marrow infiltrate or B-lymphoid nodules	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 ^c	Change of –49% to +49%
Hemoglobin	> 11.0 g/dL ⁱ	> 11.0 g/dL or increase ≥ 50% over baseline ⁱ	Decrease of > 2 g/dL from baseline secondary to CLL ^c	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	N/A	N/A

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

- a. CR also requires the lack of disease-related constitutional symptoms.
- b. Transformation to a more aggressive histology (e.g., Richter Syndrome) would also qualify as a PD.
- c. Worsening of cytopenias cannot define PD unless a bone marrow biopsy is performed to show unequivocal progression.
- d. Sum of the products of multiple LNs (as evaluated by CT scans).
- e. Increase in SPD of multiple nodes, or in greatest diameter of any previous site, or appearance of any new lymphadenopathy or organomegaly. For only Cohort 2, subjects with treatment-related lymphocytosis should remain on study treatment in the absence of other evidence of progressive disease.
- 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.
- j. The de novo appearance of hepatomegaly or splenomegaly and Transformation to a more aggressive histology (e.g., Richter syndrome) should consider progressive disease. For Transformation to a more aggressive histology, whenever possible, the diagnosis should be established by lymph node biopsy. For Only Cohort 2, it is defined as PD that a ≥50% increase count confirmed on ≥2 serial assessments if the ALC is ≥30,000/μL and lymphocyte doubling time is rapid, unless considered treatment-related lymphocytosis.

Complete Remission with an Incomplete Marrow Recovery (CRi):

Complete remission with an incomplete marrow recovery is defined as a complete remission (CR) with peripheral cytopenia and incomplete recovery of the bone marrow, manifested by persistent cytopenias. Subjects who have a CRi fulfill the criteria for a CR, but continue to have persistent anemia, thrombocytopenia, and/or neutropenia, with a hypocellular bone marrow confirmed by bone marrow biopsy. These cytopenias are considered due to drug toxicity in the bone marrow and are not related to CLL.

Nodular Partial Remission (nPR):

Nodular partial remission is a response that meets the criteria for CR, but the bone marrow biopsy shows lymphoid nodules, reflecting residual disease.

Partial Remission with Lymphocytosis (Only for Cohort 2 [V+I])

Partial response with lymphocytosis (PRL) is a response where subjects meet the criteria for a PR and have persistent lymphocytosis.*

Stable Disease:

Subjects who do not meet the criteria for CR, CRi, nPR, PR, PRL, or progressive disease (PD).

***Treatment-related Lymphocytosis:**

Treatment-related lymphocytosis is defined as an elevation in blood lymphocyte count of ≥50% compared with baseline that occurs in the setting of unequivocal improvement in at least 1 other disease-related parameter, including lymph node size, spleen size, blood counts (hemoglobin and platelet count), or disease-related symptoms. Treatment-related lymphocytosis is isolated lymphocytosis that occurs when no other criteria for PD are met. It will not be considered PD.

APPENDIX E. STANDARD COCKCROFT AND GAULT FORMULA FOR CALCULATED CREATININE CLEARANCE

For serum creatinine concentration in mg/dL:

$$\text{CrCl} = \frac{(140 - \text{age} +) \times (\text{wt}) \times 0.85 \text{ (if female), or } \times 1.0 \text{ (if male)}}{(\text{mL/min}) 72 \times \text{serum creatinine (mg/dL)}}$$

For serum creatinine concentration in $\mu\text{mol/L}$:

$$\begin{aligned} \text{CrCl} &= \frac{(140 - \text{age} +) \times (\text{wt}) \times 0.85 \text{ (if female), or } \times 1.0 \text{ (if male)}}{(\text{mL/min}) 0.81 \times \text{serum creatinine}} \\ &= (\mu\text{mol/L}) \end{aligned}$$

+ age in years, weight (wt) in kilograms

Source: Cockcroft and Gault 1976²¹

APPENDIX F. THE MODIFIED CUMULATIVE ILLNESS RATING SCALE

Please take into account that CLL-induced illness or organ damage are not included in this rating scale. The goal of this rating scale is to assess comorbidity other than CLL in the patient.

Body System	Score				
1. Cardiac (heart only)	0	1	2	3	4
2. Hypertension (rating is based on severity; organ damage is rated separately)	0	1	2	3	4
3. Vascular (blood, blood vessels and cells, bone marrow, spleen, lymphatics)	0	1	2	3	4
4. Respiratory (lungs, bronchi, trachea below the larynx)	0	1	2	3	4
5. EENT (eye, ear, nose, throat, larynx)	0	1	2	3	4
6. Upper GI (esophagus, stomach, and duodenum; pancreas; do not include diabetes)	0	1	2	3	4
7. Lower GI (intestines, hernias)	0	1	2	3	4
8. Hepatic (liver and biliary tree)	0	1	2	3	4
9. Renal (kidneys only)	0	1	2	3	4
10. Other GU (ureters, bladder, urethra, prostate, genitals)	0	1	2	3	4
11. Musculo-skeletal-integumentary (muscle, bone, skin)	0	1	2	3	4
12. Neurological (brain, spinal cord, nerves, do not include dementia)	0	1	2	3	4
13. Endocrine-Metabolic (includes diabetes, thyroid; breast; systemic infections; toxicity)	0	1	2	3	4
14. Psychiatric/Behavioral (includes dementia, depression, anxiety, agitation/delirium, psychosis)	0	1	2	3	4

Source: Linn 1968²²

PHILOSOPHY AND DEVELOPMENT OF THE SCALE

Compiling and quantifying medical problems in the elderly population would allow meaningful comparison of medical burden and treatment outcomes in elderly patients with variable and complex medical problems.

The Cumulative Illness Rating Scale (CIRS) was initially developed by Linn et al.²² and published in JAGS 1968; it appeared immediately a user friendly but comprehensive review of medical problems by organ systems, based on a 0 - 4 rating, yielding a cumulative score.

This scale was successively revised by Miller et al. to reflect common problems of the elderly with an emphasis on morbidity using specific examples and was renamed CIRS for Geriatrics (CIRS-G),²³ moreover, Miller and Towers provided also a manual of guidelines for scoring their version.²⁴

Then, in 1995, Parmelee et al. validated a Modified CIRS version, based on a 1 - 5 rating and with some differences in categories, in a geriatric residential population.²⁵

Finally, Mistry et al. used this latter Modified CIRS version with a 0 thru 4 rating to measure medical burden in psychogeriatric participants of the UPBEAT program, showing that inclusion of acute medical conditions did not undermine the usefulness of the CIRS.²⁶

Based on the version of Miller and Towers, current guidelines were adapted to the Modified CIRS version and updated.

EDUCATION OF RATER

Nurses, physician assistants, nurse practitioners, or physicians are required to have a necessary background for completing this scale. Due to the judgment required, some physician consultation may be necessary to clarify complex medical problems or their severity.

THE MINIMUM DATABASE REQUIRED

It is expected that every patient should have a complete history and physical examination with a detailed problem list, height and weight (to calculate body mass index [BMI], BMI), and baseline labs including a complete blood count and differential, chemistry profile to include electrolytes, liver and kidney function, serum B12, thyroid function, cholesterol level, hemoglobin A1c (for diabetic patients), and an EKG. For rating psychiatric conditions, the rater is expected to be familiar with the Mini Mental Status Examination,²⁷ and the Diagnostic and Statistical Manual IV APA 1994.²⁸ A checklist of needed information is available in this Appendix.

RATING SUGGESTIONS (GENERAL PRINCIPLES)

Every single disease must be classified in the appropriate system. If there are several problems in the same system, only the most severe is rated. Example: for a patient suffering from a well-controlled angina (Rated 2) and terminal heart failure (Rated 4), only the higher rated condition would be scored in the Cardiac system (e.g., rating is 4). The spread of a cancer may lead to rate the condition in more than one category. For example, a lung cancer with bone metastases treated with nonsteroidal anti-inflammatory drugs (NSAIDs) is Rated 4 in Respiratory and 2 in Musculoskeletal.

General rules for severity rating:

1. No problem affecting that system or past problem without clinical relevance.
2. Current mild problem or past significant problem.
3. Moderate disability or morbidity and/or requires first line therapy.
4. Severe problem and/or constant and significant disability and/or hard to control chronic problems (complex therapeutic regimen).
5. Extremely severe problem and/or immediate treatment required and/or organ failure and/or severe functional impairment.

LEVEL 0

No problem or healed minor injuries; past childhood illnesses (chickenpox); minor surgery (carpal tunnel completely healed, caesarean); uncomplicated healed fractures; other past problems healed without sequel, residual or complication (pneumonia).

LEVEL 1

Any current medical problem that causes mild discomfort or disability, or has occasional exacerbations, having only minor impact on morbidity (asthma controlled with PRN bronchodilators, occasional heartburn relieved with PRN antacids). Medical problems that are not currently active but were significant problems in the past (passage of a kidney stone) or required major surgery (hysterectomy, cholecystectomy, appendectomy).

LEVEL 2

Medical conditions that require daily treatment or first line therapy (asthma controlled with inhaled steroids, gastro-esophageal reflux treated with daily medication, osteoarthritis requiring daily NSAID, etc.) and/or have moderate disability or morbidity.

LEVEL 3

Chronic conditions that are not controlled with first line therapy (asthma needing continuous corticosteroid therapy, symptomatic angina despite medical regimes, heart failure with symptoms or uncontrolled hypertension despite complex therapeutic regimen) and/or constant significant disability, but not severe disability.

LEVEL 4

Any acute condition that requires immediate treatment or hospitalization (unstable angina, acute myocardial infarction (MI), stroke, but also bladder outlet obstruction) and/or extremely severe problems; organ failure (end-stage renal disease needing dialysis, oxygen-dependent chronic obstructive pulmonary disease (COPD), terminal heart failure); severe sensory impairment (almost complete blindness or deafness, being wheelchair bound) and/or severely affected quality of life, severe impairment in function; delirium by medical (organic) conditions.

RATING MALIGNANCIES

Consistent scoring of severity ratings for various malignancies is a difficult problem. Each malignancy has its own rating system and prognostic indicators, the complexity of which would quickly exceed the aim of the intended simplicity and ease of use of CIRS.

The following general guidelines are intended to provide a reasonably accurate delineation of medical burden for cancer without excessive complexity.

- Level 1: Cancer diagnosed in the remote past without evidence of recurrence or sequel in the past 10 years or skin cancer excised in the past without major sequel (other than melanoma).
- Level 2: No evidence of recurrence or sequel in the past 5 years.

- Level 3: Required chemotherapy, radiation, hormonal therapy or surgical procedure for cancer in the past 5 years.
- Level 4: Recurrent malignancy or metastasis (other than to lymph glands) or palliative treatment stage.

These ratings are to be made in the appropriate organ category for a given malignancy.

ORGAN-SPECIFIC CATEGORIES

The following organ-specific categories will attempt to provide guidelines for consistent rating of comparable severity. Common conditions will be stressed with the focus on the "judgment strategy" that can be applied to other problems not listed.

If there are several problems in the same system, only the most severe is rated.

HEART

In this category, only heart and coronary disease have to be considered (not vascular): coronary arteries disease, heart failure, valvular heart diseases, heart disease secondary to hypertension, endocarditis, myocarditis, pericarditis, arrhythmias (extrasystoles, bundle-branch blocks, atrial fibrillation, PMK placement), heart malignancies. Functional impact must be considered too (e.g., NYHA 2 heart failure has different value between dependent and independent persons).

- 0 No problems
- 1 Remote MI (> 5 years ago); occasional [exertion] angina; asymptomatic valvular disease
- 2 Congestive heart failure (CHF) compensated with meds (NYHA 1-2); daily anti-angina meds; left ventricular hypertrophy; atrial fibrillation, bundle branch block, daily anti-arrhythmic drugs (even for prophylaxis); PMK placement for asymptomatic bradycardia (relieved by Holter EKG monitoring); valvular disease requiring medical treatment
- 3 Previous MI (< 5 years ago); abnormal stress test; status post (previous) percutaneous coronary angioplasty, coronary artery bypass graft surgery or other cardiac surgery (valve replacement); moderate CHF (NYHA 2-3) or complex medical treatment; bifascicular block; PMK placement for cardiogenic syncope; pericardial effusion or pericarditis
- 4 Acute coronary syndrome, unstable angina or acute MI; intractable CHF (NYHA 3-4 acute or chronic); marked restriction to the normal activity of daily living secondary to cardiac status

HYPERTENSION

Consider only hypertension severity; organ damage (complications) should be considered into the respective categories.

- 0 Normotension
- 1 Borderline hypertension; hypertension compensated with salt restriction and weight loss, drug free (when drug therapy is indicated, but the patient does not take meds, the score is at least 2)

- 2 Daily antihypertensive meds: hypertension controlled by 1 pill therapy (even fixed doses combinations)
- 3 Hypertension requiring two or more pills for control
- 4 Malignant hypertension, or hypertension non-controlled by complex therapeutic regimen

VASCULAR-HEMATOPOIETIC

Artery disease: carotid atherosclerosis, peripheral arteries disease (PAD), aneurysms (every site);

Venous disease: venous insufficiency, varices, deep venous thrombosis (DVT), pulmonary embolism, primary pulmonary hypertension;

Hematopoietic disease: anemia, leucopenia, thrombocytopenia, hematological malignancy;

Lymphopoietic disease: chronic lymphatic edema, lymphoma, spleen and thymus disease;

Immunologic disease: systemic lupus erythematosus, systemic sclerosis (scleroderma), sarcoidosis, hypersensitivity

- 0 No problem
- 1 Venous insufficiency, varices, lymphedema; carotid stenosis < 70%; hemoglobin 10 - 12 g/dL (in females), 12 - 14 g/dL (in males); anemia of chronic "inflammatory" disease
- 2 Previous DVT; one symptom of atherosclerosis disease (claudication, bruit, amaurosis fugax, absent pedal pulses) or daily meds (e.g., anti-platelets drugs); PAD IIa/IIb by Fontaine; carotid stenosis > 70%; aortic aneurysm < 4 cm; hemoglobin 8 - 10 g/dL (in females), 10 - 12 g/dL (in males); anemia secondary to iron, B12 vitamin or folate deficiency, or to chronic renal failure; total white blood cell (WBC) 2000 - 4000/mm³; mild thrombocytopenia (50000 - 150000/mm³)
- 3 Deep venous thrombosis or recent DVT (< 6 months ago); two or more symptoms of atherosclerosis (see above); PAD Fontaine III or recent/previous angioplasty (with or without stenting); hemoglobin < 8g/dL (in females), <10 g/dL (in males); dyserythropoietic anemia; WBC < 2000/mm³; severe thrombocytopenia (< 50000/mm³)
- 4 Pulmonary embolism (acute or recent/previous); atherosclerosis requiring surgical intervention (e.g., aortic aneurysm > 4 cm, symptomatic carotid stenosis > 70%, PAD Fontaine IV or amputation for vascular causes, etc.); recent/previous vascular surgery; any hematological or vascular malignancy (including multiple myeloma)

In case of immunological disease, score should be assigned by considering blood abnormalities, stadium of organ damage and/or functional disability (2: symptoms controlled by daily meds; 3: symptoms not well controlled; 4: symptoms impossible to be controlled or short time poor prognosis).

RESPIRATORY

In this category COPD, asthma, emphysema, restrictive pulmonary interstitial lung diseases, malignancies of lung and pleura, pneumonia, and smoking status are considered.

- 0 No problem
- 1 Recurrent episodes of acute bronchitis; currently treated asthma with prn inhalers when required; cigarette smoker > 10 but < 20 pack years
- 2 Instrumental diagnosis of COPD or pulmonary interstitial disease (X-ray, TC, spirometry); daily prn inhalers (≤ 2 pharmacological classes); two or more episodes of pneumonia in the last 5 years; cigarette smoker < 20 but < 40 pack-years
- 3 Exertion dyspnea secondary to limited respiratory capacity, not well controlled by daily meds; required oral steroids for lung disease; daily prn inhalers (3 pharmacological classes); acute pneumonia treated as an outpatient
- 4 Chronic supplementation of oxygen; respiratory failure requiring assisted ventilation, or previous (at least one episode); any lung or pleural neoplasm; acute pneumonia requiring hospitalization

Smoking is an important respiratory and cardiovascular risk, so it is considered as a disease, and it is rated according to *lifetime pack-years*:

Number of cigarette packs smoked per day $\times$ Number of years smoked in their lifetime

e.g., 1 pack-year = 20 cigarettes/day (1 pack) $\times$ 1 year

Ex-smokers should be rated too, but those who have been smoke-free for the most recent 20 years would merit a lower rating than those who are currently smoking.

Examples:

- a. Patient smoking 20 cig/day (1 pack) for 25 years = 25 pack-years CIRS score: 2
- b. Patient smoking 40 cig/day (2 packs) for 25 years = 50 pack-years CIRS score: 3
- c. Ex-smoker of 20 cig/day (1 pack) for 25 years, he stopped 5 years ago CIRS score: 2
- d. Ex-smoker of 20 cig/day (1 pack) for 25 years, he stopped 20 years ago CIRS score: 1

Classification of COPD could be more specific when instrumental data (objective evidence) are available: blood gases, forced expiratory volume in 1 second, etc.

EYES, EARS, NOSE & THROAT, AND LARYNX

To simplify the potential complexity of this category it was decided to score according to the severity of the disability created by sensory diseases (degree of limited autonomy and communication), and avoid rating each type of pathology. Sensory impairments should be rated after instrumental correction (corrective lenses, hearing aid, etc.).

Eyes: glaucoma, cataracts, macular degeneration (diabetic/hypertensive retinopathy), any other pathology

Ears: otitis, dizziness, any cause of hearing impairment

Nose & Throat: rhinitis, pharyngitis, nasal polyps, sinusitis, malignancies

Larynx: dysphonia, acute and chronic laryngitis, malignancies

- 0 No problems
- 1 Corrected vision with glasses; mild hearing loss; chronic sinusitis
- 2 Difficulty in reading newspaper or drive although glasses; required hearing aid; chronic sinonasal complaints requiring medication; vertigo/dizziness requiring daily meds
- 3 Severe low vision, partially blind (required an escort to venture out, unable to read newspaper); severe ear impairment (conversational heading still impaired with hearing aid); laryngeal dysphonia (not neurological dysarthria)
- 4 Functional blindness/deafness: unable to read, recognize a familiar face, unable to conversational heading, even if "organically" he is not completely blind or deaf; laryngectomy (every cause, especially malignancies); required surgical intervention for vertigo; aphonia secondary to laryngeal impairment.

UPPER GASTROINTESTINAL SYSTEM

This category is comprehensive of the intestinal tract from esophagus to duodenum, and pancreatic trees: dysphagia, gastroesophageal reflux disease (GERD), hiatal hernia, esophageal diverticula, any type of gastritis (consider also *H. Pylori* eradication or not), gastric/duodenal ulcer, acute or chronic pancreatitis, malignancies (comprehensive of gastric lymphoma).

Ensure that type 1 diabetes is rated under "metabolic."

- 0 No problem
- 1 Hiatal hernia, GERD or gastritis requiring prn meds; previous ulcer (> 5 years ago); previous *H. Pylori* eradication therapy (> 5 years ago)
- 2 Daily proton pump inhibitor/anti-acid meds; documented gastric or duodenal ulcer or *H. Pylori* eradication therapy within 5 years
- 3 Active gastric or duodenal ulcer; positive fecal occult blood test; any swallowing disorder or dysphagia; chronic pancreatitis requiring supplemental pancreatic enzymes for digestion; previous episode of acute pancreatitis
- 4 Any type of malignancies (see "Rating Malignancies"); previous gastric surgery because of cancer; history of perforated ulcer (gastric surgery not because of cancer, ulcorrhaphy); melena/heavy bleeding from upper gastrointestinal (GI) source; acute pancreatitis

LOWER GASTROINTESTINAL SYSTEM

Comprehensive of the rest of the GI system, from small bowel to anus: Whipple's disease, diverticulosis, irritable bowel, malignancies. Constipation is rated, too, by type and frequency of laxatives required, or by history of impaction.

- 0 No problems, previous appendectomy, previous hernia repair (without complications)

- 1 Constipation managed with prn meds; active hemorrhoids; intestinal hernia requiring surgery; previous hernia repair with complications (intestinal adhesions, laparocoele, etc.); irritable bowel syndrome (few symptoms)
- 2 Constipation requiring daily bulk laxatives (psyllium, polycarbophil, sterculia, guar gum, etc.), or stool softeners; diverticulosis (previous diverticulitis); inflammatory bowel disease in remission with meds (> 5 years ago)
- 3 Bowel impaction/diverticulitis within the last year; daily use of stimulant (irritant) or osmotic laxatives (bisacodyl, senna, glycerol, sodium docusate; lactulose, polyethylene glycol) or enemas; chronic bowel inflammation in remission with meds (< 5 years ago)
- 4 Diverticulitis flare up; active inflammatory disease; current impaction; hematochezia/active bleeding from lower GI source; bowel carcinoma

LIVER AND BILIARY TREES

Comprehensive of liver, gallbladder, biliary trees, portal system: acute and chronic hepatitis (viral, alcoholic, toxic, autoimmune, idiopathic), cirrhosis, portal hypertension, hemochromatosis, primary biliary cirrhosis, cholelithiasis, cholangitis, primary malignancies. As the hepato-biliary system is difficult to assess through the physical examination, therefore, laboratory results must be used.

- 0 No problem
- 1 History of hepatitis (actually normal values of transaminases); cholecystectomy
- 2 Cholelithiasis; chronic hepatitis or previous hepatitis (< 5 years ago) or any other liver disease (hemochromatosis, primary biliary cirrhosis) with mildly elevated transaminases (within 3-times normal values); heavy alcohol use within 5 years (to rate in "psychiatric," too)
- 3 Chronic hepatitis or any other liver disease with marked elevation of transaminases (> 3-times normal values); elevated bilirubin
- 4 Acute cholecystitis; any biliary obstruction; active hepatitis/liver cirrhosis; any liver or biliary tree carcinoma

RENAL

This category is exclusive of kidney: kidney stones, acute/chronic renal failure, glomerulonephritis; nephrosic/nephritic syndrome; active/chronic pyelonephritis, diabetic or hypertensive nephropathy (albuminuria/proteinuria), renal carcinoma. Bence-Jones proteinuria in multiple myeloma should not be considered.

- 0 No problem
- 1 Asymptomatic kidney stone; kidney stone passage within the last ten years; pyelonephritis within 5 years; kidney cysts without hematuria
- 2 Serum creatinine > 1.5 but < 3 mg/dL without diuretic or antihypertensive medication (particularly angiotensin-converting enzyme-inhibitors or SRAA blockers); kidney calculi requiring daily meds

- 3 Serum creatinine > 3 mg/dL or < 1.5 mg/dL in conjunction with diuretics, antihypertensive, or bicarbonate therapy; active pyelonephritis; nephrosic syndrome; colic symptoms treated as an outpatient
- 4 Required dialysis; renal carcinoma; colic symptoms requiring hospitalization

GENITOURINARY

Ureters, bladder, urethra. Genitals, prostate, testicles, penis, seminal vesicles. Uterus, ovaries.

Mammary gland is rated under "metabolic." This category is comprehensive of all GU tract impairments: ureteral or bladder stones, benign prostate hypertrophy (BPH), urinary tract infections (UTIs), prolapses, etc. Urinary incontinence and indwelling catheter should also be considered.

- 0 No problem
- 1 Stress incontinence; BPH without urinary symptoms; hysterectomy or ovariectomy (uterine fibroma, benign neoplasm)
- 2 Pathological pap smear (or 2 consecutives abnormal); frequent UTIs (3 or more in the past year) in female or current UTIs; urinary incontinence (not stress) in females; BPH with urinary symptoms (frequency, urgency, hesitancy); status post TURP; any urinary diversion procedure; indwelling catheter; bladder calculi
- 3 Prostatic cancer in situ (e.g., incidentally found during TURP); vaginal bleeding; cervical carcinoma in situ; hematuria (any cause); urinary incontinence (not stress) in males; bladder polyps
- 4 Acute urinary retention; current urosepsis; any GU malignancies except as above

MUSCULOSKELETAL/INTEGUMENT

This is a very broad category, including: osteoarthritis, osteoporosis, any bone fracture; primary neoplasm (bone, muscle, connective tissue, skin), distinguishing melanoma from other localized skin cancers; rheumatoid arthritis and polymyalgia rheumatica; muscular injuries (rotator cuff, long head of the biceps); pressure sores; any dermatological disease.

The scores of this category are strictly correlated to the disability they cause; for the evaluation of the level of disability, refer to BADL and IADL.

NOTICE: Score the severity of each illness according to the level of disability caused by the same illness in this category, without considering the disability caused by other diseases. For example: a patient affected both by osteoarthritis and hemiplegia from a previous stroke has a high level of disability, but you have to score 2 for disability by osteoarthritis (in this category) and 4 for disability by stroke (in the neurological category); for a patient with both a deforming rheumatoid arthritis and a previous stroke without remaining outcomes you have to score 4 for disability from arthritis (in this category) and 2 for disability from stroke (in the neurological category).

- 0 No problem

- 1 Requires PRN meds for osteoarthritis (NSAID) or has mildly limited IADL from joint pathology; excised skin cancers (except melanoma); skin infections requiring antibiotics within a year
- 2 Daily anti-osteoarthritis meds (NSAID) or use of assistive devices or little limitation in activities of daily living (ADL; previous arthroprosthesis or treated fracture with a low level of remaining disability); osteoporosis without vertebral fractures; daily meds for chronic skin diseases (even local, as psoriasis or pressure sores); non-metastatic melanoma; daily meds for rheumatoid arthritis (except steroids) with a low level of disability
- 3 Osteoarthritis with a moderate level of disability in ADL; requires chronic treatment with steroids for arthritic conditions or joints' deformities or severely impaired; osteoporosis with vertebral compression fractures
- 4 Wheelchair bound for osteomuscular disease; severe joint deformities or severely impaired usage; osteomyelitis; any bone or muscle or connective tissue neoplasm (see "Rating Malignancies"); metastatic melanoma.

Fractures and/or arthroprosthesis (both recent and old) have to be scored according to the level of disability they cause (considering outcomes too), in order to avoid confusion about possible classifications of different fractures or joints. The same is true for muscular diseases.

This category includes the "somatic" pathologies of the central and peripheral nervous system: any kind of stroke, neurodegenerative diseases (Parkinson's disease and parkinsonism, multiple sclerosis, amyotrophic lateral sclerosis, etc.), myelopathies, traumas with neurological outcomes, primary or secondary epilepsy, neuropathies (diabetic, alcoholic, any other etiology), primary tumors, chronic headaches (migraine), insomnia, etc. It must carefully estimate the severity and prognosis of the illness but also the functional impairment that the illness causes.

- 0 No problem (or fewer convulsions in childhood)
- 1 Frequent headaches requiring PRN meds without impairment in Advanced ADL; previous transient ischemic attack (TIA) (one event); previous epilepsy, actually not treated, without crisis since more than 10 years ago.
- 2 Chronic headache requiring daily meds (even for prophylaxis) or with regularly functional impairment in Advanced ADL (bed rest, job withdrawal, etc.); actual TIA or more than one previous TIA; previous stroke without significant residual; mild severity neurodegenerative diseases (see above), treated and well controlled; epilepsy controlled with drugs.
- 3 Previous stroke with mild residual dysfunction (hemiparesis, dysarthria); any neurosurgical procedure; moderate severity neurodegenerative diseases (see above), not well controlled by meds; epilepsy in treatment but with periodic crisis.
- 4 Acute stroke or previous stroke with severe residual dysfunction (hemiplegia, aphasia, severe vascular dementia) or more than one previous stroke (multi-infarct encephalopathy); severe neurodegenerative diseases (see above) causing disability in ADL; neurological coma.

Alzheimer's disease and dementia should not be rated into this category (Psychiatric and behavioral diseases): Alzheimer's disease should be listed only under psychiatric disorders; if dementia stems from vascular and/or mixed dementia and/or other neurological condition (e.g., Parkinson's Disease), both

"neurologic" and "psychiatric" categories should be endorsed at the appropriate level for severity, considering in this category the stroke and the multi-infarct encephalopathy responsible for the cognitive impairment (score 3 for stroke with remaining outcomes, score 4 for multi-infarct encephalopathy).

ENDOCRINE-METABOLIC SYSTEM AND BREAST (SYSTEMIC INFECTIONS AND POISONINGS)

Type 1 and Type 2 diabetes (organ damage should be considered into the respective categories, like for hypertension), obesity and dyslipidemia (hypercholesterolemia) represent the core of this category; it includes also hypo- and hyper-thyroidism, hypo- and hyper-parathyroidism, adrenal pathologies (Cushing' or Addison' disease), hypogonadism, hypopituitarism, etc. Malignancies of these glands, both benign (like thyroid nodules) and malignant (like thyroid or adrenal cancer, vipoma, etc.) are included too.

Even if it is an exocrine gland, breast was included in this category because the authors did not find a more appropriate one; so it also includes breast cancer. Moreover, it includes: electrolyte disorders, sepsis, systemic infections (like tuberculosis, syphilis, AIDS) scored according to their severity and the functional impairment they cause (see general indications) and poisonings (chronic by metals or acute by pesticides or carbon monoxide).

- 0 No problem
- 1 Diabetes and/or dyslipidemia compensated with diet; mild obesity (BMI 30-35 kg/m²); hypothyroidism in replacement therapy (L-thyroxin); hyperthyroidism caused by Plummer' adenoma surgically treated.
- 2 Diabetes compensated with oral hypoglycemic drugs or insulin (hemoglobin A_{1c} < 7%); dyslipidemia well controlled by daily meds (c-LDL lower than the recommended target according to the individual global cardiovascular risk); moderate obesity (BMI 35-45 kg/m²); hyperthyroidism in pharmacologic treatment; asymptomatic or surgically treated hyperparathyroidism; fibrocystic breast disease.
- 3 Diabetes not well compensated by therapy (hemoglobin A_{1c} 7-8.5%, presence of complications); dyslipidemia not well controlled (c-LDL higher than the recommended target according to the individual global cardiovascular risk; for instance, c-LDL > 100 mg/dL in patients with previous MI or stroke); severe obesity (BMI > 45 kg/m²); symptomatic hyperparathyroidism (e.g., hypercalcaemia); replacement therapy for adrenal failure; any electrolytes disorder requiring hospitalization.
- 4 Uncontrolled diabetes (hemoglobin A_{1c} > 8.5%) or one diabetic ketoacidosis or nonketotic hyperosmolar coma during the past year; genetic uncontrolled dyslipidemia; acute adrenal failure during hormonal replacement therapy; any neoplasm of thyroid, breast, adrenal gland (see "Rating Malignancies").

NOTICE: when the patient is not treated with drug therapy for diabetes or dyslipidemia but he should be for the optimal control of the pathology (for instance, hemoglobin A_{1c} > 7%, total cholesterol > 250 mg/dL), score the pathology according to the laboratory values, which really define its severity.

PSYCHIATRIC AND BEHAVIORAL DISEASES

This category includes both dementia and related behavioral disorders (psychosis, anxiety, depression, agitation) and all the pre-existing and/or not related to dementia psychiatric disorders. Since this is the only item analyzing patient's mental status (all the others refer to physical status), it is very important to evaluate it considering carefully further information derived from the Comprehensive Geriatric Assessment (MMSE; Geriatric Depression Scale,²⁹ Neuro-Psychiatric Inventory³⁰ if available).

- 0 No psychiatric problem or history thereof.
- 1 Minor psychiatric condition or history thereof: previous (occasional) psychiatric treatment without hospitalization; major depressive event and/or use of antidepressants more than 10 years ago without hospitalization; occasional use of minor tranquilizers (e.g., BDZ; even if as hypnotherapy for insomnia); mild cognitive impairment (MMSE 25-28).
- 2 A history of major depression (according to DSM-IV criteria) within the last 10 years (treated or untreated); mild dementia (MMSE 20-25); previous admission to Psychiatric Department for any reason; history of substance abuse (more than ten years ago, including alcoholism).
- 3 Current major depression (according to DSM-IV criteria) or more than two previous major depression episodes in the past 10 years; moderate dementia (MMSE 15-20); current and usual usage of daily anti-anxiety meds (even as hypnotherapy for insomnia); current or within the past ten years substance abuse or dependence (according to DSM-IV criteria); requires daily antipsychotic medication; previous attempt at suicide.
- 4 Current mental illness requiring psychiatric hospitalization, institutionalization, or intensive outpatient management (psychiatric emergency, as attempt at suicide or severe depression with suicide purpose, acute psychosis or acute decompensation of chronic psychosis, severe substance abuse; severe agitation from dementia); severe dementia (MMSE < 15); delirium (acute confusion or altered mental status for medical (organic) reasons: in this case you have to codify also the medical cause in its own category with the appropriate level of severity).

It could be requested psychiatric consult for this category; dementia and depression, the most frequent diseases in the elderly, can be scored in details using the MMSE and GDS. The severity of any mental disorder (dementia, depression, anxiety, psychosis, substance abuse and all the others) has to be scored according to the level of functional impairment or disability they cause.

CHECKLIST

Medical history

1. Timing of events and/or interventions (how long ago underwent surgery for...; how long ago had MI or stroke, etc.) and evaluation of functional impairment
2. Drugs list (fundamental), including laxatives and tranquilizers (even hypnoinducents)
3. Symptoms of atherosclerotic disease (TIA, angina, claudication, amaurosis)
4. Etiological diagnosis (reasonably reliable) of anemia

5. Degree of vascular stenosis or aneurism dimension (by Doppler and/or ultrasound and/or TC data, when available)
6. Information about smoking status (how many cigarettes per day for how many years, when stopped)
7. Glasses use? With this aid, the patient is able to read a newspaper? Requires an escort to venture out?
8. Any hearing aid? (You should evaluate possibility to communicate with patient)
9. "Peptic history" of the patient (including previous eradication therapy for H. Pylori)
10. Urinary symptoms, incontinence, presence of bladder catheter (even from BADL)

PHYSICAL EXAMINATION

- a. Height (m²) and weight (kg) (measured, not reported, if possible) to calculate BMI
- b. Blood pressure, heart rate, cardiac murmurs, peripheral arterial pulses
- c. Joint pain or passive stiffness limitation (non-X-ray-based diagnosis of osteoarthritis)
- d. Neurological residual (dysarthria/aphasia, hemiparesis/hemiplegia)

BASELINE LABORATORY SAMPLES

- Blood count: hemoglobin, WBC and platelets
- Creatinine, electrolytes
- Cholesterol levels (total, HDL) and triglycerides
- AST, ALT, fractioned bilirubin
- Thyroid function and serum B12 (when indicated)
- Hemoglobin A_{1c} (for diabetic patients)

APPENDIX G. SAMPLE LIST OF EXCLUDED AND CAUTIONARY MEDICATIONS

Excluded During Initiation and Dose-Titration (Ramp-Up) of Venetoclax and Cautionary at [REDACTED] mg Steady Daily Dose of Venetoclax:
Strong CYP3A inducers – apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort Moderate CYP3A inducers[^] – bosentan, efavirenz, etravirine, phenobarbital, primidone Strong CYP3A inhibitors[†] – Boceprevir, cobicistat, danoprevir/ritonavir, elvitegravir/ritonavir, idelalisib,* indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, paritaprevir/ritonavir combinations, ritonavir, posaconazole, saquinavir, telaprevir, telithromycin, tipranavir/ritonavir, telithromycin, troleanomycin, voriconazole Moderate CYP3A inhibitors^{††} – aprepitant, conivaptan, ciprofloxacin, crizotinib,* cyclosporine,* diltiazem,# dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib,* tofisopam, verapamil P-gp inhibitors^{††} – Amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir and ritonavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, verapamil
Cautionary During Initiation and Dose-Titration (Ramp-Up) and Cautionary at [REDACTED] mg Steady Daily Dose of Venetoclax:
Coumarins (vitamin K antagonists): Warfarin (Coumadin)** phenprocoumon (Marcumar)** P-gp substrates Dabigatran etexilate, digoxin, fexofenadine BCRP substrates rosuvastatin, sulfasalazine OATP1B1/1B3 substrates asunaprevir, atorvastatin, bosentan, danoprevir, docetaxel, fexofenadine, glyburide, nateglinide, paclitaxel, pitavastatin, pravastatin, repaglinide, rosuvastatin, simvastatin acid BCRP inhibitors curcumin, cyclosporine A, eltrombopag

Note that this is not an exhaustive list. For an updated list, see the following link: <https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers>.

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 ramp-up 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 H. GUIDELINES FOR DEFINING TUMOR LYSIS SYNDROME

Howard Criteria³¹ for 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	
Hyperphosphatemia	Phosphorus > 4.5 mg/dL (1.5 mmol/liter) in adults	
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 < 4.5 mg/dL (1.12 mmol/liter) ^a	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 ^b
Acute kidney injury ^c	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 of < 0.5 mL/kg/hr for 6 hours

TLS = tumor lysis syndrome

* In laboratory TLS, 2 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 days afterward. Clinical TLS requires the presence of Laboratory TLS plus one or more findings from the Clinical TLS column.

- The corrected calcium level in milligrams per deciliter=measured calcium level in milligrams per deciliter + 0.8 × (4 – albumin in grams per deciliter).
- Not directly attributable to a therapeutic agent.
- Acute kidney injury is defined as an increase in the creatinine level of ≥ 0.3 mg/dL (26.5 µmol/L) or a period of oliguria lasting ≥ 6 hours. By definition, if acute kidney injury is present, the patient has clinical TLS.

APPENDIX I. IWCLL GRADING SCALE FOR HEMATOLOGIC TOXICITY IN CLL SUBJECTS

Decrease in Platelets or Hemoglobin From Pre-Treatment (%)	Toxicity Grade	ANC/ μ L
0 – 10	0	≥ 2000
11 – 24	1	≥ 1500 and < 2000
25 – 49	2	≥ 1000 and < 1500
50 – 74	3	≥ 500 and < 1000
≥ 75	4	< 500

ANC = absolute neutrophil count

Reference: Hallek 2008⁵

APPENDIX J. RECOMMENDATIONS FOR INITIAL MANAGEMENT OF ELECTROLYTE IMBALANCES AND PREVENTION OF TUMOR LYSIS SYNDROME

PRIOR TO OBINUTUZUMAB INFUSION (COHORT 1 ONLY)

Patients with a high tumor burden (absolute lymphocyte count [ALC] $\geq 25 \times 10^9/\text{L}$ or bulky lymphadenopathy) must receive prophylaxis for tumor lysis syndrome (TLS) prior to the initiation of treatment. These patients must be well-hydrated. It is desirable to maintain a fluid intake of approximately 3 liters/day, 1–2 days before the first dose of obinutuzumab. All such patients with a high tumor burden must be treated with allopurinol or a suitable alternative treatment starting 12–24 hours prior to the first infusion. Patients should continue to receive repeated prophylaxis with allopurinol and adequate hydration prior to each subsequent infusion, if deemed appropriate by the investigator.

FIRST DOSE OF VENETOCLAX OR DOSE ESCALATION (COHORT 1 and COHORT 2)

- Within the first 24 hours after either the first dose or dose escalation, if any laboratory criteria below are met, the patient should be hospitalized for monitoring and the investigator notified. No additional venetoclax doses should be administered until resolution. A rapidly rising serum potassium level is a medical emergency.
- Nephrology (or acute dialysis service) must be consulted/contacted on admission (per institutional standards to ensure emergency dialysis is available).
- Intravenous (IV) fluids (e.g., D5 1/2 normal saline) should be initiated at a rate of at least 1 mL/kg/h rounded to the nearest 10 mL (target 150–200 mL/hr; not < 50 mL/hr). Modification of fluid rate should also be considered for individuals with specific medical needs.
- Monitor for symptoms or signs of TLS (e.g., fever, chills, tachycardia, nausea, vomiting, diarrhea, diaphoresis, hypotension, muscle aches, weakness, paresthesias, mental status changes, confusion, and seizures). If any clinical features are observed, recheck potassium, phosphorus, uric acid, calcium, and creatinine within 1 hour STAT.
- Vital signs should be taken at time of all blood draws or any intervention.
- The management recommendations below focus on the minimum initial responses required. If a diagnosis of TLS is established, ongoing intensive monitoring and multidisciplinary management will be as per institutional protocols.

In addition to the recommendations for patients with chronic lymphocytic leukemia/ small lymphocytic lymphoma receiving first dose of venetoclax in the table below:

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

- For phosphorus increase of > 0.5 mg/dL AND > 4.5 mg/dL, administer phosphate binder and recheck potassium, phosphorus, uric acid, calcium, and creatinine within 1 hour STAT.

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

Abnormality	Management Recommendations
Potassium ≥ 6.0 mmol/L (6.0 mEq/L) and/or symptomatic (e.g., muscle cramps, weakness, paresthesias, nausea, vomiting, diarrhea)	• Perform STAT ECG and commence telemetry. • Nephrology (or other acute dialysis service) notified with consideration of initiating dialysis. • Administer Kayexalate 60 g (or Resonium A 60 g). • Administer furosemide 20 mg IV $\times$ 1. • Administer insulin 0.1 U/kg IV + D25 2 mL/kg IV. • Administer sodium bicarbonate 1 to 2 mEq IV push. • If sodium bicarbonate is used, rasburicase should not be used as this may exacerbate calcium phosphate precipitation. • Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. Do not administer in same IV line as sodium bicarbonate. • Recheck potassium, phosphorus, uric acid, calcium and creatinine.
Hyperuricemia	
Uric acid ≥ 8.0 mg/dL (476 μ mol/L)	• Consider rasburicase (0.2 mg/kg as an intravenous infusion over 30 minutes). • If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Recheck potassium, phosphorus, uric acid, calcium and creatinine.
Uric acid ≥ 10 mg/dL (595 μ mol/L) OR Uric acid ≥ 8.0 mg/dL (476 μ mol/L) with 25% increase and creatinine increase ≥ 0.3 mg/dL (≥ 0.027 mmol/L) from predose level	• Administer rasburicase (0.2 mg/kg as an intravenous infusion over 30 minutes). • When rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Notify nephrology (or other acute dialysis service). • Recheck potassium, phosphorus, uric acid, calcium and creatinine. • If uric acid < 8.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours, later, if no other evidence of tumor lysis.

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

ECG = electrocardiogram; IV = intravenous; ULN = upper limit of normal; WNL = within normal limits

Ongoing Dosing of Venetoclax (COHORT 1 and COHORT 2)

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

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

- For potassium, admit subject for any increase $\geq$ 1.0 mmol/L (1.0 mEq/L), or any level $>$ ULN.
 - Refer to the management guidelines for electrolyte changes observed within the first 24 hours after either the first dose or dose escalation (see table above).
- If a smaller potassium increase is observed that does not meet the criteria for admission above, recheck potassium, phosphorus, uric acid, calcium, and creatinine in 24 hours and confirm no evidence of tumor lysis prior to further venetoclax dosing.

- For uric acid, calcium, phosphorus and creatinine, refer to the management guidelines for electrolyte changes observed within the first 24 hours after either the first dose or dose escalation (see table above).

APPENDIX K. CHILD-PUGH SCORES FOR SUBJECTS WITH CHRONIC LIVER IMPAIRMENT

Measure	1 point	2 points	3 points
Total bilirubin, $\mu\text{mol/L}$ (mg/dL)	< 34 (< 2)	34 to 50 (2 to 3)	> 50 (> 3)
Serum albumin, g/L (g/dL)	> 35 (> 3.5)	28 to 35 (2.8 to 3.5)	< 28 (< 2.8)
PT/INR	< 1.7	1.71 to 2.30	> 2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade 1 to 2 (or suppressed with medication)	Grade 3 to 4 (or refractory)
Points	Class		
5 to 6	A		
7 to 9	B		
10 to 15	C		

INR = international normalized ratio; PT = prothrombin time

Source: Child 1964³² and Pugh 1973.³³

APPENDIX L. ACTIVITY SCHEDULE

The following table shows the required activities. The individual activities are described in detail in the **Operations Manual**. Allowed modifications due to COVID-19 are detailed in the Operations Manual.

Cohort 1 Study Activities Table

Cohort 1 (V+G)	Screening	Cycle 1							Cycle 2							Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8	Cycle 9	Cycle 10	Cycle 11	Cycle 12	Follow-Up			
Activity																													
🗨️ INTERVIEWS & QUESTIONNAIRES																													
Informed consent	✓																												
Eligibility criteria	✓																												
Medical history	✓																												
Adverse event assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓				
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓				
Survival status																										✓			
🏥 LOCAL LABS & EXAMS																													
HBV/HCV test	✓																												
12 lead ECG	✓	As clinically indicated.																											
Height (screening only) and weight	✓	✓						✓																		✓			
Vital signs (temperature, blood pressure, heart rate, respiratory rate)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			

Cohort 1 (V+G)	Screening	Cycle 1						Cycle 2						Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8	Cycle 9	Cycle 10	Cycle 11	Cycle 12	Follow-Up					
Activity																													
Complete physical examination	✓															✓			✓		✓					✓	✓		
Symptom directed physical examination		✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓		✓		✓	✓	✓					
Pregnancy test (urine/serum)	✓ S	✓ U	Additional tests can be performed per local regulations.																										
Clinical chemistry	✓	✓	✓	✓	✓	Refer to Section 6.2 for chemistry collection timepoints associated with TLS risk and venetoclax dosing.										✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Hematology	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Coagulation panel	✓																												
Urinalysis	✓	As clinically indicated.																											
ECOG performance	✓	✓						✓								✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Coombs test	✓																												
Creatinine clearance (Cockcroft Gault)	✓																												
Response Assessment																	✓			✓		✓					✓	✓	
CT scan (refer to Ops Manual)	✓																✓			✓		✓					✓	✓	

Cohort 1 (V+G)	Screening	Cycle 1						Cycle 2						Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8	Cycle 9	Cycle 10	Cycle 11	Cycle 12	Follow-Up				
Activity																												
Bone marrow biopsy/aspirate (refer to Ops Manual)	✓															✓			✓		✓					✓	✓	
CIRS score	✓																											
Child Pugh score	✓																											
Clinical Staging	✓																											
Serum β2 microglobulin	✓																											
17pDEL by FISH	✓																											
B Symptoms (constitutional symptoms)	✓	✓						✓								✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Assess occurrence of new malignancy																												✓
Assess for transformation to a more aggressive histology (Richter's transformation)																												✓
Assess for criteria supporting subsequent CLL therapy																												✓

Cohort 1 (V+G)	Screening	Cycle 1						Cycle 2						Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8	Cycle 9	Cycle 10	Cycle 11	Cycle 12	Follow-Up	
Activity																									
Record subsequent anti leukemic therapy																									✓
 CENTRAL LABS																									
Biomarker samples for blood CLL profiling		✓																					✓		
MRD peripheral blood analysis		✓																	✓					✓ 12 wks after EOT only	
Optional Biomarker Sample: Whole Blood DNA		✓																							
Peripheral blood for venetoclax PK																✓	✓								
Peripheral blood for obinutuzumab PK																✓	✓								

Cohort 1 (V+G)	Screening	Cycle 1					Cycle 2					Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8	Cycle 9	Cycle 10	Cycle 11	Cycle 12	Follow-Up		
Activity																								
Rx TREATMENT & TLS MANAGEMENT																								
Obinutuzumab administration (with premeds per Section 6.2)		mg Day 1 + mg Day 1 (if appropriate conditions met) or mg Day 2	mg	mg			mg									mg on Day 1 of each cycle								
Venetoclax dispensing/ dosing						mg	mg	mg	mg	mg	Dosing is once daily and begins on C1D22 and continues with weekly ramp up					mg once daily								
TLS Prophylaxis (oral antihyperuricemic agents and Hydration)		Refer to Prophylaxis and Management of TLS in Section 6.2																						
Hospitalization	Refer to Prophylaxis and Management of TLS in Section 6.2				Required for high TLS risk subjects on Day 1 of mg and mg doses and as needed on Day 1 of mg, mg, and mg doses																			
TLS risk assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓									
Dispense subject dosing diary						✓		✓		✓		✓		✓		✓	✓	✓	✓	✓	✓	✓		

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CIRS = cumulative illness rating scale; CLL = chronic lymphocytic leukemia; CR = complete remission; CRI = complete remission with an incomplete marrow recovery; CT = computed tomography; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ECOG = eastern cooperative oncology group; EOT = end of treatment; FISH = fluorescence in situ hybridization; HBV = hepatitis B virus; HCV = hepatitis C virus; MRD = minimal residual disease; PK = pharmacokinetic(s); S = serum; TLS = tumor lysis syndrome; U = urine

Cohort 2 Study Activities Table

Cohort 2 (V+I)	Screening	Cycle 1	Cycle 2	Cycle 3	Cycle 4				Cycle 5	Cycle 6	Cycle 7	Cycle 8	Cycle 9	Cycle 10	Cycle 11	Cycle 12	Cycles 13 - 14	Cycle 15	Follow-Up		
Activity																					
🗨 INTERVIEWS & QUESTIONNAIRES																					
Informed consent	✓																				
Eligibility criteria	✓																				
Medical history	✓																				

	Screening	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8	Cycle 9	Cycle 10	Cycle 11	Cycle 12	Cycles 13 - 14	Cycle 15	Follow-Up
Cohort 2 (V+)																
Activity																
Adverse event assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Survival status																✓
 LOCAL LABS & EXAMS																
HBV/HCV testing	✓															
12 lead ECG	✓	As clinically indicated.														
Height (screening only) and weight	✓	✓	✓	✓		✓				✓						✓
Vital signs (temperature, blood pressure, heart rate, respiratory rate)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Complete physical examination	✓					✓					✓				✓	✓
Symptom directed physical examination		✓	✓	✓					✓		✓	✓	✓	✓		
Pregnancy test (urine/serum)	✓ S	✓ U	Additional tests can be performed per local regulations.													
Clinical chemistry	✓	✓	✓	✓	✓	Refer to Section 6.2 for chemistry collection timepoints associated with TLS risk and venetoclax dosing.				✓	✓	✓	✓	✓	✓	✓
Hematology	✓	✓	✓	✓	✓	✓				✓	✓	✓	✓	✓	✓	✓

	Screening	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8	Cycle 9	Cycle 10	Cycle 11	Cycle 12	Cycles 13 - 14	Cycle 15	Follow-Up
Cohort 2 (V+)																
Activity																
Coagulation panel	✓															
Urinalysis	✓	As clinically indicated.														
ECOG Performance	✓														✓	✓
Coombs test	✓															
Creatinine clearance (Cockcroft Gault)	✓															
Response Assessment					✓					✓					✓	✓
CT Scan (refer to Ops Manual)	✓			✓						✓					✓	✓
Bone marrow biopsy/aspirate (refer to Ops Manual)	✓				✓					✓					✓	✓
CIRS score	✓															
Child Pugh score	✓															
Clinical Staging	✓															
Serum β 2 microglobulin	✓				✓						✓				✓	
17pDEL by FISH	✓															
B Symptoms (constitutional symptoms)	✓				✓					✓					✓	✓
Assess occurrence of new malignancy																✓

	Screening	Cycle 1	Cycle 2	Cycle 3	Cycle 4				Cycle 5	Cycle 6	Cycle 7	Cycle 8	Cycle 9	Cycle 10	Cycle 11	Cycle 12	Cycles 13 - 14	Cycle 15	Follow-Up		
Cohort 2 (V+)																					
Activity																					
Assess for transformation to a more aggressive histology (Richter's transformation)																					✓
Assess for criteria supporting subsequent CLL therapy																					✓
Record subsequent anti leukemic therapy																					✓
 CENTRAL LABS																					
Biomarker samples for blood CLL profiling		✓																	✓		
MRD peripheral blood analysis		✓												✓						✓ 12 weeks after EOT only	
Optional biomarker sample: whole blood DNA		✓																			
Peripheral blood for venetoclax PK									✓	✓	✓										
Peripheral blood for ibrutinib PK			✓	✓					✓	✓	✓										

	Screening	Cycle 1	Cycle 2	Cycle 3	Cycle 4			Cycle 5	Cycle 6	Cycle 7	Cycle 8	Cycle 9	Cycle 10	Cycle 11	Cycle 12	Cycles 13 - 14	Cycle 15	Follow-Up			
Cohort 2 (V+)																					
Activity																					
Rx TREATMENT & TLS MANAGEMENT																					
Venetoclax dispensing/dosing						mg	mg	mg	mg	mg	mg once daily										
						Dosing is once daily and begins on C4D1 and continues with weekly ramp up															
Ibrutinib dispensing/dosing		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			
TLS risk assessment	✓	✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			
TLS Prophylaxis (oral antihyperurimic agents and hydration)						Refer to Prophylaxis and Management of TLS in Section 6.2															
Hospitalization						Refer to Prophylaxis and Management of TLS in Section 6.2															
Dispense subject dosing diary		✓	✓	✓		✓				✓	✓	✓	✓	✓	✓	✓	✓	✓			
Review and copy subject dosing diary and perform drug reconciliation			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		

CIRS = Cumulative Illness Rating Scale; CLL = Chronic lymphocytic leukemia; CR = Complete remission; CRI = Complete remission with an incomplete marrow recovery; CT = computed tomography; DNA = deoxyribonucleic acid; ECG = Electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FISH = fluorescence in situ hybridization; HBV = hepatitis B virus; HCV = hepatitis C virus; MRD = minimal residual disease; PK = Pharmacokinetic(s); TLS = tumor lysis syndrome

APPENDIX M. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date

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