Official Title: A Prospective, Open-Label, Multicenter Randomized Phase III Study to Compare the Efficacy and Safety of a Combined Regimen of Venetoclax and Obinutuzumab Versus Fludarabine, Cyclophosphamide, and Rituximab (FCR)/ Bendamustine and Rituximab (BR) in FIT Patients with Previously Untreated Chronic Lymphocytic Leukemia (CLL) Without Del(17P) or TP53 Mutation

NCT Number: NCT04285567

Document Date: Protocol Version 5: 07-Jun-2023

PROTOCOL

TITLE:	**A PROSPECTIVE, OPEN-LABEL, MULTICENTER RANDOMIZED PHASE III STUDY TO COMPARE THE EFFICACY AND SAFETY OF A COMBINED REGIMEN OF VENETOCLAX AND OBINUTUZUMAB VERSUS FLUDARABINE, CYCLOPHOSPHAMIDE, AND RITUXIMAB (FCR)/ BENDAMUSTINE AND RITUXIMAB (BR) IN FIT PATIENTS WITH PREVIOUSLY UNTREATED CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) WITHOUT DEL(17P) OR *TP53* MUTATION**
PROTOCOL NUMBER:	CO41685
VERSION NUMBER:	5
TEST COMPOUND:	Venetoclax (GDC-0199 [ABT-199]; RO5537382), Obinutuzumab (GA101, RO5072759)
REGULATORY AGENCY IDENTIFIER NUMBERS:	*EUDRACT Number: 2019-003327-37* *IND Number: 115,045* *EU CT Number: 2023-504036-17-00* *NCT Number: NCT04285567*
SPONSOR ***AND LEGAL REGISTERED ADDRESS*****:**	F. Hoffmann-La Roche Ltd *Grenzacherstrasse 124* *4070 Basel, Switzerland*
APPROVAL:	See electronic signature and date stamp on the final page of this document

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
5	See electronic date stamp on final page of this document
4	19 April 2022
3	19 October 2021
2	12 April 2021
1	1 October 2019

PROTOCOL AMENDMENT, VERSION 5: RATIONALE

Protocol CO41685 has been amended primarily to update the planned statistical analyses. Changes to the protocol, along with a rationale for each change, are summarized below:

- The advice for contraception for female patients following treatment with cyclophosphamide has been updated to 12 months (Section 4.1.1) to align with the guidance provided in the cyclophosphamide label.
- The guidance on collection of concomitant medications during the follow-up period of the study has been updated (Section 4.5.3) for clarity.
- Clarification on reporting of adverse events and serious adverse events that occur outside the adverse event reporting period to the Sponsor has been provided (Section 5.6).
- Response criteria has been updated (Section 4.5.11) to align with the iwCLL guidelines.
- The following updates were made to align with the SAP:
  - Determination of sample size has been updated (Section 6.1).
  - Analysis timing has been updated (Section 6.2).
  - Intercurrent events identified in the study have been updated (Section 6.5.1.1).
  - The secondary endpoints to be formally tested have been updated (Section 6.5.2).
  - The planned progression-free survival interim and final analyses have been defined (Section 6.5.3, 6.8.1).
- Personal identifiable information (i.e., name and telephone number) for the Medical Monitor has been removed from the protocol to align with Clinical Trial Regulation (CTR) requirements (front page and Section 5.4.1).
- A section describing duration of participation has been added to align with CTR requirements (Section 3.2.1)
- A comprehensive list of investigational medicinal products and auxiliary medicinal products have been added to align with CTR requirements (Section 4.3 and Appendix 18).
- The threshold for ionized calcium has been corrected in the Guidelines for Defining Tumor Lysis Syndrome (Appendix 15) to align with the threshold published in the Howard et al. 2018 publication.
- The email address for withdrawal from the Research Biosample Repository after site closure has been corrected (Section 4.5.17).
- A description of the technical and organizational security measures taken to protect personal data has been added to align with CTR requirements (Section 4.5.17.4 [Confidentiality]).

- Due to certain local requirements and an alignment of Sponsor process, it has been clarified that summaries of clinical study results may be available in health authority databases for public access in addition to redacted Clinical Study Reports (Section 9.6 Dissemination of Data and Protection of Trade Secrets)
- The synopsis has been simplified to align with CTR and other guidelines.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PROSPECTIVE, OPEN-LABEL, MULTICENTER RANDOMIZED PHASE III STUDY TO COMPARE THE EFFICACY AND SAFETY OF A COMBINED REGIMEN OF VENETOCLAX AND OBINUTUZUMAB VERSUS FLUDARABINE, CYCLOPHOSPHAMIDE, AND RITUXIMAB (FCR)/ BENDAMUSTINE AND RITUXIMAB (BR) IN FIT PATIENTS WITH PREVIOUSLY UNTREATED CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) WITHOUT DEL(17P) OR *TP53* MUTATION**
PROTOCOL NUMBER:	CO41685
VERSION NUMBER:	5
TEST *COMPOUNDS*:	Venetoclax (GDC-0199 [ABT-199]; RO5537382), Obinutuzumab (GA101, RO5072759)
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form to the Sponsor or their designee.

PROTOCOL SYNOPSIS

TITLE:	**A PROSPECTIVE, OPEN-LABEL, MULTICENTER RANDOMIZED PHASE III STUDY TO COMPARE THE EFFICACY AND SAFETY OF A COMBINED REGIMEN OF VENETOCLAX AND OBINUTUZUMAB VERSUS FLUDARABINE, CYCLOPHOSPHAMIDE, AND RITUXIMAB (FCR)/ BENDAMUSTINE AND RITUXIMAB (BR) IN FIT PATIENTS WITH PREVIOUSLY UNTREATED CHRONIC LYMPHOCYTIC LEUKEMIA (CLL) WITHOUT DEL(17P) OR TP53 MUTATION**
PROTOCOL NUMBER:	CO41685
REGULATORY AGENCY IDENTIFIER NUMBERS:	EUDRACT Number: 2019-003327-37 IND Number: 115,045 EU CT Number: 2023-504036-17-00 NCT Number: NCT04285567
TEST PRODUCT:	Venetoclax (GDC-0199 [ABT-199]; RO5537382), Obinutuzumab (GA101, RO5072759)
PHASE:	III
INDICATION:	Chronic Lymphocytic Leukemia (CLL)
SPONSOR:	F. Hoffmann-La Roche Ltd

STUDY RATIONALE

This study will evaluate the efficacy and safety of venetoclax (Venclexta® or Venclyxto®) in combination with obinutuzumab (Gazyva® or Gazyvaro®) (VEN + G) compared with fludarabine, cyclophosphamide, and rituximab (FCR), and bendamustine and rituximab (BR) in FIT patients (FIT defined by a CIRS/score ≤6 and a normal creatinine clearance of ≥70 mL/min) with previously untreated chronic lymphocytic leukemia (CLL) without del(17p) or TP53 mutations. Specific objectives and corresponding endpoints for the study are outlined in this section.

OBJECTIVES AND ENDPOINTS

Primary Objective	Corresponding Endpoint
• Evaluate the efficacy of VEN + G compared with FCR/BR	• MRD response rate, determined as the proportion of patients with MRD-negativity (defined as <1 CLL cell in 10,000 leukocytes), measured in PB using NGS at Month 15
• evaluate the safety of VEN + G compared with FCR/BR	• Nature, frequency, and severity of adverse events and serious adverse events • Changes in vital signs, physical findings, and clinical laboratory test results during and following study treatment • Premature withdrawals
Secondary Objective	**Corresponding Endpoint**
• Evaluate the efficacy of VEN + G compared with FCR/BR	• PFS, defined as the time from randomization to the first occurrence of disease progression, or death from any cause; disease progression assessed by the investigators using the iwCLL criteria • MRD response rate, in PB at the end of treatment response visit (8–12 weeks after the last dose of FCR/BR [~9 months] vs. 8–12 weeks after last dose of VEN + G [~15 months]) MRD response rate in BM at the end of treatment response visit (9 months FCR/BR vs. 15 months VEN + G) vs. 8–12 weeks after last dose of VEN + G [approximately 15 months from first dose]) ORR, which includes CR, complete remission with CRi, and PR at the Month 15 assessment • CR rate, which includes CR and CRi at the Month 15 assessment • MRD response rate in PB of patients with a CR/CRi at Month 15MRD response rate in the BM of patients with a CR/CRi at the end of treatment visit (8–12 weeks after the last dose of FCR/BR [~9 months] vs. 8–12 weeks after the last dose of VEN + G [~15 months]) • DOR, defined as the time from the first response to the time of PD or death from any cause, whichever comes first • Best response achieved (CR, CRi, PR, SD, or PD) up to and including the assessment at Month 15 • EFS, defined as the time between the date of randomization and the date of disease

Secondary Objective	Corresponding Endpoint
	progression/relapse, death, or start of a new anti-leukemic therapy • OS, defined as the time from randomization to the date of death from any cause TLS risk reduction rate in Arm A, defined as the reduction in the proportion of participants who were TLS high-risk after 3 doses of obinutuzumab compared to the proportion of participants who were TLS high-risk at baseline • Reduction in mandatory hospitalizations during venetoclax ramp-up in Arm A participants, defined as the actual number of protocol-mandated hospitalizations for TLS monitoring during venetoclax ramp-up periodafter 3 doses of obinutuzumab compared to the number of protocol-mandated hospitalizations for TLS monitoring during venetoclax ramp-up expected at baseline

BM = bone marrow; BR = bendamustine and rituximab; CLL = chronic lymphocytic leukemia; CRi = incomplete blood count recovery; DOR = duration of objective response; EFS = event-free survival; FCR = fludarabine, cyclophosphamide, and rituximab; iwCLL = International Workshop on CLL; MRD = minimal residual disease; NGS = next generation sequencing; OS = overall survival; PB = peripheral blood; PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease; TLS = tumor lysis syndrome; Ven + G = Venetoclax (Venclexta or Venclyxto) in combination with Obinutuzumab (Gazyva or Gazyvaro)

Primary and selected secondary objectives for the study are expressed using the estimand framework in accordance with the International Conference on Harmonization E9 (R1) statistical principles for clinical trials (ICH 2020) in Section 3.

Overall Design and Study Population

Several key aspects of the study design and study population are summarized below.

Phase:	Phase III	**Population Type:**	Adult Patients
Control Method:	Active Comparator	**Population Diagnosis or Condition:**	FIT patients with previously untreated CLL without del(17p) or TP53 mutation requiring treatment
Interventional Model:	Parallel	**Population Age:**	≤ 65 or >65 years
Test Compounds}:	Venetoclax/RO5537382 Obinutuzumab/RO5072759	**Site Distribution:**	Multi-site and multi-region
Active Comparator:	Fludarabine, Cyclophosphamide, and Rituximab (FCR)/Bendamustine and Rituximab (BR)	**Study Intervention Assignment Method:**	Randomization and stratification
Number of Arms:	2	**Number of Participants to Be Enrolled:**	165

STUDY TREATMENT

The investigational medicinal products (IMPs) for this study are venetoclax, obinutuzumab, fludarabine, cyclophosphamide, bendamustine, and rituximab.

ARM A

Patients randomized to Arm A (VEN + G) will receive 12 cycles of treatment, each with a precise duration of 28 days. During the first cycle, obinutuzumab will be administered intravenously on Days 1 (and 2), 8, and 15 as well as on Day 1 of Cycles 2–6. Continuous daily administration, with a 5-week ramp-up period, of venetoclax starts on Cycle 1, Day 22. Venetoclax will be administered until the end of Cycle 12.

Because it is possible that de-bulking from obinutuzumab therapy before starting venetoclax dosing already significantly reduces the risk of tumor lysis syndrome (TLS), TLS prophylactic measures will be re-assessed at the time of starting the first dose of venetoclax.

Arm B

Patients randomized to Arm B (FCR/BR 50:50) will receive 6 cycles of FCR consisting of a single cycle of a single infusion of rituximab on Day 1 and fludarabine and cyclophosphamide infusions on Days 1–3 of each 28-day cycle or bendamustine as infusions on Days 1 and 2 and a single cycle of rituximab on Day 1 of each 28-day cycle.

All patients in Arm B can be considered for treatment with BR, whereas only patients ≤65 years of age will be eligible for FCR. The choice between FCR or BR in Arm B will be at the investigator's discretion.

During this study, adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0.

The primary endpoint for assessing efficacy will be MRD response rate in PB at Month 15 in both arms (~3 months after the last dose of venetoclax in Arm A and approximately 9 months after the last cycle of FCR/BR in Arm B). The primary MRD assessment will be conducted in approximately 165 patients enrolled in the study.

All patients will be assessed for minimal residual disease (MRD) response in PB samples using next generation sequencing (NGS) and will also be assessed for MRD response in the BM sample using NGS. For both, response is defined as achieving MRD negativity at a cutoff of $<10^{-4}$ ($<$1 CLL cell in 10,000 leukocytes).

DURATION OF PARTICIPATION

The total duration of study participation for each individual is expected to be approximately 3.5 years after the last patient is enrolled, allowing for completion of the maximum duration of planned therapy (in the absence of disease progression) as well as at least 2.5 years of follow up for all patients in order to reach the estimated number of events needed for the PFS final analysis.

Patients are expected to be on study for a minimum of 3.5 years up to a maximum of 6.2 years, subject to their date of enrollment in relation to the last patient enrolled.

Committees

Independent Committees:	independent Data Monitoring Committee
Other Committees:	Not Applicable

1. BACKGROUND

1.1 BACKGROUND ON CHRONIC LYMPHOCYTIC LEUKEMIA

Chronic lymphocytic leukemia (CLL) is the most common leukemia in Western countries, representing approximately 30% of all adult leukemias. The incidence of CLL varies by race and geographic location, with a lower incidence in Asia (<5% of leukemias) compared with Western countries. The incidence is higher in males than females and increases with age (NIH SEER 2018). CLL is a clonal disease of unknown etiology, characterized by the accumulation of mature B cells in the 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 (Hallek et al. 2008). The clonality of the disease is confirmed by the presence of a single immunoglobulin light chain.

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. Two clinical staging systems have been developed by Rai et al. (1975) and Binet et al. (1977). Both systems are widely used and are an accepted prognostic tool, albeit with limitations (notably for predicting disease progression in early stage disease). In both systems, patients are classified into low-, intermediate-, and high-risk groups on the basis of the degree of lymphocytosis, presence of lymphadenopathy, hepatomegaly or splenomegaly, anemia, and thrombocytopenia. There are also a number of biomarkers that can predict the patient prognosis with CLL. Patients with del(17p) or *TP53* mutations have the poorest prognosis. Approximately 5%–10% of patients with early stage CLL have del(17p) and/or *TP53* mutations, and this rate increases with treatment lines up to 40% in advanced refractory CLL (Zenz et al. 2008; Stilgenbauer and Zenz 2010; Zenz et al. 2010). Other biomarkers, such as mutations in NOTCH1, SF3B1, MYD88, or BIRC3, may also be predictive of an unfavorable prognosis in the absence of a TP53 mutation. Patients with CLL cells with unmutated immunoglobulin heavy chain variable region (IgVH/IGHV) have a higher risk of unfavorable genetic mutations and, therefore, a poorer prognosis.

In the United States, a recent Surveillance, Epidemiology, and End Results (SEER) report estimated an overall age-adjusted mortality rate for CLL of 1.3 per 100,000 persons per year with the median age at diagnosis of 70 years, the median age at death of 80 years, and an approximate 5-year survival rate of 84.2% for the period of 2008–2014 (NIH SEER 2018). The mortality estimates of the total number of CLL

deaths in Europe are limited; therefore, survival estimates are also presented. The 5-year mortality rate for Spanish patients diagnosed with CLL between 1995 and 2004 was 24 per 1000-patient years while the 10-year mortality rate was 41 per 1,000-patient years (Abrisqueta et al. 2009). In Europe, the 5-year relative survival rate of patients with CLL and small lymhocyclic lymphoma (SLL) in the period 2000–2002 was 69.1% (Marcos-Gragera et al. 2011). Since the incidence rate increases with age, the prevalence and mortality of CLL are likely to increase in the coming decades because of the demographic changes associated with an aging population.

In multiple studies in patients with CLL, achieving disease reduction below reliable limits of detection ($<$1 CLL cell/10^4 leukocytes) using sensitive techniques, such as multicolor flow cytometry, allele-specific oligonucleotide polymerase chain reaction (ASO-PCR), and next-generation sequencing (NGS), has been shown to be the strongest independent predictor of progression-free survival (PFS) and overall survival (OS). Thus, minimal residual disease (MRD) negativity rates, independent of the depth of clinical response, may predict overall clinical benefit, as previously demonstrated with the use of chemo-immunotherapy treatment (Rawstron et al. 2007, 2013, 2015; Böttcher et al. 2013; Kovacs et al. 2016; Dimier et al. 2018). MRD negativity rates have similarly shown to be predictable of the outcome regardless of clinical response in targeted therapy with a time-limited venetoclax plus rituximab regimen (Kater et al. 2018) and are, therefore, considered an established clinically significant endpoint to differentiate treatment options.

1.2 BACKGROUND ON VENETOCLAX

Venetoclax (Venclexta®; also known as Venclyxto®, GDC-0199, or ABT-199) was first approved in the United States on 11 April 2016 through an accelerated approval for the treatment of patients with CLL with del(17p). On 8 June 2018, the U.S. Food and Drug Administration (FDA) approved the combination therapy venetoclax and rituximab and the venetoclax expanded monotherapy. This approval confirmed the clinical benefit of venetoclax in the relapsing/refractory (R/R) CLL population with or without del(17p); thus, the initial accelerated approval has been converted to a full approval. On 20 November 2018, the European Commission approved venetoclax Type II variation to fulfill the Specific Obligation relating to the conditional status of the license, thus converting the conditional E.U. marketing authorization into a full E.U. marketing authorization. On 15 May 2019, the FDA approved venetoclax in combination with obinutuzumab (Gazyva® or Gazyvaro®) (VEN+G) in previously untreated patients with CLL or SLL based upon the pivotal Study BO25323/CLL14 and supporting Study GP28331. The VEN+G regimen and dose used in the BO25323/CLL14 study is the same regimen and dose used in this study.

Venetoclax is a highly selective, orally bioavailable, small-molecule, B-cell lymphoma (Bcl) 2 family inhibitor in the biarylacylsulfonamide chemical class. Venetoclax binds with high affinity (Ki $<$ 0.010 nM) to anti-apoptotic protein Bcl-2 and with lower affinity to

other anti-apoptotic Bcl-2 family proteins, including Bcl-XL and Bcl–w (>4000-fold and >2000-fold to >20,000-fold lower affinity than to Bcl-2, respectively) (Souers et al. 2013).

Anti-apoptotic Bcl-2 family members are associated with tumor initiation, disease progression, and chemotherapy resistance (Fesik 2005), as well as autoimmunity (Mérino et al. 2009). Overexpression of Bcl-2 is a major contributor to the pathogenesis of some lymphoid malignancies. Antagonism of the action of these proteins may enhance response to therapy and overcome resistance, thus, these proteins are compelling targets for anti-tumor therapy. Constitutively elevated expression of the anti-apoptotic protein Bcl-2 renders CLL cells resistant to apoptosis, resulting in the accumulation of long-lived, clonal lymphocytes that characterize the disease (Cimmino et al. 2005, Robertson et al. 1996, Del Gaizo Moore et al. 2007). In vitro, venetoclax demonstrated cell-killing activity against patient derived CLL cells, acute myeloid leukemia (AML) cells, and a variety of lymphoma and leukemia cell lines, including B-cell follicular lymphoma (FL), mantle-cell lymphoma (MCL), diffuse large B-cell lymphoma (DLBCL), and multiple myeloma (MM) (Venetoclax Investigator's Brochure). Venetoclax was especially potent against cell lines expressing high levels of Bcl-2. Venetoclax inhibits subcutaneous xenograft growth of human tumor-cell lines derived from acute lymphoblastic leukemia, non-Hodgkin lymphoma (NHL), and AML and is highly efficacious when using various doses and combined with other regimens. Venetoclax is also active in a model of disseminated acute lymphocytic leukemia (ALL). It enhanced the activity of a broad variety of chemotherapeutic agents in other human hematological models (Venetoclax Investigators Brochure). Specifically, venetoclax enhances the efficacy of obinutuzumab and rituximab in models of MCL and DLBCL (Venetoclax Investigator's Brochure and Obinutuzumab Investigator's Brochure). Furthermore, venetoclax demonstrated potential to enhance the efficacy of bortezomib in a transgenic murine lymphoma model (Vandenberg and Cory 2013) and shows single-agent efficacy in a human model of MM (Touzeau et al. 2014).

See the Venetoclax Investigator's Brochure for additional details on nonclinical and clinical studies.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

1.3.1 Efficacy

Despite the progress made in the treatment of patients with CLL, a significant number of patients experience relapsed disease that is associated with progressively shorter durations of response to therapy. The only potentially curative strategy for CLL is an allogeneic hematopoietic stem-cell transplantation for which the majority of patients with CLL are not eligible because of age or co-existing medical conditions. As a result, a cure for patients with CLL necessitates more effective drugs that also have an acceptable safety profile. A chemotherapy-free regimen could meet these expectations.

On 15 May 2019, the U.S. FDA approved the use of venetoclax in combination with obinutuzumab in previously untreated patients with CLL or SLL based on the findings from the pivotal Study BO25323/CLL14. This was an open-label, prospective, multicenter, randomized, Phase III trial to compare the efficacy and safety of VEN+G versus obinutuzumab+chlorambucil (GClb) in previously untreated CLL patients with comorbidity. This study is also under assessment by other competent authorities worldwide. Study BO25323/CLL14 not only demonstrates unprecedented MRD rates representing a depth of anti-CLL activity that differentiates treatment with VEN+G, it also provides compelling PFS data in the first-line (1L) setting.

Based on the results of a protocol-specified interim analysis (as of 17 August 2018 clinical cutoff date [CCOD]), the Independent Data Monitoring Committee (IDMC) recommended that Study BO25323/CLL14 had met its primary endpoint of investigator-assessed PFS, with a significant and clinically meaningful improvement in patients in the VEN+G arm (investigator-assessed PFS: stratified HR=0.35 [95% CI: 0.23 to 0.53], Independent Review Committee (IRC)-assessed PFS: stratified HR=0.33 [95% CI: 0.22, 0.51], $p<0.0001$) versus patients in the GClb arm. A consistent trend showing that VEN+G was superior to GClb was observed across key secondary efficacy endpoints (e.g., complete response [CR] rates, objective response rate [ORR]) and across all of the pre-specified subgroups based on baseline characteristics, stratification factors, and other key prognostics markers.

1.3.2 Safety

Known risks associated with venetoclax administration include tumor lysis syndrome (TLS), hematological effects (including neutropenia/febrile neutropenia), serious and/or opportunistic infections, nausea, and diarrhea (Venetoclax Investigator's Brochure).

Clinical evaluations of the risks identified from previous preclinical studies (e.g., single-cell necrosis, allergic reactions, liver enzyme elevations, and hair color change) did not reveal any clinically significant concerns, thus, routine surveillance is recommended in ongoing studies. Clinical evaluation of adverse events that could potentially be associated with decreased left ventricular ejection fraction (LVEF) and evaluation of available pre- and postdose LVEF data showed no risk of decreased LVEF following venetoclax dosing. Since study populations in venetoclax oncology studies are likely to be elderly and have received multiple prior chemotherapeutic agents, baseline LVEF assessments are recommended per the investigator's discretion.

Principal risks identified for the combination regimen of VEN+G include the following: TLS, infusion-related reactions (IRRs) to obinutuzumab, cytopenia (e.g., neutropenia and thrombocytopenia, especially during the first cycle of obinutuzumab, or lymphopenia), infections, transient transaminitis, and other malignancies.

However, toxicities expected to be associated with the combined treatment of VEN+G can largely be managed (e.g., first dose TLS and IRRs), or are commonly encountered

with the treatment of CLL and can be mitigated with the measures outlined in this protocol.

The protocol includes the following features to address these risks:

- In the BO25323/CLL14 study, treatment with obinutuzumab before treatment with venetoclax was an effective method to reduce the risk of TLS occurring during the venetoclax ramp-up period. The same regimen and schedule will be followed in this protocol.
- TLS appears to be an adverse event that can be mitigated by starting therapy with venetoclax at the low dose of 20 mg, by slow dose ramp-up, and by appropriate preventive measures. Measures to prevent TLS include prophylactic hydration and medication prior to initial dosing with careful monitoring during the first 24 hours after dosing for metabolic or clinical signs of impending TLS (Section 5.1.7.1).
- Staggered dosing of venetoclax initiated on Day 22 during the first cycle of chemoimmunotherapy (Section 4.3.2.1.1)
- Prophylactic medication (Section 5.1.6.1 and Section 5.1.6.2) will be administered, and careful monitoring guidelines will be used to manage IRRs to obinutuzumab.
- Frequent blood testing throughout the treatment period to monitor for cytopenia (Appendix 1 and Appendix 2)
- Dose delays or dose reductions are mandated for severe cytopenia. In addition, all supportive measures, including transfusion, antibiotics, and the use of growth factors are allowed (Section 4.3.2.2, Section 4.5.3, Section 5.1.2.6, Section 5.1.6).
- Neutropenia will be closely monitored and may be treated with growth factors, and any signs of infection will be treated with appropriate medication (Section 5.1.6).

  Note: Anti-infection prophylaxis is not mandated for all patients because of the potential risks of adding additional concomitant medications but may be prescribed by the investigator in specific cases where patients are at especially high risk. Patients with preexisting infections and past hepatitis are excluded from the study to avoid reactivation.
- Incidences of prolonged neutropenia are of concern and will be monitored carefully (Appendix 1 and Appendix 2).
- A list of excluded and cautionary mediations for patients randomized to Arm A is provided in view of the possible drug–drug interactions.

1.3.3 Benefit-Risk Assessment

Study BO25323/CLL14 provided evidence that the combination of venetoclax and obinutuzumab is a very efficacious treatment regimen with an acceptable safety profile in the 1L CLL setting. Safety profiles of both drugs seem to be compatible, especially in light of a chemotherapy-free setting. The head-to-head design of the study, precautionary safety measures, and regular monitoring of safety by the Sponsor enabled early identification of safety signals in the study and minimized the risk to the patients enrolled. In conclusion, it is considered that the benefit-risk ratio for this study is

favorable and that a chemotherapy-free fixed treatment therapy would be a very important option for patients with CLL in the 1L FIT setting. FIT is defined by a cumulative illness rating scale [CIRS] score ≤6 and a normal creatinine clearance of ≥70 mL/min.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy and safety of VEN+G compared with fludarabine, cyclophosphamide, and rituximab (FCR), and bendamustine and rituximab (BR) in FIT patients with previously untreated CLL without del(17p) or *TP53* mutations. Specific objectives and corresponding endpoints for the study are outlined in this section.

2.1 EFFICACY OBJECTIVES

2.1.1 Primary Efficacy Objective

The primary efficacy objective for this study is to evaluate the efficacy of VEN+G compared with FCR/BR on the basis of the following endpoint:

- MRD response rate, determined as the proportion of patients with MRD-negativity (defined as<1 CLL cell in 10,000 leukocytes), measured in peripheral blood (PB) using NGS at Month 15.

2.1.2 Exploratory Efficacy Objective

The exploratory objectives of this study are as follows:

- To investigate the relationship between various baseline markers and clinical outcome parameters in both arms of the study

  Baseline markers will include, but are not limited to, CLL fluorescence in situ hybridization (FISH) (17p-, 11q-, 13p-, +12q), immunoglobulin heavy chain variable region (IgHV) mutation status, p53 mutation status, serum parameters, and other CLL disease markers.

2.1.3 Secondary Efficacy Objective

The secondary efficacy objective for this study is to evaluate the efficacy of VEN+G compared with FCR/BR on the basis of the following endpoints:

- PFS, defined as the time from randomization to the first occurrence of disease progression, or death from any cause; disease progression assessed by the investigators using the International Workshop on CLL (iwCLL) criteria (Hallek et al. 2018)
- MRD response rate, in PB at the end of treatment response visit (8–12 weeks after the last dose of FCR/BR [~9 months] vs. 8–12 weeks after last dose of VEN+G [~15 months])
- MRD response rate in BM at the end of treatment response visit (8–12 weeks after the last dose of FCR/BR [approximately 9 months from first dose] vs. 8–12 weeks after last dose of VEN+G [approximately 15 months from first dose])

- ORR, which includes CR, complete remission with incomplete blood count recovery (CRi), and partial response (PR) at the Month 15 assessment
- CR rate, which includes CR and CRi at the Month 15 assessment
- MRD response rate in PB of patients with a CR/CRi at Month 15
- MRD response rate in the BM of patients with a CR/CRi at the end of treatment visit (8–12 weeks after the last dose of FCR/BR [~9 months] vs. 8–12 weeks after the last dose of VEN+G [~15 months])
- Duration of objective response (DOR), defined as the time from the first response to the time of progressive disease (PD) or death from any cause, whichever comes first
- Best response achieved (CR, CRi, PR, stable disease [SD], or PD) up to and including the assessment at Month 15
- Event-free survival (EFS), defined as the time between the date of randomization and the date of disease progression/relapse, death, or start of a new anti-leukemic therapy
- OS, defined as the time from randomization to the date of death from any cause
- TLS risk reduction rate in Arm A, defined as the reduction in the proportion of participants who were TLS high-risk after 3 doses of obinutuzumab compared to the proportion of participants who were TLS high-risk at baseline
- Reduction in mandatory hospitalizations during venetoclax ramp-up in Arm A patients, defined as the actual number of protocol-mandated hospitalizations for TLS monitoring during venetoclax ramp-up period after 3 doses of obinutuzumab compared to the number of protocol-mandated hospitalizations for TLS monitoring during venetoclax ramp-up expected at baseline

2.2 SAFETY OBJECTIVES

The safety objective for this study is to evaluate the safety of VEN+G compared with FCR/BR on the basis of the following endpoints:

- Nature, frequency, and severity of adverse events and serious adverse events
- Changes in vital signs, physical findings, and clinical laboratory test results during and following study treatment
- Premature withdrawals

2.3 BIOMARKER OBJECTIVE

The exploratory biomarker objectives of this study are as follows:

- To evaluate the relationship between efficacy outcomes and potential biomarkers, including Bcl-2 expression, for patients treated with VEN+G compared with those treated with FCR/BR
- To evaluate potential biomarkers, including CLL driver mutations and genomic complexity that are prognostic and/or predictive of response and resistance to treatment with VEN+G or with FCR/BR

- To assess new technologies, such as the circulating tumor DNA (ctDNA) assessment, in measuring MRD and monitoring disease clonal evolution

2.4 PATIENT-REPORTED OUTCOME OBJECTIVES

The quality of life (patient-reported outcome [PRO]) objectives for this study are as follows:

- To compare disease and treatment-related symptoms following treatment with the combination of VEN+G compared with FCR/BR in patients with previously untreated CLL without del(17p) or *TP53* mutation as measured by the M.D. Anderson Symptom Inventory (MDASI-CLL; see Appendix 5)
- To evaluate changes in physical functioning, role functioning, and global health status/quality of life (QoL) following treatment with the combination of VEN+G compared with FCR/BR in patients with previously untreated CLL without del(17p) or *TP53* mutation as measured by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30; see Appendix 6)

2.5 HEALTH ECONOMIC OBJECTIVE

The health economic objective for this study should be considered as a special PRO and is as follows:

- To compare the health utility effects of treatment with the combination of VEN+G compared with FCR/BR in patients with previously untreated CLL without del(17p) or *TP53* mutation as measured by the EuroQol 5 Dimension questionnaire (EQ-5D-5L; see Appendix 7)

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is an open-label, international, multicenter, randomized, Phase III study to investigate the efficacy and safety of VEN+G compared with FCR/BR in FIT patients (FIT defined by a CIRS/score ≤6 [Appendix 8] and a normal creatinine clearance of ≥70 mL/min [Appendix 9]) with previously untreated CLL without del(17p) or *TP53* mutation requiring treatment.

Approximately 165 patients will be recruited from approximately 40 centers globally and randomly assigned in a 1:1 ratio to receive either VEN+G (Arm A) or FCR/BR (Arm B). Randomization will be stratified according to the following factors:

- IGHV mutation: yes or no
- Binet stage (3 levels): A, B, or C
- Age: ≤65 or >65 years

Patients randomized to Arm A (VEN+G) will receive 12 cycles of treatment, each with a precise duration of 28 days. During the first cycle, obinutuzumab will be administered

intravenously (IV) on Days 1 (and 2), 8, and 15 as well as on Day 1 of Cycles 2–6. Continuous daily administration, with a 5-week ramp-up period, of venetoclax starts on Cycle 1, Day 22. Venetoclax will be administered until the end of Cycle 12.

Because it is possible that de-bulking from obinutuzumab therapy before starting venetoclax dosing already significantly reduces the risk of TLS, TLS prophylactic measures will be re-assessed at the time of starting the first dose of venetoclax (see Section 5.1.7.1).

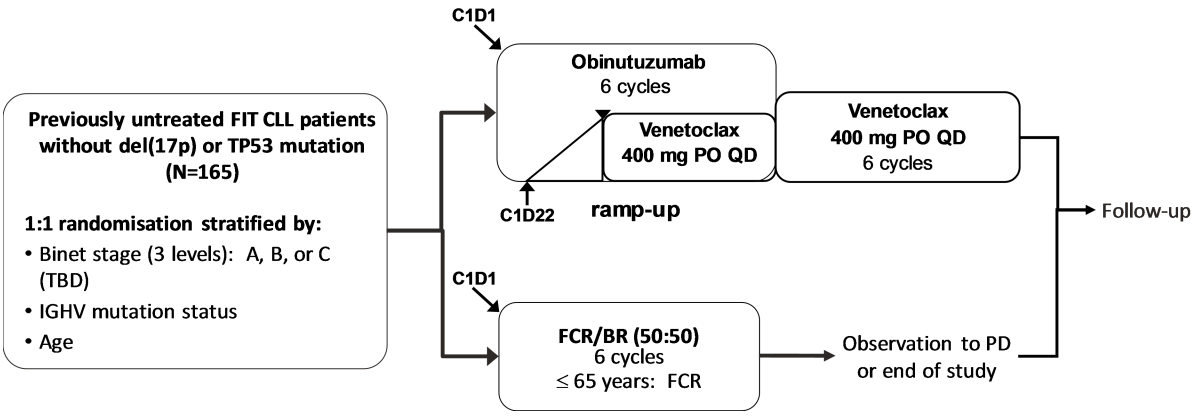
Patients randomized to Arm B (FCR/BR 50:50) (see Figure 1) will receive 6 cycles of FCR consisting of a single cycle of a single infusion of rituximab on Day 1 and fludarabine and cyclophosphamide infusions on Days 1–3 of each 28-day cycle or bendamustine as infusions on Days 1 and 2 and a single cycle of rituximab on Day 1 of each 28-day cycle.

All patients in Arm B can be considered for treatment with BR, whereas only patients ≤65 years of age will be eligible for FCR. The choice between FCR or BR in Arm B will be at the investigator's discretion.

During this study, adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0) (Appendix 10).

Figure 1 presents an overview of the study design. The schedules of activities for Arm A and Arm B are provided in Appendix 1 and Appendix 2, respectively.

Figure 1 Study Scheme



BR = bendamustine and rituximab; C = Cycle; CIRS = cumulative illness rating scale; CLL = chronic lymphocytic leukemia; D = Day; FCR=fludarabine, cyclophosphamide, and rituximab; FIT = defined by a cumulative illness rating scale [CIRS] score ≤6 and a normal creatinine clearance of ≥70 mL/min; IGHV = immunoglobulin heavy chain variable region; PD = progressive disease; PO = orally (by mouth); QD = once daily; TBD = to be determined.
Note: Each cycle will consist of 28 days.

3.1.1 Minimal Residual Disease Assessments

The primary endpoint for assessing efficacy will be MRD response rate in PB at Month 15 in both arms (~3 months after the last dose of venetoclax in Arm A and approximately 9 months after the last cycle of FCR/BR in Arm B). The primary MRD assessment will be conducted in $approximately\ 165$ patients enrolled in the study.

All patients will be assessed for MRD response in PB samples using NGS and will also be assessed for MRD response in the BM sample using NGS. For both, response is defined as achieving MRD negativity at a cutoff of $<10^{-4}$ (<1 CLL cell in 10,000 leukocytes).

3.1.2 Disease Response Assessment

Disease response assessments to determine ORR, response (CR/CRi and PR), SD, and PD will be completed according to iwCLL guidelines (Hallek et al. 2018).

3.1.3 Timing of Assessments

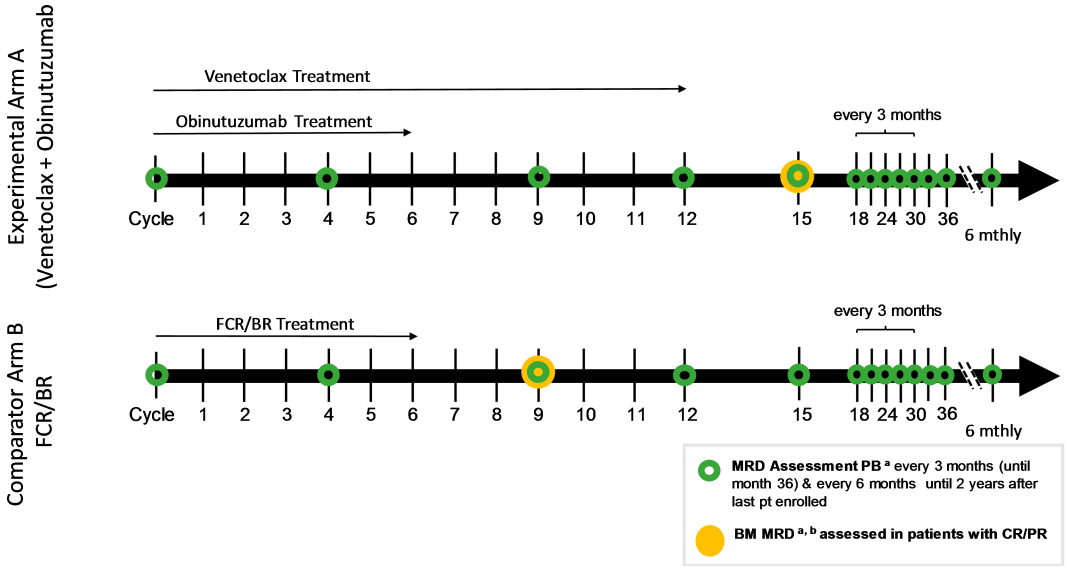
3.1.3.1 MRD Assessments

All patients will be assessed for MRD in PB at the following timepoints in both arms:

- Screening (to be collected prior to randomization before first dose)
- Cycle 4, Day 1 interim MRD assessment
- End of combination treatment (EOCT) response visit (8–12 weeks after last dose of combination therapy; ~Month 9 in both arms)
- Every 3 months after EOCT until 36 months (e.g., 12, 15, 18, 21, 24, 27, 30, 33, and 36 month visits), then every 6 months until the end of study

A BM sample will be taken 8–12 weeks after the end of treatment in both arms (~15 months in Arm A and ~9 months in Arm B). A schedule of MRD assessments is presented in Figure 2.

Figure 2 Schedule of Minimal Residual Disease Assessments



BM = bone marrow; BR = bendamustine and rituximab; CR = complete response; CRi = complete remission with incomplete blood count recovery; FCR = fludarabine, cyclophosphamide, and rituximab; MRD = minimal residual disease; mthly = monthly; PB = peripheral blood; PR = partial response; pt = patient.

[a] A BM aspirate must be taken within 8 weeks from patients who achieve a CR/PR for assessment of MRD and confirmation of molecular CR.

[b] BM aspirate at completion of treatment assessment (a minimum of 8–12 weeks after last treatment) for patients with CR/CRi and PR).

To minimize the risk of missing MRD sample collections, the Sponsor will inform the sites about the importance of MRD sample collection throughout the study. Furthermore, the Sponsor will check the collection status of MRD samples weekly. The Sponsor will be notified by the contract research organization (CRO) managing the sample collection if a sample is missing, received in poor condition, or cancelled, or exceeding the time window for sample processing. Acceptance of MRD by regulatory authorities as a marker of efficacy requires missing and unevaluable assessments of MRD to be kept to a minimum. If a sample is missing or cannot be analyzed, the patient might be asked to return to the site for another collection in a timely fashion.

3.1.3.2 Tumor and Response Assessments

All patients will have a baseline tumor assessment and will be assessed for response to treatment by the investigator using standard clinical and laboratory examinations and computed tomography (CT) scans according to iwCLL guidelines (Hallek et al. 2018) at the following timepoints:

- Clinical response assessment, only Day 1 of every cycle of combination therapy
- In Arm B (FCR/BR), a full response assessment, including CT scan in all patients and BM biopsy in responding patients (CR/PR), 12 weeks after the last dose of study treatment (no earlier than 8 weeks after the end of study treatment)

All other follow-up tumor assessments will be clinical assessments conducted within ±14 days for 3-month and within a month for 6-month assessments of the scheduled visits described in Appendix 1.

- In Arm A (VEN+G), a full response assessment, including CT assessment in all patients and BM biopsy in responding patients (CR/PR) at Month 15 (from cycle 1, day 1 [C1D1]), which corresponds to approximately 8–12 weeks after the last dose of drug received in patients that complete the full 12 cycles of venetoclax therapy.

  All other follow-up tumor assessments will be clinical assessments conducted within ±14 days for 3-month and within a month for 6-month assessments of the scheduled visits described in Appendix 1.

At each follow-up visit, patients will be assessed for response/progression by physical examination and laboratory tests. If at any time during follow-up when clinical or laboratory findings suggest that the response may have improved from SD to PR, or from PR to CR, a CT scan may be performed to confirm the response.

Imaging is not routinely required to determine PD because objective evidence of PD is most often documented by measurement of elevated peripheral CLL cells. However, when PD cannot be documented by increasing PB counts, imaging is required to document PD as detected by physical examination or suspected based on symptoms.

Annual follow-up assessments may be conducted by telephone. Patients who discontinue all components of study therapy, either prior to completion of planned therapy or prior to disease progression (e.g., for toxicity), will continue to be followed up for MRD levels, PD, and OS (regardless of whether they subsequently receive new anti-CLL therapy).

3.1.4 Summary of Study Procedures

Written informed consent will be obtained before any study specific procedures are undertaken.

3.1.4.1 Screening/Baseline Tests

All screening assessments documented in the schedule of assessments will be performed a maximum of 28 days prior to starting study treatment (Appendix 1 and Appendix 2) with the exception of a CT scan and optional bone marrow biopsy, which are allowed 8 weeks prior to randomization. Those patients who fail screening based on no immediate requirement for treatment can be rescreened in the future when their CLL is in need of treatment. Similarly, potential patients who fail screening because of recent infection (e.g., patients with infections requiring IV treatment [Grade 3 or 4] within the last 8 weeks prior to enrollment) may be rescreened once their infections resolve (see Section 4.1.2). For patients who fail screening based on creatinine clearance levels, a repeat blood test can be performed, or a urine test can be conducted within 24 hours of dosing for a more accurate assessment. If a patient is not randomized within the 28-day screening window, the site has to screen fail and can re-screen the patient using an interactive voice/web-response system (IxRS). The patient will get a new

screening number and all prior assessments that fall outside of the 28-day window from randomization will need to be repeated. This includes biomarker samples. A patient can be re-screened up to 3 times.

Randomization will be performed by IxRS. Patients will be assigned to the two treatment arms via a 1:1 randomization procedure. Patients will be stratified by Binet stage, IgHV, and age. Screening tests will be used to assess the Binet stage allowing for stratification and completion of the IxRS screening call. If a patient's Binet stage progresses between screening and randomization, then the Binet stage at the screening timepoint should be used for stratification.

3.1.4.2 Treatment Period

3.1.4.2.1 Treatment Arm A: Venetoclax and Obinutuzumab

The doses of venetoclax and obinutuzumab to be administered at each study visit is presented in Table 1.

Table 1 Treatment Arm A: VEN+G Doses per Study Visit

Cycle, Day	Dose
Obinutuzumab [a]	
Cycle 1, Day 1 [b]	100 mg or 1000 mg (follow splitting rules)
Cycle 1, Day 2 [b]	900 mg (if 100 mg on Cycle 1 Day 1)
Cycle 1, Day 8	1000 mg
Cycle 1, Day 15	1000 mg
Cycles 2–6, Day 1	1000 mg
Venetoclax [c, d, e]	
Cycle 1, Day 22–28	20 mg daily
Cycle 2, Day 1–Day 7	50 mg daily
Cycle 2, Day 8–Day 14	100 mg daily
Cycle 2, Day 15–Day 21	200 mg daily
Cycle 2, Day 22–Day 28	400 mg daily
Cycle 3, Day 1–end of Cycle 12	400 mg daily

Table 1 Treatment Arm A: VEN+G Doses per Study Visit (cont.)

TLS=tumor lysis syndrome; VEN+G=venetoclax+obinutuzumab.

Note: Cycles will comprise 28 days. Treatment with obinutuzumab will continue for 6 cycles, and venetoclax will end at Cycle 12.

[a] IV infusion; overnight hospitalization may be required on Day 1 following the first infusion of obinutuzumab (100 mg).

[b] Only the first dose (1000 mg) of obinutuzumab administration can be split over 2 days. Two infusion bags should be prepared for the infusion on Days 1 and 2 (100 mg for Day 1 and 900 mg for Day 2). If the first bag is completed without modifications of the infusion rate or interruptions, the second bag may be administered on the same day (no dose delay necessary, no repetition of premedication), provided that appropriate time, conditions, and medical supervision are available throughout the infusion. If there are any modifications of the infusion rate or interruptions during the first 100 mg, the second bag should be administered the following day. If patients require a delay of greater than 24 hours between the 100-mg and 900-mg infusions of obinutuzumab, please consult Section 4.3.2.2 and the Obinutuzumab Investigator's Brochure regarding drug stability.

[c] All patients will be assessed at screening and categorized in a TLS-risk category. Because of possible tumor de-bulking after obinutuzumab therapy, investigators will reassess TLS risk after obinutuzumab induction and prior to starting the venetoclax ramp-up (Days 16–21) and may assign patients to a lower risk group (see Section 5.1.7.1 for more details).

[d] The 20-mg and 50-mg doses of venetoclax will be administered in the hospital for patients who are at high risk of TLS, or if indicated to hospitalize, and thereafter at home daily for 7 days. The dose will increase every 7 days to the target dose of 400 mg, and venetoclax will be administered at home unless a patient is indicated to hospitalize.

[e] Oral tablets.

Guidance on patient management for TLS prophylaxis prior to and following venetoclax dosing is provided in Section 5.1.7.1.

Because it is possible that de-bulking from obinutuzumab therapy before starting venetoclax dosing already significantly reduces the risk of TLS, TLS prophylactic measures will be re-assessed at the time of starting the first dose of venetoclax (see Section 5.1.7.1).

3.1.4.2.2 Treatment Arm B: FCR/BR
3.1.4.2.3 Fludarabine, Cyclophosphamide, and Rituximab

Only patients ≤65 years of age will be eligible for FCR due to the associated high risk of severe neutropenias and infections. Patients will receive 6 cycles of fludarabine, cyclophosphamide, and rituximab each cycle with a duration of 28 days:

- Fludarabine IV will be given on Days 1–3 (Cycles 1–6) at a dosage of 25 mg/m^2
- Cyclophosphamide IV will be given on Days 1–3 (Cycles 1–6) at a dosage of 250 mg/m²
- Rituximab IV will be given before the administration of chemotherapy at a dosage of 375 mg/m^2 in the first cycle and at a dosage of 500 mg/m^2 in Cycles 2–6 with premedication according to the clinical practice of the participating sites (Eichorst et al. 2016)

Bendamustine and Rituximab

All patients in Arm B, regardless of age, can be considered for treatment with BR. Patients will receive 6 cycles of bendamustine and rituximab, each cycle with a duration of 28 days:

- Bendamustine IV will be given on Days 1 and 2 (Cycles 1–6) at a dosage of 90 mg/m^2
- Rituximab IV will be given before the administration of chemotherapy at a dosage of 375 mg/m^2 in the first cycle and at a dosage of 500 mg/m^2 in Cycles 2–6 with premedication according to the clinical practice of the participating sites (Eichorst et al. 2016)

3.1.4.3 Monitoring of Disease Progression during Treatment Period

All patients should be continually monitored for PD during the treatment period, and this should be clearly documented in the electronic Case Report Form (eCRF). Interim staging assessments will be performed at Cycle 4, Day 1; Cycle 7, Day 1; and Cycle 9, Day 1. In addition to an assessment of hematological status, this will also include a full physical examination to assess any lymphadenopathy and hepatomegaly/splenomegaly.

Unless disease progression is confirmed, the patient is withdrawn due to toxicity, the patient withdraws consent, or the patient has died, patients should receive up to 6 cycles of study treatment of obinutuzumab and 12 cycles of venetoclax in Arm A or 6 cycles of FCR/BR in Arm B.

3.1.4.4 Post-Treatment Follow-Up Visits

All patients will be followed until the end of the study (see Section 3.2). Response will be followed at all visits by clinical/laboratory signs and symptoms until progression is identified. A CT scan should be performed 8–12 weeks after the end of treatment in both arms in order to confirm CR and PR if lymphadenopathy was present at baseline. In those patients who achieve a CR or CRi, a BM aspirate and biopsy will be obtained. If PD is detected by physical examination in the absence of any objective hematological progression, a CT scan of the involved nodes will be performed. After PD, patients will be followed until the next anti-leukemic treatment is given and then for survival until the study is completed. To capture PRO assessments, post-progression among those receiving subsequent therapies, PRO assessments will be conducted at the time of the subsequent treatment visit, but before any procedures or drug infusions are performed. A schedule of assessments is provided in Appendix 1.

3.2 END OF STUDY AND LENGTH OF STUDY

3.2.1 *Duration of Participation*

The *total duration* of study *participation for each individual* is *expected to be approximately 3.5* years after the last patient is enrolled, allowing for completion of the maximum duration of planned therapy (in the absence of disease progression) as well as

at least *2.5 years* of follow-up for all patients *in order to reach the estimated number of events needed for the PFS final analysis.*

Patients are expected to be on study for a minimum of 3.5 years up to a maximum of 6.2 years, subject to their date of enrollment in relation to the last patient enrolled.

In addition, the Sponsor may decide to terminate the study at any time.

3.2.2 Long-Term Follow Up

To be able to collect long-term follow-up data until a patient´s death after the end of the study, each patient will be informed of the importance of long-term follow-up data and asked for his/her consent to the long-term follow-up for OS according to national guidelines or in a separate non-interventional or extension study.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Dose and Schedule

3.3.1.1 Venetoclax

The approved venetoclax monotherapy dose and regimen for the treatment of patients with R/R CLL is 400 mg once daily (QD). This monotherapy dose was based on the experience from the Phase I dose-escalation Study M12-175, which examined single-agent venetoclax in patients with R/R CLL and NHL, and the safety analysis of 58 patients enrolled in the study after enhanced TLS prophylaxis measures were introduced and who completed the dosing ramp-up period (Roberts et al. 2016).

This experience has demonstrated that starting venetoclax at 20 mg for 1 week followed by a gradual ramp up of venetoclax over a period of 5 weeks is an adequate measure in order to safely administer venetoclax. The dosing regimen proved to reduce the risk for TLS by more gradually reducing the leukemia-cell burden prior to administration of the full-target dose with no loss of effect.

The 400-mg dose was further supported by the results of Study GO28667/MURANO, which compared venetoclax + rituximab (VenR) with BR in patients with R/R CLL (Seymour et al. 2018).

The 400-mg QD regimen is also being used in Study BO25323, which is an ongoing, open-label, multi-center, international, randomized, Phase III study investigating the efficacy and safety of VEN + G compared with GClb in patients with 1L CLL who have coexisting medical conditions.

To date, no evidence of unexpected late toxicities has emerged from continued treatment with venetoclax beyond 6 months.

3.3.1.2 Obinutuzumab

The recommended dose of obinutuzumab for front-line treatment will be used in this study:

- Cycle 1: 1000 mg Day 1 (or split dose Day 1 and Day 2), 8, and 15 (see Section 4.3.2)
- Cycles 2–6: 1000 mg on Day 1

Treatment will be on a 28-day cycle for a total of 6 cycles.

3.3.1.3 Rationale for the Combination of Venetoclax with Obinutuzumab

Obinutuzumab is a novel, humanized, type II, glycoengineered, monoclonal antibody (mAb) 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.

As obinutuzumab and venetoclax exhibit different mechanisms of action, there is strong scientific rationale to support treatment with a combination of both drugs. The addition of venetoclax to obinutuzumab treatment results in a greatly enhanced anti-cancer activity compared with either agent alone, based on in vitro and in vivo results (Venetoclax Investigator's Brochure). It was, therefore, anticipated that VEN+G would show more anti-CLL activity than when each drug is administered alone, resulting in a greater, more durable and deeper effect in CLL-disease remission for patients with 1L CLL. In addition, the safety profiles of both drugs seem to be compatible, especially in light of a fixed treatment-duration and chemotherapy-free setting. Thus, VEN+G was considered to have the potential to be an attractive combination for patients with 1L CLL.

3.3.2 Rationale for Patient Population

More than 50% of patients with CLL are asymptomatic at diagnosis and require no treatment. Treatment is initiated when a patient's disease becomes symptomatic or progressive as defined by the iwCLL updated guidelines for diagnosis and treatment of CLL (Hallek et al. 2018). Allogeneic stem cell transplant is still the only treatment option for CLL patients that is potentially curative; however, the procedure is only appropriate for a small number of younger patients and is associated with high morbidity and mortality (Gribben 2005).

The clinical course of CLL is highly variable and can be predicted by clinical staging (Rai et al. 1975; Binet et al. 1981) as well as genetic (Dohner et al. 2000), serum, and other markers (Smith et al. 2006). *TP53* mutation/deletion is so far the strongest prognostic factor predicting non-response to chemotherapy (Zenz et al. 2008). Patients harboring *TP53* mutation/deletion should be treated with chemotherapy-free regimens.

The treatment landscape for 1L CLL is evolving. Deep remissions and clinically significant PFS can be achieved in patients without del17p or *TP53* mutation with FCR (Hallek et al. 2010). However, due to the high risk of severe neutropenias and infections with FCR, BR must also be considered for these patients. Novel agents, such as ibrutinib (a Bruton's tyrosine kinase inhibitor), have resulted in improvements in long-term clinical outcomes (Barr et al. 2018; Farooqui et al. 2015, Shanafelt et al. 2019). However, the majority of patients remain uncured, only achieve a PR, and do not achieve MRD negativity requiring treatment for unlimited time (i.e., until disease progression or unacceptable side effects) in order to control the disease, leading to potential increase in toxicities. Therefore, the aim of therapy is to control disease, improve symptoms, prolong survival, and maintain QoL while minimizing toxicity with regimens that are well tolerated and acceptable to patients.

3.3.3 Rationale for Control Group

For physically fit patients, the combination of FCR is currently considered the standard treatment, as a median PFS of 57 months and an OS of 85% 3 years after start of treatment with FCR was achieved in the CLL8 trial (Hallek et al. 2010). However, 90.8% of all patients treated with FCR experienced at least one Grade 3–4 toxicity: 90.0% hematological toxicities, 81.7% neutropenias, and 39% infections; the treatment-related mortality with FCR was 3.9%. Experience with bendamustine, an alkylating agent, used in routine practice, and results from Phase II trials evaluating the combination of bendamustine and rituximab (BR) (Fisher et al. 2011; Fisher et al. 2012) were promising, with a lower incidence of CTCAE Grade 3–4 neutropenias and infections (10.3% and 6.8% of patients receiving BR as 1L treatment). The CLL10-trial, therefore, prospectively evaluated if the BR regimen was indeed equally effective and less toxic compared to the current standard treatment FCR for the 1L treatment of a total of 564 physically fit patients (Eichhorst et al. 2016). The final analysis demonstrated a higher efficacy of the FCR compared to the BR regimen with regard to CR rate, MRD negativity, and PFS, and therefore, FCR remains the standard of care in the 1L treatment of physically fit patients (Eichhorst et al. 2016). However, as FCR is associated with a higher risk for severe neutropenias and infections, BR must be kept as standard front-line therapy in FIT patients with a high risk of infections (Eichhorst et al. 2016).

3.3.4 Rationale for MRD as the Primary Endpoint

3.3.4.1 MRD Negativity Leads to Improved Clinical Outcomes

For CLL disease, MRD assessment has been increasingly used in clinical studies since the development of the iwCLL 2008 guidelines and has been established as an independent prognostic factor that correlates with clinical outcomes in both the front-line setting and for patients with R/R disease (Böttcher et al. 2012; Kwok et al. 2016). Furthermore, MRD has been recognized as an intermediate endpoint for licensure in CLL studies by the European Medicines Agency (EMA) (EMA/CHMP/703715/2012 Rev. 2). Prospective clinical trials have provided substantial evidence that therapies that

are able to eradicate MRD usually result in an improved clinical outcome (Hallek et al. 2018). Patients achieving MRD-negative status in PB or BM had a better PFS and/or OS outcome irrespective of the treatment they received compared with those who could not achieve MRD negativity (chemo-immunotherapy regimens [Böttcher et al. 2012; Goede et al. 2014; Santacruz et al. 2014; Eichhorst et al. 2016; Kwok et al. 2016]; MAbs [Moreton et al. 2005]; *and* targeted therapies with VenR [Kater et al. 2018]). The positive association between MRD negativity and PFS in patients with previously untreated CLL is further supported by a meta-regression model demonstrating a statistically significant relationship between treatment effect on PB MRD and treatment effect on PFS at the end-of-induction treatment with chemo-immunotherapy in patients with previously untreated CLL (Dimier et al. 2018). In addition, MRD negativity seems to be a stronger predictor of PFS than the clinical response assessment. In a recent meta-analysis in 1L CLL studies, no statistically significant difference in PFS was observed between MRD-negative CR and MRD-negative PR patients; however, PFS was significantly longer for MRD-negative PR than for MRD-positive CR ($p < 0.048$) (Kovacs et al. 2016). Thus, the recently revised iwCLL guidelines highlight the increased value of MRD as an endpoint (Hallek et al. 2018).

3.3.4.2 High and Promising Rates of MRD Negativity Achieved by Venetoclax

Survival of CLL cells is highly dependent on Bcl-2; therefore, targeting CLL cells with a highly potent and selective inhibitor (e.g., venetoclax) can lead to deeper response. Studies in venetoclax monotherapy and VenR demonstrated that clinical response was more durable in patients who achieved MRD-negative status. As of 4 April 2017, results from Study M13–982, an ongoing, Phase II, open-label study investigating the efficacy of venetoclax in patients with R/R CLL with del(17p), the Kaplan-Meier estimate for PFS at 18 months was 78% (95% CI: 54%, 91%) for the 48 patients achieving PB MRD negativity ($< 10^{-4}$ by multiple-color flow) compared with 51% (95% CI: 32%, 68%) for the 53 non-MRD-negative patients (Stilgenbauer et al. 2018). Moreover, as of 4 March 2016, after a median follow-up of 28 months, results from Study M13-365, an ongoing, Phase 1b study evaluating the safety and tolerability of VenR in patients with relapsed CLL or SLL showed only 1 of 22 patients (4.5%) who achieved BM MRD negativity ($< 10^{-4}$ by multi-color flow) by Month 7 had disease progression, whereas disease progression was observed in 5 of 15 patients (33.3%) who remained MRD positive at this time (Seymour et al. 2017). Furthermore, with a median follow-up of 36 months (as of 8 May 2018) in Study GO28667/MURANO, an ongoing, randomized, Phase III study comparing a fixed-duration chemotherapy-free regimen of VenR with BR in patients with R/R CLL, landmark analysis showed a similar association between PB MRD-negativity status at the EOCT and longer PFS in the chemo-free VenR arm (HR = 0.38 [95% CI: 0.20–0.72]) and in the control chemoimmunotherapy BR arm (HR = 0.27 [95% CI: 0.14–0.52]). In addition, patients in the VenR arm who achieved an investigator-assessed PR and MRD negativity had a PFS outcome similar with that of

patients who achieved CR with MRD negativity (HR = 0.71 [95% CI: 0.24–2.14]) (Kater et al. 2018).

3.3.4.3 Venetoclax in Combination with Obinutuzumab Show Compelling PFS and MRD Data in 1L CLL

On 15 May 2019, the FDA approved venetoclax in combination with obinutuzumab in previously untreated patients with CLL or SLL based on pivotal Study BO25323/CLL14 (see Section 1.3.1 for study details). This study demonstrates unprecedented MRD rates representing a depth of anti-CLL activity that differentiates treatment with VEN + G, and also provides compelling PFS data in the 1L CLL setting.

Based on the results of a protocol-specified interim analysis (as of 17 August 2018 CCOD), the IDMC recommended that Study BO25323/CLL14 had met its primary endpoint of investigator-assessed PFS, with a significant and clinically meaningful improvement in patients in the VEN + G arm (investigator-assessed PFS: stratified HR = 0.35 [95% CI: 0.23–0.53], IRC-assessed PFS: stratified HR = 0.33 [95% CI: 0.22, 0.51], $p < 0.0001$) versus patients in the GClb arm.

In Study BO25323/CLL14, PB and BM MRD responses were assessed using real-time quantitative ASO-PCR centrally for all patients at the University of Kiel; the laboratory participated in the analytical validation of ASO-PCR.

PB samples were taken at baseline; at Cycle 4, Day 1 (each cycle = 28 days); Cycle 9, Day 1 (3 months after the last dose of obinutuzumab [EOCT assessment]), 3 months after treatment completion/early termination (end-of-treatment [EOT] assessment), at 3-month intervals until 24 months after treatment completion, and then at 6-month intervals thereafter. BM aspirate samples for MRD assessment were taken from responding patients at 2 landmark timepoints: Cycle 9, Day 1 (3 months after the last dose of obinutuzumab [EOCT assessment]) and 3 months after treatment completion/early termination (EOT assessment). MRD was considered negative if the result was < 1 CLL cell in 10,000 leukocytes. All MRD analyses were conducted using the intent-to-treat (ITT) population.

The majority of patients treated with VEN + G achieved PB MRD negativity at the EOCT and EOT assessments and continued to maintain MRD-negative status after completion of the 1-year fixed duration therapy through follow-up at the time of this CCOD.

At the EOT assessment (3 months after treatment completion/early termination), MRD negativity in PB was observed in 163 patients (75.7%) in the VEN + G arm compared with 76 patients (35.2%) in the GClb arm. The difference between treatment arms (40.28%; 95% CI: 31.45, 49.10) was statistically significant in favor of the VEN + G arm ($p < 0.0001$). The rate of MRD test positivity was low in VEN + G at 11.1%. Of note, the missing rates were comparable between the 2 arms: 10.2% in the GClb arm and 8.8% in the VEN + G arm.

At the EOCT assessment (Cycle 9, Day 1; 3 months after the last dose of obinutuzumab), MRD-negativity in PB was observed in 154 patients (71.3%) in the VEN+G arm compared with 83 patients (38.4%) in the GClb arm. The difference between treatment arms (32.87%; 95% CI: 23.76, 41.98) was statistically significant in favor of the VEN+G arm ($p<0.0001$). The rate of MRD test positivity was lower in VEN+G at only 7.9% versus 40.3% in GClb.

At the EOT assessment (3 months after treatment completion/early termination), MRD-negativity in BM in the ITT population was achieved in 123 patients (56.9%) in the VEN+G arm compared with the GClb arm with 37 patients (17.1%). The difference in MRD-negative rates was 39.81% (95% CI: 31.27, 48.36) and was statistically higher in the VEN+G arm than in the GClb arm ($p<0.0001$). The rate of MRD test positivity was low in VEN+G at 12.5%. Of note, the missing rates were again generally comparable between the 2 arms.

At the EOT assessment, patients with CR treated with VEN+G achieved higher MRD-negativity rates in both PB and BM than those treated with GClb: in PB, 87% (87/100) patients versus 62% patients (29/47), respectively, and in BM, 69% patients (69/100) versus 45% patients (21/47), respectively.

The high MRD-negative rate in PB observed in the VEN+G arm was maintained through follow-up and up to 1 year after completion of treatment (58.3% at follow-up Month 12 visit, the last visit for which complete data were available prior to the CCOD).
At follow-up Month 12, the PB MRD-negativity rate had decreased to only 9.3% in the GClb arm. At the time of the CCOD, all patients had been off treatment for at least 12 months.

At the EOT assessment, high concordance between PB and BM MRD-negativity status in paired samples was observed in the VEN+G arm, 93.5% (of 138 PB MRD-negative patients, 129 were also MRD negative in BM), suggesting VEN+G is very effective in clearing disease in both PB and BM compartments compared with GClb. Moreover, landmark analysis based on EOT assessment PB or BM MRD status by ASO-PCR showed that the majority of patients in the VEN+G arm who achieved MRD negativity had a longer duration of PFS compared with a minority of patients who did not (PB: HR=0.12 [0.05, 0.30], p-value<0.0001; BM: HR=0.12 [0.04, 0.39], p-value=0.0004), confirming the association between MRD negativity with PFS similar to mentioned literature above. Furthermore, similar to Study GO28667/MURANO, landmark analyses showed that in both arms of the BO25323/CLL14 study, patients who achieved a PR with PB MRD-negativity had a PFS outcome similar with that of patients who achieved CR with PB MRD-negativity. The same observations were noted for BM MRD status and PFS. Collectively, the high PB and BM MRD status concordance, the similarity of PFS correlation between the PB MRD negativity and the BM MRD negativity, and similar PFS outcome of PB MRD negative patients regardless of clinical outcome highlight the potential of PB MRD negativity as a surrogate for BM MRD

negativity. This provides evidence that the less invasive PB MRD assessment at EOT alone is able to appropriately predict PFS outcome in 1L patients with CLL treated with VEN+G.

Overall, Study BO25323/CLL14 showed that a substantially large portion of the patients were able to achieve MRD-negativity status with VEN+G regimen and that was associated with prolonged PFS benefit. This association between high MRD levels at the end of venetoclax treatment and prolonged PFS benefit is further supported by the results observed in all 1L CLL patients and in the subset of FIT patients treated in the GP28331 Phase 1b study (Flinn et al. 2019). As such, similar to what have been reported with chemo-immunotherapies in the 1L CLL setting, the totality of evidence show that MRD response at the end of treatment is associated with favorable outcomes, such as PFS and OS. The Sponsor anticipates similar or better MRD response and longer PFS could be achieved in a Phase III study with a 1L FIT CLL patient population treated with a VEN+G regimen. MRD response at the end of venetoclax treatment as a primary endpoint in a Phase III study can ensure timely patient access to more efficacious therapies. Therefore, the Sponsor believes that the use of MRD response rate in PB as the primary endpoint in the proposed Phase III study is adequate to establish the efficacy of venetoclax in combination with obinutuzumab as a treatment for FIT patients with previously untreated CLL.

3.3.5 Rationale for Biomarker Assessments

Venetoclax inhibits the ability of cancer cells to evade cell death (apoptosis) by blocking the activity of the anti-apoptotic protein Bcl-2. Nonclinical studies have demonstrated a pattern of response to venetoclax on the basis of the levels of Bcl-2 family proteins. High levels of Bcl-2 and low levels of MCL-1 are generally predictive of response to this drug in vitro. In addition, high levels of at least one pro-apoptotic “sensor”, such as Noxa or Bim, is required. Measurement of relevant RNAs and proteins (including those in the Bcl-2 family) in CLL cells will be examined pre-treatment for correlation with outcome.

Additionally, several prognostic markers have been described that can be used as stratification factors for CLL therapies, including del(11q), del(13q14), and trisomy 12, IGHV, serum parameters (thymidine kinase, β2 microglobulin) as well as complex karyotype or genetic complexity. There is increasing evidence from prospective clinical trials indicating that the detection of certain chromosomal deletions has prognostic significance in CLL. For example, patients with leukemia cells that have del(17p) and/or p53 mutations have an inferior prognosis and appear resistant to standard chemotherapy regimens. Therefore, detection of these and other cytogenetic abnormalities could have prognostic value and may guide therapeutic decisions (Fink et al. 2013; Goede et al. 2014; Zenz et al. 2009).

Recurrent somatic mutations, (i.e., in genes such as *NOTCH1*, *SF3B1*, *TP53*), which have recently been identified in CLL in small subsets of patients (~2%−10% of patients), might evolve over time (clonal evolution) and associate with clinical long-term prognosis (Dreger et al. 2013; Schnaiter et al. 2013; Stilgenbauer et al. 2014). A CD19-enriched

blood sample will be used to sequence commonly mutated genes mentioned above, as well as genomic variation in genes associated with the cellular DNA damage response, cellular key pathways in CLL, (e.g., B-cell receptor signaling), and genes encoding for new treatment targets, including Bcl-2.

Biomarkers described here may have both predictive and prognostic value; both arms of study will be evaluated and their potential association with disease progression will also be explored. These studies may help identify responsive patient populations and to develop better therapies for patients with CLL. The analyses described in this section are exploratory and will be done retrospectively.

Recently new technological approach, such as ctDNA measurement in plasma, allows assessing MRD potentially representing multiple disease compartments (i.e., blood, BM, and lymph nodes). This type of approach may provide a more comprehensive view of a patient's overall molecular response to treatment and may offer additional information on disease monitoring and clonal evolution. Therefore, the exploratory analysis of plasma ctDNA measurement will be conducted at relevant timepoints in concordance with MRD assessments by NGS.

Biomarkers described here may have both predictive and prognostic value; both arms of study will be evaluated and their potential association with achieving MRD negativity and disease progression will also be explored. These studies may help identify responsive patient populations and develop better therapies for patients with CLL. The analyses described in this section are exploratory and will be conducted retrospectively.

3.3.6 Rationale for Chronic Lymphocytic Leukemia Diagnostic Laboratory Assessments

3.3.6.1 Lymphocyte Count

The clinical diagnosis of CLL requires an absolute lymphocytosis with a lower threshold of at least 5000 mature-appearing lymphocytes/μL in the PB. Lymphocyte counts may fluctuate from time of diagnosis to the point at which treatment is required.

3.3.6.2 Lymphocyte Immunophenotyping

Patients must have documented CD20-positive CLL according to the iwCLL criteria (Hallek et al. 2018) and the Matutes Scoring system (Matutes et al. 1994; see Appendix 11). CLL cells co-express the T-cell antigen CD5 and B-cell antigen (CD19, CD20, and CD23). The levels of surface immune-globulins, CD20 and CD79b, are characteristically low compared with those found on normal B cells. Each B cell is monoclonal with regard to expression of either κ or λ. Variations of the intensity of expression of these markers may exist and do not exclude entry in the study.

3.3.7 Rationale for Not Assessing Pharmacokinetics in Study CO41685

Collection of pharmacokinetic (PK) samples for venetoclax and obinutuzumab in Study CO41685 (CRISTALLO) is not planned. Both the patient population and the proposed treatment combination (VEN+G) have been previously evaluated in Studies BO25323/CLL14 (N=142 in VEN+G arm, 1L FIT) and GP28331 (N=32 1L; N=22 1L FIT, N=45 R/R). For each of these studies, venetoclax and obinutuzumab exposures were consistent with those reported in prior studies and confirmed that there were no significant drug-drug interactions (DDI) between venetoclax and obinutuzumab. Therefore, no new insights on the PK profile and/or DDI potential of VEN+G is anticipated upon further PK evaluation in Study CO41685 (CRISTALLO).

Venetoclax is primarily metabolized by CYP3A4. Monoclonal antibodies do not interact directly with CYP but may interact with CYP through cytokine modulation. Treatment with obinutuzumab results in transient increases in cytokine levels at time of first infusion only. Therefore, significant effects on CYP proteins and subsequent DDI are considered highly unlikely. Consequently, the risk for obinutuzumab to significantly alter the pharmacokinetics of venetoclax is expected to be low.

Tumor burden affects clearance of obinutuzumab, especially at the beginning of treatment. Consequently, some patients with a high-tumor burden may appear to clear the drug from the blood faster than patients with a low-tumor burden because obinutuzumab binds to the CD20+ tumor cells and is effectively removed from the blood. As a result, the clearance of the drug is expected to vary with time because repeated doses of obinutuzumab should reduce the number of CD20+ tumor cells. Venetoclax has the potential to alter tumor burden and, therefore, impact the exposure of obinutuzumab.

The drug interaction potential between venetoclax and obinutuzumab was previously investigated in the pivotal Study BO25323/CLL14 and the Phase 1b Study GP28331.

3.3.8 Rationale for Patient-Reported Outcome (PRO) Assessments

Patients with CLL experience a symptom burden from the underlying disease process that is compounded by the side effects of currently available therapies. These symptoms and treatment-related side effects can impact function and, subsequently, health-related QoL. There is strong reason to believe that if the anticipated clinical benefit is observed between the combination of VEN+G in the trial, patients might report an accompanying improvement in distinct key symptoms of the disease (i.e., reduction in fatigue, reduction in nodular pain, and decrease in night sweats). PROs will be used to comprehensively capture patient reports of disease symptom and functional impact changes as well as evaluate treatment-related side effects. Using PROs to quantify the importance of MRD from the patient perspective can further support the primary endpoint, while understanding time to disease progression in terms of how patients perceive disease symptoms and functional impacts can support assessment of PFS.

4. MATERIALS AND METHODS

4.1 PATIENTS

A target of 165 patients will be randomized at a 1:1 ratio to receive either VEN + G (Arm A) or FCR/BR (Arm B).

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Signed Informed Consent Form
- Ability to comply with the study protocol, in the investigator's judgment
- Aged 18 years or older
- Have previously untreated documented CLL according to the iwCLL criteria
- CLL requiring treatment according to the iwCLL criteria
- CIRS score $\leq$6 and creatinine clearance (CrCl) $\geq$70 mL/min as calculated by the Standard Cockcroft and Gault Formula
- Hematology values within the following limits, unless cytopenia is caused by the underlying disease (i.e., no evidence of additional BM dysfunction; e.g., myelodysplastic syndrome, hypoplastic BM):
  - Absolute neutrophil count $\geq 1.0 \times 10^9$/L, unless there is BM involvement
  - Platelet count $\geq 75 \times 10^9$/L and more than 7 days since last transfusion, or $\geq 30 \times 10^9$/L if there is BM involvement
- Adequate liver function as indicated by a total bilirubin, AST, and ALT $\leq$2 times the institutional upper limit of normal (ULN) value, unless directly attributable to the patient's CLL
- Life expectancy $>$6 months
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception and agreement to refrain from donating eggs, as defined below:

  Women must remain abstinent or use contraceptive methods with a failure rate of $<$1% per year during the treatment period and for at least 30 days after the last dose of venetoclax or 18 months after the last dose of obinutuzumab for patients in Arm A, and for at least 6 months after the last dose of bendamustine *or* fludarabine or 12 months after the last dose of rituximab *or cyclophosphamide* for patients in Arm B, whichever is later. Women must refrain from donating eggs during this same period.

  A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state ($\geq$12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator

(e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.

Examples of contraceptive methods with a failure rate of <1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable methods of contraception.
If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

- For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods, and agreement to refrain from donating sperm, as defined below:

  With a female partner of childbearing potential who is not pregnant, men who are not surgically sterile must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of <1% per year during the treatment period and for at least 90 days after the last dose of venetoclax or 18 months after the last dose of obinutuzumab for patients in Arm A, and for at least 6 months after the last dose of bendamustine, fludarabine, or cyclophosphamide or 12 months after the last dose of rituximab for patients in Arm B, whichever is later. Men must refrain from donating sperm during this same period.

  With a pregnant female partner, men must remain abstinent or use a condom during the treatment period and for at least 90 days after the last dose of venetoclax or 18 months after the last dose of obinutuzumab for patients in Arm A, and for at least 6 months after the last dose of bendamustine, fludarabine, or cyclophosphamide or 12 months after the last dose of rituximab for patients in Arm B, whichever is later, to avoid exposing the embryo.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.
  If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry:

- Transformation of CLL to aggressive NHL (Richter's transformation or prolymphocytic leukemia)

- Patients with SLL only (a diagnosis of CLL/SLL is permitted)
- Known central nervous system involvement
- Patients with a history of confirmed progressive multifocal leukoencephalopathy (PML)
- Detected del(17p) or *TP53* mutation (valid test within 6-months from screening is required for randomization)
- An 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, throat organ system (note that symptoms related to CLL should not be included in the patient's screening CIRS score)
- Patients with uncontrolled autoimmune hemolytic anemia or immune thrombocytopenia
- History of prior malignancy, 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 randomization
  - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
  - Adequately treated cervical carcinoma in situ without evidence of disease
  - Surgically/adequately treated low grade, early stage, localized prostate cancer without evidence of disease
  - Patients with infections requiring IV treatment (Grade 3 or 4) within the last 8 weeks prior to enrollment
- Evidence of other clinically significant uncontrolled condition(s) including but not limited to active or uncontrolled systemic infection (e.g., viral, bacterial, or fungal)
- History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies or known sensitivity or allergy to murine products
- Hypersensitivity to fludarabine, bendamustine, cyclophosphamide, rituximab, obinutuzumab, or venetoclax or to any of the excipients (e.g., trehalose)
- Pregnant women and nursing mothers
- Vaccination with a live vaccine ≤28 days prior to randomization
- Prisoners or patients who are institutionalized by regulatory or court order or persons who are in dependence to the Sponsor or an investigator
- History of illicit drug or alcohol abuse within 12 months prior to screening, in the investigator's judgment
- Positive test results for chronic hepatitis B virus (HBV) infection (defined as positive hepatitis B surface antigen [HBsAg] serology)

Patients with occult or prior HBV infection (defined as negative HBsAg and positive total hepatitis B core antibody [HBcAb]) may be included if HBV DNA is undetectable, provided that they are willing to undergo monthly DNA testing. Patients who have protective titers of hepatitis B surface antibody (HBsAb) after vaccination or prior but cured hepatitis B are eligible.

- Positive test result for hepatitis C (hepatitis C virus [HCV] antibody serology testing)

  Patients who are positive for HCV antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.

- Patients with known infection with HIV or human T-cell leukemia virus 1 (HTLV-1)

  In countries where mandatory testing by health authorities is required, HIV testing will be performed.

  HTLV testing is required in patients from endemic countries (Japan, countries in the Caribbean basin, South America, Central America, sub-Saharan Africa, and Melanesia).

- Any 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
- Received any of the following agents within 28 days prior to the first dose of study treatment:
  - Immunotherapy
  - Radiotherapy
  - 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)
- Patients who have received the following agents:
  - Strong and moderate CYP3A inhibitors within 7 days prior to the initiation of study treatment
  - Strong and moderate CYP3A inducers within 7 days prior to the initiation of study treatment
  - Steroid therapy for anti-neoplastic intent with the exception of inhaled steroids for asthma, topical steroids, or replacement/stress corticosteroids 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 administration
- Inability to swallow a large number of tablets

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

4.2.1 Treatment Assignment

This is a randomized, open-label study. After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a patient, the study site will obtain the patient's identification number and treatment assignment from an IxRS.

Patients will be randomly assigned to one of two treatment arms: Arm A (VEN+G) or Arm B (FCR/BR). Randomization will occur in a 1:1 ratio using a block-stratified randomization method to ensure a balanced assignment to each treatment arm. Randomization will be stratified according to the following criteria:

- IGHV mutation: yes or no
- Binet stage (3 levels): A, B, or C
- Age: ≤65 or >65

In Arm B, the investigator at each site will determine whether the FCR or BR regimen will be used for the individual patient, based on their local practice. All patients in Arm B can be considered for treatment with BR, whereas only patients ≤65 years of age will be eligible for FCR.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal products (IMPs) for this study are venetoclax, obinutuzumab, fludarabine, cyclophosphamide, bendamustine, and rituximab. Appendix *18 identifies all IMPs and auxiliary* medicinal products for this study.

Where regulations require, all IMPs will be provided by the Sponsor. For the U.S. region, sites will locally source (to be fully reimbursed by the sponsor) the following IMPs: fludarabine, cyclophosphamide, bendamustine, and rituximab. Generic formulation, with the exception of IMPs provided by the Sponsor, are permitted for locally sourced IMPs.

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Venetoclax

Venetoclax will be supplied by the Sponsor. For information on the formulation, packaging, and handling of venetoclax, see the pharmacy manual and the Venetoclax Investigator's Brochure.

4.3.1.2 Obinutuzumab

Obinutuzumab will be supplied centrally for all countries participating in the study as a single-dose, sterile liquid formulation in a 50-mL pharmaceutical grade glass vial containing a nominal 1000 mg obinutuzumab. The vial contains 40 mL of solution with

2.5% overfill. For information on the formulation, packaging, and handling of obinutuzumab, see the local prescribing information.

Compatibility of the obinutuzumab with 0.9% sodium chloride has been tested in a concentration range from 0.2 mg/mL to 20 mg/mL. Dilutions of obinutuzumab in 0.9% sodium chloride have been found to be stable for 24 hours at 2°C–8°C and an additional 24 hours at ambient temperature and ambient room lighting. Storage conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C–8°C.

Administration sets with polyvinyl chloride, polyurethane, or polyethylene as product contact surfaces and IV bags with polyolefin, polypropylene, polyvinyl chloride, or polyurethane as product contact surfaces are compatible and may be used.

For further details, see the Obinutuzumab Investigator's Brochure.

4.3.1.3 Fludarabine

For information on the formulation and handling of fludarabine, see the local prescribing information for fludarabine. For sites in the United States, fludarabine will be packaged as indicated in the local prescribing information. For sites not in the United States, fludarabine will be repackaged and relabeled by the Sponsor before distribution to sites.

4.3.1.4 Cyclophosphamide

For information on the formulation and handling of cyclophosphamide, see the local prescribing information for cyclophosphamide. For sites in the United States, cyclophosphamide will be packaged as indicated in the local prescribing information. For sites not in the United States, cyclophosphamide will be repackaged and relabeled by the Sponsor before distribution to sites.

4.3.1.5 Rituximab

Rituximab is manufactured by Genentech, Inc., as the licensed product Rituxan® in the United States and Canada. For the rest of the world, rituximab is manufactured by F. Hoffmann–La Roche Ltd. (Roche) as the licensed product MabThera®. It is a sterile, clear, colorless, preservative-free liquid concentrate for IV administration. Rituximab is supplied at a concentration of 500-mg (50-mL) single-use vials. The product is formulated for IV administration in 9.0 mg/mL sodium chloride, 7.35 mg/mL sodium citrate dihydrate, and 0.7 mg/mL polysorbate 80, after reconstitution with sterile water for injection. The pH is adjusted to 6.5. Vials are for single use. Each vial and carton will be labeled (i.e., either single-panel or booklet) per individual country requirements. The label must remain affixed to the supplies.

Rituximab vials must be stored at 2°C–8°C (36°F–46°F). Rituximab vials should be stored in the outer carton in order to protect them from light. Rituximab solution for infusion may be stored at 2°C–8°C (36°F–46°F) for 24 hours and has been shown to be

stable for an additional 12 hours at room temperature. However, since rituximab does not contain a preservative, diluted solutions should be stored refrigerated (2°C–8°C). No incompatibilities between rituximab and polyvinylchloride or polyethylene bags have been observed.

For further details, see the local prescribing information for Rituxan®/MabThera®.

4.3.1.6 Bendamustine

Bendamustine HCl is marketed by Cephalon as the licensed product Treanda® for the United States and is marketed in Europe by Mundipharma International Corporation Ltd, under the name Levact®. In Australia it is marketed by Jansenn as the licensed product Ribomustin®. Bendamustine will be supplied in individual cartons containing single-use vials of 100 mg bendamustine HCl as lyophilized powder. Each vial and carton will be labeled (i.e., either single-panel or booklet) per individual country requirements. The label must remain affixed to the supplies.

Bendamustine should be stored at 15°C–25°C (59°F–77°F). It is to be retained in the original carton until time of use to protect from light. Bendamustine should be prepared for administration as close as possible to the time of administration. Once diluted with sodium chloride or dextrose/sodium chloride, the final admixture is stable for 24 hours if Treanda® is used and for 2 days if Levact® is used and when stored refrigerated (2°C–8°C or 36°F–47°F) or for 3 hours when stored at room temperature (15°C–30°C or 59°F–86°F) and room light. Administration of bendamustine must be completed within this period.

For further details, see the local prescribing information for Treanda®/Levact®.

4.3.2 Study Treatment Dosage, Administration, and Compliance

4.3.2.1 Venetoclax

Study patients will self-administer venetoclax tablets by mouth daily. Each dose of venetoclax will be taken with approximately 240 mL of water within 30 minutes after the patient's first meal of the day (e.g., breakfast).

On days when both venetoclax and obinutuzumab are given, the order of study treatment administration will be venetoclax followed by obinutuzumab (there is no minimum time required between the administration of venetoclax and the start of the obinutuzumab infusion). If vomiting occurs within 15 minutes of taking venetoclax and all expelled tablets are still intact, another dose may be given and the second dose noted in the drug log. Otherwise, no replacement dose is to be given. In cases where a dose of venetoclax is missed or forgotten, the patient should take the dose as soon as possible, ensuring that the dose is taken within 8 hours of the missed dose with food. Otherwise, the dose should not be taken. Venetoclax must be stored according to labeled storage conditions. There is to be no break between cycles.

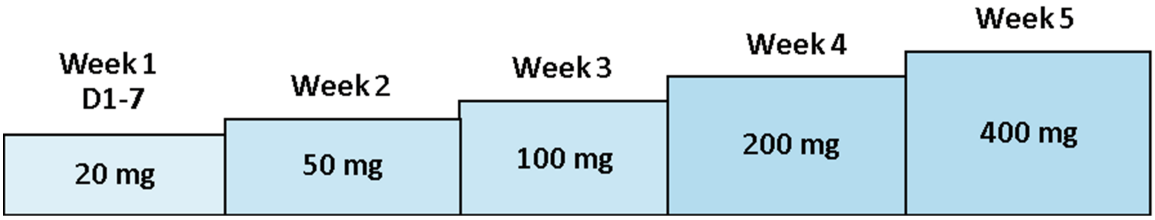
4.3.2.1.1 Venetoclax Ramp-Up Period

To mitigate potential serious complications of TLS, patients will require close clinical and laboratory monitoring during the venetoclax ramp-up period. See Section 5.1.7.1 for details of the TLS prophylaxis and monitoring guidelines.

All patients randomized to Arm A will start venetoclax treatment on Cycle 1, Day 22. They will start by receiving 20 mg of venetoclax daily for at least 7 days. Patients who demonstrate evidence of electrolyte abnormalities suggestive of TLS during the 24 hours following the initial 20-mg dose will receive appropriate treatment to resolution prior to receiving their next daily dose of venetoclax. See Appendix 12 for recommendations for initial management of electrolyte imbalances and prevention of TLS.

Venetoclax dose increases will then occur weekly, starting with 50 mg/day for 1 week followed by 100 mg/day for 1 week, 200 mg/day for 1 week, and the final dose of 400 mg/day for 1 week. All patients should receive any intended dose for at least 7 days before increasing to the next higher dose. The duration of the venetoclax ramp-up period will be 5 weeks as shown in Figure 3. Patients will then continue taking venetoclax 400 mg daily as directed by the investigator.

Figure 3 Venetoclax Dosing Scheme during the Ramp-Up Period



D = day.

Any dose modification of venetoclax should be noted on the venetoclax administration eCRF. Cases of overdose, medication error, drug abuse, or drug misuse, along with any associated adverse events, should be reported as described in Section 5.3.5.12.

Guidelines for venetoclax dosage modification and treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.6.

4.3.2.2 Obinutuzumab

4.3.2.2.1 Obinutuzumab: First Infusion

Obinutuzumab will be administered by IV infusion as an absolute (flat) dose of 1000 mg. Obinutuzumab may be administered in a single day; however, (as per local prescribing information), for the first administration, patients can receive their first dose of obinutuzumab over 2 consecutive days (split dose) in Cycle 1: 100 mg on Day 1 and 900 mg on Day 2. Two infusion bags should be prepared for the infusion on Days 1 and 2 (100 mg for Day 1 and 900 mg for Day 2). If the first bag is completed without

modifications of the infusion rate or interruptions, the second bag may be administered on the same day (no dose delay necessary, no repetition of premedication), provided that appropriate time, conditions, and medical supervision are available throughout the infusion. If there are any modifications of the infusion rate or interruptions during the first 100 mg, the second bag should be administered the following day. If patients require a delay of greater than 24 hours between the 100-mg and 900-mg infusions of obinutuzumab, see Section 4.3.2.2, Table 2, and the Obinutuzumab Investigator's Brochure regarding drug stability.

From a microbiological perspective, the prepared infusion solution should be used immediately. If it is not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C–8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Obinutuzumab should be prepared by a healthcare professional using aseptic technique. Do not shake the vial.

For storage conditions of the infusion bags see Section 4.3.1.2.

Obinutuzumab must be administered in a clinical setting (inpatient or outpatient). Full emergency resuscitation facilities should be immediately available, and patients should be under close supervision of the investigator at all times. Obinutuzumab should be given as a slow IV infusion through a dedicated line. IV infusion pumps (such as Braun Infusomat® Space) should be used to control the infusion rate of obinutuzumab. Do not administer as an IV push or bolus. After the end of the first infusion, the IV line should remain in place for at least 2 hours in order to be able to administer IV drugs if necessary. If no adverse events occur after 2 hours, the IV line may be removed. For subsequent infusions, the IV line should remain in place for at least 1 hour from the end of infusion, and if no adverse events occur after 1 hour, the IV line may be removed.

Hypotension may be expected with infusions; therefore, withholding of anti-hypertensive treatment should be considered for 12 hours prior to the obinutuzumab infusions, throughout the obinutuzumab infusions, and for the first hour after obinutuzumab infusions.

The first infusion of obinutuzumab should be started only after administration of prophylactic medications to mitigate the risks of IRRs and TLS and after pre-infusion laboratory values are checked.

The first obinutuzumab infusion will be administered at an initial rate of 25 mg over 4 hours. In the absence of IRRs/hypersensitivity, the rate of the infusion will be escalated in increments of 50 mg/hour every 30 minutes to a maximum rate of 400 mg/hour. If the start of infusion is delayed or adverse events occur that require

delaying or stopping the infusion such that infusion in a single day is not feasible, the infusion may be split and completed on the next day.

During the initial infusion of obinutuzumab, vital signs will be obtained pre-infusion, then every 15 minutes for 90 minutes, then every 30 minutes until the end of infusion, and then every 60 minutes until the infusion line is removed. If obinutuzumab is well tolerated without significant infusion-related symptoms, vital signs for subsequent infusions can be obtained every 30 minutes until the infusion line is removed.

Patients with pre-existing cardiac and/or pulmonary conditions or who have had a prior clinically significant cardiopulmonary adverse event with obinutuzumab should be monitored very carefully throughout the infusion and post-infusion period. Patients with prior clinically significant cardiac disease are excluded per eligibility criteria.

4.3.2.2.2 Prophylaxis for Infusion-Related Reactions

All obinutuzumab infusions should be administered 30−60 minutes after premedication with oral 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 100 mg dose on Cycle 1, Day 1 and the 900-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 $\geq$3 IRR with the previous infusion, to patients with lymphocyte counts $>25 \times 10^9$/L, and at the investigator's discretion.

For patients who do not experience Grade $\geq$3 infusion-related symptoms with their previous infusion (i.e., do not receive medication to treat the reaction symptoms and do not experience infusion interruption), 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 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.

4.3.2.2.3 Obinutuzumab TLS Prophylaxis

Prophylaxis of hyperuricemia and dehydration as well as laboratory monitoring are similar as described below for venetoclax dosing.

- Patients with a high tumor burden (absolute lymphocyte count [ALC] $\geq 25 \times 10^9$/L or bulky lymphadenopathy (nodal mass $\geq$10 cm) 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 Tumor Lysis Syndrome (see Appendix 12).
- Hematology and chemistry samples will be obtained prior to obinutuzumab dosing, 24 hours after the initiation of the obinutuzumab infusion (Cycle 1, Day 3 if split dose is given; see Appendix 1 for details). Discharge of patient is dependent upon review of the 24-hour laboratory values by the investigator or designee.

4.3.2.2.4 Subsequent Infusions of Obinutuzumab

If the patient's previous infusion of obinutuzumab was well tolerated (defined by an absence of Grade 2 IRRs during a final infusion rate of $\geq$100 mg/hour), subsequent infusions will be administered at an initial rate of 100 mg/hour and increased by 100 mg/hour increments at 30-minute intervals, as tolerated, to a maximum rate of 400 mg/hour (Table 2). 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 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 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. If the previous infusion rate was not well tolerated as defined above, instructions for the first infusion rate will be used.

On days when both venetoclax and obinutuzumab are given, the order of study treatment administration will be venetoclax followed by obinutuzumab (there is no minimum time required between the administration of venetoclax and the start of the obinutuzumab infusion).

Table 2 Administration of First Infusion of Obinutuzumab, if Split Over Two Days, and Subsequent Infusions of Obinutuzumab

First Infusion	Subsequent Infusions
On Day 1: All patients will receive an infusion at a fixed dose of 100 mg obinutuzumab administered at a fixed rate of 25 mg/hr with no increase in infusion rate (total duration of the first infusion: 4 hours). If the patient experiences an IRR, follow the protocol (Section 4.3.4 regarding treatment but at the resolution of symptoms, restart at half the initial rate (12.5 mg/hr). Increase to 25 mg/hr after an hour but do not increase further. If the patient tolerates 100 mg without dose modification and local label permits, the Investigator may continue to administer the remaining 900 mg on the same day at the infusion rate described below. **On Day 2**: All patients will receive 900 mg starting at the rate of 50 mg/hr, and the rate of the infusion will be escalated in increments of 50 mg/hr every 30-minutes to a maximum rate of 400 mg/hr. 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 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.	If the first infusion of obinutuzumab was well tolerated (defined by an absence of IRRs during a final infusion rate of ≥100 mg/hr), subsequent infusions will be administered at an initial rate of 100 mg/hr and increased by 100 mg/hr increments at 30-minute intervals, as tolerated, to a maximum rate of 400 mg/hr. 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 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. If the previous infusion rate was not well tolerated, as defined above, instructions for the first infusion rate will be used.

IRR = infusion-related reaction.

Any change in the infusion rate or interruption in the administration of obinutuzumab should be noted on the obinutuzumab administration eCRF. Cases of overdose, medication error, drug abuse, or drug misuse, along with any associated adverse events, should be reported as described in Section 5.3.5.12.

Guidelines for obinutuzumab treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.6.

4.3.2.3 Fludarabine, Cyclophosphamide plus Rituximab

4.3.2.3.1 Rituximab

Rituximab will be administered as an IV infusion before the administration of FC.

Rituximab will be administered to patients at 375 mg/m^2 IV on Cycle 1, Day 1 followed by 500 mg/m^2 on Day 1 of Cycles 2–6 (total of 6 infusions of rituximab).

The patient's body surface area (BSA) calculated at screening should be used to calculate the dose of rituximab throughout the study unless the patient's weight increases or decreases by >10% from screening (Appendix 13). In obese patients, there is no cap on BSA, and actual body weight, not adjusted weight, is recommended. Nonetheless, empiric dose adjustment is permitted in obese patients (obesity defined as body mass index ≥30 as measured in kilograms divided meters squared).

During the treatment period, rituximab must be administered to patients in a clinical (inpatient or outpatient) setting. Rituxan should be administered only by a healthcare professional with appropriate medical support to manage severe infusion reactions that can be fatal if they occur.

Rituximab should be administered as a slow IV infusion through a dedicated line. IV infusion pumps (such as the Braun Infusomat Space) should be used to control the infusion rate of rituximab. Administration sets with polyvinyl chloride, polyurethane, or polyethylene as a product contact surface and IV bags with polyolefin, polypropylene, polyvinyl chloride, or polyethylene as a product contact surface are compatible and can be used. Do not use an additional in-line filter because of potential adsorption. See Table 3 for instructions regarding first and subsequent infusions of rituximab.

After the end of each dose of rituximab, patients should be observed for 1 hour. If no adverse events occur after 1 hour, the IV line may be removed, or the central venous catheter may be de-accessed.

Rituximab should not be administered as an IV push or bolus. IRRs may occur.

Premedication consisting of acetaminophen, diphenhydramine (or other suitable antihistamine), and a single dose of hydrocortisone (up to 100 mg or an equivalent dose of methylprednisolone) may also be administered beginning with the first infusion. Premedication may attenuate IRRs. Because transient hypotension may occur during

rituximab infusion, consideration should be given to withholding antihypertensive medications for 12 hours prior to rituximab infusion.

Table 3 Administration of First and Subsequent Infusions of Rituximab

First Infusion (Cycle 1, Day 1)	Subsequent Infusions
Begin infusion at an initial rate of 50 mg/hr. If no infusion-related or hypersensitivity reaction occurs, increase the infusion rate in 50-mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. If an infusion reaction develops, stop or slow the infusion. Administer infusion-reaction medications and supportive care in accordance with institutional guidelines. If the reaction resolves, resume the infusion at a 50% reduction in rate (i.e., 50% of rate being used at the time that the reaction occurred).	If the patient experienced an infusion-related or hypersensitivity reaction during the prior infusion, begin infusion at an initial rate of 50 mg/hr and follow instructions for the first infusion. If the patient tolerated the prior infusion well (defined as an absence of Grade 2 reactions during a final infusion rate of ≥100 mg/hr), begin the infusion at a rate of 100 mg/hr. If no infusion reaction occurs, increase the infusion rate in 100-mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. If an infusion reaction develops, stop or slow the infusion. Administer infusion-reaction medications and supportive care in accordance with institutional guidelines. If the reaction resolves, resume the infusion at a 50% reduction in rate (i.e., 50% of rate being used at the time that the reaction occurred).

Note: A fast infusion is not allowed.

Any change in the infusion rate or interruption in the administration of rituximab should be noted on the rituximab administration eCRF. Cases of accidental overdose, medication error, drug abuse, or drug misuse, along with any associated adverse events, should be reported as described in Section 5.3.5.12.

Guidelines for rituximab treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.6.

4.3.2.3.2 Fludarabine

Fludarabine will be administered in a dosage of 25 mg/m² over 15–30 minutes IV on Days 1, 2, and 3 of each cycle.

Any dose modification of fludarabine should be noted on the fludarabine administration eCRF.

4.3.2.3.3 Cyclophosphamide

Cyclophosphamide will be administered in a dosage of 250 mg/m² over 15–30 minutes IV on Days 1, 2, and 3 of each cycle.

Fludarabine and cyclophosphamide can be administered immediately one after the other. The dose of fludarabine and/or cyclophosphamide may be capped for patients

with a BSA above a certain level (2.0 or higher) according to local practice and the investigator's clinical judgement. The dose of rituximab should not be capped.

Any dose modification of cyclophosphamide should be noted on the cyclophosphamide administration eCRF.

4.3.2.3.4 Bendamustine

Patients will receive bendamustine 90 mg/m^2 administered IV on 2 consecutive days of each 28-day cycle for 6 cycles, in combination with rituximab administered intravenously on Day 1 of each 28-day cycle for 6 cycles (see Section 4.3.2.3.1 for details of rituximab dosage and administration).

BSA will be calculated at screening and on Cycle 1, Day 1. The BSA calculated at screening should be used to calculate the dose of bendamustine throughout the study unless the patient's weight increases or decreases by >10% from screening. In obese patients, there is no BSA cap and actual body weight, not adjusted weight, is recommended. Nonetheless, empiric dose adjustment is permitted in obese patients (obesity defined as body mass index ≥30 kg/m^2).

Bendamustine will be administered over 30 to 60 minutes on Days 1 and 2 of each 28-day cycle for a total of 6 cycles. On days when rituximab and bendamustine are to be administered, rituximab will be administered before bendamustine.

Premedication with anti-emetics may be administered as per institutional guidelines (see Section 4.4.1). Granulocyte colony-stimulating factor (G-CSF) may be administered as primary prophylaxis in each cycle of therapy, per the American Society of Clinical Oncology (ASCO) guidelines or each site's institutional standards.

Any dose modification of bendamustine should be noted on the bendamustine administration eCRF.

Guidelines for bendamustine dosage modification and treatment interruption or discontinuation for patients who experience adverse events are provided in Section 5.1.6.2.2.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (venetoclax, obinutuzumab, fludarabine, cyclophosphamide, rituximab, and bendamustine) will be provided by the Sponsor where required by local regulations. The study site will acknowledge receipt of IMPs supplied by the Sponsor, using the IxRS, to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor (if supplied by the Sponsor)

with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.4 Non-Investigational Medicinal Products

4.3.4.1 Non-Investigational Medicinal Products for this Study

The non-investigational medicinal products (NIMPs) for this study are rasburicase, acetaminophen, paracetamol, prednisolone, dexamethasone, methylprednisolone, diphenhydramine, allopurinol, and ondansetron.

4.3.4.2 Rasburicase

Rasburicase (Fasturtec™ in Europe; Elitek™ in the United States) enzymatically converts uric acid in the blood to allantoin and hydrogen peroxide, thereby preventing the formation of uric acid crystals and potential renal blockage. It reduces uric acid levels within 4 hours both in pediatric and adult patients, and several studies confirm its safety, effectiveness, and tolerability both in the prevention and treatment of TLS, although the prevention of acute renal failure fails in over 25% of patients.

4.3.5 Continued Access to Venetoclax, Obinutuzumab, Fludarabine, Cyclophosphamide, Rituximab, and Bendamustine

The Sponsor will offer continued access to Roche IMPs (venetoclax, obinutuzumab, fludarabine, cyclophosphamide, rituximab, and bendamustine) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A patient will be eligible to receive Roche IMPs (venetoclax, obinutuzumab, fludarabine, cyclophosphamide, rituximab, and bendamustine) after completing the study if all of the following conditions are met:

- The patient has a life-threatening or severe medical condition and requires continued Roche IMP treatment for his or her well-being
- There are no appropriate alternative treatments available to the patient
- The patient and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A patient will not be eligible to receive Roche IMPs (venetoclax, obinutuzumab, fludarabine, cyclophosphamide, rituximab, and bendamustine) after completing the study if any of the following conditions are met:

- The Roche IMP is commercially marketed in the patient's country and is reasonably accessible to the patient (e.g., is covered by the patient's insurance or would not otherwise create a financial hardship for the patient)
- The Sponsor has discontinued development of the IMP or data suggest that the IMP is not effective for CLL
- The Sponsor has reasonable safety concerns regarding the IMP as treatment for CLL
- Provision of the Roche IMP is not permitted under the laws and regulations of the patient's country

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following website:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

4.4 CONCOMITANT THERAPY, PROHIBITED FOOD, AND ADDITIONAL RESTRICTIONS

4.4.1 Permitted Therapy

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 30 days prior to the screening period and until study drug completion or early discontinuation visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF. Patients who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination any time prior to, during, or after the study should be recorded on the concomitant medications eCRF.

Necessary supportive measures for optimal medical care will be given throughout the study according to institutional standards, including the use of growth factors (e.g., erythropoietin) if clinically indicated. G-CSF may be administered as primary prophylaxis in each cycle of therapy, per the ASCO guidelines (Smith et al. 2006) or each site's institutional standards.

Anti-emetic therapy may be instituted for any patient if clinically indicated. Bendamustine has a moderate risk of emesis (Cheson et al. 2010). It is recommended that bendamustine infusions be administered following premedication with a serotonin (5-HT3) antagonist (i.e., dolasetron, ondansetron, etc.) or per institutional practice.

4.4.1.1 Premedication before Rituximab

Premedication may attenuate IRRs. The following premedication is required prior to rituximab therapy:

- Acetaminophen (650–1000 mg) at least 30 minutes prior to the start of all infusions
- Diphenhydramine (25–50 mg) approximately 30 minutes prior to the start of the first infusion and mandatory for all subsequent infusions unless previous antibody infusions did not result in an IRR greater than NCI CTCAE Grade 1 and there was no interruption to the infusion (Appendix 10). (Another suitable antihistamine is also acceptable and must follow the preceding guidelines.)

A single dose of hydrocortisone (up to 100 mg or an equivalent dose of methylprednisolone) may also be administered with rituximab if this is the usual practice at the site.

Because transient hypotension may occur during rituximab infusion, consideration should be given to withholding antihypertensive medications for 12 hours prior to rituximab infusion.

4.4.1.2 Concomitant administration with SARS-CoV-2 Vaccine

In all instances, the SARS-CoV-2 vaccines should be given in accordance with the approved/authorized vaccine label and official immunization guidance. The SARS-CoV-2 vaccines (covering mRNA, inactivated virus, and replication deficient viral vector vaccines) are not live vaccines and are therefore permitted per protocol. The decision to administer a SARS-CoV-2 vaccine should be made on a per patient basis according to an individual's risk of COVID-19 disease, their general condition, as well as the severity and seriousness of the underlying disease/condition for which the patient is receiving study treatment together with the prevalence of local SAR-CoV-2 infection rates.

Venetoclax

Due to the immunosuppressive properties of venetoclax, patients who plan to receive any SARS-CoV-2 vaccine should do so prior to treatment initiation, unless a delay in administration of venetoclax is clinically unacceptable. If administration of a SARS-CoV2 vaccine is indicated during venetoclax treatment, consider monitoring the complete blood count to time with recovery of cytopenias, specifically lymphopenia.

Obinutuzumab

Due to the immunosuppressive properties of obinutuzumab, patients who plan to receive any SARS-CoV-2 vaccines should do so prior to treatment initiation. Currently, for SARS-CoV-2 vaccines that require two doses, it is recommended that patients should aim to complete vaccination (i.e., they should receive the second dose) at least 7 days before starting immunosuppressive therapy, in order to maximize vaccine efficacy.

Since it is possible that B-cell recovery could persist for 12–18 months following treatment with obinutuzumab, there is no strong rationale for withholding or delaying obinutuzumab therapy to allow immune recovery prior to vaccination.

Rituximab

Patients treated with MabThera/Rituxan may receive non-live vaccinations. However, with non-live vaccines response rates may be reduced. Patients who plan to receive any SARS-CoV-2 vaccines should do so prior to treatment initiation. At this time there is no experience with use of MabThera IV/SC in patients receiving vaccines based on RNA and DNA technology platforms and those using live viral vectors. Hence no recommendations concerning use of SARS-CoV-2 vaccines based on these technologies in patients receiving immunosuppressive therapy, including rituximab, can be made.

Fludarabine, Cyclophosphamide or Bendamustine

Roche is not the Marketing Authorisation Holder (MAH) for fludarabine, cyclophosphamide, or bendamustine. Therefore, please assess the benefit/risk to the patient, follow the recommendation from the respective label and if necessary, consult with the respective MAH for fludarabine, cyclophosphamide, or bendamustine.

4.4.2 Prohibited and Cautionary Therapy

Patients who require the use of any of the excluded therapies listed below will be discontinued from study treatment. Patients who are discontinued from study treatment will be followed for safety outcomes for 28 days following the patient's last dose of study drug, or until initiation of another anti-cancer therapy, whichever occurs first. All patients who discontinue study treatment for any reason should be followed until progression.

Use of the following therapies is prohibited during the study and 28 days prior to first dose of study drug:

- Immunotherapy
- Radiotherapy
- 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)

4.4.2.1 Drug-Drug Interaction

4.4.2.1.1 Patients Randomized to Arm A (Venetoclax + Obinutuzumab)

Excluded and cautionary medications for patients randomized to Arm A are shown in Table 4, and venetoclax dose reductions for strong and moderate CYP3A inhibitors are listed in Table 5. For lists of examples prohibited and cautionary medications, please see Appendix 3.

These above lists are not comprehensive, and the investigator should consult the applicable prescribing information for any concomitant medication when determining the drug-drug interaction potential.

Table 4 Excluded and Cautionary Medications for Patients Randomized to Arm A (Venetoclax + Obinutuzumab)

Excluded
Any live, attenuated vaccine including live, attenuated influenza vaccine (e.g., FluMist®): • Prohibited during treatment and within 28 days following the last dose of venetoclax. **Anti-cancer therapies, including chemotherapy, radiotherapy, or other investigational therapy (which includes targeted small molecule agents):** • Excluded 5 half-lives prior to first dose and throughout venetoclax administration. **Biologic agents (e.g., monoclonal antibodies) for anti-neoplastic intent:** • Excluded 8 weeks prior to first dose of study drug.
Excluded during the venetoclax ramp-up period and cautionary thereafter:
Strong and moderate CYP3A inhibitors: • Excluded 7 days prior to and during the venetoclax ramp-up period; consider alternative medications. If a patient requires use of these medications while they are receiving 400 mg per day of venetoclax, use with caution and reduce the venetoclax dose by 2-fold for moderate inhibitors and 4-fold for strong inhibitors during co-administration or refer to appropriate product label. After discontinuation of CYP3A inhibitor, wait for 3 days before venetoclax dose is increased back to the target dose. **Strong and moderate CYP3A inducers**: • Excluded 7 days prior to and during the venetoclax ramp-up period; consider alternative medications. If a patient requires use of these medications while they are receiving 400 mg per day of venetoclax, use with caution and contact the Medical Monitor for guidance.
Cautionary
• Warfarin (seek the guidance of the Medical Monitor; additional INR monitoring may also be required) • Weak CYP3A inducers • Weak CYP3A inhibitors • P-gp substrates • BCRP substrates • OATP1B1/1B3 substrates • P-gp inhibitors • BCRP inhibitors • OATP1B1/B3 inhibitors

Note: For examples of these medications see Appendix 5.

Table 5 Venetoclax Dose Reductions for Strong and Moderate CYP3A Inhibitors

Venetoclax Assigned Dose (mg)	Venetoclax Reduced Dose (mg)	
	Strong CYP3A Inhibitors	Moderate CYP3A Inhibitors
50	10	20
100	20	50
200	50	100
300	70	150
400	100 (70 for posaconazole in U.S. and countries with USPI-based approval	200

U.S. = United States; USPI = United States Prescribing Information.

If clinically indicated, anti-herpes and anti-pneumocystis prophylaxis should be considered. Although there is a potential for DDI, there are likely to be limited potential clinical effects; therefore, trimethoprim-sulfamethoxazole can be considered for pneumocystis prophylaxis, with close clinical monitoring.

4.4.2.2 Herbal Therapies

Concomitant use of herbal therapies is not recommended 14 days prior to, during the study, and for 28 days after the last dose of study treatment because their pharmacokinetics, safety profiles, and potential drug–drug interactions are generally unknown.

4.4.3 Prohibited Food

Use of the following foods by patients randomized to Arm A is prohibited for at least 3 days prior to initiation of venetoclax treatment, throughout venetoclax administration and for 28 days after last dose of study treatment.

Constituents of these foods have been shown to inhibit CYP3A4, the major enzyme responsible for the metabolism of venetoclax. Consumption of these foods could lead to increased venetoclax exposure:

- Grapefruit
- Grapefruit products
- Seville oranges (including marmalade containing Seville oranges)
- Star fruit

4.4.4 Other Prohibited Medication

Steroid therapy for anti-neoplastic intent with the exception of inhaled steroids for asthma, topical steroids, or replacement/stress corticosteroids are not permitted during the study at any time.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities should be performed and documented for each patient.

Patients will be closely monitored for safety and tolerability throughout the study. Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

4.5.1 Informed Consent Forms and Screening Log

Written informed consent for participation in the study must be obtained before performing any study-related procedures (including screening evaluations). Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. The investigator will maintain a detailed record of all patients screened to document eligibility or record reasons for screening failure, as applicable.

4.5.2 Procedures for Enrollment of Eligible Patients

All patients in the randomized part of the study must commence treatment within 7 days of randomization.

For patients who experience a Grade 3 or 4 adverse event between randomization and the start of study drug, the start of the treatment may be delayed for up to 28 days. If the Grade 3 or 4 event does not improve within 28 days, the patient will be withdrawn from the study.

After initial written informed consent has been obtained, all screening procedures and assessments have been completed, and eligibility has been established for a patient, the study site will obtain the patient's identification number and treatment assignment from an IxRS.

A Subject Enrollment and Identification Code List must be maintained by the investigator.

4.5.3 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures and prior SARS-CoV-2 infection), reproductive status, smoking history, and use of alcohol and drugs of abuse, will be recorded at baseline.

Prior SARS-CoV-2 vaccination, regardless of when it was administered, shall be reported at baseline. All other medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to initiation of study treatment will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded. *Any concomitant medications that are related to adverse events that occur up to 28 days post-last treatment, or related to adverse events and serious adverse events that are required per protocol to be reported indefinitely (e.g., drug-related serious adverse events, second primary malignancies, and SARS-CoV-2 infections) should be recorded.*

Demographic data will include age, sex, and self-reported race/ethnicity.

4.5.4 Physical Examinations

A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

At subsequent visits (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

4.5.5 Performance Status

Performance status (PS) will be measured using the Eastern Cooperative Oncology Group (ECOG) Performance Status Scale (see Appendix 14). It is recommended, where possible, that a patient's PS be assessed by the same person throughout the study.

4.5.6 Clinical Staging

During screening, patients should be assessed according to Binet Staging criteria. Staging is based on the number of involved areas, as defined by the presence of enlarged lymph nodes of >1 cm in diameter (by physical examination only) or organomegaly, and on whether anemia or thrombocytopenia are present.

Areas of involvement to be assessed for staging:

- Head and neck, including the Waldeyer ring (this counts as one area, even if more than one group of nodes is enlarged)
- Axillae (involvement of both axillae is counted as one area)
- Groins, including superficial femoral arteries (involvement of both groins is counted as one area)

- Palpable spleen
- Palpable liver (clinically enlarged)

Binet Stage A:
Hemoglobin $\geq$100 g/L (10 g/dL) and platelets $\geq 100 \times 10^9$/L and up to 2 areas involved

Binet Stage B:
Hemoglobin $\geq$100 g/L (10 g/dL) and platelets $\geq 100 \times 10^9$/L and 3–5 areas involved

Binet Stage C:
Hemoglobin $<$100 g/L (10 g/dL) and/or platelets $<100 \times 10^9$/L and irrespective of nodal or organ enlargement

4.5.7 Criteria for Initiation of First-Line Treatment

At the time of screening, the patient must satisfy at least 1 of the following criteria for active disease requiring treatment according to the iwCLL:

- Evidence of progressive marrow failure as manifested by the development or worsening of anemia and/or thrombocytopenia. Cutoff levels of Hb $<$10 g/dL or platelet counts $<100 \times 10^9$/L are generally regarded as indication for treatment. However, in some patients, platelet counts $<100 \times 10^9$/L may remain stable over a long period; this situation does not automatically require therapeutic intervention.
- Massive (i.e., $\geq$6 cm below the left costal margin) or progressive or symptomatic splenomegaly
- Massive nodes (i.e., $\geq$10 cm in the longest diameter) or progressive or symptomatic lymphadenopathy
- Progressive lymphocytosis with an increase of more than 50% over a 2-month period or lymphocyte doubling time (LDT) of less than 6 months. LDT can be obtained by linear regression extrapolation of absolute lymphocyte count obtained at intervals of 2 weeks over an observation period of 2–3 months; patients with initial blood lymphocyte counts of $<30 \times 10^9$/L may require a longer observation period to determine LDT. Factors contributing to lymphocytosis or lymphadenopathy other than CLL (e.g., infections, steroid administration) should be excluded.
- Autoimmune complications including anemia and/or thrombocytopenia poorly responsive to corticosteroids.
- Symptomatic or functional extranodal involvement (e.g., skin, kidney, lung, spine).
- Disease-related symptoms as defined by any of the following:
  - Unintentional weight loss of $\geq$10% within the previous 6 months
  - Significant fatigue (ECOG PS 2 or worse; inability to work or perform usual activities)
  - Fevers $>$100.5°F or 38.0°C for $\geq$2 weeks without other evidence of infection
  - Night sweats for $>$1 month without evidence of infection

Hypogammaglobinemia, monoclonal paraproteinemia, or oligoclonal paraproteinemia does not by itself constitute a basis for initiating therapy. However, it is recommended to assess the change in these protein abnormalities, if patients are treated. Also, patients with CLL may present with a markedly elevated leukocyte count; however, leukostasis rarely occurs in patients with CLL. Therefore, the absolute lymphocyte count should not be used as the sole indicator for treatment.

4.5.8 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

4.5.9 MRD Response Criteria

4.5.9.1 MRD Evaluation

For the evaluation of MRD as the primary endpoint of this study, MRD response rate will be determined as the proportion of patients with MRD-negativity measured in the PB at Month 15 using NGS using a cutoff of $<10^{-4}$. MRD was considered negative if the result was <1 CLL cell in 10,000 leukocytes.

For the evaluation of MRD as part of the secondary endpoints, assessment of MRD in BM is also required in patients with CR or PR and will be used to determine MRD response rate in BM at end of treatment response visit (8–12 weeks after last dose of FCR/BR (~9 months) vs. 8–12 weeks after last dose of VEN + G (~15 months). Additionally, MRD response rates in the PB at completion of combination treatment assessment (Cycle 9, Day 1 or 8–12 weeks after last IV infusion) will also be determined. MRD response rate in PB in patients with a CR/CRi at Month 15 will also be evaluated.

4.5.9.2 Additional Exploratory Assessments of MRD Response

For the evaluation of MRD as part of the exploratory endpoints, MRD response rate in PB using a cutoff of $<10^{-4}$ will be evaluated at each MRD assessment timepoint. Furthermore, MRD response rate will be evaluated at each timepoint by NGS using additional cutoffs ($<10^{-5}$ and $<10^{-6}$) within the limit of sensitivity of this methodology.

4.5.10 Tumor and Response Evaluations

Baseline tumor assessments must be assessed a maximum of 4 weeks before randomization. Given that response is a secondary endpoint of the trial and PD will be followed by physical examination, CT scans (e.g., thorax, neck, abdomen, pelvis) performed prior to screening as part of the regular clinical work-up of the patient will be allowed up to 8 weeks before randomization. This is to prevent the re-irradiation of patients who have recently undergone a CT scan. However, a CT scan must be

performed within the 4-week period prior to randomization for those patients with signs of rapidly progressing disease at screening.

All patients should be continuously monitored for PD during the treatment period. At any time, if progression is confirmed, it should be clearly documented in the eCRF.

In Arm A (VEN+G), a full response assessment of hematological status will also include a CT scan and a full physical examination to assess any lymphadenopathy and hepato/splenomegaly and BM biopsy in responding patients (CR/PR), will occur 8–12 weeks after the last dose of venetoclax at the end of Cycle 12 or 8–12 weeks after the last dose of drug received in the case of early termination. All other follow-up tumor assessments will be clinical assessments conducted within ±14 days for the 3-month assessments and within a month for the 6-month assessments of the scheduled visits described in Appendix 1.

In Arm B (FCR/BR), a full response assessment of hematological status will also include a CT scan and a full physical examination to assess any lymphadenopathy and hepato/splenomegaly and BM biopsy in responding patients (CR/PR), will occur 8–12 weeks after the last dose of study treatment. All other follow-up tumor assessments will be clinical assessments conducted within ±14 days of the 3-month assessments and within a month of the 6-month assessments of the scheduled visits described in Appendix 1.

At each follow-up visit, patients will be assessed for response/progression by physical examination and laboratory tests. If at any time during follow-up when clinical or laboratory findings suggest that the response may have improved from SD to PR or PR to CR, a scan may be performed to confirm the response.

Imaging is not routinely required to determine PD because objective evidence of PD is most often documented by measurement of elevated peripheral CLL cells. However, when PD cannot be documented by increasing PB counts, imaging is required to document PD as detected by physical examination or suspected based on symptoms.

Unless disease progression is confirmed, the patient is withdrawn due to toxicity, the patient withdraws consent, or the patient has died, patients should receive a maximum of 12 cycles of venetoclax, 6 cycles of obinutuzumab (Arm A), or 6 cycles of FCR/BR (Arm B). If there is suspicion of PD given clinical or laboratory findings before the next scheduled assessment, an unscheduled assessment should be performed.

The end of treatment response assessment must be performed 12 weeks after the last study treatment (i.e., no earlier than 8 weeks after the end of study treatment). For those patients with a CR and PR confirmed by laboratory and physical examination and CT scan, a BM aspirate and biopsy must also be performed. The BM aspirate sample will also be tested for MRD status by NGC.

All other follow-up tumor assessments will be done within ±14 days for the 3-month assessments and within a month for the 6-month assessments of the scheduled visits described in Appendix 1.

If a patient inadvertently misses a prescribed tumor evaluation or a technical error prevents the evaluation, the patient may continue treatment until the next scheduled assessment unless signs of clinical progression are present.

4.5.11 Response Criteria

4.5.11.1 Complete Response

To be considered to have a CR, patients are required to meet all of the following criteria*, which should be sustained for at least 8 weeks*:

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

  Hepatomegaly considered to be due to CLL disease is defined as >3 cm below costal margin.
- No splenomegaly by physical examination and CT scan as determined by measurement below the costal margin

  A spleen size of ≥13 cm is considered to be related to CLL disease.
- Absence of disease or constitutional symptoms (B-symptoms)
- Blood counts above the following values:
  - Neutrophils $\geq 1.5 \times 10^9$/L [1500/μL] (without growth factors)
  - Platelets $\geq 100 \times 10^9$/L [100,000/μL] (without platelet transfusion or growth factors)
  - Hemoglobin ≥110 g/L [11 g/dL] (without blood transfusions or erythropoietin).
- BM at least normocellular for age, ≤30% of nucleated cells being lymphocytes; lymphoid nodules should be absent

  BM aspirate and biopsy should be performed 8-12 weeks after the last treatment when clinical and laboratory results listed above demonstrate that a CR/cytopenic CR has been achieved. If the BM is hypocellular, a repeat determination should be made in 4 weeks or when PB counts have recovered. However, this time interval should not exceed 6 months. Patients who are otherwise in a complete remission but have BM nodules that can be identified histologically should be considered to have a PR. Immunohistochemistry should be performed to define whether these nodules are composed of primarily T cells, lymphocytes other than CLL cells, or CLL cells.

4.5.11.2 Complete Response and Incomplete Bone Marrow Recovery

For patients who fulfil the criteria for CR (including BM) but who have persistent cytopenia, anemia, thrombocytopenia, or neutropenia, the marrow evaluation described above should be performed with scrutiny and should not show any clonal infiltrate.

4.5.11.3 Partial Response

To be considered to have a PR, patients must exhibit the following features for at least 8 weeks:

- ≥50% decrease in PB lymphocyte count from the pre-treatment value

AND either

- ≥50% reduction in lymphadenopathy (sum of longest diameter of up to 6 largest lymph nodes by physical exam and 50% reduction in the sum of product of the diameter of up to 6 of the largest lymph nodes measured by CT scan)

  There can be no increase in any node and no new enlarged lymph node (diameter ≥15 mm). In small lymph nodes (<15 mm in diameter), an increase of less than 25% is not considered to be significant.

OR

- ≥50% reduction of liver enlargement, or normalization in size, if enlarged at baseline, as assessed by physical examination.

OR

- ≥50% reduction of spleen enlargement, or normalization in size, if enlarged at baseline, as assessed by physical examination. When assessed by CT, scan spleen size must have regressed by ≥50% in length beyond normal.

AND at least one of the following

- Neutrophil count $>1.5 \times 10^9$/L (1500/μL) (without growth factors) or ≥50% increase of pretreatment value
- Platelet count $>100 \times 10^9$/L (100,000/μL) (without platelet transfusion or growth factors) or ≥50% increase of pretreatment value
- Hemoglobin concentration >110 g/L (11 g/dL) (without blood transfusions or erythropoietin) or ≥50% increase of pretreatment value

4.5.11.4 Progressive Disease

PD that occurs during or after therapy will be characterized by at least one of the following, when compared with nadir values:

- Increase of ≥50% in the absolute number of circulating lymphocytes, to at least 5×10^9/L.

  Interim cycle absolute lymphocyte counts may not be stable as certain therapies may cause lymphocytosis. In the setting of therapy with such agents, an increase in blood lymphocyte count by itself does not uniformly indicate an increased tumor burden but may reflect redistribution of leukemia cells from lymphoid tissues to the blood. Therefore, please use caution and clinical

interpretation when assessing a potential PD in the context of interim cycle absolute lymphocyte count.

- Appearance of new palpable lymph nodes (>15 mm in longest diameter) or any new extra nodal lesion (regardless of size)

  Transient increases of lymph node size during treatment with novel inhibitors may occur and should not be counted as PD.

- Increase of ≥50% in the longest diameter of any previous site of clinically significant lymphadenopathy (i.e., any lesion >15 mm)
- An increase in the spleen size by ≥50% or the *de novo* appearance of splenomegaly

  In the setting of splenomegaly, the splenic length must increase by ≥50% of the extent of its prior increase beyond baseline (e.g., a 15 cm spleen must increase to ≥16 cm). If no prior splenomegaly was observed at baseline of if splenomegaly has resolved with treatment, the spleen must increase by at least 2 cm from baseline.

- An increase in the liver size of ≥50% of the extend of enlargement of the liver below the intercostal margin defined by palpation, or the de novo appearance of hepatomegaly

  Given the impact of numerous medical conditions, liver size by physical examination or by CT scan is not a reliable measure of hepatic involvement by CLL and should only be counted if hepatomegaly is clearly attributable to lymphoid involvement.

- Transformation to a more aggressive histology (e.g., Richter syndrome or pro-lymphocytic leukemia with >55% prolymphocytes)

  Whenever possible, this diagnosis should be supported by lymph node biopsy.

- After treatment, the progression of any cytopenia (unrelated to autoimmune cytopenia) as documented by:
  - A decrease of hemoglobin levels by more than 20 g/L (2 g/dL) or to <100 g/L (10 g/dL), OR
  - A decrease of platelet counts by >50% or to $<100 \times 10^9$/L (100,000/μL), OR
  - A decrease of neutrophil counts by >50% or to $<1 \times 10^9$/L that occurs no earlier than 12 weeks after end of therapy defines progression if the marrow biopsy demonstrates an infiltrate of clonal CLL cells.

4.5.11.5 Stable Disease

Patients who have not achieved a CR or a PR, or who have not exhibited PD, will be considered to have SD (which is equivalent to a nonresponse).

4.5.12 Other Disease-Specific Assessments

Details on the required hematology panel necessary to assess response are provided in Section 4.5.13.

4.5.12.1 Bone Marrow

A BM aspirate and biopsy are generally not requested at study entry. Nevertheless, CLL is a disease of the BM, and it may be appropriate to evaluate a major site of involvement. In such cases, the aspirate smear must show ≥30% of all nucleated cells to be lymphoid. The percentage of atypical cells (e.g., pro-lymphocytes) should be ≤55%.

A BM aspirate and biopsy should be performed at least 12 weeks after the last treatment when clinical and laboratory results listed above demonstrate that a CR/CRi has been achieved. If the BM is hypocellular, a repeat determination should be made in 4 weeks or when PB counts have recovered. However, this time interval should not exceed 6 months. A marrow biopsy should be compared to a pre-treatment marrow if available. Patients who are otherwise in a complete remission, but BM nodules can be identified histologically should be considered to have PR. Immunohistochemistry should be performed to define whether these nodules are composed of primarily T cells, lymphocytes other than CLL cells, or CLL cells.

4.5.12.2 Lymphadenopathy and Hepatomegaly/Splenomegaly

A full physical examination should be performed to assess the extent of disease involvement. Up to a maximum of the 6 largest palpable lymph nodes, hepatomegaly, and splenomegaly should be recorded in the eCRF.

A CT scan (i.e., thorax, neck, abdomen, pelvis) will be performed at screening. Up to a maximum of the 6 largest bi-dimensional lesions should be reported in the eCRF. Note that these may be different from those lesions assessed by physical examination. A repeat CT scan of involved sites at baseline will be performed in patients who satisfy the clinical criteria for PR or CR after the end of treatment. When PD is detected by physical examination in the absence of any objective hematological progression, a CT scan of the involved nodes will be performed. In addition, CT scans may be performed at any time at the investigator's discretion or if clinically indicated. In patients with severe renal insufficiency at screening, CT contrast should be used according to local practice. If necessary, magnetic resonance imaging (MRI) scans can be performed. CT without contrast is not recommended except for patients that develop renal insufficiency during treatment and have previously been assessed by CT scan. It is obligatory to use the same imaging technique for all tumor evaluations.

4.5.12.3 B-Symptoms

B-symptoms are considered to be constitutional symptoms defined as any one or more of the following disease-related symptoms or signs:

- Unintentional weight loss of 10% or more within the previous 6 months
- Significant fatigue (i.e., ECOG PS 2 or worse; inability to work or perform usual activities)
- Fevers >100.5°F or 38.0°C for ≥2 weeks without other evidence of infection

- Night sweats for >1 month without evidence of infection

B-symptoms should not be reported as adverse events. Worsening is generally considered a symptom (but not an objective criterion) of progression.

4.5.13 Laboratory, Biomarker, and Other Biological Samples

The following laboratory tests will be performed at the study site's local laboratory for analysis.

4.5.13.1 During Screening Only (Days –28 to –1)

- Lymphocyte count and immunophenotyping (this is to be performed centrally, but in exceptional circumstances [e.g., sample could not be shipped in time to the central laboratory], it can be performed locally)
- Assessment of major site involvement using BM aspirate or biopsy at baseline
- Hematology (hemoglobin, WBC with differentials, platelets)
- Coagulation (aPTT, PT, INR)
- Biochemistry (biochemistry and electrolytes [including lactate dehydrogenase, sodium, potassium, calcium, phosphorus, chloride, bicarbonate, blood urea nitrogen, uric acid, aspartate aminotransferase, alanine aminotransferase, total bilirubin, serum creatinine, alkaline phosphatase, total protein, albumin])
- Coombs test (indirect and direct Coombs test should be repeated if positive)
- CrCl (should be estimated using the standard Cockcroft-Gault formula for calculated CrCl)

  A 24-hour urine collection may be undertaken to determine CrCl in patients with a borderline value for eligibility.
- Serum pregnancy test (in women of childbearing potential only)

  If a serum pregnancy test has not been performed 14 days prior to dosing, a urine pregnancy test must be performed 7 days prior to dosing. If the test result is positive, patient dosing will be postponed until the patient's status is confirmed by a serum pregnancy test.
- Immunoglobulins (total IgA, IgG, IgM)
- A dipstick urinalysis for proteinuria will be performed at screening and follow-up for all patients.
- Hepatitis B (HBsAg) status in serum and HBcAb status in serum (using the same sample) for patients who were HBsAg-negative
- In HBcAb-positive patients, hepatitis B viral DNA (HBV DNA) and HCV RNA will be assessed

4.5.13.2 Further Assessments

Patients who are HBsAg-negative/HBcAb-positive with undetectable serum HBV DNA should be monitored closely (every month) for HBV DNA by a real-time PCR

quantification assay (lower limit of detection: approximately 10 IU/mL) until at least 12 months after the last treatment cycle. If the HBV DNA assay becomes positive, patients should pre-emptively be treated with a nucleoside analog (i.e., lamivudine) for at least 12 months after the last cycle of therapy or be referred to a specialist, such as a gastroenterologist for management. This may not be relevant in all participating countries.

If a BM aspirate and/or biopsy is performed as part of the routine clinical work-up for the patient, this information should be collected in the eCRF. A BM aspirate or biopsy is recommended in patients with an absolute neutrophil count (ANC) $<1.5\times10^9$/L or platelets $<75\times10^9$/L to demonstrate BM infiltration by CLL as the cause of cytopenia or may be taken during the study to elucidate the cause of cytopenia.

Samples for the following laboratory tests will be sent to one or several central laboratories for analysis as per instructions in the laboratory manual:

MRD measurements (in peripheral blood and in bone marrow aspirate [when applicable]):

- MRD by Next Generation Sequencing:
  - Approximately 4-mL whole blood will be collected during screening (prior to randomization) and approximately 10 mL whole blood at repeated timepoints during treatment and follow-up (as per the schedule of assessments; see Appendix 1 and Appendix 2) A patient will not be randomized until a viable sample has been collected and received at the testing laboratory. If a sample is found not to be viable, a further sample will be requested.
- MRD by ASO-PCR
  - Approximately10-mL whole blood will be collected during screening (prior to randomization) and at repeated timepoints during treatment and follow-up (as per the schedule of assessments; see Appendix 1 and Appendix 2). The baseline CLL count required for the ASO-PCR assay will be determined by flow cytometry for B-CLL cell count at screening (described below). The 'paired' MRD ASO-PCR and B-CLL cell count whole blood sample collections are required for a patient to be randomized. A patient will not be randomized until a viable sample has been collected and received at the testing laboratory. If either the MRD ASO-PCR and/or B-CLL cell count sample is found not to be viable, a further sample set will be requested *(*i.e., the MRD ASO-PCR and B-CLL cell count whole blood sample*)* are required to be collected again.

Lymphocyte counts and immunophenotyping for confirmation of diagnosis, IRR prediction and safety monitoring:

- B-CLL cell count by flow cytometry
  - Approximately 6-mL whole blood will be collected during screening (prior to randomization) and at subsequent visits during follow up (see Appendix 1 and

Appendix 2) for the quantification of CLL cells (namely CD5, CD19, CD20, CD23, CD79b, kappa, lambda)

- Lymphocyte subset counts by flow cytometry
  - Approximately 5-mL whole blood will be collected during screening (prior to randomization) and at subsequent visits during follow up (see Appendix 1 and Appendix 2) for B cells (CD19+) and T cell subsets (CD3+, CD4+, CD8+) and NK cells (CD16+, CD56+)
- Additional immunophenotyping samples may be collected if required for safety reasons at the discretion of the physician

Serum parameters (β2 microglobulin):

- Approximately 10-mL whole blood (approximately 5-mL serum) will be taken at baseline for the testing of serum parameters (including, but not limited to, β2 microglobulin)

CLL prognostic factors, genetic and expression analysis:

- Approximately 20 mL whole blood will be taken during screening (prior to randomization) and at other applicable visits

  Analysis will include but is not limited to:

  - Cytogenetic aberrations by FISH (13q, 11q, 17p, trisomy [12]), TP53 mutations, and somatic hypermutation by analysis of IGHV mutational status.
  - Analysis of tumor specific (non-inherited) genetic aberrations by next generation sequencing of genes, including commonly mutated genes in CLL (including but not limited to ATM, TP53, NOTCH1, SF3B1, BIRC3)
  - Genomic complexity by aCGH
  - RNA expression to understand mechanism of action and resistance of Venetoclax treatments (including but not limited to BCL2 family, genes regulating apoptosis, and disease relevant markers)
  - DNA isolation for evaluation of gene expression and mutation status of somatic genetic aberrations in Bcl 2 family genes (i.e., genes regulating apoptosis as well as other CLL disease related markers)

The analysis will include ctDNA measurement in plasma

- Approximately 10-mL whole blood will be collected during screening (prior to randomization), at Month 15 and at time of progression (early termination, if applicable) (see Appendix 1 and Appendix 2)

Pregnancy Test: All women who are not postmenopausal (≥ 12 months of non-therapy-induced amenorrhea) or surgically sterile will have a serum pregnancy test performed monthly while receiving study drug and at the Treatment Completion/Early Termination visit.

Note: sample shipment for central laboratory assessments must be made to designated laboratories as per instructions in the laboratory manual.

Total blood loss during screening is approximately100 mL (7 tablespoons). Total blood loss during the study is approximately 1.3 L (86 tablespoons) but varies slightly, depending upon TLS risk assessment. All samples will be destroyed at the end of analysis or at the end of the study, unless otherwise specified (see Section 4.5.17).

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

Unless the patient gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.17), biological samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exception:

- Blood, plasma, and serum samples and any derivatives thereof (e.g., PBMCs, DNA, RNA, proteins, and peptides) collected for biomarker research will be destroyed no later than 5 years after the final Clinical Study Report has been completed. However, the storage period will be in accordance with the Institutional Review Board/Ethics Committee (IRB/EC) -approved Informed Consent Form and applicable laws (e.g., health authority requirements).

When a patient withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the patient specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis, including data on genomic variants, will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

4.5.14 Electrocardiograms

Single ECG recordings will be obtained as outlined in the Schedule of Assessments (Appendix 1 and Appendix 2) and may be obtained at unscheduled timepoints as indicated.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be

performed after the patient has been resting in a supine position for at least 10 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws) and should not be obtained within 3 hours after any meal. Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation), should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. Digital recordings will be stored at site. The following should be recorded in the appropriate eCRF: heart rate, RR interval, QRS interval, PR duration, uncorrected QT interval, and corrected (Fridericia's correction) QTc interval (QTcF) on the basis of the machine readings of the individual ECG tracings. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF. If considered appropriate by the Sponsor, ECGs may be analyzed retrospectively at a central laboratory.

If, at a particular postdose timepoint, the mean QTcF is >500 ms and/or >60 ms longer than the baseline value, another ECG must be recorded, ideally within the next 5 minutes, and ECG monitoring should continue until QTcF has stabilized on two successive ECGs. The Medical Monitor should be notified. Standard-of-care treatment may be instituted per the discretion of the investigator. A decision on study drug discontinuation should be made (Section 5.1.6). The investigator should also evaluate the patient for potential concurrent risk factors (e.g., electrolyte abnormalities, co-medications known to prolong the QT interval, severe bradycardia).

4.5.15 Patient-Reported Outcome (PRO) Assessments and Health Economic Assessments

PRO data will be elicited from the patients in this study to more fully characterize the clinical profile of the combination of VEN+G compared with FCR/BR in patients with previously with previously untreated CLL without del(17p) or *TP53* mutation. The PRO instruments, translated as required into the local language, will be distributed by the investigator staff and completed in their entirety by the patient at specified timepoints during the study. To ensure instrument validity and that data standards meet health authority requirements, PRO questionnaires should be self-administered at the investigational site prior to the completion of other study assessments and the administration of study treatment.

4.5.15.1 MDASI-CLL

The MD Anderson Symptom Inventory for Chronic Lymphocytic Leukemia (MDASI-CLL) (see Appendix 5) is a cancer-related multi-symptom, valid, and reliable self-report questionnaire for clinical and research use. It consists of 25 items over two scales that assess symptom severity and symptom interference with different aspects of a patient's life. Thirteen items (i.e., pain, fatigue, nausea, disturbed sleep, distressed, shortness of

breath, remembering things, lack of appetite, drowsy, dry mouth, sadness, vomiting, and numbness or tingling) from the original MDASI-CLL ask patients to rate how severe the symptoms were when “at their worst” in the last 24 hours. An additional six items ask patients to rate how much the symptoms have interfered with six areas of function (i.e., general activity, walking, work, mood, relations with other people, and enjoyment of life) in the last 24 hours. Additionally, the MDASI-CLL contains a tumor-specific module to assess additional disease-specific symptoms (night sweats, fevers and chills, lymph node swelling, diarrhea, bruising easy or bleeding, and constipation). The MDASI-CLL items are rated 0−10 with 0 indicating that the symptom is either not present or does not interfere with the patient’s activities and 10 indicating that the symptom is “as bad as you can imagine” or “interfered completely” with the patient’s life. The MDASI-CLL takes approximately 5 minutes to complete. The MDASI-CLL assessment will be conducted during Day 1 of each treatment cycle. The MDASI-CLL will be administered at all follow-up visits until new leukemia treatment (NLT).

4.5.15.2 EORTC QLQ-C30

The European Organization for the Treatment and Research of Cancer Quality of Life (EORTC QLQ-C30) (see Appendix 6) is a validated and reliable self-report measure (Aaronson et al. 1993; Fayers et al. 1999; Fitzsimmons et al. 1999) consisting of 30 questions incorporated into five functional scales (physical, role, cognitive, emotional, and social scales), three symptom scales (fatigue, pain, nausea, and vomiting scales), and a global health status/global quality-of-life scale. The remaining single items (dyspnea, appetite loss, sleep disturbance, constipation, and diarrhea) assess the additional symptoms experienced by patients with cancer and the perceived financial burden of treatment. The EORTC QLQ-C30 assessment will be conducted during Day 1 of each treatment cycle. The EORTC QLQC30 will be administered at all follow-up visits until NLT.

4.5.15.3 EQ-5D-5L

The EQ-5D-5L is a validated self-report health status questionnaire that is used to calculate a health status utility score for use in health economic analyses (EuroQol Group 1990; Brooks 1996; Herdman et al. 2011; Janssen et al. 2013) (see Appendix 7). This questionnaire is a generic, preference-based health utility measure with two components: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a visual analogue scale (VAS) that measures health state. The EQ-5D-5L is designed to capture the patient's current health status. Published weighting systems allow for creation of a single composite score of the patient's health status.

The EQ-5D-5L will be utilized in this study to estimate quality adjusted life years (QALY) for economic modeling. The EQ-5D-5L also contains a visual analog scale (VAS) to assess the patient’s overall health. The EQ-5D-5L questionnaire takes 5 minutes or less to complete, and assessments are made on Day 1 of each treatment cycle at the same time as the MDASI-CLL and QLQ-C30.

4.5.16 Data Collection Methods for Clinical Outcome Assessments

PRO instruments will be self-administered at the clinic at specified timepoints during the study (see schedule of activities in Appendix 1 and Appendix 2). At the clinic, instruments will be administered before the patient receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment, unless otherwise specified.

PRO instruments, translated into the local language as appropriate, will be completed through use of an electronic device provided by the Sponsor. The device will be preprogrammed to enable the appropriate instruments to be administered in the correct order at each specified timepoint. The electronic device and instructions for completing the instruments electronically will be provided by the site staff. The data will be transmitted to a centralized database maintained by the electronic device vendor. The data will be available for access by appropriate study personnel.

A web-based platform will be used as back-up to collect PRO data in the event of electronic device malfunction or unavailability.

During clinic visits, PRO instruments should be administered as outlined below:

- Patients' health status should not be discussed prior to administration of the instruments.
- Sites must administer the official version of each instrument, as provided by the Sponsor. Instruments must not be copied from the protocol.
- Sites should allow sufficient time for patients to complete the instruments, estimated to be 20 minutes at each specified visit.
- Sites should administer the instruments in a quiet area with minimal distractions and disruptions.
- Patients should be instructed to answer questions to the best of their ability; there are no right or wrong answers.
- Site staff should not interpret or explain questions, but may read questions verbatim upon request.
- Patients should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.

4.5.17 Optional Samples for Research Biosample Repository

4.5.17.1 Overview of the Research Biosample Repository

The Research Biosample Repository (RBR) is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

Samples for the RBR will be collected from patients who give specific consent to participate in this optional research. RBR samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

4.5.17.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.17) will not be applicable at that site.

4.5.17.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to venetoclax and apoptosis, diseases, or drug safety:

- Leftover blood, BM aspirate, serum, plasma, PBMC, and any derivatives thereof (e.g., DNA, RNA, proteins, peptides)

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via whole genome sequencing (WGS), whole exome sequencing (WES), or other genomic analysis methods. Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches or new methods for monitoring efficacy and safety or predicting which patients are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR samples are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.17.4 Confidentiality

RBR samples and associated data will be labeled with a unique patient identification number.

Patient medical information associated with RBR samples is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Given the complexity and exploratory nature of the analyses of RBR samples, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

Data generated from RBR samples must be available for inspection upon request by representatives of national and local health authorities, and Sponsor monitors, representatives, and collaborators, as appropriate.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of the RBR data will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

4.5.17.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RBR. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RBR samples. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

In the event of an RBR participant's death or loss of competence, the participant's samples and data will continue to be used as part of the RBR research.

4.5.17.6 Withdrawal from the Research Biosample Repository

Patients who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the patient. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a patient wishes to withdraw consent to the testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the patient's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a patient wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and patient number to the following email address:

global.rcr-withdrawal@roche.com

A patient's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a patient's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

4.5.17.7 Monitoring and Oversight

RBR samples will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system, to ensure compliance with data confidentiality as well as adherence to authorized use of samples as specified in this protocol and in the Informed Consent Form. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RBR for the purposes of verifying the data provided to the Sponsor. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RBR samples.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Patients must permanently discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient (including high-grade toxicities when continuing treatment is deemed detrimental)
- Pregnancy
- Patient non-compliance
- Disease progression

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF. Patients who discontinue study treatment prematurely will not be replaced.

Patients will return to the clinic for a treatment completion or treatment discontinuation visit 28 (±7) days after the final dose of study drug (see Appendix 1, Appendix 2, and Appendix 3 for additional details).

After disease progression, information on survival follow-up and new anti-cancer therapy will be collected via telephone calls, patient medical records, and/or clinic visits approximately every year until death or study completion (unless the patient withdraws consent or the Sponsor terminates the study).

4.6.2 Patient Discontinuation from the Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time.

Reasons for patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent
- Study termination or site closure
- Adverse event
- Loss to follow-up
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study will not be replaced.

If a patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status.

4.6.3 Study Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory

- Insufficient management of TLS

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.6.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Venetoclax is currently approved in various countries/regions including the United States (US), the European Union (EU), Canada, Switzerland, and Australia for the treatment of adult patients with R/R CLL either as monotherapy or in combination with rituximab. In 2019, venetoclax was also approved by the FDA for the treatment of previously untreated CLL or SLL patients in combination with obinutuzumab (see Venetoclax US Prescribing Information 2019).

Clinical experience with venetoclax in CLL is based on several ongoing Phase I, II, and III studies evaluating monotherapy or combination regimens in relapsed/refractory or previously untreated patients (see Venetoclax Investigator's Brochure). The safety plan for this study is designed to ensure patient safety and will include specific eligibility criteria and monitoring assessments.

5.1.1 Risks Associated with Venetoclax

Clinical experience gained thus far with venetoclax has demonstrated that it is generally well tolerated, and toxicities appear to be mostly manageable and/or reversible; see the Venetoclax Investigator's Brochure for more information.

On the basis of clinical data to date, the following known and potential risks with venetoclax are described below. Guidelines around the management of these risks through dose and schedule modifications are described in Section 5.1.6.

5.1.1.1 Tumor Lysis Syndrome

In patients with CLL, TLS is a rare, but potentially life-threatening event. TLS is characterized by cytolysis leading to hyperkalemia, hyperphosphatemia, hyperuricemia

and/or hypocalcemia, as defined by the Howard criteria (Appendix 15). Analyses of patients treated with venetoclax monotherapy have reported TLS frequencies of up to 5%. TLS prophylaxis and monitoring measures implemented in all protocols involving patients with CLL/SLL since May 2013, including initiation of therapy at the 20-mg dose and more gradual, five-step−dose ramp-up, have effectively reduced the severity and risk of TLS in patients with CLL/SLL.

In the BO25323/CLL14 study, in which elderly, unfit patients were randomized to receive 12 cycles of VEN+G or GClb, impaired renal function was reported for most patients at study entry. Therefore, patients in Study BO25323/CLL14 were particularly at risk of TLS. However, TLS was a very rare finding in this study. The incidence of adverse events of TLS was 2.3% in the GClb arm compared with 1.4% in the VEN+G arm. In the VEN+G arm, all events occurred prior to initiation of venetoclax treatment and were associated with obinutuzumab treatment. There were no adverse events of clinical TLS consistent with Howard criteria reported; however, 1 event in each arm was reported where clinical manifestations were described (both did not meet laboratory Howard criteria). All events were managed per standard of care and resolved.

There were additional laboratory abnormalities identified from blood test reports, consistent with Howard criteria, but that were not reported as adverse events of TLS by the investigator. Medical review by the Sponsor revealed that some of these events were associated with pre-dose laboratory abnormalities and were not considered medically significant. There was no venetoclax dose adjustment identified, or other treatment given as a result of these laboratory abnormalities.

TLS is an important identified risk for venetoclax, and requires ongoing prophylactic measures and blood test monitoring to manage and reduce the risks associated with TLS, as per current prescribing information. In this study rigorous TLS monitoring and prophylaxis will be instituted (Section 5.1.7.1; see Appendix 12 for TLS prophylaxis, monitoring plan, and management recommendations). All patients in Arm A will be re-evaluated by laboratory assessment and can be re-categorized in a lower TLS-risk group during the venetoclax ramp-up period, as described in Section 5.1.7.1.

5.1.1.2 Serious Infections

Serious infection is an important identified risk for venetoclax and obinutuzumab and will be closely monitored by routine surveillance. The current prescribing information provides treating physicians with appropriate guidance on how to mitigate and manage this risk. Most common infections reported with venetoclax include pneumonia, sepsis, upper respiratory tract infections, and urinary tract infections. Fatalities resulting from pneumonia and sepsis have been reported in patients receiving venetoclax.

In Study BO25323/CLL14, the frequency of Grade ≥3 infections was similar in the GClb arm compared with the VEN+G arm (16.4% vs. 19.3%, respectively). Pneumonia was the most frequently reported Grade ≥3 event (4.2% of patients in both treatment arms).

Grade ≥3 sepsis was reported in 3.3% of patients in the VEN+G arm compared with 0.9% in the GClb arm.

Grade 3–4 infections were comparable across treatment groups (15.0% in the GClb arm vs. 17.5% in the VEN+G arm), and comparable across treatment periods (combination, single-agent and post-treatment periods).

The overall frequency of serious infections was numerically higher in the VEN+G arm compared with the GClb arm (18.9% vs. 14.0%, respectively). Pneumonia was the most frequently reported SAE (4.7% in the VEN+G arm vs. 4.2% in the GClb arm). The largest difference between treatment groups by individual PT was for sepsis (2.8% in the VEN+G arm vs. 0.9% in the GClb arm).

Infections are well-known to increase morbidity and mortality in patients with CLL (Hilal et al. 2018). This is primarily due to disease-related (inherent immune dysfunction caused by the disease process, affecting both humoral and cell-mediated immunity, and complement activity) and therapy-related elements (most anti-CLL treatments are responsible for causing lymphopenia, either B-cell or T-cell, and/or neutropenia to some degree).

Patients in this study will be closely monitored for infections and prompt therapy will be instituted, as necessary. Patients are allowed to receive concomitant prophylactic anti-infective therapy at the investigator's discretion. Refer to Section 5.1.6.1 for management of infections.

5.1.1.3 Neutropenia and Cytopenias

5.1.1.3.1 Neutropenia

Neutropenia is an important identified risk for venetoclax. Effects on lymphocyte numbers are expected on the basis of the mechanism of action, and modest reductions in neutrophils have been observed with venetoclax therapy in oncology patients. The majority of serious events of neutropenia and febrile neutropenia were confounded with poor BM reserves, multiple prior therapies, disease infiltrating the BM, and the use of growth factor prior to entering the studies.

Clinical data from the oncology studies suggest that adverse events of neutropenia are observed among patients who receive venetoclax as a single agent or in combination with other therapeutic agents, with slightly higher frequency observed in some combination studies. Serious adverse events of neutropenia or neutropenia that lead to discontinuations are few across the entire venetoclax oncology program. Neutropenia management guidelines are provided in Section 5.1.6.1. Granulocyte colony-stimulating factors are permitted for supportive measures per local practice guidelines.

5.1.1.3.2 Cytopenias

Thrombocytopenia and anemia have been reported with venetoclax in the single-agent Phase I dose−escalation Study M12-175 that is being conducted in heavily pretreated patients with CLL and NHL. In most cases, the condition was preexisting.

Treatment-emergent adverse events of neutropenia, anemia, and thrombocytopenia showed a higher incidence in a combination study with rituximab (Study M13-365). Cytopenias, including neutropenia, anemia, and thrombocytopenia, are known adverse reactions of anti-CD20 monoclonal antibodies.

In this study, blood counts will be monitored closely throughout treatment (see the Schedule of Activities in Appendix 1. Growth factors are permitted according to local practice, and patients will be monitored and treated promptly in case of infections. Dose interruptions or reductions will be allowed on the basis of toxicity. Refer to Section 5.1.6.1 for management of cytopenias.

5.1.1.4 Effects on Cardiac Function

No patterns of adverse events indicating changes in cardiac function have been reported in clinical studies to date. However, since study populations in venetoclax oncology studies are likely to be elderly and have received multiple prior chemotherapeutic agents, patients enrolled in this study are required to have ECGs and assessments of LVEF at screening per investigator's discretion and as clinically indicated afterward.

5.1.1.5 Effects on Fertility and Reproductive Toxicity

Given non-clinical data, there is a potential for decreased spermatogenesis. Male patients considering preservation of fertility should bank their sperm before treatment with venetoclax.

Two human pregnancies have been reported in the clinical program with venetoclax so far, including one pregnancy of a partner; in both cases, a live infant with no neonatal complication, congenital anomalies, or birth defects was delivered. In nonclinical embryo-fetal development studies, venetoclax had the potential to cause embryo-fetal developmental toxicities. Consequently, venetoclax should not be administered to pregnant women, and must be discontinued if a patient becomes pregnant.

Long-term effects of venetoclax on either male or female reproductive potential are unknown. Male and female patients should agree to remain abstinent or use contraceptive methods as described in Section 4.1.1.

5.1.1.6 Drug Interactions

Drug-drug interactions may occur with venetoclax. Venetoclax is eliminated almost entirely through the hepatic route via metabolism by CYP3A4. Specific recommendations are provided for co-administration of venetoclax with inhibitors and inducers of CYP3A (see Section 4.4.2.1, Table 4, and Appendix 4.) Venetoclax does

not appear to be a clinically significant inhibitor of CYP2C9 or CYP2C8. Venetoclax is not an inducer of CYP1A2, CYP2B6, or CYP3A4; therefore, it is not expected to have any potential for drug-drug interaction via CYP induction. Venetoclax is a substrate of the transporters P-gp and BCRP and an inhibitor of P-gp, BCRP, and OATP1B1.

On a case-by-case basis, equivalent drugs, which do not interact with venetoclax, will be selected. If there is no substitute available for a vital drug, withdrawal of the patient from the study is necessary.

5.1.1.7 Treatment-Emergent Malignancies (Second Primary Malignancies)

Events of second primary malignancies (including non-melanoma skin cancers) have been reported across the venetoclax hematologic oncology program. However, no causal association with venetoclax administration has been confirmed, and no pattern has been observed. The overall observed incidence rate of malignancy in the venetoclax clinical trial programs was comparable to that reported in the general population. Second primary malignancies will be closely monitored in this study.

5.1.1.8 Toxicity in Patients with Severe Hepatic Impairment

Mean venetoclax AUC exposures in patients with severe hepatic impairment were approximately 2.3- to 2.7-fold higher as compared with participants with normal hepatic function. On the basis of these results, a dose adjustment in patients with severe hepatic impairment is recommended.

5.1.1.9 Food Effect

Administration of venetoclax with a low-fat meal increased venetoclax exposure by approximately 3.4-fold, and administration with a high-fat meal increased venetoclax exposure by 5.1- to 5.3-fold compared with fasting conditions. Based on these results, venetoclax should be administered with a meal (see Section 4.3.2.1), to ensure adequate and consistent bioavailability of venetoclax.

5.1.2 Risks Associated with Obinutuzumab

Important risks associated or potentially associated with obinutuzumab are IRRs and hypersensitivity reactions, TLS, thrombocytopenia (including acute thrombocytopenia), neutropenia (including prolonged and late-onset neutropenia), prolonged B-cell depletion, infections (including PML and HBV reactivation), worsening of pre-existing cardiac conditions, impaired immunization response, immunogenicity, gastrointestinal (GI) perforation, and second malignancies. Physicians should exercise caution when treating patients with a history of recurring or chronic infections or with underlying conditions that may predispose patients to infections. Signs and/or symptoms of infection should result in prompt evaluation and collection of appropriate samples for bacteriological investigation prior to starting antibiotic or other treatment. Patients may receive concomitant prophylactic anti-infective therapy at the physician's discretion.

5.1.2.1 Infusion-Related Reactions and Hypersensitivity Reactions

IRRs are seen with the first infusion in virtually all patients with CLL treated with obinutuzumab. The IRRs are most commonly characterized by symptoms of hypotension, fever, chills, flushing, nausea, vomiting, hypertension, dyspnea, and fatigue. IRRs occur predominantly during the first infusion, and their incidence and intensity decrease with subsequent infusions. They generally appear early during the infusion or shortly after, or in some cases, up to 24 hours after the completion of infusion of obinutuzumab. Some patients have developed severe IRRs resulting in permanent discontinuation of obinutuzumab. In some instances, concurrent signs of TLS are observed. To mitigate the risk for IRRs, the following measures are included in the study protocol:

- Patients who have preexisting cardiac or pulmonary conditions or who have had a prior clinically-significant cardiopulmonary adverse event with obinutuzumab should be monitored carefully throughout the infusion and the post-infusion period.
- Dosing should be split for the first infusion only (100 mg on Cycle 1, Day 1 and 900 mg on Cycle 1, Day 2).

IRRs may be clinically indistinguishable from IgE-mediated allergic or anaphylactic reactions; anaphylaxis has been reported in patients treated with obinutuzumab.

Hypotension may occur during obinutuzumab IV infusions. Therefore, withholding of anti-hypertensive treatments should be considered for 12 hours prior to and throughout each obinutuzumab infusion and for the first hour after administration. Patients at acute risk of hypertensive crisis should be evaluated for the benefits and risks of withholding their anti-hypertensive medication.

Guidelines for medical management of IRRs and anaphylaxis are provided in Section 5.1.6.1 and Appendix 16.

Hypersensitivity reactions with immediate (e.g., anaphylaxis) and delayed onset (e.g., serum sickness) have been reported in patients treated with obinutuzumab. Hypersensitivity reactions typically occur after previous exposure and very rarely with the first infusion. In the case a hypersensitivity reaction is suspected during or after an infusion, the infusion should be stopped and treatment permanently discontinued.

5.1.2.2 Tumor Lysis Syndrome

Both venetoclax and obinutuzumab cause rapid cell breakdown after initial dosing of patients with CLL, and administration of both agents individually has been associated with events of laboratory and/or clinical TLS, which can be fatal. Management of TLS is described in Appendix 12.

5.1.2.3 Neutropenia

Some patients who were treated with obinutuzumab developed NCI CTCAE Grade 3–4 neutropenia, including febrile neutropenia. Neutropenia resolved spontaneously or with

use of hematopoietic growth factors. Patients who experience Grade 3 or 4 neutropenia should be closely monitored until neutrophil values return to at least Grade 2. Cases of late-onset neutropenia (ANC <1000 cells/μL occurring=28 days after obinutuzumab treatment has been completed or stopped) or prolonged neutropenia (ANC <1000-cells/μL) that does not resolve after 28 days without obinutuzumab treatment have also been reported.

Increased infections may occur due to neutropenia. Growth factors may be given during treatment with the combination, and patients will be monitored and treated promptly in case of infections. Guidelines for the treatment of neutropenia are provided in Section 5.1.6.1.

5.1.2.4 Lymphopenia

There is a potential for clinically significant lymphopenia. Given the mechanism of action of B-cell depletion with obinutuzumab and inhibition of Bcl-2 with venetoclax, it is possible that there could be a delay in B-cell recovery.

5.1.2.5 Thrombocytopenia

Cases of Grade 3–4 thrombocytopenia, including acute thrombocytopenia (occurring within 24 hours after the infusion), have been reported with obinutuzumab.

A higher incidence of thrombocytopenia and hemorrhagic events was observed during the first cycle in patients with CLL with coexisting medical conditions treated with GClb as compared with patients treated with rituximab+chlorambucil (RClb) or chlorambucil alone in the Phase III pivotal Study BO21004/CLL11. The incidence of all grade and fatal hemorrhagic events was similar across the study arms. However, all four fatal hemorrhagic events in GClb patients occurred in Cycle 1, compared with none in RClb-treated patients and one in chlorambucil-treated patients.

Due to the small number of patients with fatal hemorrhagic events, lack of laboratory data (platelet count), specifically on the day of the hemorrhagic event, and the presence of confounding factors in all cases (pre-existing thrombocytopenia due to CLL, concomitant medical conditions, and concomitant treatments such as platelet inhibitors, and anticoagulants), no clear relationship could be established between thrombocytopenia and fatal hemorrhagic events.

Patients receiving concomitant medication that could possibly worsen thrombocytopenia related events (e.g., platelet inhibitors and anticoagulants) may be at greater risk of bleeding. When possible, replace prior vitamin K antagonist therapy with low molecular weight heparin (LMWH) prior to Cycle 1, Day 1. Patients should be closely monitored for thrombocytopenia, especially during the first cycle. For patients who experience thrombocytopenia, regular laboratory tests should be performed until the event resolves, and dose delays should be considered in case of severe or life-threatening

thrombocytopenia. Transfusion of blood products (i.e., platelet transfusion) may be performed at the discretion of the treating physician, according to institutional practice.

5.1.2.6 Coagulation Abnormalities Including Disseminated Intravascular Coagulation

Disseminated intravascular coagulation (DIC) has been reported in patients receiving obinutuzumab for the treatment of FL and CLL. In the majority of cases, the events have involved subclinical (asymptomatic) changes in platelets and laboratory coagulation parameters following the first infusion, with spontaneous resolution usually occurring by Day 8. In some cases, the events were associated with IRRs and/or TLS. No specific baseline risk factors for DIC have been identified.

5.1.2.7 Infections

Consistent with its intended mode of action resulting in profound B-cell depletion, obinutuzumab has been shown to be associated with an increased risk of infections.

Serious bacterial, fungal, and new or reactivated viral infections can occur during and following the completion of obinutuzumab therapy. Fatal infections have been reported. Serious viral infections may include herpes virus infections (including cytomegalovirus, John Cunningham virus infection (JCV), PML, and HCV infection).

The Medical Monitor is available for guidance regarding the eligibility of patients who are thought to have passive transfer of HCV or HBV core surface antibodies from IV immunoglobulin administration. Patients with HCV or HBV antibody following administration of IV immunoglobulin may be eligible only if PCR is negative for HCV or HBV, respectively. Patients with positive HBV antibodies must be willing to undergo monthly HBV DNA testing. Patients with serological evidence of HBV or HCV will not be eligible for treatment in this study.

Hepatitis B Virus Reactivation

Reactivation of hepatitis B in patients with chronic hepatitis (HBsAg positive) with evidence of prior hepatitis B exposure, or in patients who are carriers (HBsAg negative and HBcAb positive) has been reported with other anti-CD20 antibodies. The risk is increased particularly when anti-CD20 antibodies are administered with immunosuppressive therapies, such as steroids or chemotherapy.

For the subset of patients who are HBsAg negative and HBcAb positive and have undetectable HBV DNA levels at screening, HBV DNA levels must be followed approximately every 3−4 weeks during the treatment phase and then approximately every 4 weeks during the follow-up phase of the study. For the management of Hepatitis B Virus reactivation, follow the guidance provided in Table 6.

Table 6 Management of Hepatitis B Virus Reactivation

Symptom	Action to be Taken
HBV DNA level of ≥29 IU/mL	• Hold VEN + G. • Begin anti-viral medication immediately after the first report showing HBV DNA ≥29 IU/mL • Retest HBV DNA level as soon as possible to rule out a false-positive report and to confirm HBV-reactivation (≥29 IU/mL) (best prior to treatment; e.g., when prescribing the anti-viral treatment). • If HBV reactivation is confirmed in second test, continue to treat for at least 1 year after the last dose of obinutuzumab and refer the patient to a gastroenterologist or hepatologist for additional management. • If a second test does not confirm HBV reactivation and was taken prior to start of anti-viral therapy, then anti-viral therapy may be stopped again, and VEN + G may be resumed. Retest the patient at close intervals (every 3–4 weeks). • If a second test does not confirm HBV reactivation but was potentially confounded because it was taken only after the start of ant-viral therapy, then continue to treat for at least 1 year after the last dose of obinutuzumab and refer the patient to a gastroenterologist or hepatologist for additional management. • Resume VEN + G once HBV DNA levels decrease to undetectable levels (<10 IU/mL) or if retest does not confirm hepatitis B reactivation.
HBV DNA level of >100 IU/mL and increasing while on appropriate anti-viral medication	Discontinue venetoclax + obinutuzumab.
HBV DNA level detectable but <29 IU/mL	• Continue with VEN + G, but retest at close intervals (e.g., every 3–4 weeks). • If HBV DNA still detectable, but <29 IU/mL on retest, continue to administer treatment and retest at close intervals (e.g., every 3–4 weeks). • If HBV DNA ≥ 29 IU/mL on retest, follow instructions for HBV DNA level of ≥29 IU/mL (see above).

HBV = hepatitis B virus; VEN + G=venetoclax + obinutuzumab

Progressive Multifocal Leukoencephalopathy

JCV infection resulting in PML has been reported in patients who have received obinutuzumab. Particular attention should be given to patients who have had significant prior immunosuppressive treatment, such as high-dose chemotherapy or a stem cell transplant, and physicians should be aware of symptoms that are suggestive of PML and consider the diagnosis of PML in any patient presenting with new-onset neurologic manifestations.

The symptoms of PML are very unspecific and can vary depending on the affected region of the brain. Motor involvement with corticospinal tract findings, sensory involvement, cerebellar deficits, and visual field defects are common. Some syndromes regarded as “cortical” (e.g., aphasia or visual-spatial disorientation) can occur.

Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture to quantify DNA of JCV in the cerebrospinal fluid.

Therapy with obinutuzumab should be withheld during the investigation of potential PML and permanently discontinued in case of PML. Discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy should also be considered.

The patient should be referred to a neurologist for the treatment of PML.

Physicians should exercise caution when treating patients with a history of recurring or chronic infections or with underlying conditions that may predispose patients to infections. Signs and/or symptoms of infection should result in prompt evaluation and appropriate samples for bacteriological investigation prior to starting antibiotic or other treatment. Patients may receive concomitant prophylactic anti-infective therapy at the physician's discretion.

5.1.2.8 Immunization

The safety of immunization with live viral vaccines following obinutuzumab therapy has not been studied. Patients who participate in this study may not receive vaccination with a live vaccine for a minimum of 28 days prior to randomization.

Investigators should review the vaccination status of potential study patients being considered for this study and follow the U.S. Centers for Disease Control and Prevention guidelines for adult vaccination with non-live vaccines intended to prevent infectious diseases prior to study therapy.

5.1.2.9 Gastrointestinal Perforation

Gastrointestinal perforations, including fatal events, have been reported in patients treated with obinutuzumab. Patients with GI involvement should be monitored for signs of GI perforation.

5.1.2.10 Worsening of Preexisting Cardiac Conditions

In patients with underlying cardiac disease and treated with obinutuzumab, adverse events such as angina pectoris, acute coronary syndrome, myocardial infarction, heart failure, and arrhythmias, including atrial fibrillation and tachyarrhythmia, have been observed. These events may occur as part of an IRR and can be fatal. Therefore, patients with a history of cardiac disease should be monitored closely. In addition, these patients should be hydrated with caution to prevent a potential fluid overload.

5.1.2.11 Risks Associated with the Combination of Venetoclax and Obinutuzumab

Given their mechanisms of action and review of available single-agent safety data, additive or overlapping acute toxicities for the combination of venetoclax and obinutuzumab could potentially include neutropenia and TLS. In terms of chronic toxicity, it is possible that inhibition of Bcl-2 could delay B-cell recovery following

completion of obinutuzumab treatment and/or lead to combined B- and T-cell depletion. These effects, if they occur, would likely manifest as an increased incidence of infections only after several months of exposure to the combination. However, in Study BO25323/CLL14, no increase in TLS or infections were observed. Given the degree of immunodeficiency associated with the underlying disease, all patients will be monitored closely for infection and treated aggressively according to institutional guidelines.

5.1.3 Risks Associated with Rituximab

The following adverse events are considered to be important risks associated or potentially associated with rituximab: IRRs, infections (including PML and HBV reactivation), neutropenia (including prolonged), rTLS, impaired immunization response, GI perforation, and severe mucocutaneous reactions. Details for some of these risks are provided below; refer to the Rituximab Investigator's Brochure for full information.

5.1.3.1 Infusion-Related Reactions

Acute IRRs are very common in patients receiving rituximab (occurring in ≥10% of patients) based on clinical trial experience. However, serious IRRs are uncommonly reported (occurring in ≥1/1,000 and <1/100 patients) and are rarely fatal (occurring in ≥1/10,000 and <1/1,000 patients). Most IRRs occur with the first administration of rituximab. Rituximab-induced IRRs consist of a cluster of symptoms and signs occurring during or within 24 hours of a rituximab infusion. These are related to cytokine release, and these acute IRRs overlap with "cytokine release syndrome". Anaphylactic and other hypersensitivity reactions also occur following rituximab administration, and clinical manifestations of these reactions are similar to cytokine release syndrome. In contrast to cytokine release syndrome, true hypersensitivity reactions typically occur within minutes of starting the rituximab infusion.

5.1.3.2 Infections (Including Serious Infections)

Serious infections, including fatal bacterial, fungal, and new or reactivated viral infections, can occur during and up to 1 year following completion of rituximab-based therapy. New or reactivated viral infections include cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis B and C viruses.

5.1.3.3 Neutropenia

Neutropenia is very common in patients receiving rituximab (occurring in ≥10% of patients) based on clinical trial experience. However, delayed onset neutropenia is very rare (occurring in <1/10,000 patients), and the incidence of prolonged neutropenia is unknown. Neutropenia may lead to serious or overwhelming infection, especially if profound (Grade 3/4), prolonged, associated with breaches in natural mucosal barriers (e.g., diarrhea and/or mucositis), and/or other immunological defects (e.g., lymphopenia, hypogammaglobulinemia, acquired immunodeficiency syndrome). Despite an increase

in incidence of neutropenia and Grade 3/4 neutropenia associated with rituximab, most studies have not reported a significant increase in serious neutropenic infections.

5.1.3.4 Tumor Lysis Syndrome

Patients treated with rituximab may be at risk for TLS. Severe tumor TLS is very rare in patients receiving rituximab (occurring in <1/10,000 patients), based on postmarketing experience. Signs and symptoms (e.g., hyperuricemia, hyperkalemia, hypocalcaemia, hyperphosphatemia, acute renal failure, and elevated LDH) that are consistent with TLS have been reported to occur after the first MabThera/Rituxan IV infusion in patients with high numbers of circulating malignant lymphocytes. A high number of circulating malignant cells (≥25,000/mm^3) or high tumor burden confers a greater risk of TLS. For patients with evidence of TLS, rituximab should be discontinued, and the patient should be treated as clinically indicated.

5.1.3.5 Hepatitis B Reactivation

Reactivation of hepatitis B ranges from asymptomatic reactivations (detected by changes in laboratory parameters only) to fulminant liver failure and death. Patients with chronic hepatitis B (HBsAg positive) viral infection are at risk for reactivation and will be excluded from the study. Patients with evidence of prior hepatitis B exposure or who are carriers (defined as HBsAg negative and anti-HBcAb positive) are at a lower risk for reactivation. Patients who demonstrate evidence of reactivation while receiving an appropriate anti-viral therapy will be discontinued from study treatment.

5.1.3.6 Progressive Multifocal Leukoencephalopathy

Rare cases of PML have also been reported in patients treated with rituximab alone or in combination with other immunosuppressive medications (Goldberg et al. 2002; Calabrese et al. 2007; Carson and Bennett 2009). In a review of 57 patients who developed PML after rituximab administration, all patients had received prior therapies with alkylating agents, corticosteroids, purine analogs, or drugs to prevent allogeneic stem cell or solid-organ graft rejection. The diagnosis of PML in any patient treated with rituximab is rare, but it should be suspected in any patient who develops new-onset neurologic manifestations. The majority of patients with hematologic malignancies diagnosed with PML received rituximab in combination with chemotherapy or as part of a hematopoietic stem cell transplant. Most cases of PML were diagnosed within 12 months of the patients' last infusion of rituximab.

5.1.3.7 Severe Mucocutaneous Reactions

Severe reactions, including fatal mucocutaneous reactions, can occur in patients receiving rituximab. These reactions include paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis (TEN). The onset of these reactions in patients treated with rituximab has varied from 1–13 weeks following rituximab exposure.

5.1.3.8 Gastrointestinal Perforation

Abdominal pain, bowel obstruction, and perforation, in some cases leading to death, can occur in patients receiving rituximab in combination with chemotherapy. Patients with gastrointestinal involvement should be monitored for signs of gastrointestinal perforation.

5.1.4 Risks Associated with FCR/BR

Potential risks relevant for the FCR/BR arm of this trial as well as specific risks for each drug alone are briefly described below. Refer to the prescribing information for fludarabine, cyclophosphamide, and bendamustine for risks related to FCR/BR chemotherapy. Risks associated with rituximab are detailed in Section 5.1.3.

5.1.4.1 Tumor Lysis Syndrome

Detailed instructions and premedication are described in Appendix 12.

Patients with a high tumor burden (i.e., larger lymph nodes and/or high lymphocyte count ($>25\times10^9$/L) are at increased risk of TLS, especially if treated with fast-acting, effective agents as used in this trial. The overwhelming activity of these agents leading to a rapid destruction of CLL cells can cause electrolyte imbalances, such as hyperkalemia, hyperuricemia, hyperphosphatemia, hypocalcemia, and hyperuricosuria; thereby leading to cardiac arrhythmias, acute uric acid nephropathy/acute renal failure and epileptic seizures if not timely and properly managed.

Patients with TLS should be treated per institutional practice (including correction of electrolyte abnormalities, monitoring of renal function and fluid balance, in some cases even dialysis as indicated).

5.1.4.2 Cytopenias and Infections

All drugs tested in this trial cause or may cause cytopenias with decreased levels of hemoglobin, neutrophil, and platelet count. However, it needs to be considered that patients with CLL commonly have pre-existing myelosuppression due to BM infiltration or previous therapy. These abnormal laboratory values are clinically relevant and should be treated at the investigator´s discretion. Prophylactic measures are strongly recommended as described in Section 5.1.6.

Treatment should not be administered in the presence of an active or severe infection including bacterial, viral and fungal infections. Caution should be exercised when considering the application of study drugs in patients with a history of recurring or chronic infections or with underlying conditions that may predispose patients to infections. If clinically indicated, anti-infective prophylaxis should be implemented at the investigator's discretion. Signs and/or symptoms of infection should result in prompt evaluation and appropriate samples for bacteriological investigation prior to starting antibiotic or other treatment. Serious, bacterial, fungal, and new or reactivated viral infections (including cytomegalovirus [CMV], JC virus infection [PML], and HBV/HCV

infection) can occur during and following the completion of therapy. Fatal infections related to all drugs used in this trial have been reported.

5.1.4.3 Worsening of Preexisting Cardiac Conditions

In CLL patients with underlying cardiac disease, adverse events such as angina pectoris, acute coronary syndrome, myocardial infarction, heart failure and arrhythmias, including atrial fibrillation and tachyarrhythmia have been observed during treatment with cyclophosphamide, and bendamustine. These events may also occur as part of an IRR and can be fatal. Therefore, patients with a history of cardiac disease should be monitored closely. In addition, these patients should be hydrated with caution in order to prevent a potential fluid overload.

However, as CLL patients are often elderly and sometimes have cardiac comorbidities, ECG and cardiac ultrasound for assessment of LVEF is mandatory at screening and recommended as clinically indicated afterwards. In addition, patients with a history of cardiac disease should be monitored closely and should be hydrated with caution in order to prevent a potential fluid overload.

5.1.4.4 Teratogenicity and Mutagenicity

Fludarabine, cyclophosphamide and bendamustine are known to be teratogenic and mutagenic; a pregnancy must be prevented in both, female patients and partners of male patients during and at least 6 months after treatment.

Potential risks with fludarabine

For detailed information and further guidance on fludarabine please see the prescribing information. Aside from the above-described risks the following side effects are relevant:

- Autoimmune diseases
- Neurotoxicity
- Transfusion-associated graft-versus-host-reaction
- Renal insufficiency
- Secondary malignancies, especially of the skin

Potential risks with cyclophosphamide

For detailed information and further guidance on cyclophosphamide please see the prescribing information. Aside from the above described risks, the following side effects are relevant:

- Impairment of the urinary tract and the kidneys
- Pulmonal toxicity
- Veno-occlusive disease (VOD)
- Secondary malignancies

5.1.5 Potential Risks with Bendamustine

For detailed information on bendamustine please see the prescribing information. Aside from the above-described risks allergies and toxic skin reactions are the most common and relevant risks.

Stevens-Johnson-Syndrome/ toxic epidermal necrolysis

Cases of Stevens-Johnson-Syndrome (SJS)/TEN, some fatal, have been reported in patients who were treated with allopurinol and bendamustine with/without rituximab. Therefore, allopurinol should be avoided in combination with bendamustine and if the concomitant use of allopurinol is indispensable, allopurinol must be stopped ≥24 hours before administration of bendamustine and reinitiated ≥24 hours after administration of the last dose of bendamustine. If patients experience any skin reactions during treatment, they should be monitored closely and in case of any suspicion of evolving to a serious mucocutaneous reaction, treatment with any suspected drugs including but not limited to bendamustine and allopurinol should be discontinued until complete resolution of event.

5.1.6 Management of Patients Who Experience Adverse Events

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 BM 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 2–4 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 the NCI grading scale for hematological toxicity in CLL studies (see Table 7). For patients with a normal neutrophil count, platelet count, and/or hemoglobin value at baseline, the NCI CTCAE v5.0 will be used.

Table 7 National Cancer Institute Grading Scale for Chronic Lymphocytic Leukemia

Decrease in Platelets or Hemoglobin from Pre-Treatment (%)	Grade	ANC/μL
No change to 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.

5.1.6.1 Guidelines for Management of Specific Adverse Events in ARM A (Venetoclax + Obinutuzumab)

Guidelines for management of specific adverse events in Arm A are outlined in Table 8. Additional guidelines are provided in the subsections below.

Table 8 Guidelines for Management of Specific Adverse Events for Patients Randomized to Arm A

Event	Dose Delay or Dose Modification
Grade 3 or 4 (NCI CTCAE v5.0 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.
Severe thrombocytopenia, (platelets <25 000/μL) and/or symptomatic bleeding	• Withhold venetoclax (and obinutuzumab if event occurs during Cycles 1–6) for severe thrombocytopenia (platelets <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 doses 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, contact the Medical Monitor regarding continuation on the protocol.
Grade 4 IRR	• Discontinue obinutuzumab permanently. Patients may continue venetoclax
Grade 3 IRR on first dose; the same Grade 3 IRR on two 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 Appendix 12.

Table 8 Guidelines for Management of Specific Adverse Events for Patients Randomized to Arm A (cont.)

Non-hematologic toxicity	
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 Cycles 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. • Delay obinutuzumab if event occurs during Cycles 1–6 for a maximum of 28 days. First episode: If improvement to Grade ≤1 or baseline, resume previous doses of obinutuzumab. • 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 v5.0 definitions. In such cases, if a patient is clinically stable, resumption of study drug may be possible after consultation with the Medical Monitor.
Grade 2 non-hematologic toxicity	• Delay treatment with venetoclax (and obinutuzumab if event occurs during Cycles 1–6) until resolution to Grade ≤1 (or baseline status) for a maximum of 28 days. • After resolution, resume full dose of venetoclax and obinutuzumab.
Grade 1 non-hematologic toxicity	• No dose reduction or delay.
Active infection	• Do not administer obinutuzumab to patients with an active infection. • After resolution, reinitiate obinutuzumab.

ANC = absolute neutrophil count; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; G-CSF = granulocyte stimulating factor; HBV = hepatitis B virus; IRR = infusion-related reaction.

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 (see Table 9); however, if the toxicity recurs, the patient may continue treatment on the lower dose.

Table 9 Venetoclax Dose Reduction

Venetoclax Current Dose Level	Venetoclax Dose Reduction
400 mg	200 mg
200 mg	100 mg
100 mg	Discontinue venetoclax and obinutuzumab

There will be no change in the infusion rate or interruptions in the administration of obinutuzumab in this study.

Patients who discontinue obinutuzumab may continue venetoclax. Patients who discontinue venetoclax for toxicity should also discontinue obinutuzumab, although they are to continue evaluation per protocol Appendix 3.

Patients who interrupt all study treatments secondary to treatment-related adverse 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 1 and Appendix 2. For patients who interrupt all study treatments for longer than 28 days due to reasons other than treatment-related adverse events, resumption of study drug may be possible only after consultation with the Medical Monitor. TLS risk should be reassessed to determine if restarting venetoclax at a reduced dose is necessary (for example, all or some levels of the dose ramp-up).

5.1.6.2 Guidelines for Management of Specific Adverse Events in ARM B (FCR/BR)

5.1.6.2.1 Rituximab Dosage Modifications

There will be no change in the infusion rate or interruptions in the administration of rituximab in this study. Patients at high risk for IRRs may, at the investigator's discretion, receive their initial dose of rituximab split over 2 consecutive days (e.g., 125 mg/m^2 on Cycle 1, Day 1 and 250 mg/m^2 on Cycle 1, Day 2).

Rituximab may be temporarily held. Any NCI CTCAE v5.0 toxicity Grade $\geq$3 in severity that is deemed related to rituximab treatment will require interruption of study treatment until resolution to Grade $\leq$1.

Patients receiving BR who discontinue rituximab for rituximab-related toxicity may continue to receive bendamustine as a single agent for the full 6 cycles if deemed to be in the best interest of the patient as assessed by the investigator. Patients who discontinue both bendamustine and rituximab are to continue evaluation per protocol as described in Section 4.6.1.

5.1.6.2.2 Bendamustine Dosage Modifications

On the first day of each new treatment cycle and before each bendamustine dose, the patient will be evaluated for possible toxicities that may have occurred after the previous dose(s). The following dose-reduction rules for bendamustine should be followed (see Table 10 and Table 11).

If toxicities occurred at 70 mg/m^2, reduce dose to 50 mg/m^2; if toxicity occurred at 50 mg/m^2, discontinue bendamustine. If the dose of bendamustine is reduced due to toxicity, it will not be re-escalated later in the study.

Table 10 Bendamustine Dose Reduction

Bendamustine Current Dose Level	Bendamustine Dose Reduction
90 mg/m^2	70 mg/m^2
70 mg/m^2	50 mg/m^2
50 mg/m^2	Discontinue bendamustine

If a patient has disease-related splenomegaly or significant bone marrow involvement as the etiology of cytopenias at enrollment, treatment may be continued without meeting the hematologic criteria for subsequent cycles of induction chemotherapy. In such cases, the decision to continue dosing of bendamustine at the current dose is at the investigator's discretion.

Table 11 Dose Modification Guidelines for Bendamustine

NCI CTCAE Category	Severity	Dose Modification
Hematologic [a]	Neutrophil <1000/μL on Day 1 of Cycles 2–6	Initiation (Day 1) of Cycles 2–6 should be delayed until the neutrophil count is ≥1000/μL (or returns to baseline level obtained at screening) and the platelet count is ≥75,000/μL.[a] If Day 1 is delayed by more than 2 weeks, then bendamustine should be resumed at the next lower dose level.
	Platelets <75,000/μL on Day 1 of Cycles 2–6	
	Grade 4 neutropenia with fever/infection	Initiation (Day 1) of Cycles 2–6 should be delayed until the neutrophil count is ≥1000/μL without evidence of fever or infection and the platelet count is ≥75,000/μL.[a] Bendamustine should then be resumed at the next lower dose level.
	Grade 4 neutropenia lasting ≥7 days	
	Grade 4 platelets for ≥7 days or a platelet count <10,000/μL at any time	
Nausea, emesis, or diarrhea in the absence of maximal prophylaxis	Grade ≥3	Continue treatment, but with institution of maximum prophylactic therapy, including a 5-HT_3 antagonist for nausea and emesis, and loperamide, or a comparable antidiarrheal agent, for diarrhea. Events of Grade 4 toxicity require holding treatment until resolution of toxicity to Grade ≤2 with use of maximum prophylaxis.
Nausea, emesis, or diarrhea with maximal prophylaxis	Grade ≥3	Hold bendamustine for up to 2 weeks or until the toxicity returns to Grade ≤2, and restart at the next lower dose. If treatment is delayed by more than 2 weeks, treatment with bendamustine must be discontinued.
All other toxicities related to bendamustine	Grade ≥3	

5-HT_3 = 5-hydroxytryptamine 3; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

[a] If patients have disease-related splenomegaly or significant bone marrow involvement as the etiology of cytopenias at enrollment, treatment may be continued without meeting the hematologic criteria for subsequent cycles of induction chemotherapy. In such cases, the decision to continue dosing of bendamustine at the current dose is at the investigator's discretion.

5.1.6.2.3 Dose Modification for FCR

Before starting treatment on day 1 of every cycle, the following retreatment criteria must be fulfilled:

- No active infection
- No CTCAE Grade 3/4 adverse events (except hematological adverse events that are due to BM involvement of the CLL, these must be recovered to at least baseline value)

If these criteria are not met treatment must be delayed for up to 14 days.

Afterwards the patient must continue with a reduced dose of 75% of the normal dose of fludarabine and cyclophosphamide.

The rituximab dose will not be reduced (except for dose reductions of 100% that may occur due to side effects) but will be delayed by the same amount.

If the patient does not meet the retreatment criteria within the 14-day-period again a further delay of 14 days (resulting in a total delay of 28 days) is permitted.

The patient will than continue with a reduced dose of 50% of the normal dose of the fludarabine and cyclophosphamide. Again, the rituximab dose will not be reduced.

The reduced dosage must be applied in all consecutive treatment cycles.

If the retreatment criteria are not met after 4 weeks, the study treatment must be permanently discontinued.

If, after the first dose reduction to 75%, retreatment criteria are not met by day 1 of one of the following treatment courses, treatment can be delayed again for up to 2 weeks with a following reduction to 50% of fludarabine and cyclophosphamide for subsequent cycles. The rituximab dose will not be reduced. Further delay is not permitted.

If the retreatment criteria are not met on day 1 of the subsequent cycles after dose reduction to 50%, treatment can be delayed again for up to 2 weeks without further dose reduction. If the event does not resolve after two additional weeks, the study treatment has to be discontinued.

Besides the above described circumstances for permanent discontinuation of standard chemo-immunotherapy, it must be performed in the following cases:

- CTCAE GRADE 4 infections
- Treatment related autoimmune disease
- Grade ≥3 non-hematological toxicity related to study treatment

Patients receiving FCR who discontinue rituximab for rituximab-related toxicity may continue to receive FC for the full 6 cycles if deemed to be in the best interest of the patient as assessed by the investigator. Patients who discontinue both FC and rituximab are to continue evaluation per protocol as described in Section 4.6.1 and Appendix 3.

5.1.7 Dose Modifications of Fludarabine and Cyclophosphamide Due to Decreased Renal Function

Both fludarabine and cyclophosphamide are excreted mainly via the kidneys. If a decrease of renal function occurs during therapy (creatinine clearance <70 mL/min) the

dose of fludarabine and cyclophosphamide has to be adjusted (Table 12). A dose reduction of fludarabine to 80% and of cyclophosphamide to 75% must be instituted when the creatinine clearance is within the range from 30 to 70 mL/min. If creatinine clearance falls to <30 mL/min, FC should be discontinued.

Table 12 Dose Adjustments for Fludarabine and Cyclophosphamide in Renal Impairment

Creatinine Clearance (mL/min)	Fludarabine (mg/m^2/day)	Cyclophosphamide (mg/m^2/day)
>70	25	250
30-70	20	187 (75%)
<30	No further treatment	No further treatment

5.1.7.1 Prophylaxis and Management of Tumor Lysis Syndrome for Patients Being Treated with Venetoclax

TLS is a risk for patients with CLL who are treated with high cell-killing agents or obinutuzumab. 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.

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 13). 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 (see Section 4.5.12.2). 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 13 Risk Categories for Developing Tumor Lysis Syndrome

TLS Risk Category	Definition
Low	All measurable lymph nodes with the largest diameter <5 cm and $<25 \times 10^9$/L ALC. Lymph node size will be determined by radiologic assessment.
Medium	Any measurable lymph node with the largest diameter ≥5 cm but <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. Lymph node size will be determined by radiologic assessment.

ALC=absolute lymphocyte count; TLS=tumor lysis syndrome.

Note: The TLS Risk Assessment MUST be made based on measurements of nodal disease burden based on radiologic assessments (CT scan or MRI, see Section 4.5.12.2) performed during the screening period.

All patients enrolling in the study will be assessed at screening and categorized in a risk category as described above. Because of possible tumor de-bulking after obinutuzumab therapy, investigators will reassess TLS risk after obinutuzumab induction for all patients in Arm A 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 will have a re-evaluation of their TLS risk category based on their most recent ALC after the obinutuzumab run in period and before initiating venetoclax on Cycle 1, Day 22. If the patient's ALC decreases to $<25 \times 10^9$/L, the patient may be categorized as TLS medium-risk and may follow the management guidelines for the TLS medium-risk category during the venetoclax ramp-up period. Only patients who are classified as high-risk because they have a lymph node with largest diameter ≥10 cm will have a repeat CT scan after obinutuzumab induction and before starting venetoclax on Cycle 1, Day 22. If the patient's lymph node size decreases to <10 cm, the investigator may follow the management guidelines for the TLS medium-risk category for the venetoclax 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.

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.

This section describes the management of patients throughout dosing (as described in Section 4.3.2) given their risk factors for developing TLS identified upon study entry. A summary of TLS prophylaxis for venetoclax and monitoring measures is presented in Table 14.

Table 14 Summary of Tumor Lysis Syndrome Prophylaxis for Venetoclax and Monitoring Measures

TLS Risk Category	Day 1 of Dose Level	Prophylaxis Medication	Hosp.	Hydration [a]	Laboratory Assessments [b, e]
TLS low-risk	20, 50, 100, 200, 400 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 (C3D1).	No	Oral hydration of 1.5–2 L/day beginning at least 48 hours prior to dose and continuing for at least 24 hours after dose.	For first dose of 20 mg and 50 mg: hematology and chemistry samples will be taken predose and 6–8 and 24 hours after dosing. For subsequent ramp-up doses: hematology and chemistry will be taken predose. 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 results from a sample taken up to 4 hours predose, then it is acceptable to take a predose hematology and 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 chemistry samples drawn on the day of venetoclax administration prior to dosing are not required to be reviewed prior to dose administration. The 6–8-hour chemistry results must be reviewed before the patient 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 medium-risk	20 and 50 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 (C3D1).	No [c,d]	Oral hydration of 1.5–2 L/day beginning at least 48 hours prior to dose and continuing for at least 24 hours after dose. In addition to oral hydration, IV hydration (1.5–2 L) will be given in the outpatient setting during the clinic stay.	For first dose of 20 mg and 50 mg: hematology and chemistry samples will be taken predose and 6–8 and 24 hours after dosing. For subsequent ramp-up doses: hematology and chemistry will be taken predose. 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 results from a sample taken up to 4 hours predose, then it is acceptable to take a predose hematology and chemistry sample within 24 hours prior to dosing. The

Table 14 Summary of Tumor Lysis Syndrome Prophylaxis for Venetoclax and Monitoring Measures (cont.)

TLS Risk Category	Day 1 of Dose Level	Prophylaxis Medication	Hosp.	Hydration [a]	Laboratory Assessments [b, e]
	100, 200, 400 mg	Continue oral uric-acid reducer as above.		Oral hydration of 1.5–2 L/day beginning at least 48 hours prior to dose and continuing for at least 24 hours after dose.	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 chemistry samples drawn on the day of venetoclax administration prior to dosing are not required to be reviewed prior to dose administration. The 6–8-hour chemistry results must be reviewed before the patient 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 high-risk	20 and 50 mg	Oral uric acid reducer (such as allopurinol 300 mg/day) beginning at least 72 hours prior to dose and continued until the first week of combination therapy with venetoclax is completed. Rasburicase 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 Howard et al. [2011] 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 Medical	Yes [d]	Oral hydration of 1.5–2 L/day beginning at least 48 hours prior to dose and continuing for at least 24 hours after dose. Upon hospital admission, IV hydration should be started with a target of approximately 2–3 L per day or as clinically appropriate.	Hematology and chemistry samples will be taken predose and 4, 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 results from a sample taken up to 4 hours predose, then it is acceptable to take a predose hematology and 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 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 investigator or subinvestigator must review the 24-hour laboratory results prior to dosing on the next day.

Table 14 Summary of Tumor Lysis Syndrome Prophylaxis for Venetoclax and Monitoring Measures (cont.)

TLS Risk Category	Day 1 of Dose Level	Prophylaxis Medication	Hosp.	Hydration [a]	Laboratory Assessments [b, e]
		Monitor. Uric acid levels following treatment with rasburicase must be analyzed using specific guidelines described in Section 5.1.7.1.1			
TLS high-risk	100, 200, 400 mg	Continue oral uric acid reducer as above	No [c,d]	Oral hydration of 1.5–2 L/day beginning at least 48 hours prior to dose and continuing for at least 24 hours after dose. In addition to oral hydration, IV hydration (1.5–2L) will be given in the outpatient setting during the clinic stay.	Hematology and chemistry samples will be taken predose, 6–8, 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 results from a sample taken up to 4 hours predose, then it is acceptable to take a predose hematology and 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 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 investigator or subinvestigator must review the 24-hour laboratory results prior to dosing on the next day.

C = cycle; CrCl = creatinine clearance; D = day; IV = intravenous; Hosp = Hospitalization; 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.

Table 14 Summary of Tumor Lysis Syndrome Prophylaxis for Venetoclax and Monitoring Measures (cont.)

[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 ±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 ±2-hour window of the scheduled time. If it is not possible to review a sample taken up to 4 hours predose, then it is acceptable to take a predose hematology and 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 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 a baseline for later laboratory values when assessing for laboratory evidence of TLS.

[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 12. 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 20 mg (400 mg → 200 mg; 200 mg → 100 mg; 100 mg → 50 mg; 50 mg → 20 mg).

5.1.7.1.1 Initial Doses: Venetoclax 20 and 50 mg

All patients, irrespective of their TLS risk category at the first dose of venetoclax, must receive the following TLS prophylaxis measures prior to the initiation of the first doses of venetoclax:

- Administration of an oral uric acid reducer (such as allopurinol 300 mg/day) beginning at least 72 hours prior to dose and continued to the end of the venetoclax ramp-up period (Cycle 3, Day 1).
- Oral hydration consisting of fluid intake of approximately 1.5–2 L/day starting at least 48 hours prior to the start of treatment and continued for at least 24 hours after the first dose.
- Serum chemistry and hematology laboratory samples must be drawn prior to administering venetoclax (predose). If clinically significant laboratory abnormalities are observed in this baseline laboratory assessment, the first dose of venetoclax must be delayed until resolution and management per the protocol and recommendations for Initial Management of Electrolyte Imbalances and Prevention of TLS must be initiated. If needed, patient should receive additional prophylactic treatment prior to the initiation of 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 results from a sample taken up to 4 hours predose, then it is acceptable to take a predose hematology and 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 chemistry samples drawn on the day of venetoclax administration prior to dosing are not required to be reviewed prior to dose administration. If possible, 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.

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

TLS Low Risk

Low-risk patients will receive their initial doses of 20 and 50 mg venetoclax as outpatients.

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 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.

Serum chemistry, hematology, and vital signs will be obtained prior to administering venetoclax (predose) and 6–8 and 24 hours after dosing. Laboratory samples should be sent and analyzed immediately.

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 results from a sample taken up to 4 hours predose, then it is acceptable to take a predose hematology and 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 chemistry samples drawn on the day of venetoclax administration prior to dosing are not required to be reviewed prior to dose administration.

The 6–8-hour chemistry results must be reviewed before the patient leaves the outpatient clinic that day.

Furthermore, the investigator or subinvestigator must review the 24-hour laboratory results prior to dosing on the next day.

Additional laboratory assessments may be performed per investigator discretion.

TLS Medium Risk

Medium-risk patients who have CrCl ≥80 mL/min will receive their initial doses of 20 mg and 50 mg venetoclax as outpatients. Patients with CrCl <80 mL/min and/or who have higher tumor burden (defined per the discretion of the investigator) may be handled as High-Risk patients (see the TLS High Risk section below for details of hospitalization, hydration, laboratory, and so forth).

In addition to oral hydration stated above, IV hydration (1.5–2 L) will be given in the outpatient setting during the clinic stay. For patients for whom volume overload is considered a significant risk, hospitalization should be considered.

Serum chemistry, hematology, and vital signs will be obtained prior to administering venetoclax (predose) and 6–8 and 24 hours after dosing timepoints. Laboratory samples should be sent and analyzed immediately.

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 results from a sample taken up to 4 hours predose, then it is acceptable to take a predose hematology and 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 chemistry samples drawn on the day of venetoclax administration prior to dosing are not required to be reviewed prior to dose administration.

The 8-hour chemistry results must be reviewed before the patient leaves the outpatient clinic that day. Furthermore, the investigator or subinvestigator must review the 24-hour laboratory results prior to dosing on the next day.

Additional laboratory assessments may be performed per investigator discretion.

TLS High Risk

High-risk patients will be hospitalized to receive their initial doses of 20 mg and 50 mg venetoclax. Hospitalization will begin the evening prior to each initial dose of venetoclax and continue for 24 hours after each dose.

Upon admission, serum chemistry and hematology laboratory samples should be drawn, and IV hydration should be started with a target of 2–3 L per day or as clinically appropriate.

Rasburicase 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 Howard et al. [2011] 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 Medical Monitor. Uric acid levels following treatment with rasburicase must be analyzed using specific guidelines described below.

Please note that 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.
- Blood must be collected into prechilled tubes containing heparin anticoagulant. Immediately immerse plasma samples for uric acid measurement in an ice water bath.
- Plasma samples must be prepared by centrifugation in a precooled centrifuge (4°C).
- The plasma must be maintained in an ice water bath and analyzed for uric acid within 4 hours of collection.

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.

Serum chemistry, hematology, and vital signs will be obtained prior to administering venetoclax (predose) and at 4, 8, 12, and 24 hours after dosing. These samples are to

be sent immediately to the laboratory, and the results must be reviewed promptly by the investigator or subinvestigator.

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 results from a sample taken up to 4 hours predose, then it is acceptable to take a predose hematology and 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 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 24-hour postdose laboratory results must be reviewed by the investigator or subinvestigator before the patient leaves the hospital or receives any additional study drug.

Additional laboratory assessments may be performed per investigator discretion.

5.1.7.1.2 Subsequent Dose Increases during the Venetoclax Ramp-Up Period (100, 200, and 400 mg Venetoclax)

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

- Continued administration of an oral uric acid reducer as indicated above.
- Oral hydration consisting of fluid intake of approximately 1.5–2 L/day starting at least 48 hours prior to dosing. IV hydration is encouraged at subsequent dose increases for patients unable to maintain such oral hydration. IV hydration in the outpatient setting on the day of dosing during the clinic stay is recommended in order to assure this full amount of hydration is achieved. For patients for whom volume overload is considered a significant risk, hospitalization should be considered.
- Serum chemistry and hematology laboratory samples must be drawn prior to administering venetoclax (predose). If clinically significant laboratory abnormalities are observed in this laboratory assessment, dose of venetoclax must be delayed until resolution, and management per the protocol, Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome, must be initiated. If needed, patient should receive additional prophylactic treatment prior to the initiation of 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 results from a sample taken up to 4 hours predose, then it is acceptable to take a predose hematology and 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 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 to 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.

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

TLS Low Risk

Low-risk patients will receive the subsequent dose increases (100, 200, and 400 mg venetoclax) as outpatients.

Serum chemistry, hematology, and vital signs will be obtained prior to administering venetoclax (predose). Laboratory samples should be sent and analyzed immediately.

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 results from a sample taken up to 4 hours predose, then it is acceptable to take a predose hematology and 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 chemistry samples drawn on the day of venetoclax administration prior to dosing are not required to be reviewed prior to dose administration.

Additional laboratory assessments may be performed per investigator discretion.

TLS Medium Risk

Medium-risk patients who have CrCl $\geq$80 mL/min will receive their subsequent dose increases as outpatient. Patients with CrCl $<$80 mL/min and/or who have high-tumor burden (defined per the discretion of the investigator) may be hospitalized.

For patients who receive this subsequent dose increases as outpatient, serum chemistry, hematology, and vital signs will be obtained prior to administering venetoclax (predose). Laboratory samples should be sent and analyzed immediately.

Pre-dose 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 results from a sample taken up to 4 hours pre-dose, then it is acceptable to take a predose hematology and 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 chemistry samples drawn on the day of venetoclax administration prior to dosing are not required to be reviewed prior to dose administration.

Additional laboratory assessments may be performed per investigator discretion.

For patients hospitalized during subsequent dose increases, serum chemistry, hematology, and vital signs will be obtained prior to dosing (pre-dose, defined as up to 4 hours before venetoclax dose) and 6–8, 12, and 24 hours after dosing. These samples are to be sent immediately to the laboratory, and the results must be reviewed promptly by the investigator or subinvestigator. The 24-hour after dosing laboratory results must be reviewed by the investigator or subinvestigator before the patient leaves the hospital or receives any additional study drug.

IV hydration should be started with a target of approximately 2–3 L per day or as clinically appropriate for patients who are hospitalized.

TLS High Risk

High-risk patients with CrCl of ≥80 mL/min will receive the subsequent dose increases as outpatients. Patients with CrCl <80 mL/min and/or high tumor burden (defined per the discretion of the investigator) may be hospitalized. Hospitalization will begin the evening prior to the dose of venetoclax and continue for 24 hours after the dose.

IV hydration (1.5–2 L) will be given in the outpatient setting during the clinic stay. For patients who are hospitalized, IV hydration should be started with a target of approximately 2–3 L per day or as clinically appropriate.

For patients who are not hospitalized, serum chemistry, hematology, and vital signs will be obtained prior to administering venetoclax and at 6–8 and 24 hours after dosing timepoints. Laboratory samples should be sent and analyzed immediately.

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 results from a sample taken up to 4 hours predose, then it is acceptable to take a predose hematology and 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 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 to 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 6–8 hour chemistry results must be reviewed before the patient leaves the outpatient clinic that day.

Furthermore, the investigator or subinvestigator must review the 24-hour laboratory results prior to dosing on the next day.

For patients who are hospitalized during subsequent dose increases, serum chemistry, hematology, and vital signs will be obtained prior to dosing (predose, defined as up to 4 hours before venetoclax dose) and 6–8, 12, and 24 hours after dosing. These samples are to be sent immediately to the laboratory, and the results must be reviewed promptly by the investigator or subinvestigator. The 24-hour after dosing laboratory results must be reviewed by the investigator or subinvestigator before the patient leaves the hospital or receives any additional study drug.

Additional laboratory assessments may be performed per investigator 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 12, 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 20 mg (400 mg → 200 mg; 200 mg → 100 mg; 100 mg → 50 mg; 50 mg → 20 mg). All patients must receive the intended dose for at least 7 days before increasing to the next ramp-up dose.

For patients who are at high risk of TLS, the following apply:

- Hospitalized patients should receive TLS prophylaxis as described above for initial venetoclax dosing. Per institutional standards, nephrology (or acute dialysis service) can be consulted/contacted on admission to ensure emergency dialysis is available and the appropriate staff are aware and prepared to handle any necessary intervention for TLS. Telemetry should also be considered.

5.1.7.2 Prophylaxis for Infections

If clinically indicated, anti-infective prophylaxis for viral, fungal, bacterial, or Pneumocystis infections is permitted. Although there is a potential for DDI, there is likely to be limited potential clinical effects; therefore, trimethoprim sulfamethoxazole can be considered for Pneumocystis prophylaxis with close clinical monitoring. The Medical Monitor should also be consulted regarding any consideration of the use of azoles as anti-fungal prophylaxis or therapy, because of the potential for DDI.

5.1.7.3 Prophylaxis for Infusion-Related Reactions

The rate of infusion of obinutuzumab or rituximab 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.

5.1.7.4 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 or rituximab should be discontinued and no additional obinutuzumab or rituximab should be administered. Patients who experience any of these reactions should receive aggressive symptomatic treatment and will be discontinued

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Section 5.3.5.9 and Section 5.3.5.10 for more information)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Is fatal (i.e., the adverse event actually causes or leads to death)

- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that, had it occurred in a more severe form or was allowed to continue, might have caused death.
- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

5.2.3 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 5.3.5.7)
- Suspected transmission of an infectious agent by the study drug, as defined below

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

- TLS of any grade, irrespective of causality
- Second primary malignancies

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Section 5.4–Section 5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events will be reported until 28 days after the final dose of study drug, or until initiation of another anti-cancer therapy, whichever occurs first. Related serious adverse events, all second primary malignancies irrespective of causality, and SARS-CoV-2 infection irrespective of causality will be reported indefinitely (Section 5.6).

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.3.2 Eliciting Adverse Event Information

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of nondirective questions include the following:

"How have you felt since your last clinic visit?"

"Have you had any new or changed health problems since you were last here?"

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 15 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 15 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Section 5.4.2 for reporting instructions), per the definition of serious adverse event in Section 5.2.2.

5.3.4 Assessment of Causality of Adverse Events

Investigators should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be related to the study drug, indicating "yes" or "no" accordingly. The following guidance should be taken into consideration (see also Table 16):

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Table 16 Causal Attribution Guidance

Is the adverse event suspected to be caused by the study drug on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon rechallenge.
NO	An adverse event will be considered related, unless it fulfills the criteria specified below. Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).

For patients receiving combination therapy, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Infusion-Related Reactions

Adverse events considered to be IRRs that occur during or within 24 hours after obinutuzumab, cyclophosphamide, fludarabine, rituximab, or bendamustine administration and are judged to be related to obinutuzumab, cyclophosphamide, fludarabine, rituximab, or bendamustine infusion should be captured as a diagnosis (e.g., infusion-related reaction) on the Adverse Event eCRF. If possible, avoid ambiguous terms such as "systemic reaction." Associated signs and symptoms should be recorded on the dedicated Infusion-Related Reaction eCRF. If a patient experiences both a local and systemic reaction to the same dose of study drug, each reaction should be recorded separately on the Adverse Event eCRF, with signs and symptoms also recorded separately on the dedicated Infusion-Related Reaction eCRF.

5.3.5.2 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events

based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.
- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

5.3.5.4 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 5.4.2 for reporting instructions). The Adverse Event eCRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to serious adverse events.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded as a separate event on the Adverse Event eCRF.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

    Note: For oncology trials, certain abnormal values may not qualify as adverse events.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.6 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- Is accompanied by clinical symptoms
- Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention or a change in concomitant therapy
- Is clinically significant in the investigator's judgment

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.4 for details on recording persistent adverse events).

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy's Law). Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $>3\times$ULN in combination with total bilirubin $>2\times$ULN
- Treatment-emergent ALT or AST $>3\times$ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.5) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

For this protocol, mortality is an efficacy endpoint. Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of CLL should be recorded on the Death Attributed to Progressive Disease eCRF. All other deaths that occur during the adverse event reporting period, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death. The term **"sudden death"** should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.9 Pre-existing Medical Conditions

A pre-existing medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Worsening of Chronic Lymphocytic Leukemia

Events that are clearly consistent with the expected pattern of progression of the underlying disease (such as transformation to more aggressive histology) should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on iwCLL criteria. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration or monitoring for potential TLS)
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease

  The patient has not experienced an adverse event
- Hospitalization due solely to progression of the underlying cancer

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.12 Cases of Overdose, Medication Error, Drug Abuse, or Drug Misuse

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Intentional overdose: intentional administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug

  In some cases, a medication error may be intercepted prior to administration of the drug.
- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm}
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

  In cases where drug is to be self-administered by the patient, drug misuse could involve the drug being administered to someone other than the patient.

Special situations are not in themselves adverse events but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). For venetoclax, obinutuzumab, and rituximab, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the adverse event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes.

In addition, all special situations associated with venetoclax, obinutuzumab, and rituximab, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.
- Drug abuse that does not qualify as an overdose: Enter the drug name and "drug abuse" as the event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.
- Drug administered to someone other than the patient: Enter the drug name and "patient supplied drug to third party" as the event term. Check the "Drug misuse" box.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries.

5.3.5.13 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor. In addition, the Sponsor will make no attempt to reconcile patient reports of treatment-related symptoms with investigator reports of adverse events. Sites are not expected to review the PRO data for adverse events.

5.3.5.14 Safety Biomarker Data

Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on patient management.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

To ensure the safety of study patients, *access to Medical Monitors is available 24 hours per day, 7 days per week.* An Emergency Medical Call Center will *also be available 24 hours per day, 7 days per week. The* Emergency *Medical Call Center will connect the investigator with an Emergency Medical Contact*, provide medical translation service if necessary*,* and track all calls. *Contact information, including toll-free numbers for the* Emergency Medical Call Center*,* will be distributed to investigators.

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. The paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 28 days after the final dose of study drug or until initiation of another anti-cancer therapy, whichever occurs first. Related serious adverse events and all second primary malignancies irrespective of causality will be reported indefinitely (Section 5.6).

Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, the paper Clinical Trial Adverse Event/Special Situations Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur >28 days after the final dose of study treatment are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 30 days after the final dose of venetoclax (or within 18 months of the final dose of obinutuzumab) for patients in Arm A, and within 6 months of the final dose of bendamustine, fludarabine or cyclophosphamide (or within 12 months of the final dose of rituximab) for patients in Arm B, whichever is later. A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 90 days after the final dose of venetoclax (or within 18 months of the final dose of obinutuzumab) for patients in Arm A, and within 6 months of the final dose of bendamustine, fludarabine or cyclophosphamide (or within 12 months of the final dose of rituximab) for patients in Arm B, whichever is later. The investigator should report the pregnancy on the paper Clinical Trial Pregnancy Reporting Form and submit the form to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form with additional information on the pregnant partner and the course and outcome of the pregnancy as it becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.4 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to study drug or the female partner of a male patient exposed to study drug should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2).

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

5.5.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

After the end of the adverse event reporting period (defined as 28 days after the final dose of study drug or until initiation of another anti-cancer therapy, whichever occurs first), all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF.

In addition, if the investigator becomes aware of a serious adverse event that is believed to be related to prior exposure to study drug, the event should be reported through use of the Adverse Event eCRF. Investigators should also report all second primary malignancies and SARS-CoV-2 infections irrespective of whether they are believed to be related to previous study treatment or not, indefinitely. *A serious, non-drug-related adverse event, such as a serious SARS-CoV-2 infection that occurs after the adverse event reporting period does not need to be reported to the Sponsor within 24 hours of the investigator becoming aware of it. However, the site should endeavor to add this information to the eCRF in a timely manner.* If the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Adverse Event/Special Situations Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and expeditiously communicate possible new safety findings to investigators, IRBs, Ethics Committees (ECs), and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events through use of the reference safety information in the documents listed below:

Drug	Document
Venetoclax	Venetoclax Investigator's Brochure
Obinutuzumab	Obinutuzumab Investigator's Brochure
Fludarabine	Fludarabine UK Summary of Product Characteristics
Cyclophosphamide	Cyclophosphamide UK Summary of Product Characteristics
Rituximab	Rituximab Investigator’s Brochure
Bendamustine	Bendamustine UK Summary of Product Characteristics

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the applicable reference document.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

Certain adverse events are anticipated to occur in the study population at some frequency independent of study drug exposure and will be excluded from expedited reporting. These anticipated events include known consequences of the underlying disease or condition under investigation (e.g., symptoms, disease progression) and events unlikely to be related to the underlying disease or condition under investigation but common in the study population independent of drug therapy (e.g., cardiovascular events in an elderly population). These events are listed in Appendix 17.

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

The list of Medical Dictionary for Regulatory Activities (MedDRA) preferred terms associated with these events, is available upon request.

Although exempted from expedited reporting to Health Authorities and IRBs as individual cases, these Serious Adverse Events (as defined in Section 5.4.2) must be reported within 24 hours of the site being made aware of the event.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 DETERMINATION OF SAMPLE SIZE

The sample size for the primary MRD analysis is determined based on the hypothesis to be tested to establish clinically relevant statistical superiority in the MRD response rate.

To detect an improvement in MRD response rate at a two-sided significance level of 0.05, approximately 165 patients are required at the MRD primary analysis to achieve a power of 92% assuming a target improvement in MRD response rate of 30%. The minimum detectable difference of MRD response rate is 14.1%.

The primary MRD analysis is expected to occur approximately 46 months after the first-patient in.

The calculation of sample size and estimates of the MRD analysis timelines are based on the following assumptions, which are based on the completed enrollment:

- *Patients will be randomized to FCR/BR and VEN +G arms in a 1:1 ratio*
- Two-sample test for proportions at the two-sided 0.05 level of significance
- MRD response rate for FCR/BR arm at Month 15 (*52*%)
- FCR/BR ratio in the control arm is *55/45*
- *>90*% power to detect difference in MRD response rate of *30*% (response rate of 82% for VEN+G arm) at Month 15

- Proportion of patients with non-evaluable MRD including samples which cannot be assayed and patients who have died or discontinued the study prior to *Month* 15 MRD assessment (15%)
- Misclassification rate *for* MRD status assessed by clonoSEQ NGS assay

The sample size calculation was performed using rpact package in R version *4.0.*3.

6.2 ANALYSIS TIMING

A number of factors may affect the timing of the primary efficacy MRD analysis specifically the recruitment rate, since the primary efficacy analysis is triggered when the last patient has reached the 15-month MRD assessment the MRD primary analysis *will* occur *when* approximately *165 patients randomized in the study have reached the 15-month MRD assessment at approximately 46 months* after the first patient is randomized in the study. At the time of MRD primary analysis*, a first interim analysis for PFS will be conducted and approximately 25 (57% information fraction)* events are expected. *In the event the expected number of PFS events are reached before or after the time of MRD analysis, interim PFS analysis will be conducted at the time of MRD analysis regardless of the achievement of the planned number of events. In this scenario, the information fraction along with the stopping boundaries will be re-evaluated on the basis of the number of events reached* at that time.

A second interim analysis for PFS will be conducted when 33 events (75% information fraction) will be reached.

The final PFS analysis will take place when 44 events will have occurred.

6.3 SUMMARIES OF CONDUCT OF STUDY

Enrollment, major protocol deviations, study drug administration, and patient disposition will be summarized by treatment arm in all randomized patients. A summary of patient disposition will include whether treatment was completed or discontinued early and the reason for early treatment discontinuation. Descriptive statistics will be used in evaluating the conduct of the study. Median length of follow-up will be estimated overall and by-treatment in all randomized patients using the reverse Kaplan Meier (K-M) method.

6.4 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics, such as age, sex, race/ethnicity, and baseline ECOG Performance Status, previous and concurrent medical history and medications will be summarized by treatment arm in all randomized patients.

6.5 EFFICACY ANALYSES

6.5.1 Primary Efficacy Endpoint

The primary efficacy endpoint is MRD response rate (determined as the proportion of patients with MRD-negativity defined as <1 CLL cell in 10,000 leukocytes) measured in PB using NGS at Month 15.

The primary objective of the study is to test the following hypothesis:

- MRD response rate of VEN+G versus FCR/BR
  (i.e., H_0: VEN+G – FCR/BR=pre-specified difference versus H_1: VEN+G – FCR/BR ≠ pre-specified difference

MRD response rate of the 2 arms will be compared based on Cochran-Mantel-Haenszel (CMH) test stratified by IGHV mutation status, Binet stage and age. If the null hypothesis of no difference in MRD response rate is rejected and the observed MRD response rate is favorable for the VEN+G experimental arm, then it is concluded that VEN+G significantly increases the chance to respond compared to FCR/BR. Difference in MRD response rate will be estimated and two-sided 95% Anderson-Hauck CI will be provided. Within each arm, 2-sided 95% Clopper-Pearson exact CIs will also be presented.

6.5.1.1 Target of Estimation for the Primary Efficacy Endpoint

To provide clarity on the target of estimation, the five attributes in the estimand framework are defined below.

Population: Defined as all randomized patients, analyzed by randomized treatment group. FIT patients with previously untreated CLL without del(17p) or *TP53* mutation requiring treatment. Inclusion and exclusion criteria have been described in details in Section 4.1.1 and Section 4.1.2.

Variable: MRD response (defined as a patient with MRD-negativity <1 CLL cell in 10,000 leukocytes) measured in PB using NGS at Month 15. Patients with missing MRD assessment at Month 15 will be considered non-responders.

Treatment: Patients will be randomized to either Arm A (venetoclax+obinutuzumab) or Arm B (FCR or BR). During the conduct of the study patients may also receive concomitant medications as detailed in Section 4.4.

Intercurrent event: The intercurrent events which will be identified in this study are as follows.

- Exposure to new anti-CLL treatment
- Discontinuation of treatment due to *any reason (except PD)*
- Death
- *Missing*/Non-evaluable MRD sample

- Discontinuation from the study due to other reasons

In case of missing data due to death, non-evaluable MRD sample, or for any other reason, a composite strategy is planned. This means that a patient with a missing MRD value in PB at Month 15 will be considered a non-responder. In case of exposure to new anti-CLL treatment prior to Month 15, the patient will be considered as a non-responder regardless of the availability of MRD data at Month 15. Discontinuation of treatment due to *any reason (except PD),* if a Month 15 MRD result is obtained a treatment-policy strategy is planned. This means that observed MRD value in PB at Month 15 will be used ignoring the intercurrent event. However, supplementary analyses will be performed in these cases to determine the robustness of the primary analysis.

Population-level summary for the variable: Difference in the proportion of patients achieving MRD response in the 2 arms.

6.5.2 Secondary Efficacy Endpoints

The primary MRD analysis will be supported by further secondary endpoints including the following:

- PFS, defined as the time from randomization to the first occurrence of disease progression, or death from any cause; disease progression assessed by the investigators using iwCLL criteria (Hallek et al. 2018).
- MRD response rate, in PB at end of treatment response visit (8−12 weeks after last dose of FCR/BR (~9 months) vs. 8-12 weeks after last dose of VEN+G (~15 months).
- MRD response rate in BM at end of treatment response visit (9 months FCR/BR vs. 15 months VEN+G).
- ORR which includes CR, CRi, and PR at Month 15 assessment.
- Complete response (CR) rate which includes CR and CRi at Month 15 assessment.
- MRD response rate in PB in patients with a CR/CRi at Month 15.
- MRD response rate in BM in patients with a CR/CRi at end of treatment visit (8−12 weeks after last dose of FCR/BR (~9 months) vs. 8-12 weeks after last dose of VEN+G (~15 months)
- DOR, defined as the time from the first response to the time of PD or death from any cause, whichever comes first.
- Best response achieved (CR, CRi, PR, SD, or PD) up to and including the assessment at Month 15.
- EFS, defined as the time between date of randomization and the date of disease progression/relapse, death, or start of a new anti-leukemic therapy.
- OS, defined as the time between the date of randomization and the date of death due to any cause. Patients who are alive (including lost to follow-up) at the time of the analysis will be censored at the date when they were last known to be alive.

- TLS risk reduction rate in Arm A, defined as the reduction in the proportion of patients who were TLS high-risk after 3 doses of obinutuzumab compared to the proportion of patients who were TLS high-risk at baseline.
- Reduction in mandatory hospitalizations during venetoclax ramp-up in Arm A patients, defined as the actual number of protocol-mandated hospitalizations for TLS monitoring during venetoclax ramp-up period after 3 doses of obinutuzumab compared to the number of protocol-mandated hospitalizations for TLS monitoring during venetoclax ramp-up expected at baseline.

Hypotheses for response endpoints will be evaluated using CMH test and hypotheses for time-to-event endpoints will be evaluated using stratified log-rank test.

The following *key* secondary endpoints will be formally tested.

- PFS
- MRD response rate in PB at end of treatment visit
- MRD response rate in BM at end of treatment visit

The hierarchical ordering of selected secondary endpoints will be confirmed in the Statistical Analysis Plan (SAP).

6.5.3 Type-1 Error Control

Multiple endpoints and multiple decision timepoints have been proposed for this study. To establish a valid claim of efficacy it is important to control the overall type-1 error rate at a pre-specified level. In this study we propose hierarchical testing *for the three key secondary* endpoints (i.e., a hypothesis can only be tested if the previous hypothesis is rejected). For each endpoint an overall $\alpha = 0.05$ will be used for testing. Obrien-Fleming alpha spending function will be used *for PFS* to determine the boundary at the time of MRD primary analysis *(i.e., which corresponds to the time of the first PFS interim* analysis*), at the second PFS interim analysis, and at the final PFS analysis.*

6.5.4 Supplementary Analyses

To check the robustness of the primary MRD analysis and underlying assumptions, the following supplementary analyses for MRD will be performed on the ITT population:

- To assess the impact of intercurrent events (exposure to a new anti-CLL treatment, discontinuation of treatment due to adverse event, or due to lack of efficacy) on MRD status in PB at Month 15, an analysis of MRD will be performed considering patients with intercurrent events as non-responders.
- To assess the impact of missing data on primary MRD analysis, for patients who discontinued the treatment and Month 15 assessment is missing their last non-missing MRD response will be carried forward and used as the response at Month 15.
- To assess the impact of missing data on primary MRD analysis, for patients who are missing the Month 15 assessment but have an available non-missing assessment

thereafter, the subsequent available MRD response closest to Month 15 will be used as the response at Month 15.

- To address potential discrepancies between PB and BM results, proportion of patients achieving MRD negativity in both PB and BM will be compared at Month 9 for FCR/BR and Month 15 for VEN+G.

6.6 SAFETY ANALYSES

Safety endpoints include adverse events, serious adverse events, and adverse events of special interest. Safety analyses will be based on safety population which is defined as all patients who received at least one dose of any study medication.

Treatment exposure will be summarized, including the number of cycles received by each patient, and the cumulative dose will be summarized by treatment arm. Verbatim descriptions of adverse events will be mapped to MedDRA thesaurus terms. All adverse events occurring during or after the first treatment will be summarized by treatment arm and NCI CTCAE grade. In addition, all serious adverse events will be summarized.

Deaths reported during the study treatment period and those reported after treatment completion/discontinuation will be summarized by treatment arm.

Adverse events leading to early treatment discontinuation and early study withdrawal will be summarized by arm and reason. Laboratory data with values outside of the normal ranges will be identified. Additionally, select laboratory data will be summarized by treatment arm and grade using the NCI CTCAE. Of note, abnormal laboratory data that are clinically significant will be reported as adverse events and summarized in the adverse event tables. Vital signs and other physical findings will be summarized by treatment arm.

6.6.1 Patient-Reported Outcome Analyses

The secondary PRO endpoints for the study are as follows:

- Change in disease and treatment-related symptoms following treatment with the combination of VEN+G compared with FCR/BR in patients with previously with previously untreated CLL without del(17p) or *TP53* mutation as measured by MDASI-CLL.
- Change in physical functioning, role functioning and health-related quality of life (HRQoL) following treatment with the combination of VEN+G compared with FCR/BR in patients with previously with previously untreated CLL without del(17p) or *TP53* mutation as measured by EORTC QLQ-C3.

The analysis of all other scales will be considered exploratory.

Repeated-measures for mixed-model analyses will be used to compare changes from baseline between the arms.

Scoring for the MDASI-CLL and EORTC QLQ-C30 questionnaires (Appendix 5 and Appendix 6) will be based on the corresponding user manual. For scales with more than 50% of the constituent items completed, a pro-rated score will be computed that is consistent with the scoring manuals and validation papers. For subscales with less than 50% of the items completed, the subscale will be considered as missing.

Summary statistics of the MDASI-CLL and EORTC QLQ-C30 scales and their changes from baseline will be calculated at each assessment timepoint for both study arms. Analysis details of these PROs will be provided in the SAP.

6.6.2 Health Economic Analyses

Health economics data, as assessed by the EQ-5D-5L, will be evaluated for patients with a baseline assessment and at least one post-baseline EQ-5D-5L assessment that generate a score. Scores at baseline and change from baseline scores for each timepoint will be quantified using descriptive statistics.

The results from the health economics data analysis may be reported separately from the Clinical Study Report.

6.7 EXPLORATORY ANALYSES

The exploratory outcome measures for this study are as follows (provided these data are available in a sufficiently timely and complete form to perform these analyses at the time of the final analysis):

- Subgroup analyses of primary and key secondary endpoints including, but not limited to, baseline characteristics, stratification factors, FCR only patients, and BR only patients.
- The relationship between various baseline markers and clinical outcome parameters including the primary PFS outcome will be assessed in patients from both arms of the study (including but not limited to CLL FISH (17p-, 11q-, 13p-, +12q), IGHV mutation status, p53 mutation status, serum parameters, Bcl-2 expression and other CLL disease markers.
- Durability of MRD-negativity (at 10^{-4}) over time in PB measured by NGS

Relationship between MRD at EOT assessment and PFS on the basis of PB assessed using NGS.

Exploratory analyses of MRD negativity by timepoint will also be performed with MRD negativity defined using a cutoff of 10^{-4} (less than 1 CLL cell in 10,000 leukocytes) and secondly by additional cutoffs ($<10^{-5}$, and $<10^{-6}$) within the limit of sensitivity of the technology.

6.8 INTERIM ANALYSIS

6.8.1 Planned Interim Analysis

Two planned interim efficacy *analyses will be conducted for PFS as detailed in Section 7.2 . The first interim analysis* for PFS will be conducted at the time of MRD primary analysis and *the second interim analysis will be performed at the occurrence of 33 PFS events. PFS* will be tested at the significance level determined using the O*′B*rien-Fleming error spending function so that the overall two-sided type I error rate for each endpoint will be maintained at the 0.05 level. *Detailed decision rules will be reported in the SAP.*

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. Central laboratory data will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

PRO data will be collected through the use of an electronic device provided by a vendor (see Section 7.3 for details).

Back up PRO data can be collected on a web-based system. The use of this electronic back up allows for completion of all questionnaires on a web portal. This web back–up is to be used only when the electronic device (tablet) is not functioning as expected. For information on how to activate the web back up, please refer to the eCOA quick reference guide provided by the vendor.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 ELECTRONIC PATIENT-REPORTED OUTCOME DATA

An electronic device will be used to capture PRO data. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. FDA regulations for electronic records (21 CFR Part 11). The data will be transmitted to a centralized database maintained by the electronic device vendor.

The electronic data will be available for view access only, via a secure web server. Only identified and trained users may view the data, and their actions will become part of the audit trail. The Sponsor will have view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

Once the study is complete, the data, audit trail, and trial and system documentation will be archived. The investigator will receive patient data for the site in both human- and machine-readable formats that must be kept with the study records as source data. Acknowledgement of receipt of the data is required. In addition, the Sponsor will receive all data in a machine-readable format.

7.4 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, PROs, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.5 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, electronic or paper PRO data (if applicable), Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

Roche will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trials Directive (2001/20/EC) *or Clinical Trials Regulation (536/2014)* and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as an Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

If the Consent Forms are revised (through an amendment or an addendum) while a patient is participating in the study, the patient or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.7).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such

data against accidental or unlawful loss, alteration, or unauthorized disclosure or access. In the event of a data security breach, appropriate mitigation measures will be implemented.

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Given the complexity and exploratory nature of exploratory biomarker analyses, data derived from these analyses will generally not be provided to study investigators or patients unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.6).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.6).

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 MANAGEMENT OF STUDY QUALITY

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring patient safety and data integrity. Prior to study initiation, the Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and controlling these risks. Risk evaluation and control will include the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters prior to study initiation. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

9.4 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.5 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 40 sites globally will participate to enroll approximately 165 patients. Enrollment will occur through an IxRS.

Central facilities will be used for certain study assessments throughout the study (e.g., specified laboratory tests, biomarker and PK analyses), as specified in Section 4.5. Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

9.6 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and*/or summaries of clinical study results may be available in health authority databases for public access, as required by local regulation, and* will be made available upon request, provided the requirements of Roche's global policy on data sharing have been met. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:

https://www.roche.com/innovation/process/clinical-trials/data-sharing

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional

monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

9.7 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

10. REFERENCES

Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993;85:365–76.

Abrisqueta P, Pereira A, Rozman C, et al. Improving survival in patients with chronic lymphocytic leukemia (1980-2008): the Hospital Clinic of Barcelona experience. Blood. 2009;114(10):2044–50.

Barr PM, Robak T, Owen C, et al. Sustained efficacy and detailed clinical follow-up of first-line ibrutinib teatment in older patients with chronic lymphocytic leukemia: extended Phase 3 results from RESONATE-2. Haematologica 2018;103(9):1502–10.

Binet JL, Leporrier M, Dighiero G, et al. A clinical staging system for chronic lymphocytic leukemia: prognostic significance. Cancer 1977;40:855–64.

Binet JL, Auquier A, Dighiero G, et al. A new prognostic classification of chronic lymphocytic leukemia derived from a multivariate survival analysis. Cancer 1981;48:198-206.

Böttcher S, Hallek M, Ritgen M, et al. The role of minimal residual disease measurements in the therapy for CLL is it ready for prime time? Hematol Oncol Clin N Am 2013;27:267–88.

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

Brooks R. EuroQol: the current state of play. Health Policy 1996;37:53–72.

Calabrese LH, Molloy ES, Huang D, Ransohoff RM. Progressive multifocal leukoencephalopathy in rheumatic diseases: evolving clinical and pathologic patterns of disease. Arthritis Rheum. 2007;56(7):2116-28.

Carson KR, Bennett CL. Rituximab and progressive multi-focal leukoencephalopathy: the jury is deliberating. Leuk Lymphoma. 2009;50(3):323-4.

Cheson BD, Wendtner CM, Pieper A, Dreyling M, Friedberg J, Hoelzer D, Moreau P, Gribben J, Knop S, Montillo M, Rummel M. Optimal use of bendamustine in chronic lymphocytic leukemia, non-Hodgkin lymphomas, and multiple myeloma: treatment recommendations from an international consensus panel. Clinical Lymphoma Myeloma and Leukemia. 2010;10(1):21-7.

Cimmino A, Calin GA, Fabbri M, et al. miR-15 and miR-16 induce apoptosis by targeting BCL2. Proc Natl Acad Sci U S A 2005;102:13944–9.

Del Gaizo Moore V, Brown JR, Certo M, Love TM, Novina CD, Letai A. Chronic lymphocytic leukemia requires BCL2 to sequester prodeath BIM, explaining sensitivity to BCL2 antagonist ABT-737. J Clin Invest 2007;117:112-121

Dimier N, Delmar P, Ward C, et al. A model for predicting effect of treatment on progression-free survival using MRD as surrogate end point in CLL. Blood 2018;131:955-962.

Dohner H, Stilgenbauer S, Benner A, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. N Engl J Med 2000;343:1910–6.

Dreger P, Schnaiter A, Zenz T, Böttcher S, Rossi M, Paschka P, Bühler A, Dietrich S, Busch R, Ritgen M, Bunjes D. TP53, SF3B1, and NOTCH1 mutations and outcome of allotransplantation for chronic lymphocytic leukemia: six-year follow-up of the GCLLSG CLL3X trial. Blood. 2013;121(16):3284-8.

Eichhorst B, Fink AM, Bahlo J, et al. First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. Lancet Oncol 2016;17(7):928-42.

EuroQol Group. EuroQol: a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199–208.

Farooqui MZ, Valdez J, Martyr S, et al. Ibrutinib for previously untreated and relapsed or refractory chronic lymphocytic leukaemia with *TP53* aberrations: a phase 2, single-arm trial. Lancet Oncol 2015;16(2):169–76.

Fayers PM, Aaronson NK, Bjordal K, Curran D, Grønvold M. EORTC QLQ-C30 scoring manual. Eortc; 1999.

Fink AM, Böttcher S, Ritgen M, Fischer K, Pflug N, Eichhorst B, et al. Prediction of poor outcome in CLL patients following first-line treatment with fludarabine, cyclophosphamide and rituximab. Leukemia. 2013;27(9):1949.

Fesik SW. Promoting apoptosis as a strategy for cancer drug discovery. Nat Rev Cancer. 2005;5(11):876–85.

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

Fischer K, Cramer P, Busch R, et al. Bendamustine in combination with rituximab for previously untreated patients with chronic lymphocytic leukemia: a multicenter phase II trial of the German Chronic Lymphocytic Leukemia Study Group. J Clin Oncol 2012;30:3209–16.

Fitzsimmons D, Johnson CD, George S, et al. Development of a disease specific quality of life (QoL) questionnaire module to supplement the EORTC core cancer QoL questionnaire, the QLQ-C30 in patients with pancreatic cancer. EORTC Study Group on Quality of Life. Eur J Cancer 1999;35:939–41.

Flinn IW, Gribben JG, Dyer MJ, et al. Phase 1b study of venetoclax-obinutuzumab in previously untreated and relapsed/refractory chronic lymphocytic leukemia. Blood. 2019;133(26):2765-75.

Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. N Engl J Med 2014;370:1101–10.

Goldberg SL, Pecora AL, Alter RS, Kroll MS, Rowley SD, Waintraub SE, Imrit K, Preti RA. Unusual viral infections (progressive multifocal leukoencephalopathy and cytomegalovirus disease) after high-dose chemotherapy with autologous blood stem cell rescue and peritransplantation rituximab. Blood. 2002;99(4):1486-8.

Gribben JG. Salvage therapy for CLL and the role of stem cell transplantation. Hematology Am Soc Hematol Educ Program 2005:292–8.

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

Hallek M, Cheson BD, Catovsky D, et al.. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood. 2018;131:2745–60.

Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, Phase 3 trial. Lancet 2010;376:1164–74.

Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ5D-5L). Qual-Life Res 2011;20:1727–36.

Hilal T, Gea-Banacloche JC, Leis JF. Chronic lymphocytic leukemia and infection risk in the era of targeted therapies: linking mechanisms with infections. Blood reviews. 2018;32(5):387-99.

Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. New England Journal of Medicine. 2011;364(19):1844-54.

Janssen MF, Pickard AS, Golicki D, et al. Measurement properties of the EQ-5D-5L compared to the EQ5D3L across eight patient groups: a multi-country study. Qual Life Res 2013;22:1717–27.

Kater AP, Seymour JF, Hillmen P, et al. Fixed duration of venetoclax-rituximab in relapsed/refractory chronic lymphocytic leukemia eradicates minimal residual disease and prolongs survival: post-treatment follow-up of the MURANO Phase III study. J Clin Oncol. 2018;37(4):269-77.

Kovacs G, Robrecht S, Fink AM, et al. Minimal residual disease assessment improves prediction of outcome in patients with chronic lymphocytic leukemia (CLL) who achieve partial response: comprehensive analysis of two phase III studies of the German CLL study group. J Clin Oncol 2016;34(31):3758–65.

Kwok M, Rawstron A, Varghese A, et al. Minimal residual disease is an independent predictor for 10-year progression-free and overall survival in CLL. Blood 2016;128:2770–3.

Marcos-Gragera R, Allemani C, Tereanu C, et al. Survival of European patients diagnosed with lymphoid neoplasms in 2000-2002: results of the HAEMACARE project. Haematologica. 2011;96(5):720-8.

Matutes E, Owusu-Ankomah K, Morilla R, et al. The immunological profile of B-cell disorders and proposal of a scoring system for the diagnosis of CLL. Leukemia 1994;8:1640–5.

Mérino D, Bouillet P. The Bcl-2 family in autoimmune and degenerative disorders. Apoptosis. 2009 Apr;14:570−83.

Moreton P, Kennedy B, Lucas G, et al: Eradication of minimal residual disease in B-cell chronic lymphocytic leukemia after alemtuzumab therapy is associated with prolonged survival. J Clin Oncol 2005;23:2971-9.

NIH National Cancer Institute. SEER Stats Fact Sheets: Chronic Lymphocytic Leukemia. Available from: http://seer.cancer.gov/statfacts/html/clyl.html

Rai KR, Sawitsky A, Cronkite EP, et al. Clinical staging of chronic lymphocytic leukemia. Blood 1975;46:219–34.

Rawstron AC, Villamor N, Ritgen N, et al. International standardized approach for flow cytometric residual disease monitoring in chronic lymphocytic leukaemia. Leukemia 2007;21:956–64.

Rawstron AC, Bottcher S, Letestu R, et al. Improving efficiency and sensitivity: European Research Initiative in CLL (ERIC) update on the international harmonised approach for flow cytometric residual disease monitoring in CLL. Leukemia 2013;27(1):142–9.

Rawstron AC, Cohen D, de Tute R, et al. The level of residual CLL at assessment of response and in follow-up objectively predicts the outcome of patients following FCR-based therapy: >1% residual disease in the marrow 3 months post-treatment predicts early relapse and poor survival. XVI International Workshop on Chronic Lymphocytic Leukemia. 2015. Abstract 154.

Roberts AW, Davids MS, Pagel JM, et al. Targeting BCL2 with Venetoclax in Relapsed Chronic Lymphocytic Leukemia. N Engl J Med. 2016;374:311–22.

Robertson LE, Plunkett W, McConnell K, Keating MJ, McDonnell TJ. Bcl-2 expression in chronic lymphocytic leukemia and its correlation with the induction of apoptosis and clinical outcome. Leukemia 1996;10:456–9

Santacruz R, Villamor N, Aymerich M, et al. The prognostic impact of minimal residual disease in patients with chronic lymphocytic leukemia requiring first-line therapy. Haematologica. 2014;99:873-80.

Schnaiter A, Paschka P, Rossi M, Zenz T, Bühler A, Winkler D, Cazzola M, Döhner K, Edelmann J, Mertens D, Kless S. NOTCH1, SF3B1, and TP53 mutations in fludarabine-refractory CLL patients treated with alemtuzumab: results from the CLL2H trial of the GCLLSG. Blood. 2013;122(7):1266-70.

Seymour JF, Kipps TJ, Eichhorst B, et al. Venetoclax-rituximab in relapsed or Refractory chronic lymphocytic leukemia. N Engl J Med. 2018;378:1107–20.

Seymour JF, Shuo M, Brander DM, et al. Venetoclax plus rituximab in relapsed or refractory chronic lymphocytic leukaemia: a Phase 1b study. Lancet 2017;18:230-40.

Shanafelt TD, Wang XV, Kay NE, et al. Ibrutinib–Rituximab or Chemoimmunotherapy for Chronic Lymphocytic Leukemia. N Engl J Med. 2019;381(5):432–43.

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

Souers AJ, Leverson JD, Boghaert ER et al. ABT-199, a potent and selective Bcl-2 inhibitor, achieves antitumor activity while sparing platelets. Nat Med. 2013;19:202–8.

Stilgenbauer S, Eichhorst B, Schetelig J, Hillmen P, Seymour JF, Coutre S, et al. Venetoclax for patients with chronic lyhpmocytic leukemia with 17p deletion: results from the full population of a Phase II pivotal trial. J Clin Oncol. 2018;36(19):1973-80.

Stilgenbauer S, Schnaiter A, Paschka P, Zenz T, Rossi M, Döhner K, et al. Gene mutations and treatment outcome in chronic lymphocytic leukemia: results from the CLL8 trial. Blood. 2014;123(21):3247-54.

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

Touzeau C, Dousset C, Le Gouill S, Sampath D, Leverson JD, Souers AJ, Maiga S, Bene MC, Moreau P, Pellat-Deceunynck C, Amiot M. The Bcl-2 specific BH3 mimetic ABT-199: a promising targeted therapy for t (11; 14) multiple myeloma. Leukemia. 2014;28(1):210.

Vandenberg CJ, Cory S. ABT-199, a new Bcl-2–specific BH3 mimetic, has in vivo efficacy against aggressive Myc-driven mouse lymphomas without provoking thrombocytopenia. Blood. 2013;121(12):2285–8.

Zenz T, Häbe S, Denzel T, Mohr J, Winkler D, Bühler A, et al. Detailed analysis of p53 pathway defects in fludarabine-refractory chronic lymphocytic leukemia (CLL): dissecting the contribution of 17p deletion, TP53 mutation, p53-p21 dysfunction, and miR34a in a prospective clinical trial. Blood. 2009;114(13):2589-97.

Zenz T, Krober A, Scherer K, et al. Monoallelic *TP53* inactivation is associated with poor prognosis in chronic lymphocytic leukemia: results from a detailed genetic characterization with long-term follow-up. Blood 2008;112:3322-9.

Zenz T, Mertens D, Kuppers R, et al. From pathogenesis to treatment of chronic lymphocytic leukemia. Nat Rev Cancer 2010;10(1):37–50.

Appendix 1
Schedule of Activities for Arm A

Arm A: RAMP-UP to 400 mg of Venetoclax

Arm A (VEN + G) Assessments	Screening	Cycle 1								Cycle 2							
Day (VEN dose)	−28 to −1	1 [a]	2	3 [b]	8	15	16–21	22 (20 mg)	23	1 (50 mg)	2	8 (100 mg)	9	15 (200 mg)	16	22 (400 mg)	23
Informed consent [c]	x																
Demographic data	x																
TLS laboratory-based risk assessment [d]	x						x [e]										
TLS Monitoring [d]		x	x	(x)				x	x	x [f]	x	x	x	x	x	x	x
General medical history	x																
CIRS score	x																
Vital signs [g]	x	x	x	(x)	x	x		x	x	x		x		x		x	
Weight	x	x								x							
Height	x																
Complete physical examination [h]	x																
Clinical staging [h]	x																
Lymphadenopathy (during physical examination/ Binet staging at screening)	x																
Liver/spleen (by physical examination)	x																
ECG 12 lead	x	As clinically indicated															
LVEF	x	As clinically indicated															
ECOG Performance Status	x	x								x							

Appendix 1: Schedule of Activities for Arm A

Arm A (VEN+G) Assessments	Screening	Cycle 1								Cycle 2							
Day (VEN dose)	−28 to −1	1 [a]	2	3 [b]	8	15	16–21	22 (20 mg)	23	1 (50 mg)	2	8 (100 mg)	9	15 (200 mg)	16	22 (400 mg)	23
B-symptoms (see Section 4.5.12.3)	x	x								x							
CT scan assessment [i]	x						x [e]										
BM biopsy/aspirate [j]	(x)																
Hospitalization		(x)						Mandatory hospitalization for patients at high-risk for TLS on Day 1 of 20-mg and 50-mg doses and possibly Day 1 of 100-mg, 200-mg, and 400-mg doses									
Obinutuzumab [k]		x	(x)		x	x				x							
Venetoclax								Daily, as per dosing chart schedule (20, 50, 100, 200, 400 mg) starting C1D22									
Adverse events [c]	x	x	x	(x)	x	x		x	x	x	x	x	x	x	x	x	x
Concomitant medications	x	x	x	(x)	x	x		x	x	x	x	x	x	x	x	x	x
PRO questionnaires (MDASI-CLL, EQ-5D-5L, and EORTC-QLQ C30) l		x								x							
Local Laboratory [m]																	
IGHV [n]	x																
Immunoglobulins	x																
HBV, HCV, HIV, HTLV1 (if applicable) [o]	x																
Coombs test	x																
Coagulation (INR *OR* PT, *AND* aPTT or PTT)	x																
Pregnancy test [p]	x	x								x							
Urinalysis [q]	x																
Hematology [r]	x	x	x	(x)	x	x	x [e]	x	x	x	x	x	x	x	x	x	x
Chemistry [s]	x	x	x	(x)	x	x	x [e]	x	x	x	x	x	x	x	x	x	x

Appendix 1: Schedule of Activities for Arm A

Arm A (VEN + G) Assessments	Screening	Cycle 1								Cycle 2							
Day (VEN dose)	−28 to −1	1 [a]	2	3[b]	8	15	16–21	22 (20 mg)	23	1 (50 mg)	2	8 (100 mg)	9	15 (200 mg)	16	22 (400 mg)	23
Central Laboratory [m]																	
Serum parameters (β2 microglobulin,)		x [a]															
Whole blood for CLL Prognostic factors (including IGHV, 17p, *TP53*)	x																
Blood for genetic analysis (genetic complexity, gene mutations and resistance markers)	x																
Blood for lymphocyte counts/ immunophenotyping (B-CLL count, B-cell, T-cell and NK cell markers) by flow cytometry	x																
MRD in PB by NGS	x																
MRD in PB by ASO-PCR	x																
ctDNA sample	x																

ALC = absolute lymphocyte count; ASO-PCR = allele-specific oligonucleotide polymerase chain reaction; BM = bone marrow; C = Cycle; CIRS = cumulative illness rating scale; CLL = chronic lymphocytic leukemia; CR = complete remission; CT = computed tomography; D = Day; ECOG = Eastern Cooperative Oncology Group; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-5L = EuroQol 5-Dimension Questionnaire, 5-level version; HBV = hepatitis B virus; HCV = hepatitis C virus; HTLV1 = human T-cell leukemia virus 1; IRR = infusion-related reaction; IV = intravenous(ly); LVEF = left ventricular ejection fraction; MDASI-CLL = MD Anderson Symptom Inventory for Chronic Lymphocytic Leukemia; MRD = minimal residual disease; MRI = magnetic resonance imaging; NGS = next-generation sequencing; PB = peripheral blood; PR = partial response; PRO = patient-reported outcome; TLS = tumor lysis syndrome; VEN + G = venetoclax (Venclexta or Venclyxto) in combination with obinutuzumab (Gazyva or Gazyvaro).

Notes: All assessments during treatment period and at the follow-up Day 28 visit should be performed within 7 days of the scheduled visit, unless otherwise specified. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified. On treatment days: pre-infusion laboratory samples should be drawn 0–4 hours before the start of infusion. On Day 1 of each venetoclax dose ramp-up (e.g., 20 mg

[C1D22], 50 mg [C2D1], 100 mg [C2D8], 200 mg [C2D15], 400 mg [C2D22]), laboratory analyses will be required predose and at 8 and 24 hours postdose to ensure that there are no abnormal changes. If the patient is an inpatient, an additional 12-hours postdose initiation hematology and chemistry is required. Laboratory values must be read by a clinician prior to taking the next venetoclax dose.

[a] Samples should be taken after a randomization number has been assigned.

[b] In patients where the first obinutuzumab dose is administered over Days 1 and 2, the 24-hour postdose TLS monitoring will also need to occur on Day 3

[c] After informed consent has been obtained but prior to initiation of study drug, only adverse events and serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 28 days after the last dose of study drug, or until initiation of another anti-cancer therapy, whichever occurs first. After this period, the investigator is not required to actively monitor patients for adverse events; however, the Sponsor should be notified if the investigator becomes aware of any post-study serious adverse event that is believed to be related to prior exposure to study drug or any second primary malignancies, irrespective of whether they are believed to be related to previous study treatment or not. In addition, all deaths, regardless of cause, should be reported. The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

[d] TLS risk assessment and monitoring: Chemistry and hematology panels must be assessed within 0–4 hours prior and 24 hours after the first obinutuzumab dose. For TLS low-risk and TLS medium-risk patients: at the first 20 mg and 50 mg dose of venetoclax, hematology and chemistry samples are to be taken 0-4 hours predose and 6–8 and 24 hours after dosing. For subsequent ramp-up doses hematology and chemistry will be taken within 0–4 hours predose. For TLS high-risk patients: at the first 20 mg and 50 mg dose of venetoclax, patients will be hospitalized, and hematology and chemistry samples will be taken 0-4 hours predose and 4, 8, 12, and 24 hours after dosing. For subsequent ramp-up doses hematology and chemistry will be taken within 0-4 hours predose and 6-8 and 24 hours after doing. If it is not possible to review results from a sample taken up to 4 hours predose, then it is acceptable to take a predose hematology and 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 chemistry samples drawn on the day of venetoclax administration prior to dosing are not required to be reviewed prior to dose administration. However, if possible, 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.

[e] Because of possible tumor de-bulking after obinutuzumab therapy, investigators will reassess TLS risk after obinutuzumab induction for all patients in Arm A 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 will have a re-evaluation of their TLS risk category based on their most recent ALC after the obinutuzumab run-in period and before initiating venetoclax on Cycle 1, Day 22. If the patient's ALC decreases to $< 25 \times 10^9$/L, the patient may be categorized as TLS medium-risk and may follow the management guidelines for the TLS medium-risk category during the venetoclax ramp-up period. Only patients who are classified as high-risk because they have a lymph node with largest diameter ≥10 cm will have a repeat CT scan after obinutuzumab induction and before starting venetoclax on Cycle 1, Day 22.

If the patient's lymph node size decreases to <10 cm, the investigator may follow the management guidelines for the TLS medium-risk category for the venetoclax ramp-up period.

[f] For Cycle 2 only, in addition to Day 1, the TLS assessment must be performed on Day 8, Day 15, and Day 22.

[g] Vital signs include measurements of respiratory rate, pulse rate and systolic and diastolic blood pressure while the patient is in a seated position, and temperature. For TLS low-risk and TLS medium-risk patients: At the first 20-mg and 50-mg dose of venetoclax, vital signs are to be taken 0–4 hours predose, and 6–8 and 24 hours after dosing. For subsequent ramp-up doses, vital signs will be taken within 0–4 hours predose. For TLS high-risk patients: At the first 20-mg and 50-mg dose of venetoclax, vital signs will be taken 0–4 hours predose and 4, 8, 12, and 24 hours after dosing. For subsequent ramp-up, vital signs will be taken within 0–4 hours predose and 6–8 and 24 hours after doing.

[h] Physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF. Binet staging will be assessed using data collected at the screening visit. Physical examinations may be performed 1 day prior to a planned treatment visit to facilitate scheduling.

[i] CT scans are allowed 8 weeks prior to randomization and required as confirmation of CR/PR at 12 weeks after end of treatment. An MRI is only to be conducted if a contrast enhanced CT is not possible. All patients must have a baseline CT scan (or MRI if CT is not possible) of the neck (if indicated), chest, abdomen, and pelvis with IV and oral contrast. Conventional CT and MRI should be performed with contiguous cuts of 10 mm or less in slice thickness. Spiral CT should be performed by use of a 5-mm contiguous reconstruction algorithm; this specification applies to the tumors of the chest, abdomen, and pelvis. If MRIs are used instead of CT scans, MRIs should be used consistently throughout the study.

[j] A BM biopsy and aspirate is optional at screening (investigator discretion if clinically indicated) and can be performed 8 weeks prior to randomization. At the end of treatment response visit, a BM biopsy and aspirate is required to confirm response in all responding patients (CR/PR).

[k] Obinutuzumab may be given over 2 days if the patient is considered high risk for IRR or as per standard of care.

[l] PRO questionnaires scheduled for administration during a clinic visit should be completed prior to the performance of non-PRO assessments and the administration of study treatment.

[m] For samples drawn on days of study treatment, predose laboratory samples should be drawn within 0–4 hours before the dose. If these results need to be reviewed prior to dosing and if it is not possible to review results from a sample taken up to 4 hours predose, then it is acceptable to take a predose hematology and chemistry sample within 24 hours prior to dosing. The results of these samples can be reviewed prior to dosing. 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 safety. Other laboratory samples occurring on the same day should be obtained within a ±15-minute window of any scheduled time. Any laboratory tests occurring at time intervals ≥24 hours after dose should be obtained within a ±2-hour window of the scheduled time.

[n] IGHV mutational status is required for randomization. Historical results irrespective of when test was performed can be used (tests that have occurred prior to the 28–day screening window are valid indefinitely and do not need to be repeated). If IGHV mutational status is unknown at

screening, then sites will need to perform this locally prior to randomization. Patients with an undetermined IGHV mutational status cannot be randomized and will be considered a screen-fail.

[o] Certain patients (occult or prior HBV infection) require monthly DNA testing, although the data is not collected for the study.

[p] All women who are not postmenopausal (i.e., ≥12 months of non-therapy-induced amenorrhea) or surgically sterile will have a serum pregnancy test at screening. If a serum pregnancy test has not been performed 14 days prior to the first dose, a urine pregnancy test must be performed 7 days prior to the first dose. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. Further, all women who are not postmenopausal (i.e., ≥12 months of non-therapy-induced amenorrhea) or surgically sterile will have a serum pregnancy test monthly while receiving study drug and at the Treatment Completion/Early Termination visit.

[q] Urinalysis includes: dipstick pH, specific gravity, glucose, protein, ketones, blood, and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria).

[r] Hematology includes: WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[s] Chemistry includes: sodium, potassium, chloride, bicarbonate, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total and direct bilirubin, alkaline phosphatase, ALT, AST, uric acid, and LDH.

Arm A: Cycle 3-Cycle 12 and Follow-Up Day 28

Arm A (VEN+G) Assessment	C3	C4	C5	C6	Day 28 after Completion/ Early Termination of Combination Therapy[a]	C7	C8	EOCTRV 8–12 Weeks Post End of Combination[b]	C9	C10	C11	C12	Day 28 after Treatment Completion/Early Termination of Ven Monotherapy [c]
Vital signs (Day 1 of each cycle only)	x	x	x	x	x	x	x	x	x	x	x	x	x
Weight	x	x	x	x	x	x	x	x	x	x	x	x	x
Complete physical examination		x			x			x					x
Lymphadenopathy (during physical examination)		x			x			x					x
Liver and spleen by physical examination		x			x			x					x
ECG 12 lead	As clinically indicated												
LVEF	As clinically indicated												
ECOG Performance Status	x	x	x	x	x	x	x	x	x	x	x	x	x
B-symptoms (see Section 4.5.12.3)	x	x	x	x	x	x	x	x	x	x	x	x	x
Obinutuzumab	x	x	x	x									
Venetoclax	Daily dosing 400 mg for 10 cycles												

Appendix 1: Schedule of Activities for Arm A

Arm A (VEN+G) Assessment	C3	C4	C5	C6	Day 28 after Completion/ Early Termination of Combination Therapy[a]	C7	C8	EOCTRV 8–12 Weeks Post End of Combination[b]	C9	C10	C11	C12	Day 28 after Treatment Completion/Early Termination of Ven Monotherapy [c]
CLL response assessment [d]		x			x			x					
CT scan assessment (or MRI if performed at screening)								(x) [e]					
CT scan if PD detected (lymph nodes only)	x												
Adverse events	x	x	x	x	x	x	x	x	x	x	x		x
Concomitant medication	x	x	x	x	x	x	x	x	x	x	x		x
PRO questionnaires (MDASI-CLL, EQ-5D-5L, EORTC QLQ-C30) [f]	x	x	x	x	x	x	x	x	x	x	x	x	x
Local Laboratory													
Hematology (Day 1)	x	x	x	x	x		x	x		x	x	x	x
Biochemistry (Day 1)	x	x	x	x	x		x	x		x	x	x	x
Pregnancy Test [g]	x	x	x	x	x		x			x	x	x	x

Appendix 1: Schedule of Activities for Arm A

Arm A (VEN + G) Assessment	C3	C4	C5	C6	Day 28 after Completion/ Early Termination of Combination Therapy[a]	C7	C8	EOCTRV 8–12 Weeks Post End of Combination[b]	C9	C10	C11	C12	Day 28 after Treatment Completion/Early Termination of Ven Monotherapy [c]
BM biopsy/aspirate								(x)[h]					
Central Laboratory													
MRD in PB by NGS		x						x				x	
MRD in PB by ASO-PCR								x					
MRD in BM								(x) [i]					
ctDNA					(x) [j]								(x) [j]
Blood for genetic analysis (genetic complexity, gene mutations and resistance markers)					(x) [j]								(x) [j]

ASO-PCR = allele-specific oligonucleotide polymerase chain reaction; C = Cycle; CLL = chronic lymphocytic leukemia; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EOCTRV = End of Combination Treatment Response Visit; EORTC-QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-5L = EuroQol 5-Dimension Questionnaire, 5-level version; LVEF = left ventricular ejection fraction; MDASI-CLL = MD Anderson Symptom Inventory for Chronic Lymphocytic Leukemia; MRD = minimal residual disease; NGS=next-generation sequencing; PD = progressive disease; PR = partial response; PRO = patient-reported outcome; VEN + G = venetoclax (Venclexta® or Venclyxto®) in combination with obinutuzumab (Gazyva® or Gazyvaro®).

Appendix 1: Schedule of Activities for Arm A

Notes: For laboratory samples drawn on days on 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 ±15-minute window of any scheduled time. Any laboratory tests occurring at time intervals greater than or equal to 24 hours after dose should be obtained within a ±2–hour window of the scheduled time.

[a] This visit is mandatory for all patients. For patients who discontinue all study drug prior to completing the combination period, the Early Treatment Termination Visit occurs 28 days after last dose of study treatment. For patients that have completed the full 6 cycles of combination therapy, this visit should be performed at the same time as C7D1.

[b] Patients who discontinue all study drug prior to completing the combination period should have their EOCTRV visit performed 8-12 weeks after the last dose of combination therapy. Patients who discontinue study drug for reasons other than progressive disease prior to completing 12 cycles of therapy should continue to be followed for disease progression and MRD assessment per the schedule of assessments (follow-up period). For patients who have not discontinued study drugs and have completed the full 6 cycles of combination therapy, the EOCTRV visit should be performed 8-12 weeks after the last dose of combination therapy. This visit may be performed on the same day as other scheduled visits (e.g., C8D1 or C9D1)

[c] Patients who complete venetoclax monotherapy or who discontinue all study drug prior to completing 12 cycles of treatment should have their early termination visit performed 28 days after the last dose of study drug was administered. For patients in Arm A, this would be the last day of venetoclax administration. Patients who discontinue study drug prior to completing 12 cycles of therapy should continue to be followed for disease progression and MRD assessment per the schedule in schedule of assessments (follow-up period).

[d] The CLL response assessment will consist of a physical examination and laboratory tests.

[e] CT scan is only required at this visit in patients who discontinue all treatment early during the combination phase.

[f] PRO questionnaires scheduled for administration during a clinic visit should be completed prior to the performance of non-PRO assessments and the administration of study treatment.

[g] All women who are not postmenopausal (≥12 months of non-therapy-induced amenorrhea) or surgically sterile will have a serum pregnancy test monthly while receiving study drug and at the Treatment Completion/Early Termination visit.

[h] A bone marrow biopsy and aspirate (including for central assessment of MRD) must be taken in patients who discontinue all treatment early during the combination phase and achieve a CR/PR

[i] A bone marrow aspirate must be taken in patients who discontinue treatment early during the combination phase and achieve a CR/PR for central assessment of MRD.

[j] ctDNA sample and blood for genetic analysis sample collection is mandatory in patients who have discontinued due to disease progression.

ARM A: Follow-Up Period

Arm A (VEN+G) Assessments		Follow-Up Visits Duration from Last Study Drug Administration until Disease Progression			Survival (All Patients)
Assessment	+3 months after Early Termination [a]	Month 15[b]	+6, 9, 12, 15, 18, and 21 months after Treatment Completion/Early Termination	+24 months after Treatment Completion/Early Termination then every 6 months until end of study	Every year after disease progression until end of study
Complete physical examination	x	x	x	x	
Weight	x	x	x	x	
Vital signs [c]	x	x	x	x	
ECG 12-lead	As clinically indicated	As clinically indicated	As clinically indicated	As clinically indicated	
LVEF	As clinically indicated	As clinically indicated	As clinically indicated	As clinically indicated	
Physical examination [d]	x	x	x	x	
Liver/spleen (by physical examination)	x	x	x	x	
ECOG Performance Status	x	x	x	x	
B-symptoms (see Section 4.5.12.3)	x	x	x	x	
CT scan assessment (or MRI if performed at screening)	x	x			
CT scan if PD is detected by lymph nodes only	x				
CLL response assessment[e]	x	x	x	x	
PRO questionnaire (MDASI-CLL, EQ-5D-5L, and EORTC-QLQ C30) until NLT [f]	x	x	x	x	
Collection of NLT	x	x	x	x	x
Related serious adverse events	x	x	x	x	x
Concomitant medication	x	x	x	x	x
All second primary malignancies	x	x	x	x	x

Appendix 1: Schedule of Activities for Arm A

Arm A (VEN + G) Assessments		Follow-Up Visits Duration from Last Study Drug Administration until Disease Progression			Survival (All Patients)
Assessment	+ 3 months after Early Termination [a]	Month 15[b]	+ 6, 9, 12, 15, 18, and 21 months after Treatment Completion/Early Termination	+ 24 months after Treatment Completion/Early Termination then every 6 months until end of study	Every year after disease progression until end of study
Local Laboratory					
Hematology [g]	x	x	x	x	
Chemistry [h]	x	x	x	x	
Immunoglobulin (IgA, IgG, IgM)	x	x	x	x	
Urinalysis [i]	x	x			
BM biopsy/aspirate	(x)[j]	x [k]			
Central Laboratory					
Blood for Lymphocyte counts/ Immunophenotyping (B-CLL count, B-cell, T-Cell and NK cell markers) by flow cytometry			x (12 & 18 months only)	x	
MRD in PB by NGS	x	x	x	x	
MRD in PB by ASO-PCR		x			
MRD in BM	(x)[j]	x [k]			
ctDNA		x	(x)[l]	(x)[l]	
Blood for genetic analysis (genetic complexity, gene mutations and resistance markers)		x	(x)[l]	(x)[l]	

ASO-PCR = allele-specific oligonucleotide polymerase chain reaction; BM = bone marrow; C = Cycle; CLL = chronic lymphocytic leukemia; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-5L = EuroQol 5-Dimension Questionnaire, 5-level version; LVEF = left ventricular ejection fraction; MDASI-CLL = MD Anderson Symptom Inventory for Chronic Lymphocytic Leukemia; MRD = minimal residual disease; MRI = magnetic resonance imaging; NGS = next-generation sequencing; NLT = next line treatment; PD = progressive disease; PRO = patient-reported outcome; VEN + G = venetoclax (Venclexta® or Venclyxto®) in combination with obinutuzumab (Gazyva® or Gazyvaro®).

Appendix 1: Schedule of Activities for Arm A

Notes: All assessments during treatment period and at the follow-up Day 28 visit should be performed within 7 days of the scheduled visit, unless otherwise specified. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified. Following the end of treatment assessment (12 weeks after treatment completion/early termination) all other follow-up assessments, whether tumor assessments or other study assessments, will be done within ±14 days for 3-month and within a month for 6-month assessments of the scheduled visits.

[a] Visit should be performed no earlier than 8 weeks and no later than 12 weeks after last dose of study drug. If the patient is in CR or PR following the CT scan a bone marrow biopsy should be performed a minimum of 12 weeks after last dose of study drug. This visit also correlates to 8 weeks after the Day 28 after Treatment Completion/Early Termination visit.

[b] Month 15 is to be performed 15 months from C1D1 in all patients who have not developed progressive disease.

[c] Includes pulse rate, respiratory rate, and systolic and diastolic blood pressure while the patient is in a seated position, and temperature.

[d] Physical examination includes evaluation of the head, eyes, ears, nose, and throat; cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems; and assessment for lymphadenopathy. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF

[e] The CLL response assessment will consist of a physical examination and laboratory tests. A CT scan is only required at the first follow-up visit (3 months after early termination) or at Month 15. If at any time during follow-up when clinical or laboratory findings suggest that the response may have improved from SD to PR, or from PR to CR, a CT scan may be performed to confirm the response.

[f] PRO questionnaires scheduled for administration during a clinic visit should be completed prior to the performance of non-PRO assessments and the administration of study treatment.

[g] Includes: WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells.

[h] Includes: sodium, potassium, chloride, bicarbonate, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total and direct bilirubin, alkaline phosphatase, ALT, AST, uric acid, and LDH.

[i] Includes: dipstick pH, specific gravity, glucose, protein, ketones, blood, and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria).

[j] A bone marrow biopsy and aspirate (including for central assessment of MRD) must be taken in patients who discontinue treatment early during the monotherapy phase and achieve a CR/PR.

[k] A bone marrow biopsy and aspirate (including for central assessment of MRD) must be taken in patients who achieve a CR/PR. A bone marrow biopsy/aspirate is not required in patients who have discontinued and have had a BM biopsy done at their +3 months after early termination visit.

[l] ctDNA sample and blood for genetic analysis sample collection is mandatory in patients who have discontinued due to disease progression.

Appendix 2
Schedule of Activities for Arm B

Arm B: Schedule of Assessments

Arm B (FCR/BR) Assessments	Screening	Combination (FCR/BR) Therapy													Observation and Follow-Up			
		Cycle 1					Cycles 2–3					Cycle 4	Cycles 5–6	Day 28 after Treatment Completion or Early Termination [b]	EOCTR Visit / [c]	Follow-Up Visits [d]	Month 15[e]	Survival Follow-Up Visits
Day	−28 to −1	1 [a]	2	3	8	15	1	2	3	8	15	1	1					
Informed consent [f]	x																	
Demographic data	x																	
TLS laboratory-based risk assessment	x																	
General medical history	x																	
CIRS score	x																	
Vital signs [g]	x	x	x	x			x	x	x			x	x	x	x	x	x	
Weight	x	x					x					x	x	x	x	x	x	
Height	x																	
Complete physical examination [h]	x											x		x	x	x	x	
Clinical staging [h]	x																	

Appendix 2: Schedule of Activities for Arm B

Arm B (FCR/BR) Assessments	Screening	Combination (FCR/BR) Therapy													Observation and Follow-Up			
		Cycle 1					Cycles 2–3					Cycle 4	Cycles 5–6	Day 28 after Treatment Completion or Early Termination [b]	EOCTR Visit / [c]	Follow-Up Visits [d]	Month 15[e]	Survival Follow-Up Visits
Day	−28 to −1	1 [a]	2	3	8	15	1	2	3	8	15	1	1					
Lymphadenopathy (during physical examination/ Binet staging at screening)	x											x		x	x	x	x	
Liver/spleen (by physical examination)	x											x		x	x	x	x	
ECG 12 lead	x	As clinically indicated																
LVEF	x	As clinically indicated																
ECOG Performance Status	x	x					x					x	x	x	x	x	x	
B-symptoms (see Section 4.5.12.3)	x	x					x					x	x	x	x	x	x	
CT scan assessment (or MRI if performed at screening) [i]	x														x			
CT scan if PD detected (lymph nodes only)	x																	
CLL response assessment [j]												x		x	x	x	x	
BM biopsy/aspirate [k]	(x)														x			
Fludarabine		Days 1-3 (Cycles 1–6)																

Appendix 2: Schedule of Activities for Arm B

Arm B (FCR/BR) Assessments	Screening	Combination (FCR/BR) Therapy													Observation and Follow-Up			
		Cycle 1					Cycles 2–3					Cycle 4	Cycles 5–6	Day 28 after Treatment Completion or Early Termination [b]	EOCTR Visit / [c]	Follow-Up Visits [d]	Month 15[e]	Survival Follow-Up Visits
Day	−28 to −1	1 [a]	2	3	8	15	1	2	3	8	15	1	1					
Cyclophosphamide		Days 1-3 (Cycles 1–6)																
Rituximab		x	(x)				x					x	x					
Bendamustine		Day 1 & 2 (Cycles 1–6)																
Adverse events [f]	x	x	x	x			x	x	x			x	x	x	x	x	x	*x*
Concomitant medications	x	x	x	x			x	x	x			x	x	x	x	x	x	*x*
All second primary malignancies	x	x	x	x			x	x	x			x	x	x	x	x	x	x
PRO questionnaires (MDASI-CLL, EQ-5D-5L, and EORTC-QLQ-C30) [l]		x					x					x	x	x	x	x	x	
Collection of NTL															x	x	x	x
Local Laboratory [m]																		
IGHV[n]	x																	
Immunoglobulins	x																	
HBV, HCV, HIV, HTLV1 (if applicable) [o]	x																	
Coombs test	x																	

Appendix 2: Schedule of Activities for Arm B

Arm B (FCR/BR) Assessments	Screening	Combination (FCR/BR) Therapy													Observation and Follow-Up			
		Cycle 1					Cycles 2–3					Cycle 4	Cycles 5–6	Day 28 after Treatment Completion or Early Termination [b]	EOCTR Visit / [c]	Follow-Up Visits [d]	Month 15[e]	Survival Follow-Up Visits
Day	−28 to −1	1 [a]	2	3	8	15	1	2	3	8	15	1	1					
Coagulation (INR OR PT, AND aPTT or PTT)	x																	
Pregnancy test [p]	x	x					x					x	x	x				
Urinalysis [q]	x																	
Hematology [r]	x	x	x	x	x	x	x	x	x			x	x	x	x	x	x	
Chemistry [s]	x	x	x	x	x	x	x	x	x			x	x	x	x	x	x	
Central Laboratory [a]																		
Serum Parameters (β2 microglobulin, thymidine kinase)		x																
Blood for CLL Prognostic factors (including IGHV, 17p, *TP53*)	x																	
Blood for Lymphocyte counts/ Immunophenotyping (B-CLL count, B-cell, T-Cell and NK cell markers) by flow cytometry	x																	

Appendix 2: Schedule of Activities for Arm B

Arm B (FCR/BR) Assessments	Screening	Combination (FCR/BR) Therapy													Observation and Follow-Up			
		Cycle 1					Cycles 2–3					Cycle 4	Cycles 5–6	Day 28 after Treatment Completion or Early Termination [b]	EOCTR Visit / [c]	Follow-Up Visits [d]	Month 15[e]	Survival Follow-Up Visits
Day	−28 to −1	1 [a]	2	3	8	15	1	2	3	8	15	1	1					
MRD in PB by NGS	x											x			x	x	x	
MRD in PB by ASO-PCR	x														x		x	
MRD in BM															x [t]			
ctDNA	x													(x)[u]		(x)[u]	x	
Blood for genetic analysis (genetic complexity, gene mutations and resistance markers)	x													(x)[u]		(x)[u]	x	

ASO-PCR = allele-specific oligonucleotide polymerase chain reaction; BM = bone marrow; BR = bendamustine and rituximab; C = Cycle; CIRS = cumulative illness rating scale; CLL = chronic lymphocytic leukemia, CR = complete response; CT = computed tomography; D = Day; ECOG = Eastern Cooperative Oncology Group; EOCTRV = End of Combination Treatment Response Visit; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; eCFR = electronic Case Report Form; EQ-5D-5L = EuroQol 5-Dimension Questionnaire, 5-level version; FCR = fludarabine, cyclophosphamide, and rituximab; HBV = hepatitis B virus; HCV = hepatitis C virus; HTLV1 = human T-cell leukemia virus 1; LVEF = left ventricular ejection fraction; M = Month; MDASI-CLL = MD Anderson Symptom Inventory for Chronic Lymphocytic Leukemia; MRD = minimal residual disease; MRI = magnetic resonance imaging; NGS = next-generation sequencing; NTL = next treatment line; PB = peripheral blood; PD = progressive disease; PR = partial response; PRO = patient-reported outcome.

Appendix 2: Schedule of Activities for Arm B

Notes: All assessments during treatment period and at the follow-up Day 28 visit should be performed within 7 days of the scheduled visit, unless otherwise specified. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified. Following the end of treatment assessment (12 weeks after treatment completion/early termination) all other follow-up assessments, whether tumor assessments or other study assessments, will be done within ±14 days for 3-month and within a month for 6-month assessments of the scheduled visits.

[a] Samples should be taken after a randomization number has been assigned.

[b] Patients who discontinue all study drug prior to completing 6 cycles of treatment should have their early termination visit performed 28 days after the last dose of study drug was administered. Patients who discontinue study drug prior to completing 6 cycles of therapy should continue to be followed for disease progression per the schedule of assessments.

[c] Visit should be performed no earlier than 8 weeks and no later than 12 weeks after end of treatment/early termination. If the patient is in CR or PR following the CT scan a BM examination should be performed a minimum of 12 weeks after the end of the treatment. This visit also correlates to 8 weeks after the Day 28 after Treatment Completion/Early Termination visit.

[d] Follow-up visits occur every 3 months until 3 years and then every 24 weeks until PD.

[e] Month 15 is to be performed 15 months from C1D1 in all patients who have not developed progressive disease.

[f] After the informed consent has been obtained but prior to initiation of study drug, only adverse events and serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 28 days after the last dose of study drug, or until initiation of another anti-cancer therapy, whichever occurs first. After this period, the investigator is not required to actively monitor patients for adverse events; however, the Sponsor should be notified if the investigator becomes aware of any post-study serious adverse event that is believed to be related to prior exposure to study drug or any second primary malignancies, irrespective of whether they are believed to be related to previous study treatment or not. In addition, all deaths, regardless of cause, should be reported. The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

[g] Vital signs include measurements of respiratory rate, pulse rate and systolic and diastolic blood pressure while the patient is in a seated position, and temperature.

[h] Physical examination includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF. Binet staging will be assessed using data collected at the screening visit. Physical examinations may be performed 1 day prior to a planned treatment visit to facilitate scheduling.

[i] CT scans are allowed 8 weeks prior to randomization and required as confirmation of CR/PR 12 weeks after end of treatment. An MRI is only to be conducted if a contrast enhanced CT is not possible. All patients must have a baseline CT scan (or MRI if CT is not possible) of the neck (if indicated), chest, abdomen, and pelvis with IV and oral contrast. Conventional CT and MRI should be performed with contiguous cuts of 10 mm or less in slice thickness. Spiral CT should be performed by use of a 5-mm contiguous reconstruction algorithm; this specification applies to the tumors of the chest, abdomen, and pelvis. If MRIs are used instead of CT scans, MRIs should be used consistently throughout the study.

[j] The CLL response assessment will consist of a physical examination and laboratory tests.

[k] A BM biopsy and aspirate is optional at screening (investigator discretion if clinically indicated) and can be performed 8 weeks prior to randomization. At the end of treatment response visit, a BM biopsy and aspirate is required to confirm response in all responding patient (CR/PR).

[l] PRO questionnaires scheduled for administration during a clinic visit should be completed prior to the performance of non-PRO assessments and the administration of study treatment.

[m] For laboratory samples drawn on days of study treatment, predose samples should be drawn within 0–4 hours before the dose. If these results need to be reviewed prior to dosing and if it is not possible to review results from a sample taken up to 4 hours predose, then it is acceptable to take a predose hematology and chemistry sample within 24 hours prior to dosing. The results of these samples can be reviewed prior to dosing. 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 safety. Other laboratory samples occurring on the same day should be obtained within a ±15-minute window of any scheduled time. Any laboratory tests occurring at time intervals ≥24 hours after dose should be obtained within a ±2-hour window of the scheduled time.

[n] IGHV mutational status is required for randomization. Historical results irrespective of when test was performed can be used (tests that have occurred prior to the 28-day screening window are valid indefinitely and do not need to be repeated). If IGHV mutational status is unknown at screening, then sites will need to perform this locally prior to randomization. Patients with an undetermined IGHV mutational status cannot be randomized and will be considered a screen-fail.

[o] Certain patients, those with occult or prior HBV infection, require monthly DNA testing, although the data is not collected for the study.

[p] All women who are not postmenopausal (i.e., ≥12 months of non-therapy-induced amenorrhea) or surgically sterile will have a serum pregnancy test at screening. If a serum pregnancy test has not been performed 14 days prior to the first dose, a urine pregnancy test must be performed 7 days prior to the first dose. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test. Further, all women who are not postmenopausal (i.e., ≥12 months of non-therapy-induced amenorrhea) or surgically sterile will have a serum pregnancy test monthly while receiving study drug and at the Treatment Completion/Early Termination visit.

[q] Urinalysis includes: dipstick pH, specific gravity, glucose, protein, ketones, blood, and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria).

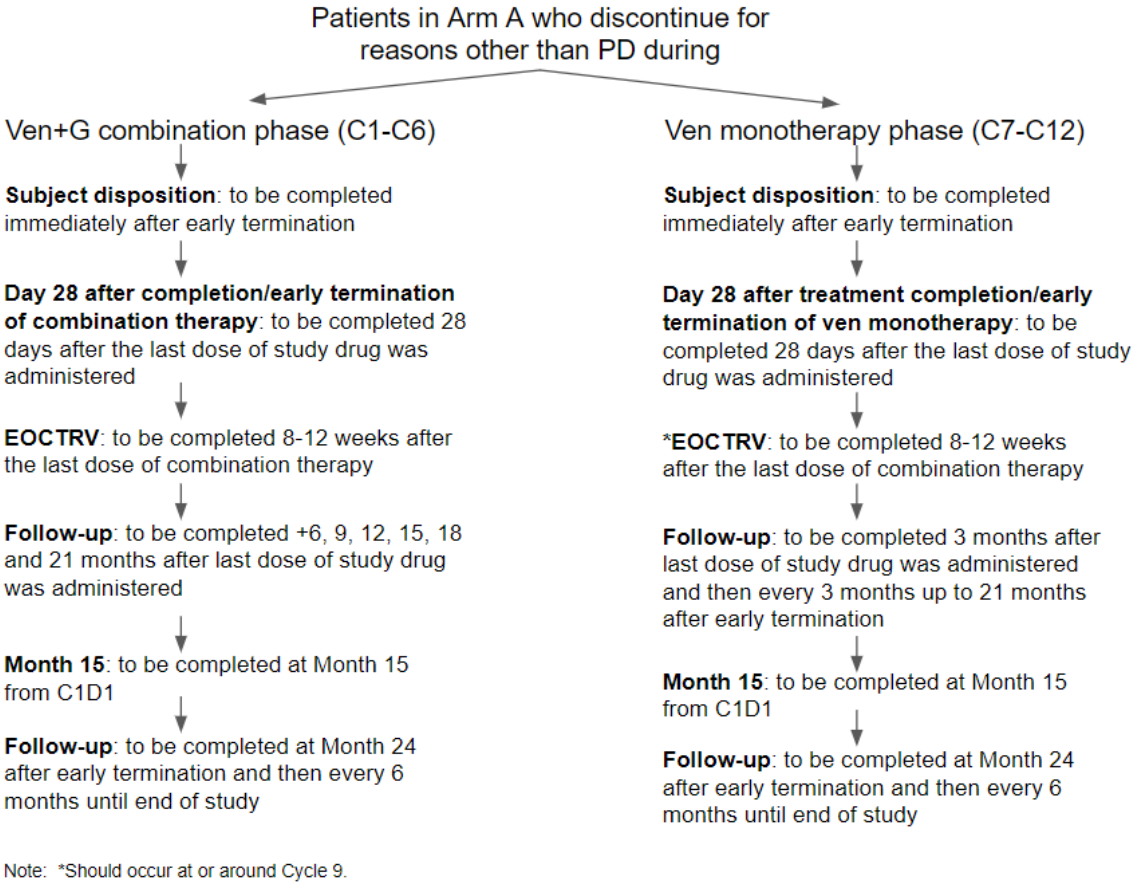
[r] Hematology includes: WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells.

[s] Chemistry includes: sodium, potassium, chloride, bicarbonate, glucose, BUN or urea, creatinine, total protein, albumin, phosphorus, calcium, total and direct bilirubin, alkaline phosphatase, ALT, AST, uric acid, LDH.

[t] A BM aspirate must be taken in patients who achieve a CR/PR for central assessment of MRD.

[u] ctDNA sample and blood for genetic analysis sample collection is mandatory in patients who have discontinued due to disease progression.

Appendix 3
Visits for Arm A Patients Who Discontinue Treatment for Reasons Other than Progressive Disease



Note: *Should occur at or around Cycle 9.

Appendix 4
Sample List of Excluded and Cautionary Medications for Patients Randomized to Arm A (Venetoclax + Obinutuzumab)

Type	Medication
Excluded 7 days prior to and during the venetoclax ramp-up period and cautionary after patients are on 400 mg/day of venetoclax	
Strong CYP3A inducers	Avasimibe, carbamazepine (Tegretol®), phenobarbital, phenytoin (Dilantin®), rifampin (Rifadin®), and St. John's wort
Moderate CYP3A inducers	Bosentan, efavirenz, etravirine, modafinil, and nafcillin
Strong CYP3A inhibitors [a]	Boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, mibefradil, lopinavir/ritonavir, nefazodone, nelfinavir, ritonavir, posaconazole, saquinavir, telaprevir, telithromycin, and voriconazole
Moderate CYP3A inhibitors [a]	Amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib [b], darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib [b], and verapamil
Cautionary throughout the study	
Warfarin	—
Weak CYP3A inducers	Amprenavir, aprepitant, armodafinil, clobazamechinacea, pioglitazone, prednisone, rufinamide, and vemurafenib [b]
Weak CYP3A inhibitors	Alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide [b], cilostazol, cimetidine, cyclosporine [b], fluoxetine, fluvoxamine, ginkgo, goldenseal, isoniazid, nilotinib [b], oral contraceptives, pazopanib [b], ranitidine, ranolazine, tipranavir/ritonavir, ticagrelor, and zileuton
P-gp substrates	Aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus [b], fexofenadine, lapatinib [b], loperamide, maraviroc, nilotinib [b], ranolazine, saxagliptin, sirolimus [b], sitagliptin, talinolol, tolvaptan, and topotecan [b]
BCRP substrates	Methotrexate [b], mitoxantrone [b], irinotecan [b], lapatinib [b], rosuvastatin, sulfasalazine, and topotecan [b]
OATP1B1/1B3 substrates	Atrasentan, atorvastatin, ezetimibe, fluvastatin, glyburide, rosuvastatin, simvastatin acid, pitavastatin, pravastatin, repaglinide, telmisartan, valsartan, and olmesartan
P-gp inhibitors	Amiodarone, azithromycin, captopril, carvedilol, dronedarone, felodipine, quercetin, ronalzine, and ticagrelor
BCRP inhibitors	Gefitinib [b], cyclosporine [b]
OATP1B1/B3 inhibitors	Gemfibrozil, eltrombopag, cyclosporine [b], tipranavir

Note: This is not an exhaustive list; refer to the label of the drug under consideration for the most current drug-drug intervention information. For an updated list, see the following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm. In addition to the medications listed in this table, patients receiving venetoclax should not consume grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges), or star fruits.

[a] After discontinuation of a strong or moderate CYP3A inhibitor, wait for 3 days before venetoclax dose is increased back to the initial maintenance/target dose.

[b] These are anti-cancer agents; contact Medical Monitor before use.

Appendix 5
M.D. Anderson Symptom Inventory (MDASI-CLL)

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

Part I. How **severe** are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been ***in the last 24 hours***. Please select a number from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

		Not Present										As Bad As You Can Imagine
		0	1	2	3	4	5	6	7	8	9	10
1.	Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
2.	Your **fatigue (tiredness)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
3.	Your **nausea** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
4.	Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
5.	Your feeling of being **distressed (upset)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
6.	Your **shortness of breath** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
7.	Your problem with **remembering things** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
8.	Your problem with **lack of appetite** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
9.	Your feeling **drowsy (sleepy)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
10.	Your having a **dry mouth** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
11.	Your feeling **sad** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
12.	Your **vomiting** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
13.	Your **numbness or tingling** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

	Not Present 0	1	2	3	4	5	6	7	8	9	As Bad As You Can Imagine 10
14. Your **night sweats** at their WORST?	○	○	○	○	○	○	○	○	○	○	○
15. **Fevers and chills** at their WORST?	○	○	○	○	○	○	○	○	○	○	○
16. **Lymph node swelling** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
17. Your **diarrhea** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
18. Your **bruising easily or bleeding** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
19. Your **constipation** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

Part II. How have your symptoms **interfered** with your life?

Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items *in the last 24 hours*? Please select a number from 0 (s… h… no…terfered) to 10 (symptoms interfered completely) for each item.

	Did Not Interfere 0	1	2	3	4	5	6	7	8	9	Interfered Completely 10
20. **General activity?**	○	○	○	○	○	○	○	○	○	○	○
21. **Mood?**	○	○	○	○	○	○	○	○	○	○	○
22. **Work (including work around the house)?**	○	○	○	○	○	○	○	○	○	○	○
23. **Relations with other people?**	○	○	○	○	○	○	○	○	○	○	○
24. **Walking?**	○	○	○	○	○	○	○	○	○	○	○
25. **Enjoyment of life?**	○	○	○	○	○	○	○	○	○	○	○

Appendix 6
European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _ _ _ _

Your birthdate (Day, Month, Year): _ _ _ _ _ _ _ _

Today's date (Day, Month, Year): 31 _ _ _ _ _ _ _ _

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 7
EuroQol 5-Dimension, 5-Level (EQ-5D-5L) Questionnaire

Do not reproduce or distribute. The Sponsor will provide sites with all instruments to be completed in this study.

Health Questionnaire

English version for the USA

Appendix 7: EuroQol 5-Dimension, 5-Level (EQ-5D-5L) Questionnaire

Under each heading, please tick the **ONE** box that best describes your health **TODAY**

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

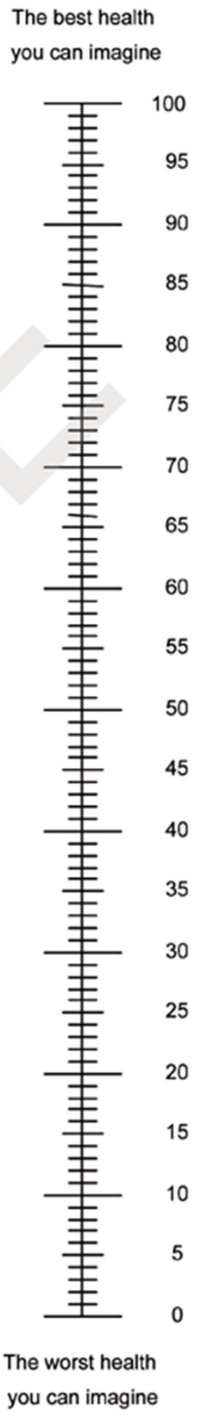
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is **TODAY**.
- This scale is numbered from **0** to **100**.
- **100** means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an **X** on the scale to indicate how your health is **TODAY**.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix 8
The Modified Cumulative Illness Rating Scale (CIRS)

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. Muscolo-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

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. 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) (Miller et al. 1992); moreover, Miller and Towers provided also a manual of guidelines for scoring their version (Miller et al. 1991).

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 (Parmelee et al. 1995).

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 (Mistry et al. 2004).

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), 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 patients with diabetes), and an EKG. For rating psychiatric conditions, the rater is expected to be familiar with the Mini Mental Status Examination (Folstein et al. 1975), and the Diagnostic and Statistical Manual IV (DSM IV) APA 1994). 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, 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, 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 II 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. CHF compensated with meds (NYHA I-II); 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 II–III) 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 III–IV 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

5. No problem
6. 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
7. 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/mmc; mild thrombocytopenia (50,000−150,000/mmc)

8. DVT 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/mmc; severe thrombocytopenia (<50,000/mmc)
9. 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.

10. No problem
11. Recurrent episodes of acute bronchitis; currently treated asthma with prn inhalers when required; cigarette smoker >10 but <20 pack years
12. 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
13. 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
14. 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 × Number of years smoked in their lifetime

e.g., 1 pack-year=20 cigarettes/die (1 pack) × 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/die (1 pack) for 25 years=25 pack-years–CIRS score: 2

b) Patient smoking 40 cig/die (2 packs) for 25 years=50 pack-years–CIRS score: 3

c) Ex-smoker of 20 cig/die (1 pack) for 25 years, he stopped 5 years ago–CIRS score: 2

d) Ex-smoker of 20 cig/die (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 (FEV_1), 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

15. No problems
16. Corrected vision with glasses; mild hearing loss; chronic sinusitis
17. Difficulty in reading newspaper or drive although glasses; required hearing aid; chronic sinonasal complaints requiring medication; vertigo/dizziness requiring daily meds
18. 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)
19. 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, GERD, hiatal hernia, esophageal diverticula, any type

of gastritis (consider also *Helicobacter 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."

20. No problem
21. Hiatal hernia, GERD or gastritis requiring prn meds; previous ulcer (>5 years ago); previous *H. pylori* eradication therapy (>5 years ago)
22. Daily proton pump inhibitor/anti-acid meds; documented gastric or duodenal ulcer or *H. pylori* eradication therapy within 5 years
23. 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
24. 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 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.

25. No problems, previous appendectomy, previous hernia repair (without complications)
26. Constipation managed with prn meds; active hemorrhoids; intestinal hernia requiring surgery; previous hernia repair with complications (intestinal adherences, laparocele, etc.); irritable bowel syndrome (few symptoms)
27. Constipation requiring daily bulk laxatives (psyllium, policarbophil, sterculia, guar gum, etc.), or stool softeners; diverticulosis (previous diverticulitis); inflammatory bowel disease in remission with meds (>5 years ago)
28. 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)
29. 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.

30. No problem
31. History of hepatitis (actually normal values of transaminases); cholecystectomy
32. 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)
33. Chronic hepatitis or any other liver disease with marked elevation of transaminases (>3-times normal values); elevated bilirubin
34. 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 MM should not be considered.

35. No problem
36. Asymptomatic kidney stone; kidney stone passage within the last 10 years; pyelonephritis within 5 years; kidney cysts without hematuria
37. Serum creatinine >1.5 but <3 mg/dL without diuretic or antihypertensive medication (particularly ACE-inhibitors or SRAA blockers); kidney calculi requiring daily meds
38. 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
39. 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 (UTI's), prolapses, etc. Urinary incontinence and indwelling catheter should also be considered.

40. No problem
41. Stress incontinence; BPH without urinary symptoms; hysterectomy or ovariectomy (uterine fibroma, benign neoplasm)
42. 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
43. 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
44. 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).

45. No problem
46. 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

47. Daily anti-osteoarthritis meds (NSAID) or use of assistive devices or little limitation in 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
48. 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
49. 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.

CENTRAL AND PERIPHERAL NERVOUS SYSTEM

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.

50. No problem (or fewer convulsions in childhood)
51. Frequent headaches requiring PRN meds without impairment in Advanced ADL; previous TIA (one event); previous epilepsy, actually not treated, without crisis since more than 10 years ago.
52. 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.
53. 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.
54. 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 benignant (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).

55. No problem
56. 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.
57. 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/m^2); hyperthyroidism in pharmacologic treatment; asymptomatic or surgically treated hyperparathyroidism; fibrocystic breast disease.
58. 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 myocardial infarction or stroke); severe obesity (BMI >45 kg/m^2); symptomatic hyperparathyroidism (e.g., hypercalcemia); replacement therapy for adrenal failure; any electrolytes disorder requiring hospitalization.

59. 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, Neuro-Psychiatric Inventory if available).

60. No psychiatric problem or history thereof
61. 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).
62. 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 10 years ago, including alcoholism).
63. 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 10 years substance abuse or dependence (according to DSM-IV criteria); requires daily antipsychotic medication; previous attempt at suicide.
64. 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 myocardial infarction or stroke, etc.) and evaluation of functional impairment
2. Drugs list (fundamental), including laxatives and tranquilizers (even hypnoinducent)
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 (m^2) 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, and fractioned bilirubin
- Thyroid function and serum B12 (when indicated)
- Hemoglobin A_{1c} (for diabetic patients)

REFERENCES

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV. 4th ed. Washington: Amer. Psychiatric Assn., 1994.

Cummings JL, Mega M, Gray K, et al. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology 1994;44:2308–14.

Folstein MF, Folstein SE, McHugh PR. "Mini Mental State": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–98.

Linn BS, Linn MW, Gurel L. Cumulative Illness Rating Scale. J Am Geriatr Soc 1968;16:622–6.

Miller MD, Paradis CF, Houck PR, et al. Reynolds CF III. Rating chronic medical illness burden in geropsychiatric practice and research: application of the Cumulative Illness Rating Scale. Psychiatry Res 1992; 41:237–48.

Miller MD, Towers A. A manual guideline for scoring the Cumulative Illness Rating Scale for Geriatrics (CIRS-G). Pittsburg, PA: University of Pittsburgh; 1991.

Mistry R, Gokhman I, Bastani R, et al. UPBEAT Collaborative Group. Measuring medical burden using CIRS in older veterans enrolled in UPBEAT, a psychogeriatric treatment program: a pilot study. J Gerontol A Biol Sci Med Sci 2004;59:1068–75.

Parmelee PA, Thuras PD, Katz IR, et al. Validation of the Cumulative Illness Rating Scale in a geriatric residential population. J Am Geriatr Soc 1995;43:130–7.

Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res 1983;17:37–49.

Appendix 9
Standard Cockcroft and Gault Formula for Calculated Creatinine Clearance

For serum creatinine concentration in mg/dL:

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

For serum creatinine concentration in μmol/L:

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

= (μmol/L)

+ age in years, weight (wt) in kilograms

Reference: *Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.*

Appendix 10
National Cancer Institute Common Terminology Criteria

In the present study, toxicities will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0.

A pdf of the NCI CTCAE v5.0 can be downloaded from the following website:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Investigators who do not have access to Internet can contact the Data Center to receive a hard copy of this document by mail.

Appendix 11
Matutes Scoring System

Flow cytometric analysis of peripheral blood or bone marrow is performed for expression of the cell surface markers listed in the table below. The scores for each marker are summed.

	0 Points	1 Point
CD5	Negative	Positive
CD23	Negative	Positive
FMC7	Positive	Negative
S Ig	Strong	Weak
CD22	Strong	Weak

Note: A score of ≥4 is indicative of CLL; a score ≤3 should prompt consideration of an alternative diagnosis.

Source: http://bloodref.com/lymphoid/cll/cll-score

REFERENCE

Matutes E, Owusu-Ankomah K, Morilla R, et al. The immunological profile of B-cell disorders and proposal of a scoring system for the diagnosis of CLL. Leukemia 1994;8:1640–5.

Appendix 12
Recommendations for Initial Management of Electrolyte Imbalances and Prevention of Tumor Lysis Syndrome

PRIOR TO OBINUTUZUMAB INFUSION

Patients with a high tumor burden (absolute lymphocyte count $\geq 25 \times 10^9$/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

- 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.
- For any blood chemistry changes requiring more than 48 hours to resolve, resume venetoclax at the reduced dose, as detailed in Table 9.
- For any events of clinical TLS (defined as laboratory TLS with clinical consequences such as acute renal failure, cardiac arrhythmias, or sudden death and/or seizures), resume venetoclax at reduced dose following resolution, as detailed in Table 9.
- 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:

- 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.

Appendix 13
Body Surface Area (BSA) Calculation Using the Mosteller Formula

The following formula is to be used when calculating BSA:

$$BSA(m^2) = ([Height\ (cm) \times Weight\ (kg)]/3600)^{1/2}$$

Appendix 14
Eastern Cooperative Oncology Group (ECOG) Performance Status

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework or office work)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about >50% of waking hours
3	Capable of only limited self-care, confined to a bed or chair >50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Appendix 15
Guidelines for Defining Tumor Lysis Syndrome

All tumor lysis syndrome events should be graded per the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 criteria.

Howard et al. (2011) defined laboratory tumor lysis syndrome as the presence of two or more electrolyte changes above or below the thresholds described above occurring during the same 24-hour period within 3 days before the start of therapy or 7 days after the start of therapy. For the purposes of this study, this window applies to the initiation of any study therapy and each dose escalation of venetoclax. Furthermore, this assessment assumes that a patient has or will receive adequate hydration (±alkalinization) and a hypouricemic agent(s).

Table 1 Howard Definition of Laboratory Tumor Lysis Syndrome

Laboratory Assessment	Range
Uric acid	>476 μmol/L (>8.0 mg/dL)
Potassium	>6.0 mmol/L (>6.0 mEq/L)
Phosphorous	>1.5 mmol/L (>4.5 mg/dL)
Corrected calcium	<1.75 mmol/L (<7.0 mg/dL) or ionized calcium <1.12 mmol/L $(4.5\ mg/dL)$ [a]

Note: Howard et al. (2011) defined laboratory tumor lysis syndrome as the presence of two or more electrolyte changes above or below the thresholds described above occurring during the same 24-hour period within 3 days before the start of therapy or 7 days afterward. For the purposes of this study, this window applies to the initiation of any study therapy and each dose escalation of venetoclax. Furthermore, this assessment assumes that a patient has or will receive adequate hydration (± alkalinization) and a hypouricemic agent(s).

[a] The corrected calcium level in mg/dL is the measured calcium in mg/dL + (0.8 × [4-albumin in g/dL]).

Table 2 Howard Definition of Clinical Tumor Lysis Syndrome

The presence of laboratory TLS and one or more of the following criteria:
Creatinine [a]: An increase in serum creatinine level of 0.3 mg/dL (26.5 μmol/L); a single value >1.5 times the ULN of the age appropriate normal range if no baseline creatinine measurement is available; or the presence of oliguria, defined as average urine output of <0.5 mL/kg/hour for 6 hours
Cardiac dysrhythmia or sudden death probably or definitely caused by hyperkalemia
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]

TLS=tumor lysis syndrome; ULN=upper limit of normal.

[a] Acute kidney injury is defined as an increase in the creatinine level of ≥0.3 mg/dL (26.5 umol/L) or a period of oliguria lasting ≥6 hours. By definition, if acute kidney injury is present, the patient has clinical TLS.

[b] Not directly attributable to a therapeutic agent.

REFERENCE

Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. New Engl J Med 2011;364:1844–54.

Erratum in The tumor lysis syndrome. New Engl J Med 2018;379:1094.

Appendix 16
Anaphylaxis Precautions

EQUIPMENT NEEDED

- Oxygen
- Epinephrine for subcutaneous, intravenous (IV), and/or endotracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- IV infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment infusion, the following procedures should be performed:

- Stop the study treatment infusion.
- Apply a tourniquet proximal to the injection site to slow systemic absorption of study treatment. Do not obstruct arterial flow in the limb.
- Maintain an adequate airway.
- Administer glucocorticoids, antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
- Continue to observe the patient and document observations.

Appendix 17
Adverse Events Commonly Associated with Chronic Lymphocytic Leukemia Study Population and/or Progression of Chronic Lymphocytic Leukemia

DISEASE-RELATED EVENTS

- Lymphadenopathy
- Splenomegaly
- Hepatomegaly
- Leukemia cutis (macules, papules, plaques, nodules, ulcers, or blisters)
- Lymphocytosis
- Cytopenias (neutropenia, anemia, and thrombocytopenia)
- Febrile neutropenia
- Autoimmune hemolytic anemia
- Autoimmune thrombocytopenia
- Hypogammaglobulinemia
- Infections (bacterial, viral, and fungal)
- Second cancers (Kaposi's sarcoma, malignant melanoma, squamous cell skin cancer, basal cell carcinoma, cancers of the larynx, colorectal cancer, and cancers of the lung)
- Fatigue
- Weight loss
- Pyrexia
- Bruising
- Minor hemorrhages
- Pain (any type)

POPULATION-RELATED COEXISTING MEDICAL CONDITIONS

- Hypertension
- Rheumatoid arthritis/osteoarthritis
- Hyperlipidemia
- Peptic ulcer
- Inflammatory bowel disease
- Coronary artery disease
- Peripheral vascular disease
- Cardiomyopathy
- Valvular disease
- Atrial fibrillation
- Diabetes mellitus
- Chronic obstructive pulmonary disease
- Cerebrovascular accident
- Transient ischemia attack

Appendix 18
Investigational Medicinal Product and Auxiliary/Non-Investigational Medicinal Product Designations (for Use in European Economic Area and United Kingdom)

Table 1 Investigational and Authorized Auxiliary Medicinal Product Designations for European Economic Area

Product Name	*IMP/AxMP Designation*	*Marketing Authorization Status in EEA*	*Used within Marketing Authorization*
venetoclax	*IMP*	*Authorized*	*Yes*
obinituzumab	*IMP*	*Authorized*	*Yes*
fluradabine	*IMP*	*Authorized*	*Yes*
cyclophosphamide	*IMP*	*Authorized*	*Yes*
rituximab	*IMP*	*Authorized*	*Yes*
bendamustine	*IMP*	*Authorized*	*Yes*
rasburicase	*AxMP (rescue medicine)*	*Authorized*	*Yes*
acetaminophen	*AxMP (rescue medicine)*	*Authorized*	*Yes*
paracetamol	*AxMP (rescue medicine)*	*Authorized*	*Yes*
prednisolone	*AxMP (rescue medicine)*	*Authorized*	*Yes*
dexamethasone	*AxMP (rescue medicine)*	*Authorized*	*Yes*
methylprednisolone	*AxMP (rescue medicine)*	*Authorized*	*Yes*
diphenhydramine	*AxMP (rescue medicine)*	*Authorized*	*Yes*
allopurinol	*AxMP (rescue medicine)*	*Authorized*	*Yes*
ondansetron	*AxMP (rescue medicine)*	*Authorized*	*Yes*

AxMP =auxiliary medicinal product; EEA =European Economic Area; IMP =investigational medicinal product.

Note: Rasburicase, acetaminophen, prednisolone, dexamethasone, methylprednisolone, diphenhydramine, allopurinol, and ondansetron are used as pre-medications to treat anticipated adverse reactions.

Appendix 19
Abbreviations

Abbreviation	Definition
1L	first-line
ALC	absolute lymphocyte count
ALL	acute lymphocytic leukemia
AML	acute myeloid leukemia
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
ASO-PCR	allele-specific oligonucleotide polymerase chain reaction
BCL	B-cell lymphoma
BM	bone marrow
BR	bendamustine and rituximab
BSA	body surface area
CCOD	clinical cut-off date
CIRS	cumulative illness rating scale
CLL	chronic lymphocytic leukemia
CMH	Cochran-Mantel-Haenszel
CMV	cytomegalovirus
CR	complete remission
CrCl	creatinine clearance
CRi	complete remission with incomplete blood count recovery
CRO	contract research organization
CRR	complete response rate
CT	computed tomography
ctDNA	circulating tumor DNA
DDI	drug-drug interactions
DIC	disseminated intravascular coagulation
DLBCL	diffuse large B-cell lymphoma
DOR	duration of objective response
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EFS	event-free survival
EMA	European Medicines Agency
EOCT	end of combination treatment
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EOT	end of treatment
EQ-5D-5L	EuroQol 5-Dimension Questionnaire, 5-level version

Appendix 19: Abbreviations

Abbreviation	Definition
EU	European Union
FCR	fludarabine, cyclophosphamide, and rituximab
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
FIT	patients with a CIRS score ≤6 and a normal creatinine clearance of ≥70 mL/min
FL	follicular lymphoma
GClb	obinutuzumab + chlorambucil
G-CSF	granulocyte colony-stimulating factor
GI	gastrointestinal
HBV	hepatitis B virus
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HTLV-1	human T-cell leukemia virus 1
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IgHV	immunoglobulin heavy chain variable region
IND	Investigational New Drug (Application)
IRB/EC	Institutional Review Board/Ethics Committee
IRC	Independent Review Committee
IRR	infusion-related reaction
ITT	intent-to-treat (population)
iwCLL	International Workshop on Chronic Lymphocytic Leukemia
IxRS	interactive voice/web-response system
JCV	John Cunningham virus
LDT	lymphocyte doubling time
LVEF	left ventricular ejection fraction
mAb	monoclonal antibody
MAH	Marketing Authorisation Holder
MCL	mantle cell lymphoma
MDASI-CLL	MD Anderson Symptom Inventory for Chronic Lymphocytic Leukemia
MM	multiple myeloma
MRD	minimal residual disease
MRI	magnetic resonance imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events

Appendix 19: Abbreviations

Abbreviation	Definition
NGS	next-generation sequencing
NHL	non-Hodgkin lymphoma
NIMP	non-investigational medicinal products
ORR	objective response rate
OS	overall survival
PB	peripheral blood
PCR	polymerase chain reaction
PD	progressive disease
PFS	progression-free survival
PK	pharmacokinetic
PML	progressive multifocal leukoencephalopathy
PR	partial response
PRO	patient-reported outcome
PS	performance status
QD	once daily
QoL	quality of life
QTc	QT interval corrected
QTcF	QT interval corrected through use of Fridericia's formula
RBR	Research Biosample Repository
R/R	relapsed/refractory
SAP	Statistical Analysis Plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	stable disease
SEER	Surveillance, Epidemiology, and End Results (report)
SJS	Stevens-Johnson Syndrome
SLL	small lymphocytic lymphoma
TEN	toxic epidermal necrolysis
TLS	tumor lysis syndrome
ULN	upper limit of normal
VEN + G	venetoclax (Venclexta® or Venclyxto®) in combination with obinutuzumab (Gazyva® or Gazyvaro®)
VenR	venetoclax in combination with rituximab

Signature Page for Protocol - CO41685 - VENCLEXTA - v5 - Published
System identifier: RIM-CLIN-489606

Approval Task	[redacted] Company Signatory 07-Jun-2023 20:06:58 GMT+0000