Official Title: **A PROSPECTIVE, OPEN-LABEL, MULTICENTER RANDOMIZED PHASE III TRIAL TO COMPARE THE EFFICACY AND SAFETY OF A COMBINED REGIMEN OF OBINUTUZUMAB AND VENETOCLAX (GDC-0199/ABT-199) VERSUS OBINUTUZUMAB AND CHLORAMBUCIL IN PREVIOUSLY UNTREATED PATIENTS WITH CLL AND COEXISTING MEDICAL CONDITIONS**

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STATISTICAL ANALYSIS PLAN

TITLE: **A PROSPECTIVE, OPEN-LABEL, MULTICENTER RANDOMIZED PHASE III TRIAL TO COMPARE THE EFFICACY AND SAFETY OF A COMBINED REGIMEN OF OBINUTUZUMAB AND VENETOCLAX (GDC-0199/ABT-199) VERSUS OBINUTUZUMAB AND CHLORAMBUCIL IN PREVIOUSLY UNTREATED PATIENTS WITH CLL AND COEXISTING MEDICAL CONDITIONS**

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STUDY DRUG:	Venetoclax
VERSION NUMBER:	2
IND NUMBER:	110159
EUDRACT NUMBER:	2014-0018101-24
SPONSOR:	F. Hoffmann-La Roche Ltd in collaboration with the German Chronic Lymphocytic Leukemia Study Group
CO-SPONSOR (United States only):	AbbVie, Inc.
PLAN PREPARED BY:	[redacted] Ph.D [redacted], M.Sc.
DATE FINAL:	See electronic date stamp below.

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GLOSSARY OF ABBREVIATIONS

AE	adverse event
AEGT	adverse event group term
ASO-PCR	allele-specific oligonucleotide polymerase chain reaction
CLL	chronic lymphocytic leukemia
CR	complete response
CRi	complete response with incomplete bone marrow recovery
CRR	complete response rate
DOR	duration of overall response
ECG	electrocardiogram
EDC	electronic data capture
EFS	Event-free survival
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EOT	end of treatment
FISH	Fluorescence In Situ Hybridization
GClb	obinutuzumab+chlorambucil
HR	hazard ratio
HRQoL	health-related quality of life
IA	interim analysis
iDCC	Independent Data Coordinating Center
iDMC	independent Data Monitoring Committee
IGHV	immunoglobulin heavy chain variable
IRC	Independent Review Committee
ITT	intent to treat
IV	intravenous
IWCLL	International Workshop on CLL
IxRS	interactive voice-/web-based system
LOD	limit of detection
MDASI	MD Anderson Symptom Inventory
MedDRA	medical dictionary for regulatory activities
MMRM	mixed-effects model repeated measures
MRD	minimal residual disease
NCI CTCAE	National Cancer Institute Common Terminology Criteria for AEs
NGS	next-generation sequencing
ORR	overall response rate

GLOSSARY OF ABBREVIATIONS

OS	overall survival
PD	progressive disease
PFS	progression-free survival
PFS FA	PFS final analysis
PR	partial response
PRO	patient reported outcome
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
TLS	tumor lysis syndrome
TTNALT	time to next anti-leukemic treatment

1. BACKGROUND AND SCOPE

This document is based on the Statistical Considerations and Analysis Plan section of the study protocol and will provide more details on the planned statistical analyses. For purposes of registration, the analyses outlined in this Statistical Analysis Plan (SAP) will supersede those specified in the protocol. The SAP will be finalized before Sponsor is unblinded to treatment assignment.

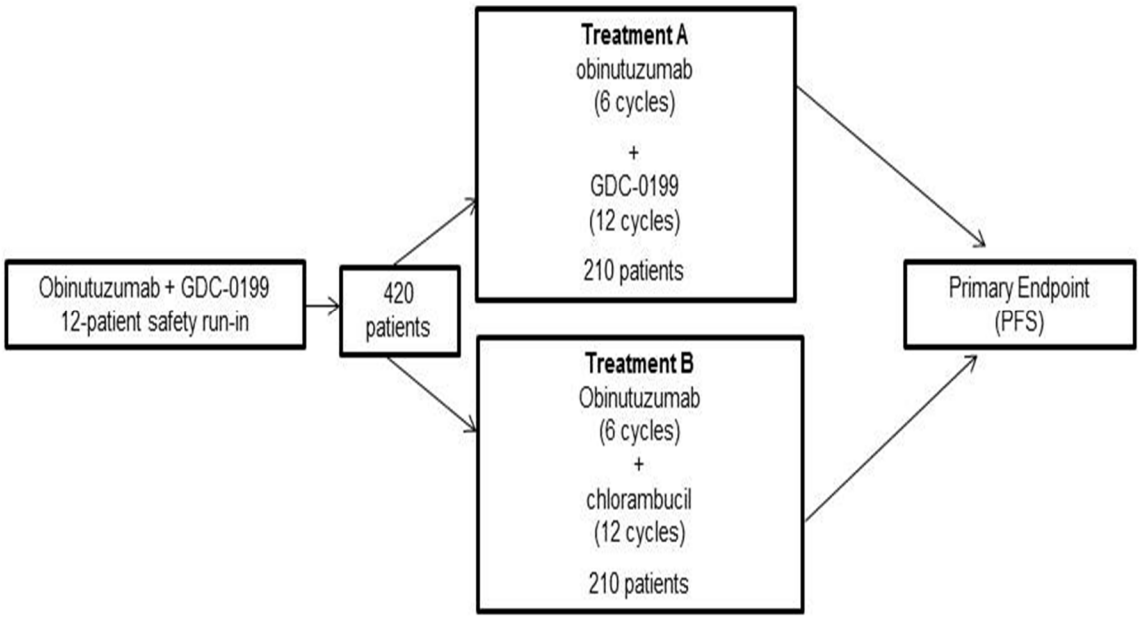
This SAP concerns the analyses of the randomized phase of the study, i.e. including all patients except those in the safety run-in period, who are summarized separately.

2. STUDY DESIGN

This is an open-label, multicenter, randomized Phase III trial to compare the efficacy and safety of a combined regimen of obinutuzumab and venetoclax versus obinutuzumab + chlorambucil (GClb) in patients with chronic lymphocytic leukemia (CLL) and coexisting medical conditions. Figure 1 illustrates the design of the study.

Initially, there was a planned 12-patient safety run-in phase. In the study 13 patients were recruited, (including at least 1 patient at high risk of developing Tumor Lysis Syndrome [TLS]) wherein patients received obinutuzumab + venetoclax in a non-randomized fashion. After the thirteenth patient had reached the end of Cycle 3, a formal review was undertaken by Roche and the German CLL Study Group ([GCLLSG]; together, hereafter referred to as the Sponsor) and an Independent Data Monitoring Committee (iDMC).

Figure 1 Study Schema



GDC-0199 = Venetoclax; PFS = progression-free survival

After the initial safety run-in phase of the study, it was planned to enroll 420 patients into the study who were randomized in a 1:1 ratio to receive either obinutuzumab and venetoclax or GClb, using a block stratified randomization procedure, using the following strata:

- Binet stage (3 levels): A, B, or C.
- Geographic region (US/Canada/Central America; Australia/New Zealand; Western Europe; Central and Eastern Europe; or Latin America).

Patients randomized to receive obinutuzumab and venetoclax have received administered study drugs according to the scheme outlined in Table 1. Patients received 6 cycles of obinutuzumab, and venetoclax until the end of Cycle 12; the duration of each cycle is 28 days. In order to help mitigate adverse events (AEs) of TLS, venetoclax was started at a low dose of 20 mg, followed by a slow ramp up to the target dose of 400 mg at Cycle 2, Day 22. Obinutuzumab treatment started on Cycle 1, Day 1 and venetoclax started on Cycle 1, Day 22.

Table 1 Treatment Arm A: Obinutuzumab + Venetoclax Study Visits

Cycle, Day	Dose
	Obinutuzumab[a]
Cycle 1, Day 1	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
Cycle 2, Day 1–Cycle 6, Day 1	1000 mg
	Venetoclax[c,d]
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

Note: Cycles will comprise 28 days. Treatment for obinutuzumab will be for six 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 drug 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- and 900-mg infusions of obinutuzumab, please consult Protocol Section 4.3.1.3 and the Obinutuzumab Investigator's Brochure regarding drug stability.

[c] 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.

[d] Oral tablets.

Patients randomized to receive GClb received study drugs according to the scheme outlined in Table 2. Patients received 6 cycles of obinutuzumab and 12 cycles of chlorambucil; the duration of each cycle was 28 days.

Table 2 Treatment Arm B: Obinutuzumab + Chlorambucil

Cycle, Day	Dose
	Obinutuzumab
Cycle 1, Day 1[a,b]	100 mg or 1000 mg (follow splitting rules)
Cycle 1, Day 2	900 mg (if 100 mg on Cycle 1, Day 1)
Cycle 1, Day 8	1000 mg
Cycle 1, Day 15	1000 mg
Cycle 2, Day 1–Cycle 6, Day 1	1000 mg
	Chlorambucil[c]
Cycle 1–Cycle 12, Day 1	0.5 mg/kg oral
Cycle 1–Cycle 12, Day 15	0.5 mg/kg oral

Note: Cycles will comprise 28 days. Treatment for obinutuzumab will be for six cycles and 12 cycles for chlorambucil.

[a] Intravenous 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 drug 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 on Day 1 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- and 900-mg infusions of obinutuzumab, please consult Protocol Section 4.3.1.3 and the Obinutuzumab Investigator's Brochure regarding drug stability.

[c] Chlorambucil is given orally on Days 1 and 15 at a dose of 0.5 mg/kg.

2.1 PROTOCOL SYNOPSIS

The Protocol Synopsis is in Appendix 1. For additional details, see the Schedule of Assessments in Appendix 2.

2.2 OUTCOME MEASURES

Response, progression and relapse will be assessed according to the 2008 International Workshop on Chronic Lymphocytic Leukemia (IWCLL) guidelines. The investigator assessment of response and progression will be considered primary for all endpoints described in the study.

The primary efficacy endpoint for this study is progression-free survival (PFS) as assessed by the investigator. However, for U.S. regulatory purposes PFS based on Independent Review Committee (IRC)-assessments will be used.

2.2.1 Primary Efficacy Outcome Measures

The primary efficacy outcome measure for this study is as follows:

- PFS, defined as the time from randomization to the first occurrence of progression, relapse, or death from any cause as assessed by the investigator. Disease progression and relapse will be assessed by the investigators using the IWCLL criteria (2008).

2.2.2 Secondary Efficacy Outcome Measures

The secondary efficacy outcome measures for this study are as follows:

- PFS based on IRC-assessments (primary outcome for U.S. regulatory purposes), defined as the time from randomization to the first occurrence of progression or relapse or death from any cause. Disease progression and relapse will be assessed using the IWCLL criteria (2008).
- Overall Response Rate (ORR) (defined as rate of a clinical response of Complete Response [CR], complete response with incomplete bone marrow recovery [CRi], or Partial Response [PR]) at the completion of treatment assessment (end of treatment [EOT] assessment i.e., 3 months after treatment completion/early termination), as determined by the investigator according to the IWCLL guidelines (2008).
- Complete response rate (CRR; defined as rate of a clinical response of CR or CRi) at the completion of treatment assessment (EOT assessment i.e., 3 months after treatment completion/early termination), as determined by the investigator according to the IWCLL guidelines (2008).
- Minimal Residual Disease (MRD) response rate (determined as the proportion of patients with MRD-negativity) measured in the peripheral blood and bone marrow at the completion of treatment assessment (EOT assessment i.e., 3 months after treatment completion/early termination), both measured by allele-specific oligonucleotide polymerase chain reaction (ASO-PCR).
- ORR at completion of combination treatment response assessment (Cycle 7 Day 1 or 28 days after last intravenous [IV] infusion).
- MRD response rates in the peripheral blood and bone marrow at completion of combination treatment assessment (Cycle 9, Day 1 or 3 months after last IV infusion), both as measured by ASO-PCR.
- MRD response rate in patients with CR (determined as the proportion of patients with MRD-negativity and in Complete Response). MRD is measured in the peripheral blood and bone marrow at the completion of treatment assessment (EOT assessment i.e., 3 months after treatment completion/early termination), both measured by allele-specific oligonucleotide polymerase chain reaction (ASO-PCR), and Clinical Response is defined as a clinical response of CR or CRi at the completion of treatment assessment as determined by the investigator according to the IWCLL guidelines (2008).

Note: the secondary endpoint analyses will be on the basis of MRD assessment performed centrally by ASO-PCR with MRD negativity defined as $< 10^{-4}$ (less than 1 CLL

cell in 10,000 leukocytes). MRD response rates at other time points during treatment and follow-up where MRD is measured in the peripheral blood will also be summarized.

- Overall Survival (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.
- Duration of overall response (DOR), defined as the time from the first occurrence of a documented overall response (CR, CRi, or PR, as assessed by the investigator) to the first occurrence of progression or relapse as determined by the investigator or death from any cause.
- Best response achieved (CR, CRi, PR, Stable Disease [SD], or Progressive Disease [PD] as assessed by the investigator) up to and including the assessment at completion of treatment assessment (within 3 months of last day of treatment).
- Event-free survival (EFS), defined as the time between date of randomization and the date of disease progression/relapse on the basis of investigator-assessment, death from any cause, or start of a new anti-leukemic therapy.
- Time to next anti-leukemic treatment (TTNALT), defined as time between the date of randomization and the date of first intake of new anti-leukemic therapy or death from any cause.

2.2.3 Exploratory Efficacy Outcome Measures

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):

- MRD negativity in peripheral blood, measured using flow cytometry and/or next-generation sequencing (NGS) with MRD negativity defined using a cutoff of 10^{-4} (less than 1 CLL cell in 10,000 leukocytes), 10^{-5} and 10^{-6}.
- Durability of MRD-negativity (at 10^{-4}) over time in peripheral blood measured by ASO-PCR.
- Relationship between MRD at EOT assessment and PFS on the basis of peripheral blood assessed using ASO-PCR.
- Relationship between various baseline markers and clinical outcome parameters in patients from both arms of the study (including but not limited to CLL fluroscence in situ hybridization (FISH) [17p-, 11q-, 13p-, +12q], immunoglobulin heavy chain variable (IGHV) mutational status, TP53 mutation status, serum parameters (β2 microglobulin and thymidine kinase), Bcl-2 expression, and other CLL disease markers).

2.2.4 Patient-Reported Outcome Measures

The patient-reported outcome (PRO) measures for this study are as follows:

- Disease and treatment-related symptoms as measured by MD Anderson Symptom Inventory (MDASI)-CLL to compare the combination of obinutuzumab+venetoclax with GClb.
- Role functioning and health-related quality of life (HRQoL) as measured by European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) to compare the combination of obinutuzumab+venetoclax with GClb.

2.2.5 Pharmacokinetic Outcome Measures

A separate analysis plan for pharmacokinetics will be used.

2.2.6 Pharmacodynamic Outcome Measures

For each visit at which CD19+, CD5+, and CD19+ CD5+ B-cell measurements are taken, B-cell data will be summarized for each visit by treatment arm. A separate analysis plan will be used for pharmacodynamic analyses.

2.2.7 Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Nature, frequency, and severity of AEs and serious adverse events (SAEs).
- Changes in vital signs, physical findings, and clinical laboratory results during and following study treatment.
- Lymphocyte immunophenotyping and incidence of human–anti-human antibodies.
- Premature withdrawals.

2.3 DETERMINATION OF SAMPLE SIZE

The sample size for the study is determined given the requirements to perform a hypothesis test for clinically relevant statistical superiority in the primary endpoint of PFS.

The assumptions used for original sample size calculation are given below. Subsequently the timing of the interim analysis has changed, and the alpha-spending function has changed. However, none of these changes require changes to the sample size.

- Log-rank test at the two-sided 0.05 level of significance.
- Median PFS for obinutuzumab and chlorambucil control arm (27 months).
- 80% power to detect HR=0.65 for the comparison of obinutuzumab+venetoclax experimental arm versus GClb, with median PFS for obinutuzumab+venetoclax increased to 41.5 months.
- Exponential distribution of PFS.

- Annual drop-out rate of 10%.
- One interim analysis for efficacy after 75% of PFS events, utilizing a stopping boundary according to the γ family error spending function with parameter $\gamma = -9.21$.

Based on these assumptions, a total of 170 PFS events are required for the final analysis of PFS. The minimum detectable difference at the final analysis corresponds approximately to an HR = 0.74.

Further details of the analysis timing and interim analysis are provided in Section 4.9 of this SAP.

The sample size calculation was performed using EAST version 6.2.

2.4 ANALYSIS TIMING

Protocol Version 7 allows that up to two formal interim efficacy analyses may be performed. The first potential interim efficacy analysis, occurring at 85 PFS events (50% of total planned PFS events), will not be performed. The only interim analysis which will be conducted is the interim analysis at 110 events. As it will not be conducted, no further detail is provided for the analysis at 85 PFS events. Further details are givein in Section 4.10.

The PFS final analysis is designed to occur after approximately 170 IRC-assessed PFS events have occurred. The OS final analysis will occur at the end of the study. If the interim analysis (IA) crosses the pre-specified boundary, the subsequent final PFS analysis (PFS FA) will not be conducted.

3. STUDY CONDUCT

3.1 RANDOMIZATION SPECIFICATIONS

This is an open-label study.

Randomization was performed by an Interactive Voice-/Web-based System (IxRS). Patients were assigned in 1:1 ratio to one of the two treatment arms through a block stratified randomization procedure.

The randomization scheme ensured approximately equal sample sizes in the two treatment groups in regard to the following stratification factors:

- Binet stage (3 levels): A, B, or C
- Geographic region (US/Canada/Central America; Australia/New Zealand; Western Europe; Central and Eastern Europe; or Latin America).

A unique patient number was assigned to all patients. This patient number is used to identify the patient in the electronic data capture (EDC) system and all other data sources.

The iDMC will review unblinded safety data by treatment arm for the purpose of interim safety reviews and the planned interim analysis of efficacy. The Sponsor and study team do not have access to the unblinded information reviewed by the iDMC. Assessments by the IRC will be blinded to treatment arm.

3.2 INDEPENDENT REVIEW COMMITTEE

Response will be assessed according to the IWCLL guidelines (2008). The investigator assessment of response and progression will be considered primary for all endpoints described in the study, except for the U.S. regulatory purposes, where IRC-assessed PFS will be used. The IRC will be composed of at least three experts (two reviewers and one adjudicator). IRC assessment will be based on peripheral blood counts, bone marrow biopsy results, CT/MRI scan reports and physical examination data. The IRC assessment will be blinded with respect to treatment arm and investigator assessment of response.

Further details about the responsibility and procedures of the IRC are available in a separate document, the IRC Charter.

3.3 DATA MONITORING

This trial includes an iDMC for periodic review of safety and efficacy data collected during the study.

The iDMC reviews the safety data once the randomization was opened. A first safety analysis was planned to occur at the earliest of the following being reached:

- 100 patients randomized and treated for 3 months,

  or
- 9 months have elapsed since the first patient was randomized

  or
- A new case of treatment-related death.

Before the first safety analysis occurs, the iDMC reviews safety data approximately every month depending on the rate of initial recruitment into the study. All further iDMC reviews take place approximately twice per year and the iDMC reviews all safety data collected during the study and the results of any interim analysis performed.

For each review, the iDMC will be provided with:

- General toxicity National Cancer Institute Common Terminology Criteria for AEs (NCI CTCAE): Grade 3 and Grade 4 AEs, all SAEs.
- Laboratory data (hematology and biochemistry).
- Any AE that required discontinuation of the study drug.
- Patient deaths.

- Concomitant medications.

Following each meeting, the iDMC recommends to the Sponsor whether the study may continue according to the protocol, or the iDMC may suggest changes to be made to the protocol on the basis of the outcome of the data review. In exceptional cases, the iDMC may recommend stopping the study or closing a treatment arm due to safety reasons or an overwhelming benefit or lack of efficacy.

An Independent Data Coordinating Center (iDCC) that is independent of the Sponsor prepares analyses for review by the iDMC.

Further details about the definition, the role as well as the responsibility of the iDMC are provided in a separate document, the iDMC Charter.

4. STATISTICAL METHODS

This section outlines the detailed statistical methods to be used for analyzing data in this study. Unless otherwise specified, all continuous variables will be summarized with use of descriptive statistics (the number of non-missing values, mean, standard deviation, median, minimum, and maximum) and all categorical variables will be summarized with use of frequency counts and percentages.

4.1 ANALYSIS POPULATIONS

4.1.1 Intent-to-Treat (ITT) (All Randomized) Population

The primary and secondary analyses will be based on the ITT population, defined as all randomized patients. Patients will be analyzed according to the treatment group to which they were randomized.

4.1.2 PRO-Evaluable Population

PRO-evaluable population will include all randomized patients who have a baseline and at least 1 post-baseline assessment of PRO scales. PRO-evaluable population will be used for descriptive analyses of visit summary and change from baseline and mixed-effects model repeated measures (MMRM) modeling. All PRO analyses will be performed based on the treatment arm assigned at randomization.

4.1.3 Safety Population

All safety analyses will be based on the safety population, defined as all patients who receive at least one dose of any study medication (i.e., obinutuzumab, venetoclax, or chlorambucil). Patients will be analyzed according to the treatment group as actually treated (i.e., patients who received at least one dose of venetoclax will be analyzed under the obinutuzumab+venetoclax arm). In the event that only chlorambucil was received, the patient will be analyzed under the obinituzumab + chlorambucil arm. In the event that only obinitizumab was received, the patient will be analyzed under the arm to which they were randomized.

4.2 ANALYSIS OF STUDY CONDUCT

Enrolment, 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 ITT population using the reverse Kaplan Meier (K-M) method.

4.3 ANALYSIS OF TREATMENT GROUP COMPARABILITY

Descriptive summaries will be provided for the ITT population by treatment groups for the following demographic and baseline variables:

- Stratification factors
  - Binet Stage (3 levels): A, B or C
  - Geographic region: US/Canada/Central America; Australia/New Zealand; Western Europe; Central and Eastern Europe; or Latin America
- Demographics
  - Gender
  - B-symptoms (no vs. yes)
  - Age (continuous and categorical ($<$40, 40–59, 60–69, $\geq$70)
  - Age group: $<$65, $\geq$65; $<$75, $\geq$75.
  - Race
  - Ethnicity
  - TLS risk category (Low, Medium and High)
  - Total Cumulative Illness Rating Scale (CIRS) score
  - Estimated creatinine clearance [according to the formula of Cockroft-Gault] (continuous and categorical with cut-off value$\geq$70 mL/min)
  - IGVH mutational status
  - Cytogenetic factors (deletion 17p, 11q and 13q, and trisomy 12)
  - TP53 mutation status
  - Serum beta2-microglobulin
  - Eastern Cooperative Oncology Group (ECOG) Performance Status at screening.
  - Time from first diagnosis to randomisation

4.4 EFFICACY ANALYSIS

The primary and secondary efficacy analyses will include all randomized patients, with patients grouped according to the treatment assigned at randomization (ITT population).

4.4.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the investigator-assessed PFS, defined as the time from randomization to the first occurrence of progression or relapse (determined using standard IWCLL guidelines [2008]), or death from any cause, whichever occurs first. PFS on the basis of an IRC assessment will be considered primary for U.S. regulatory purposes. For patients who have not progressed, relapsed, or died at the time of analysis, PFS will be censored on the date of the last disease assessment. If no disease assessments were performed after the baseline visit, PFS will be censored at the time of randomization + 1 day. All patients, including patients who discontinue all components of study therapy prior to disease progression (e.g., for toxicity), will continue in the study and will be followed for progressive disease and survival regardless of whether or not they subsequently receive new anti-leukemic therapy.

The primary objective of the study is to test the hypothesis that PFS for obinutuzumab + venetoclax is equal to that of GClb, formally:

H_0: PFS for obinutuzumab+venetoclax = PFS for GClb

H_1: PFS for obinutuzumab+venetoclax ≠ PFS for GClb

Treatment comparisons will be made using a two-sided log-rank test (at 0.05 significance-level, adjusted for the interim analysis), stratified by Binet stage and Geographic Region. If the null hypothesis is rejected and the observed stratified HR is favorable for the obinutuzumab + venetoclax experimental arm, then it is concluded that obinutuzumab + venetoclax significantly lowers the risk of PFS events more than GClb. Median PFS and the 95% confidence limits will be estimated using Brookmeyer Crowley method, with the Kaplan-Meier survival curve presented to provide a visual description. PFS rates for 1, 2, and 3 years after randomization with 95% CIs using Brookmeyer Crowley method will be reported. Estimates of the treatment effect will be expressed as HR including 95% confidence limits estimated through a Cox proportional-hazards analysis stratified by Binet stage and Geographic Region. Primary analysis for FDA submission will be based on assessment of PFS by an IRC.

Sensitivity analyses for PFS will be performed to assess the robustness of the primary analysis of PFS, as outlined in Section 4.4.4 of this SAP.

4.4.2 Secondary Efficacy Endpoints

The following endpoints will be tested in the order listed below:

1. IRC-assessed PFS
2. MRD in bone marrow at EOT assessment
3. CR (investigator-assessed) at EOT assessment
4. MRD in peripheral blood at EOT assessment
5. MRD in CR in bone marrow at EOT assessment

6. MRD in CR in peripheral blood at EOT assessment
7. ORR (investigator-assessed) at EOT assessment
8. OS

If the study meets the primary efficacy endpoint of investigator assessed PFS, then the formal statistical testing procedure for the key secondary endpoints will be performed as detailed in Section 4.4.3.

Secondary time-to-event endpoints of IRC-assessed PFS, OS, EFS, DOR and time to new anti-leukemic treatment will be analyzed using the same statistical methods described for the primary analysis of PFS.

Response rates in the treatment groups will be compared using Cochran-Mantel-Haenszel tests stratified by Binet stage and Geographic Region. Rates and 95% CIs will be reported for each treatment group.

The secondary outcome measures of MRD detailed in Section 2.2.2 of this SAP will be on the basis of assessments performed centrally by ASO-PCR with MRD negativity defined using a cutoff of 10^{-4} (less than 1 CLL cell in 10,000 leukocytes).

MRD status will be determined through the following calculations:

1. If CLL count (as a % of leukocytes) $\geq$ 0.01%; then MRD response status = positive
2. If CLL count (as a % of leukocytes) $<$ 0.01% AND limit of detection (LOD) $\leq$ 0.01% then MRD response status = negative
3. If CLL count (as a % of leukocytes) $<$ LOD, AND LOD $>$ 0.01% then MRD response status = undetermined

The MRD response rates in peripheral blood samples and bone marrow aspirate samples will each be assessed separately. Further analyses will assess MRD response rates separately for peripheral blood samples and bone marrow aspirate samples in responders, defined as CR or CRi. The MRD response rates at EOT assessment will be reported for both treatment arms. Additionally, MRD response rates at each response assessment visit will be summarized. The MRD response rates based on the bone marrow aspirate and peripheral blood samples in responders (CR, CRi, and PR) will be summarized. The best MRD response rate in two treatment arms based on the peripheral blood samples collected in the study will be analyzed. The durability of MRD-negativity in peripheral blood will be illustrated by summarizing MRD response rates at time points during treatment and follow-up. In cases where no post-baseline MRD assessment is available at a specific time point, patients will be considered as MRD-positive, except for those who have not been followed up long enough to have MRD data collected for that timepoint.

4.4.3 Type-1 Error Control

In this study we have multiple endpoints and multiple decision timepoints. To establish a valid claim of efficacy it is important to control the overall type-1 error rate at a pre-specified two-sided acceptable level $\alpha=0.05$. A number of methods are available for controlling α. In this study we have chosen Fallback Procedure (Dmitrienko and D'Agostino, 2013). This is a type of group-sequential procedure with the flexibility to be able to test hypotheses further in the sequence if a previous hypothesis is not rejected. Overall α is split for endpoints in a pre-specified order thereby controlling multiplicity. A brief overview of the steps involved in this testing procedure is outlined below with details in Section 4.10.

Step 1: Test Primary efficacy endpoint (i.e., Investigator-assessed PFS) at $\alpha=0.05$.

Step 2: If the above hypothesis is rejected, then test first secondary efficacy endpoint (i.e., IRC-assessed PFS) at $\alpha=0.05$.

Step 3: If the above hypothesis is rejected, then we move to a different pre-specified α threshold based on Fallback Procedure to test for second secondary endpoint (i.e., MRD in bone marrow).

Step 4: Depending on if the above hypothesis is rejected or accepted then we move to another pre-specified α threshold based on Fallback Procedure to test for third secondary endpoint (i.e., investigator-assesed CR). This procedure continues until the last endpoint in the hierarchy.

With the addition of several timepoints for decision-making (i.e., IA, PFS FA and OS FA) α-spent for each endpoint would be distributed over these timepoints. For the primary and first secondary endpoints (i.e., investigator-assessed PFS and IRC-assessed PFS) gamma-family α-spending method with gamma parameter $\gamma=-9.21$ is used. Assuming there are 110 Investigator-assessed PFS events at the time of the IA, α boundary of 0.0019 will allow the study to stop for efficacy if a treatment effect HR of 0.55 or better in investigator-assessed PFS is observed. For OS, an α-spending function using gamma family with parameter $\gamma=-4$ is used. This will ensure control of overall type-1 error and reserve most of the α for the final OS analysis.

α-spending boundary of each endpoint at each timepoint is provided in Table 3 below.

Table 3 Alpha-spending Boundary of Each Endpoint at Each Analysis

Endpoint		Alpha Spend at Interim Analysis	Progression-Free Survival Final Analysis	Overall Survival Final Analysis FA
1	INV-assessed PFS[a1].	0.0019	0.049	NA
2	IRC-assessed PFS[a1].	0.0019	0.049	NA
3	MRD in bone marrow at EOT assessment	0.05	NA	NA
4	CR (investigator assessed) at EOT assessment	0.05	NA	NA
5	MRD in peripheral blood at EOT assessment	0.05	NA	NA
6	MRD in CR in bone marrow at EOT assessment	0.05	NA	NA
7	MRD in CR in peripheral blood at EOT assessment	0.05	NA	NA
8	ORR (investigator assessed) at EOT assessment	0.05	NA	NA
9	OS[a2]	0.007	0.011	0.045

NA = Not applicable.

For Endpoints 3-8, full $\alpha = 0.05$ is used at IA as the full information is available. The IA dataset will be the one used for any hierarchically-controlled evaluation of endpoints 3-8.

CR = Complete response; IA = interim analysis; IRC = Independent Review Committee; PFS = progression-free survival; MRD = Minimal Residual Disease; ORR = overall response rate; OS = overall survival

a1. Actual α value will depend on number of observed PFS events at IA with Type I error control assured by gamma-family α-spending (see Section 4.4.3).

a2. Determined based on gamma family error spending function with parameter $\gamma = -4$ assuming 55% information fraction at IA and 70% information fraction at PFS FA. It is anticipated that 69 OS events in total will correspond to 100% information fraction, so 55% information fraction corresponds to 38 OS events and 70% information fraction corresponds to 48 OS events.

The testing strategy using the Fallback procedure is detailed in the tables at the end of Section 4.10.

4.4.4 Exploratory Efficacy Endpoints

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 mutational status, *TP53* mutation status, serum parameters, Bcl-2 expression and other CLL disease markers). These will be compared using forest plots.

Exploratory analyses of MRD negativity by time point will also be performed using flow cytometry and new technologies including Next-Generation Sequencing (NGS) with MRD negativity defined using a cutoff of 10^{-4} (less than 1 CLL cell in 10,000 leukocytes) for comparison with ASO-PCR and secondly by different cut-offs of each of the above technologies.

Also, exploratory analyses will be performed, including graphical analyses, of the relationship between MRD (on the basis of peripheral blood results by ASO-PCR) and PFS.

4.4.5 Sensitivity Analyses

To check robustness of the primary analysis of PFS and underlying assumptions, the following sensitivity analyses for PFS (both investigator-assessed and IRC-assessed) will be performed on the ITT population:

- An unstratified log-rank test for the primary PFS comparison between treatment arms will be conducted.
- The impact of patients' initiation of non-protocol–specified anti-CLL therapy without meeting the criteria of disease progression/relapse on PFS will be assessed by censoring these patients at the start date of the non-protocol–specified anti-CLL treatment. Stopping only one component of the randomized study treatment will not be considered a reason for censoring patients.
- To assess the impact of missing assessments on PFS, an analysis on PFS will be performed by censoring those patients who progressed, relapsed or died after missing more than one visit consecutively at their last adequate response assessment date before the missed visits.

4.4.6 Subgroup Analyses

Subgroup analyses of investigator-assessed PFS, IRC-assessed PFS, MRD, ORR, CR and OS will be performed to assess internal consistency using the ITT population. The odds ratios of response and their 95% confidence intervals, HR of time-to-event endpoints and their 95% confidence intervals (based on similar analyses to the primary endpoint), as well as the sample sizes will be reported separately for each level of the following subgroups in forest plots:

- Baseline characteristics as mentioned in Section 4.3.
- Stratification factors (Binet stage and Region)

Since the study was powered for the ITT population, all subgroup analyses will be exploratory only. Additional subgroup analyses might be performed as required.

4.5 PHARMACODYNAMIC ANALYSES

For each visit at which CD19+and CD5+and CD19+CD5- B-Cell measurements are taken, B-cell data will be listed for individual patients by treatment arm:

- Absolute counts

- Percent relative to the baseline counts for the individual
- Extent of CD19+B-cell depletion (nadir)
- Duration of depletion
- Time to Recovery

CD19+B-cell measurements will be summarized for each visit by the two treatment arms. The parameters summarized will be CD19+B-cell counts, percentage of baseline counts, nadir, time to nadir, duration of depletion, and time to recovery.

A separate analysis plan will be used for pharmacodynamic analyses.

4.6 PATIENT-REPORTED OUTCOME ANALYSIS

Scoring for the MDASI-CLL and EORTC QLQ-C30 questionnaires 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.

4.6.1 Visit score summary and change from baseline

Visit summary and change from baseline analyses will be performed for the MDASI-CLL severity, interference, and CLL scales, as well as the EORTC QLQ-C30 scales. Summary statistics (number of patients, mean, standard deviation, median, minimum, maximum) of score(s) and score change(s) from baseline to each time point will be presented by treatment arm.

4.6.2 Mixed-effect model repeated measures (MMRM) analysis

Repeated measures mixed-effects model will be used for comparing the MDASI-CLL and EORTC QLQ-C30 scale scores between treatment arms. The model will include a term for intercept, a term for linear time trend, a term for treatment group, and a term for treatment-by-time interaction. Covariates will be added as appropriate. Time points with less than 20% patients who completed the MDASI-CLL and QLQ-C30 scales, where all subsequent time points also have less than 20% completion will be excluded.

4.7 HEALTH ECONOMICS ANALYSES

Summary statistics (number of patients, mean, standard deviation, median, minimum, maximum) of score(s) and score change(s) from baseline to each time point will be presented by treatment arm on the EQ-5D-3L utility score and visual analog scale. In addition, the proportion of patients endorsing each level of the EQ-5D-3L dimensions will be provided by treatment arm at each time point. Further analyses of the results from the health economics data will be reported separately from the Clinical Study Report.

4.8 SAFETY ANALYSES

Safety analysis will be based on exposure to study medication, AEs, laboratory data and vital signs. Analysis of AEs will include SAEs and AEs of special interest.

The safety analysis will be based on the safety evaluable population.

4.8.1 Exposure of Study Medication

Treatment exposure to study medication will be summarized by treatment arm for each medication administered. The following measures will be included in the summary output:

- Duration of treatment
- Dose intensity (%) – calculated as the total cumulative dose actually received divided by the planned cumulative dose
- Number of doses/cycles
- Total cumulative dose
- Missed doses
- Number of dose discontinuation and reason for discontinuation
- Number of dose modifications and reasons for modification
  - Number of dose interruptions and reasons for dose interruptions
  - Number of dose reductions and reasons for dose reductions

In addition, the number and percentage of patients withdrawing from each treatment and the primary reason for discontinuation will be summarized by treatment arm.

4.8.2 Adverse Events

Coding of AEs will be done using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA). Verbatim terms of AEs will be mapped to MedDRA thesaurus terms and graded according to the NCI CTCAE grading system, version 4.0. All AEs occurring during or after the first treatment will be included in the summary tables.

AE summaries will be presented by system organ class, preferred term, and treatment arm, for the following:

- All AEs
- AEs by NCI CTCAE grade
- Grade 3-4 AEs
- SAEs
- Fatal AEs

- Grade 3 neutropenia rate and Grade 4 neutropenia rates along with dose interruptions due to Grade 3 and Grade 4
- Grade $\geq$3 infections
  - Opportunistic infections (Using Roche AEGT)
- Second primary malignancies
- Richter's transformation
- AEs of special interest, including:
  - 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.
  - Suspected transmission of an infectious agent by the study drug (refer to protocol for full definition)
- AEs leading to treatment discontinuation (any study drug)
- AEs leading to study withdrawal
- AEs leading to dose interruptions
- AEs leading to dose reduction
- AEs suspected to be caused by any study drug
- AEs stratification by treatment phase (combination therapy phase and single agent treatment phase)
- All AEs by phase
- Grade 3–4 AEs by phase
- SAEs by phase
- Fatal AEs by phase
- Venetoclax dose interruptions by phase
- Venetoclax dose reductions by phase
- Venetoclax withdrawal by phase

In the case of multiple occurrences of the same AE within a patient, the most extreme severity recorded will be used in the summary tables.

Deaths reported during the study treatment period and those reported after treatment completion/discontinuation will be summarized by treatment arm.

A listing of all AEs and SAEs will be presented (separately).

Note – abnormal laboratory data that are clinically significant are reported as AEs.

4.8.3 Laboratory Data

Clinical laboratory tests will be performed at local laboratories throughout the study. Laboratory tests will be grading according to the NCI CTCAE v4.0. Laboratory data outside the normal ranges will be identified.

Laboratory data including NCI CTCAE v4.0 will be presented using summary statistics of change from baseline by visit and treatment arm. Baseline will be defined as the last valid measurement before first dose of study medication.

In addition, shift tables will be generated to cross-tabulate the number of patients grouped into each NCI CTCAE v4.0 grade at baseline versus post-baseline assessments.

4.8.4 Vital Signs

Vital signs data will be summarized over time for absolute values and changes from baseline without any replacement for missing data. Descriptive statistics will be provided by treatment arm.

Electrocardiogram (ECG) data at the screening visit will be summarized by treatment arm.

4.9 MISSING DATA

Censoring rules have been defined for the survival analyses to handle cases where the event criteria are not achieved; it is assumed that such rules are non-informative. However, additional sensitivity analysis will be performed, as outlined in Section 4.4.4 of this SAP to test the robustness of these assumptions.

In general, if a response assessment is missing or not available for the analysis then it will be assumed that the patient is a non-responder for the analysis in question.

4.10 INTERIM ANALYSES

Protocol Version 7 allows that up to two formal interim efficacy analyses may be performed. The first potential interim efficacy analysis, occurring at 85 PFS events (50% of total planned PFS events), will not be performed. As it will not be conducted, no further detail is provided for this interim analysis.

Hereafter, all references to the interim analysis refers to the interim analysis at a minimum of 110 PFS events. This original interim analysis for efficacy will be performed once a minimum of 110 PFS events have occurred. PFS will be tested at the significance level determined using the gamma family error spending function with parameter $\gamma = -9.21$ so that the overall two-sided type I error rate will be maintained at the 0.05 level.

In addition to the periodic safety data reviews, the iDMC will evaluate efficacy and safety at the interim analyses of PFS and recommend if the study should be stopped early for efficacy.

Summaries and analyses will be prepared by an iDCCand presented by treatment arm for the iDMC's review.

The Sponsor will conduct an interim analysis after 110 IRC-assessed PFS events have been observed. The following tables Table 4 and Table 5 will be used as guide to perform tests on primary and secondary endpoints with corresponding α-boundaries. The detailed testing procedure is provided in Appendix 3.

Table 4 Flexible Testing Strategy at Interim Analysis Decision Point

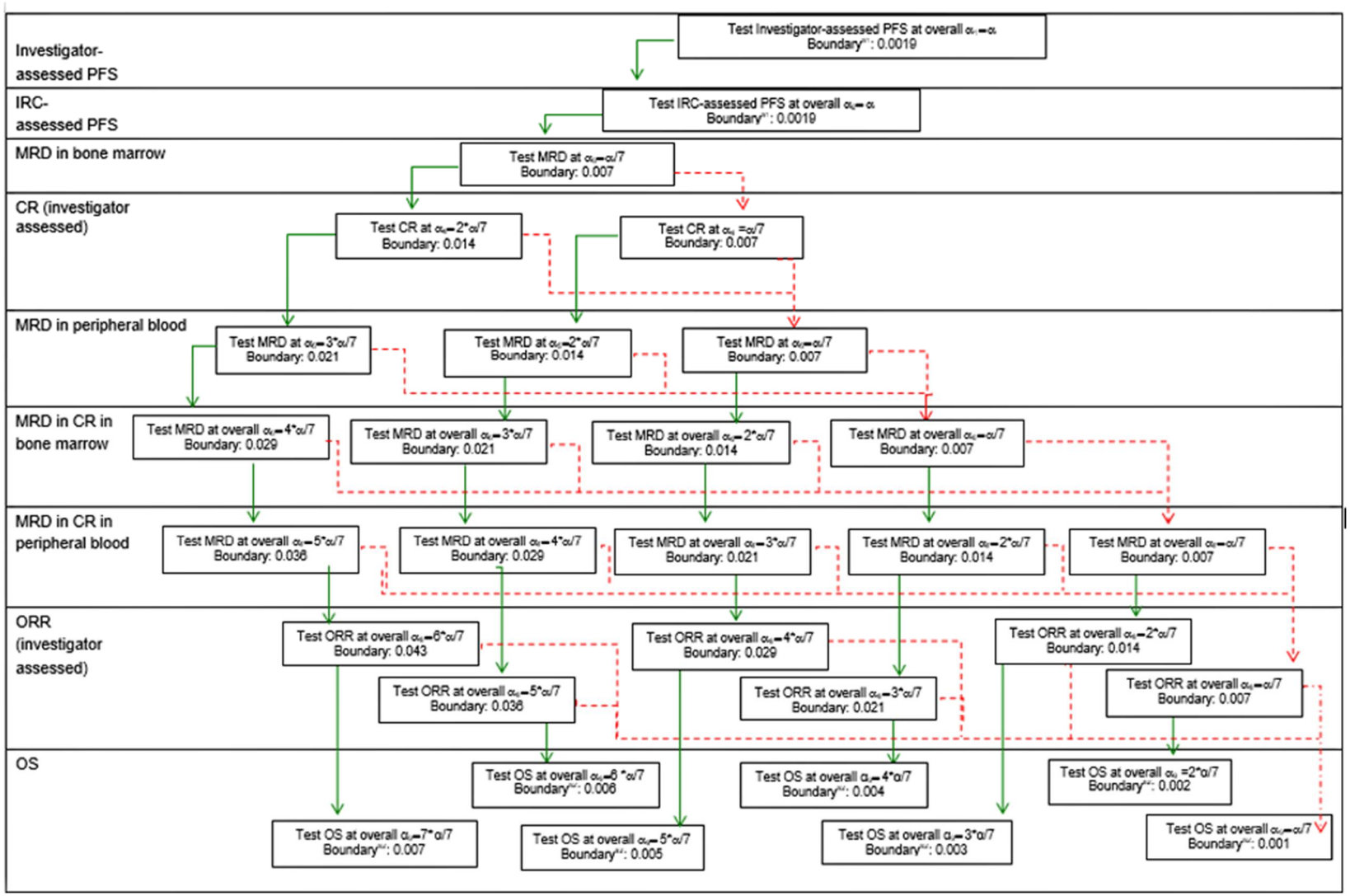


Table 4 Flexible Testing Strategy at Interim Analysis Decision Point (cont.)

CR = Complete response; IA = interim analysis; IRC = Independent Review Committee; PFS = progression-free survival; MRD = Minimal Residual Disease; ORR = overall response rate; OS = overall survival

Green solid arrow denotes hypothesis is rejected. Red dashed arrow denotes hypothesis is not rejected.

a1. Actual α value will depend on number of observed PFS events at IA with Type I error control assured by gamma-family α-spending (see Section 4.4.3). The α values shown assume 122 events (65% information fraction) for investigator-assessed PFS and 110 events (65% information fraction) for IRC-assessed PFS.

a2. Determined based on gamma family error spending function with parameter γ=-4 assuming 55% information fraction at IA. 55% information fraction corresponds to OS 38 events when 100% information fraction corresponds to OS 69 events. α values are shown rounded to 4 decimal places.

Table 5 Flexible Testing Strategy at PFS Final Analysis Decision Point if Primary Endpoint Hypothesis at IA is Not Rejected

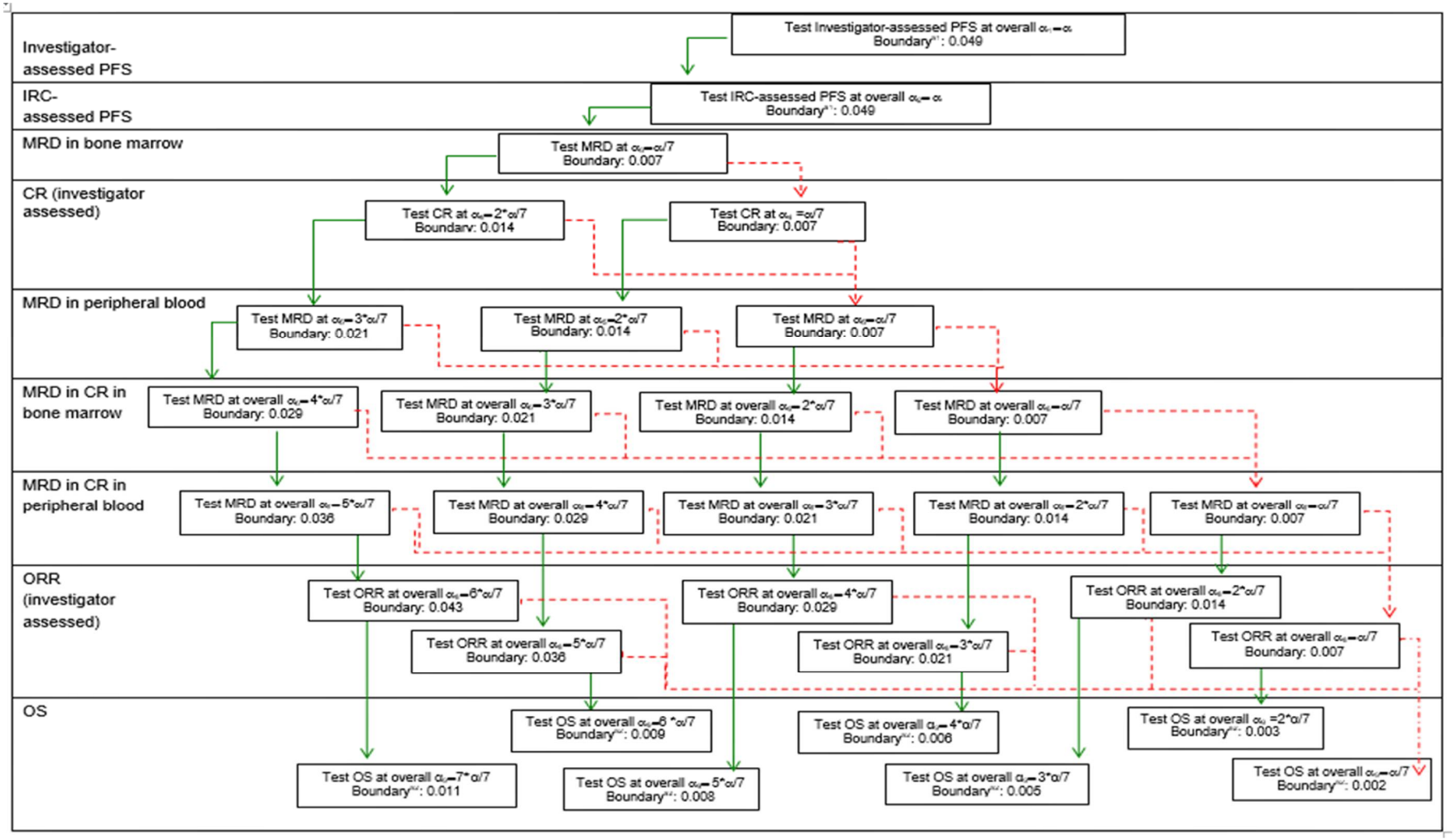


Table 5 Flexible Testing Strategy at PFS Final Analysis Decision Point if Primary Endpoint Hypothesis at IA is Not Rejected (cont.)

CR = Complete response; IA = interim analysis; IRC = Independent Review Committee; PFS = progression-free survival; MRD = Minimal Residual Disease; ORR = overall response rate; OS = overall survival

Green solid arrow denotes hypothesis is rejected. Red dashed arrow denotes hypothesis is not rejected.

a1. Actual α value will depend on number of observed PFS events at PFS FA with Type I error control assured by gamma-family α-spending (see Section 4.4.3). The α values shown correspond to 100% information fraction for investigator-assessed PFS and IRC-assessed PFS.

a2. Determined based on gamma family error spending function with parameter γ = -4 assuming 70% information fraction at PFS FA. 70% information fraction corresponds to 48 OS events when 100% information fraction corresponds to 69 OS events.

α values are shown rounded to 4 decimal places. At the end of the study, final OS will be tested at α-boundary of 0.045.

5. CHANGES TO THE ANALYSIS SPECIFIED IN THE PROTOCOL

Protocol (version 7) Section 6.5 - Safety Analysis states that the safety analyses will include all 'randomized' patients who received at least one dose of any study treatment. However, to be consistent with normal analysis and reporting conventions, the analysis of safety will be performed on all treated patients regardless of whether randomized or not, with the exception of safety run-in patients who are reported separately.

Analyses have been added for Minimal Residual Disease (MRD) response rate in patients with CR. These are not specified in the protocol.

6. SUMMARY OF POST-UNBLINDING CHANGES

The Safety population definition was changed so that patients randomized to the venetoclax + obinituzumab arm who received only obinituzumab treatment will be analysed under the obinituzumab + venetoclax arm rather than the obinituzumab + chlorambucil arm. This change is conservative as it ensures all safety data generated for patients randomized to obinituzumab + venetoclax who receive only obinituzumab will be associated with the obinituzumab + venetoclax treatment group rather than the obinituzumab + chlorambucil arm. The impact of this change will be discussed in the CSR.

The current definition of the safety population is as per section 4.1.3. The original definition of the Safety population was as follows:

All safety analyses will be based on the safety population, defined as all patients who receive at least one dose of any study medication (i.e., obinutuzumab, venetoclax, or chlorambucil). Patients will be analyzed according to the treatment group as actually treated (i.e., patients who received at least one dose of venetoclax will be analyzed under the obinutuzumab+venetoclax arm). In the event that only obinutuzumab and/or chlorambucil was received, the patient will be analyzed under the GClb arm.

7. REFERENCES

Dmitrienko A, D'Agostino R. Traditional multiplicity adjustment methods in clinical trials. Statistics in Medicine. 2013;32(29):5172-218.

Jennison C, Turnbull BW. Group sequential methods with applications to clinical trials. CRC Press; 1999 Sep 15.

Appendix 1
Protocol Synopsis

TITLE:	**A PROSPECTIVE, OPEN-LABEL, MULTICENTER RANDOMIZED PHASE III TRIAL TO COMPARE THE EFFICACY AND SAFETY OF A COMBINED REGIMEN OF OBINUTUZUMAB AND VENETOCLAX (GDC-0199/ABT-199) VERSUS OBINUTUZUMAB AND CHLORAMBUCIL IN PREVIOUSLY UNTREATED PATIENTS WITH CLL AND COEXISTING MEDICAL CONDITIONS**
PROTOCOL NUMBER:	**BO25323/CLL14**
VERSION NUMBER:	7
EUDRACT NUMBER:	2014-001810-24
IND NUMBER:	110159
TEST PRODUCT:	Venetoclax (GDC-0199 [ABT-199]; RO5537382), Obinutuzumab (GA101; RO5072759), and Chlorambucil
PHASE:	III
INDICATION:	Previously untreated patients with chronic lymphocytic leukemia with coexisting medical conditions
SPONSOR:	F. Hoffmann-La Roche Ltd in collaboration with the German CLL Study Group (GCLLSG)
CO-SPONSOR (United States only)	AbbVie, Inc.

Objectives

Efficacy Objectives

The primary efficacy objective for Study BO25323/CLL14 is as follows:

- To determine efficacy by investigator-assessed progression-free survival (PFS) of a combined regimen of obinutuzumab + venetoclax compared with obinutuzumab + chlorambucil (GClb) in previously untreated patients with chronic lymphocytic leukemia (CLL) who have coexisting medical conditions

The secondary efficacy objective for this study is as follows:

- To determine efficacy as assessed by additional outcome measures (including PFS assessed by Independent Review Committee [IRC], overall response, complete response, and MRD response rate as measured by allele-specific oligonucleotide polymerase chain reaction [ASO-PCR])

Note: IRC-assessed PFS will be considered primary for U.S. regulatory purposes.

Safety Objective

The safety objective for this study is as follows:

- To evaluate the safety of the combination of obinutuzumab and venetoclax, compared with GClb, in patients with previously untreated CLL and coexisting medical conditions, focusing on the nature, frequency, and severity of Grade 3 and 4 adverse events and of serious adverse events

Pharmacokinetic Objectives

The pharmacokinetic (PK) objective for this study is as follows:

- To characterize the pharmacokinetics of venetoclax and of obinutuzumab (including population PK [popPK] techniques). Standard non-compartmental analysis (NCA)/descriptive tables, listings, and graphs (TLGs) and popPK approaches will be considered.

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 obinutuzumab+venetoclax compared with GClb in patients with previously untreated CLL and coexisting medical conditions as measured by M.D. Anderson Symptom Inventory (MDASI-CLL)
- To evaluate changes in role functioning and global health status/quality of life (QoL) following treatment with the combination of obinutuzumab+venetoclax compared with GClb in patients with previously untreated CLL and coexisting medical conditions between arms as measured by European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)

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 combination of obinutuzumab and venetoclax compared with GClb in patients with previously untreated CLL and coexisting medical conditions measured by the EuroQol 5 Dimension questionnaire (EQ-5D-3L).

Exploratory Objectives

The exploratory objectives for this study are as follows:

- To assess MRD using new technologies, including flow cytometry and next-generation sequencing, to compare results with MRD measured by ASO-PCR
- To evaluate the relationship between PFS and MRD response rate
- To evaluate the relationship between various baseline prognostic markers and clinical outcome parameters
- To evaluate the relationship between biomarkers measured at baseline and disease progression to understand mechanisms of response and resistance

Study Design

Description of Study

This is an open-label, multicenter, randomized Phase III trial to compare the efficacy and safety of a combined regimen of obinutuzumab and venetoclax versus GClb in patients with CLL and coexisting medical conditions.

Initially, there will be a 12-patient safety run-in phase, (including at least 1 patient at high risk of developing TLS) wherein patients will receive obinutuzumab+venetoclax in a non-randomized fashion. After the twelfth patient has reached the end of Cycle 3, a formal review will be undertaken by Roche and the German CLL Study Group ([GCLLSG]; together, hereafter referred to as the Sponsor) and an independent Data Monitoring Committee (iDMC).

The following are stopping criteria for the run-in phase of this study:

- One treatment-related death

  or

- One Grade 4 adverse event related to a clinical tumor lysis syndrome (TLS) despite protocol-specified prophylaxis, either following the administration of the first dose of venetoclax or during dose escalation

If any of these criteria are met, the main study will not be opened for recruitment, and the Sponsor will then re-evaluate the study design and amend the protocol accordingly. If the stopping criteria are not met, randomization into the trial will commence.

Number of Patients

A total of 420 patients will be enrolled in the randomized part of the study, and 12 patients will be enrolled in the safety run-in phase.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

- Have documented previously untreated CLL according to International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria
- CLL that requires treatment according to the IWCLL criteria
- Total Cumulative Illness Rating Scale (CIRS) score >6 or creatinine clearance (CrCl) <70 mL/min
- Adequate marrow function independent of growth factor or transfusion support within 2 weeks of screening as follows, unless cytopenia is due to marrow involvement of CLL:

  Absolute neutrophil count $\geq 1.0 \times 10^9$/L

  Platelet counts $\geq 30 \times 10^9$/L; in cases of thrombocytopenia clearly due to marrow involvement of CLL (per the discretion of the investigator); platelet count should be $\geq 10 \times 10^9$/L if there is bone marrow involvement

  Total hemoglobin $\geq$ 9 g/dL (without transfusion support, unless anemia is due to marrow involvement of CLL)
- 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
- For those patients with a screening lymphocyte count $<$5,000 cells/μL, historical data that confirms a lymphocyte count $\geq$5,000 cells/μL at the time of diagnosis is required
- 18 years of age or older
- Life expectancy >6 months
- Signed informed consent and, in the investigator's judgment, able to comply with the study protocol
- For women who are not postmenopausal ($\geq$12 months of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent or use single or combined contraceptive methods that result in 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, whichever is longer

  Abstinence is only acceptable if it is in line with 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.

  Examples of contraceptive methods with a failure rate of $<$ 1% per year include tubal ligation, male sterilization, hormonal implants, established, proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices. Alternatively, two methods (e.g., two barrier methods such as a condom and a cervical cap) may be

combined to achieve a failure rate of $<$ 1% per year. Barrier methods must always be supplemented with the use of a spermicide.

- For men: agreement to 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, whichever is longer, and agreement to refrain from donating sperm during the treatment period and for at least 90 days after the last dose of venetoclax

  Men with a pregnant partner must agree to remain abstinent or use a condom for the duration of the pregnancy.
- Abstinence is only acceptable if it is in line with 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.

Exclusion Criteria

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

- Transformation of CLL to aggressive non-Hodgkin's lymphoma (NHL) (Richter's transformation or pro-lymphocytic leukemia)
- Known central nervous system involvement
- Patients with a history of confirmed progressive multifocal leukoencephalopathy
- 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). Investigators should consult the General Rules for Severity Rating as well as the Organ-Specific Categories when assigning scores for certain conditions (i.e., pulmonary embolism) and consider the level of morbidity associated with a patient's condition.
- Patients with uncontrolled autoimmune hemolytic anemia or immune thrombocytopenia
- Inadequate renal function: CrCl $<$ 30 mL/min
- 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 $\geq$ 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 active infections requiring IV treatment (Grade 3 or 4) within the last 2 months prior to enrollment
- History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies or known sensitivity or allergy to murine products
- Hypersensitivity to chlorambucil, obinutuzumab, or venetoclax or to any of the excipients (e.g., trehalose)
- Pregnant women and nursing mothers
- Vaccination with a live vaccine $\leq$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 PCR is negative for HCV RNA.
- Patients with known infection with human immunodeficiency virus (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
- Patients who have received:

  Strong and moderate CYP3A inhibitors within 7 days prior to the first dose of study drug administration

  Strong and moderate CYP3A inducers within 7 days prior to the first dose of study drug administration

  Consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges), or star fruit within 3 days prior to the first dose of study drug and throughout venetoclax administration
- Inability to swallow a large number of tablets

Length of Study

The approximate length of study will be 6 years and 8 months calculated from an estimated 20-month recruitment period, and the end of study is defined below.

End of Study

The end of this study is defined as 5 years from last patient enrolled (unless all patients have died).

Outcome Measures

Efficacy Outcome Measures

The primary efficacy outcome measure for this study is as follows:

- PFS, defined as the time from randomization to the first occurrence of progression, relapse, or death from any cause as assessed by the investigator. Disease progression will be assessed by the investigators using the IWCLL criteria (2008).

The secondary efficacy outcome measures for this study are as follows:

- PFS based on Independent Review Committee (IRC)-assessments (primary outcome for U.S. regulatory purposes), defined as the time from randomization to the first occurrence of progression or relapse or death from any cause
- Overall response rate (ORR; defined as rate of a clinical response of complete response [CR], complete response with incomplete bone marrow recovery [CRi], or PR) at the completion of treatment assessment, as determined by the investigator according to the IWCLL guidelines (2008)

- Complete response rate (CRR; defined as rate of a clinical response of CR or CRi) at the completion of treatment assessment, as determined by the investigator according to the 2008 IWCLL guidelines
- MRD response rate (determined as the proportion of patients with MRD-negativity) measured in the peripheral blood at the completion of treatment assessment and MRD response rate as measured in the bone marrow at the completion of treatment, both measured by ASO-PCR
- ORR at completion of combination treatment response assessment (Cycle 7, Day 1 or 28 days after last intravenous [IV] infusion)
- MRD response rates in the peripheral blood at completion of combination treatment assessment (Cycle 9, Day 1 or 3 months after last IV infusion) and also MRD response rate in the bone marrow, both as measured by ASO-PCR

Note: the secondary endpoint analyses will be on the basis of MRD assessment performed centrally by ASO-PCR with MRD negativity defined using a cutoff of 10^{-4} (less than 1 cell in 10,000 leukocytes). As well as evaluating MRD response rate, it will further be evaluated using results of both measures, where a patient will be considered MRD-positive if either blood or bone marrow result is positive or both are missing. MRD response rates at other timepoints during treatment and follow-up where MRD is measured in the peripheral blood will also be summarized.

- Overall survival (OS), defined as the time between the date of randomization and the date of death due to any cause
- Duration of objective response, defined as the time from the first occurrence of a documented objective response to the time of progressive disease (PD) as determined by the investigator or death from any cause
- Best response achieved (CR, CRi, partial response [PR], stable disease, or PD) up to and including the assessment at completion of treatment assessment (within 3 months of last day of treatment)
- Event-free survival, defined as the time between date of randomization and the date of disease progression/relapse on the basis of investigator-assessment, death, or start of a new anti-leukemic therapy
- Time to next anti-leukemic treatment, defined as time between the date of randomization and the date of first intake of new anti-leukemic therapy

Safety Outcome Measures

The safety outcome measures for this study are as follows:

- Nature, frequency, and severity of adverse events and serious adverse events
- Changes in vital signs, physical findings, and clinical laboratory results during and following study treatment
- Lymphocyte immunophenotyping and incidence of human–anti-human antibodies
- Premature withdrawals

Pharmacodynamic Outcome Measures

For each visit at which CD19 + CD5 + and CD19 + CD5 − B-cell measurements are taken, B-cell data will be listed for individual patients by treatment arm.

Pharmacokinetic Outcome Measures

The PK outcome measure for this study is as follows:

- Apparent clearance, apparent volume of distribution, and/or other appropriate PK parameters of venetoclax and of obinutuzumab characterized with the use of popPK techniques. Standard NCA/descriptive TLGs and popPK approaches will be considered.

Patient-Reported Outcome Measures

The PRO measures for this study are as described below. The first assessment will be done during the first obinutuzumab infusion, and PROs will be followed until end of study as defined by 5 years after last randomized patient:

- To evaluate changes following treatment in disease and treatment-related symptoms in MDASI-CLL scores.
- To evaluate changes in role functioning and global health status/QoL scales following treatment with the EORTC QLQ-C30.

Health Economic Outcome Measures

The health economic outcome measure for this study is as follows:

- The EQ-5D-3L questionnaire

Exploratory Outcome Measures

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 primary analysis):

- MRD negativity in peripheral blood measured using new technologies, including flow cytometry and next-generation sequencing with MRD negativity defined using a cutoff of 10^{-4} (less than 1 cell in 10,000 leukocytes) for comparison with ASO-PCR, and secondly by the limit of sensitivity of each of the above technologies.
- Relationship between MRD and PFS on the basis of peripheral blood assessed using ASO-PCR
- Relationship between various baseline markers and clinical outcome parameters in patients from both arms of the study (including but not limited to CLL fluorescence in-situ hybridization [FISH; 17p-, 11q-, 13p-, + 12q], immunoglobulin heavy chain variable [IGHV] mutation status, p53 mutation status, serum parameters, Bcl-2 expression and other CLL disease markers)

Investigational Medicinal Products

All investigational medicinal products (IMPs) required for completion of this study (chlorambucil, obinutuzumab, and venetoclax) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs and 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 returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any 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.

Venetoclax

Venetoclax, a highly selective, orally bioavailable, small-molecule Bcl-2 family inhibitor in the biarylacylsulfonamide chemical class, will be administered as an oral tablet. Patients will receive venetoclax as follows:

- 20 mg daily during Cycle 1, Days 22–28
- 50 mg daily during Cycle 2, Days 1–7
- 100 mg daily during Cycle 2, Days 8–14
- 200 mg daily during Cycle 2, Days 15–21
- 400 mg daily during Cycle 2, Days 22–28 and on Days 1–28 for all subsequent cycles until the end of Cycle 12

Obinutuzumab

Obinutuzumab, a novel, humanized, type II glycoengineered monoclonal antibody (mAb) directed against the CD20 antigen, will be administered as an IV infusion. Patients will receive obinutuzumab as follows:

- 100 mg or 1000 mg, depending on splitting rules, at Cycle 1, Day 1 (if 100 mg was received on Day 1, 900 mg will be administered on Cycle 1, Day 2).
- 1000 mg at Cycle 1, Day 8 and Day 15
- 1000 mg at Day 1 for all subsequent cycles until the end of Cycle 6

Chrorambucil

Chlorambucil will be administered orally. Patients will receive chlorambucil as follows:

- 0.5 mg/kg at Day 1 and Day 15 for Cycles 1−12

Non-Investigational Medicinal Products

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.

Note: Rasburicase may be supplied by the Sponsor in countries where rasburicase is not approved or cannot be supplied locally.

Statistical Methods

Primary Analysis

The primary efficacy endpoint is investigator-assessed PFS, defined as the time from randomization to the first occurrence of progression or relapse (determined using standard IWCLL guidelines [2008]), or death from any cause, whichever occurs first. Progression-free survival on the basis of IRC assessments will be considered primary for U.S. regulatory purposes (details will be provided in the Statistical Analysis Plan [SAP]). For patients who have not progressed, relapsed, or died at the time of analysis, PFS will be censored on the date of the last disease assessment. If no disease assessments were performed after the baseline visit, PFS will be censored at the time of randomization + 1 day. All patients, including patients who discontinue all components of study therapy prior to disease progression (e.g., for toxicity), will continue in the study and will be followed for progressive disease and survival regardless of whether or not they subsequently receive new anti-leukemic therapy.

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

- Progression-free survival of obinutuzumab + venetoclax versus GClb (i.e., H0: obinutuzumab + venetoclax = GClb versus H1: obinutuzumab + venetoclax ≠ GClb)

Treatment comparisons will be made using a two-sided log-rank test (at 0.05 significance-level, adjusted for the interim analyses), stratified by Binet stage. If the null hypothesis is rejected and the observed HR is favorable for the obinutuzumab + venetoclax experimental arm, then it is concluded that obinutuzumab + venetoclax significantly lowers the risk of PFS events more than GClb. A two-sided non-stratified log-rank test will be performed to support the primary analysis. Median PFS and the 95% confidence limits will be estimated using Kaplan-Meier survival methodology, with the Kaplan-Meier survival curve presented to provide a visual description. PFS rates for 1, 2, and 3 years after randomization with 95% CIs will be reported. Estimates of the treatment effect will be expressed as HR including 95% confidence limits estimated through a Cox proportional-hazards analysis stratified by Binet stage. Primary analysis for U.S. Food and Drug Administration (FDA) submission will be based on assessment of PFS by an IRC.

Determination of Sample Size

The sample size for the study is determined given the requirements to perform a hypothesis test for clinically relevant statistical superiority in the primary endpoint of PFS.

Estimates of the number of events required to demonstrate efficacy with regard to PFS are based on the following assumptions:

- Log-rank test at the two-sided 0.05 level of significance
- Median PFS for obinutuzumab and chlorambucil control arm (27 months)
- 80% power to detect HR = 0.65 for the comparison of obinutuzumab + venetoclax experimental arm versus GClb, with median PFS for obinutuzumab + venetoclax increased to 41.5 months
- Exponential distribution of PFS
- Annual drop-out rate of 10%
- One interim analysis for efficacy after 75% of PFS events, utilizing a stopping boundary according to the γ family error spending function with parameter $\gamma = -9.21$.

The addition of an optional early analysis requires no adjustment to the sample size, as the impact on the statistical power calculation is negligible.

Based on these assumptions, a total of 170 PFS events are required for the final analysis of PFS.

The minimum detectable difference at the final analysis corresponds approximately to an HR = 0.74.

The sample size calculation was performed using EAST version 6.2.

Interim Analyses

In addition to the periodic safety data reviews, the iDMC will evaluate efficacy and safety at up to two formal interim analyses of PFS and recommend if the study should be stopped early for efficacy.

Summaries and analyses will be prepared by an independent data coordinating center and presented by treatment arm for the iDMC's review.

An interim efficacy analysis may be conducted at or after 1 year after the last patient's last venetoclax dose (i.e., Month 37 of the study [August 2018]), provided that at least 85 PFS events (50% of the total of 170 PFS events) have occurred. If 85 PFS events have not been observed by 1 year after the last patient's last venetoclax dose, then the interim analysis will be conducted once a minimum of 85 PFS events have occurred. PFS will be tested at the significance level determined using the gamma family error spending function with parameter $\gamma = -21.12$ so that the overall two-sided type I error rate will be maintained at the 0.05 level. This gamma family boundary only allows the study to stop for efficacy if a treatment effect HR of 0.35 or better is observed when the interim analysis is based on 85 events.

Because this option is added to mitigate a potential delay in the study read-out, the Sponsor's decision to conduct this interim analysis will be based on a number of factors including, but not limited to, the number of events observed by 1 year after the last patient's last venetoclax dose and the subsequent predicted time to reach 110 events. If the Sponsor does not conduct this interim analysis or if this interim analysis is conducted and is negative, then the Sponsor will proceed with the later original interim analysis as follows.

Provided the above early interim analysis is not done or not passed, the original interim analysis for efficacy will be performed once a minimum of 110 PFS events have occurred. PFS will be tested at the significance level determined using the gamma family error spending function with parameter $\gamma = -9.21$ so that the overall two-sided type I error rate will be maintained at the 0.05 level. If the early interim analysis (at a minimum of 85 events) is performed and is passed, the later original interim analysis will not be undertaken.

The final analysis will be performed after 170 events have occurred. The significance level will be adjusted to incorporate the α spent at either interim analysis, so that the overall two-sided type I error rate will be maintained at the 0.05 level.

Appendix 2
Schedule of Assessments

Schedule of Assessments Treatment-Period Visits (RAMP-UP to 400 mg)

	Screening	Cycle 1						Cycle 2							
Day	−28 to −1	1 [a]	2	8	15	22 (20 mg)	23	1 (50 mg)	2	8 (100 mg)	9	15 (200 mg)	16	22 (400 mg)	23
Informed Consent [b]	x														
Consent for GCLLSG biobanking (optional) [b]	x														
Demographic data	x														
TLS Lab-Based Risk Assessment and monitoring [c]	x	x	x			x	x	x[d]	x	x	x	x	x	x	x
General medical history, CIRS score, IADL and baseline conditions	x														
Vital signs [e]	x	x	x	x	x	x	x	x		x		x		x	
Weight	x	x						x							
Height	x														
Complete physical examination [f]	x														
Clinical Staging [f]	x														

Appendix 2
Schedule of Assessments (cont.)

Schedule of Assessments Treatment-Period Visits (RAMP-UP to 400 mg) (contd…)

	Screening	Cycle 1						Cycle 2							
Day	−28 to −1	1 [a]	2	8	15	22 (20 mg)	23	1 (50 mg)	2	8 (100 mg)	9	15 (200 mg)	16	22 (400 mg)	23
Lymphadenopathy (during physical exam/Binet staging at screening)	x														
Liver/spleen (by physical examination)	x														
ECG 12 lead	x	As clinically indicated													
LVEF	As clinically indicated														
ECOG performance status	x	x						x							
B symptoms	x	x						x							
CT scan assessment [g]	x	If PD is detected and confirmation of CR/PR at 3 months post treatment													
Bone marrow biopsy [h]	(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 in treatment Arm A only									
Obinutuzumab (Arms A and B) [i]		x	(x)	x	x			x							

Appendix 2
Schedule of Assessments (cont.)

Schedule of Assessments Treatment-Period Visits (RAMP-UP to 400 mg) (contd…)

	Screening	Cycle 1						Cycle 2							
Day	−28 to −1	1 [a]	2	8	15	22 (20 mg)	23	1 (50 mg)	2	8 (100 mg)	9	15 (200 mg)	16	22 (400 mg)	23
Venetoclax Arm A						Daily, as per dosing chart schedule (20, 50, 100, 200, 400mg) for 12 cycles starting C1D22									
Chlorambucil Arm B		x			x			x				x			
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events [b]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Serious AEs and Grade 3 and 4 infections [b]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
PRO questionnaires (MDASI-CLL, EQ-5D-3L, and EORTC-QLQ C30) [t]		x						x							
Local laboratory [j]															
Immunoglobulins	x														
HBV, HCV, HTLV1 (if applicable) [k]	x														
Coombs test	x														
Coagulation (aPTT, PT, INR)	x														

Appendix 2
Schedule of Assessments (cont.)

Schedule of Assessments Treatment-Period Visits (RAMP-UP to 400 mg) (contd…)

	Screening	Cycle 1						Cycle 2							
Day	−28 to −1	1 [a]	2	8	15	22 (20 mg)	23	1 (50 mg)	2	8 (100 mg)	9	15 (200 mg)	16	22 (400 mg)	23
Pregnancy test [l]	x	x						x							
Urinalysis [m]	x														
Hematology [n]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Chemistry [o]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
[redacted] **Central Laboratory** [j]															
Serum parameters (β2 microglobulin, thymidine kinase)		x[p]													
CLL markers (DNA/RNA)		x[p]													
Flow cytometry (BCL2 family and CLL counts)	x														
Optional tumor tissue for Bcl-2 family analysis by IHC (formalin fixed tissue)		x[q]													
MRD (ASO-PCR)[r]	x														
MRD (NGS)	x														

Appendix 2
Schedule of Assessments (cont.)

Schedule of Assessments Treatment-Period Visits (RAMP-UP to 400 mg) (contd…)

	Screening	Cycle 1						Cycle 2							
Day	−28 to −1	1 [a]	2	8	15	22 (20 mg)	23	1 (50 mg)	2	8 (100 mg)	9	15 (200 mg)	16	22 (400 mg)	23
[redacted] **Laboratory** [j]															
Evaluation of resistance by CD40L, simulation		x[p,s]													
Metaphase cytogenetics		x[p]													
GCLLSG Biobanking sample		x[s]													
Genetic analysis, (IGVH mutation status, cytogenetics (FISH), gene mutations and resistance markers	x														
Blood for lymphocyte immunophenotyping (for diagnosis, safety monitoring, IRR prediction, ZAP70/CD38)	x														
MRD (flow)	x														

Appendix 2
Schedule of Assessments (cont.)

Schedule of Assessments Treatment-Period Visits (RAMP-UP to 400 mg) (contd…)

AE = adverse event; ASO-PCR = allele-specific oligonucleotide polymerase chain reaction; C = cycle; CIRS = Cumulative Illness Rating Scale; CLL = chronic lymphocytic leukemia; CR = complete response; CT = computed tomography; D = day; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EORTC = European Organization for Research and Treatment of Cancer; EQ-5D-3L = EuroQol 5-Dimension questionnaire; GCLLSG = German CLL Study Group; IADL = Instrumental Activity of Daily Living IHC = immunohistochemistry; INR = international normalized ratio; IRR = infusion-related reaction; LVEF = left ventricular ejection fraction; MDASI-CLL = M.D. Anderson Symptom Inventory-Chronic Lymphocytic Leukemia; MRD = minimal residual disease; MRI = magnetic resonance imaging; NGS = next-generation sequencing; PD = disease progression; PR = partial response; PRO = patient-reported outcome; Tmt = treatment; TLS = tumor lysis syndrome.

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 post-dose 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 randomization number has been assigned.

[b] 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. 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 events or adverse events of special interest. 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.

[c] Chemistry and hematology must also be assessed within 0–4 hours prior and 24 hours after the first obinutuzumab and venetoclax dose, and within 0–4 hours prior and 24 hours after each new (increased) venetoclax dose during the venetoclax dose-ramp up phase. 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.

[d] For Cycle 2 only, in addition to Day 1, the TLS assessment must be performed on Day 8, Day 15, and Day 22.

Appendix 2
Schedule of Assessments (cont.)

Schedule of Assessments Treatment-Period Visits (RAMP-UP to 400 mg) (contd…)

[e] Includes: pulse rate and systolic and diastolic blood pressure while the patient is in a seated position, and temperature.
High TLS risk subjects must have vital signs performed before and 8, 12, 24 hours after venetoclax 20mg and 50 mg dose ramp up.

[f] 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.

[g] CT Scan allowed 8 weeks prior to randomization and required as confirmation of CR/PR at 3months after end of treatment. MRI only if contrast enhanced CT not possible.

[h] A bone marrow aspirate and biopsy is optional at screening (investigator discretion if clinically indicated) and must be taken at the end of treatment response assessment at the end of combination therapy at 9 months (Cycle 9) in patients with a CR or a PR.

[i] Obinutuzumab may be given over two days if subject is considered high risk for infusion related reaction (IRR),or as per standard of care (SOC).

[j] For 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 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.

[k] Certain patients (occult or prior HBV infection) require monthly DNA testing, although the data is not collected for the study.

[l] All women who are not postmenopausal (≥ 12 months of non-therapy-induced amenorrhea) or surgically sterile will have a serum pregnancy test at screening. If 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 (≥ 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.

[m] Includes: dipstick pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria).

[n] Includes: WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells.

[o] 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.

[p] Sample should be taken after randomization number is assigned and before first dose.

Appendix 2
Schedule of Assessments (cont.)

Schedule of Assessments Treatment-Period Visits (RAMP-UP to 400 mg) (contd…)

[q] If formalin fixed specimen of bone marrow biopsy (also including lymph node or other biopsies) are collected at baseline by the site as per standard clinical assessment of the patient, a sample should be provided for IHC analysis of Bcl-2 family.

[r] Blood. Additional bone marrow aspirate at completion of combination therapy (Cycle 9, Day 1 or 3 months after last IV infusion) and at the completion of treatment assessment (a minimum of 3 months after last treatment) for patients with CR/CRi and PR.

[s] For patients who have signed the additional consent for GCLLSG biobanking, residual sample will be sent to the GCLLSG for analysis.

[t] 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.

Schedule of Assessments Cycle 3–Cycle 12 and Follow-Up Day 28

Assessment	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	Day 28 after Treatment Completion/Early Termination [a]
General medical history											
Vital signs (Day 1 of each cycle only)	x	x	x	x	x	x	x	x	x	x	x
Weight	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	
B-symptoms	x	x	x	x	x	x	x	x	x	x	
CT scan if PD is detected lymph nodes only	x										
Bone marrow aspirate and biopsy (MRD) CR/PR							x				
Obinutuzumab Arm A and B	x	x	x	x							
Chlorambucil Arm B (Days 1 and 15)	x	x	x	x	x	x	x	x	x	x	
Venetoclax Arm A	Daily dosing 400 mg for 10 cycles										
Staging and response assessment		x			x		x				x
CT scan confirmation of CR/PR											

Schedule of Assessments Cycle 3–Cycle 12 and Follow-Up Day 28 (contd..)

Assessment	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	Day 28 after Treatment Completion/Early Termination [a]
Concomitant medication	x	x	x	x	x	x	x	x	x	x	x
AEs	x	x	x	x	x	x	x	x	x	x	x
SAEs/Grade3/4 infections	x	x	x	x	x	x	x	x	x	x	x
PRO questionnaires (MDASI-CLL, EQ-5D-3L, EORTC QLQ C30) [b]	x	x	x	x	x	x	x	x	x	x	x
Local laboratory											
Hematology (Days 1 and 15)	x	x	x	x	x	x	x	x	x	x	x
Biochemistry (Days 1 and 15)	x	x	x	x	x	x	x	x	x	x	x
Pregnancy Test [c]	x	x	x	x	x	x	x	x	x	x	
[redacted] **Central Laboratory**											
MRD (ASO-PCR)					x		x			x	
MRD (NGS)					x		x			x	
PK samples for obinutuzumab [d]		x (Arm A only)									
PK samples for venetoclax [d]		x (Arm A only)									
[redacted] **Laboratory**											
MRD (flow)					x		x			x	
Blood for safety monitoring/B-cell recovery											x

Schedule of Assessments Cycle 3–Cycle 12 and Follow-Up Day 28 (contd..)

AE = adverse event; ASO-PCR = allele-specific oligonucleotide polymerase chain reaction; C = cycle; CR = complete response; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EORTC = European Organization for Research and Treatment of Cancer; EQ-5D-3L = EuroQol 5-Dimension questionnaire; IRR = infusion-related reaction; LVEF = left ventricular ejection fraction; MDASI-CLL = M.D. Anderson Symptom Inventory-Chronic Lymphocytic Leukemia; MRD = minimal residual disease; NGS = next-generation sequencing; PD = disease progression; PK = pharmacokinetic; PR = partial response; PRO = patient-reported outcome; SAE = serious adverse event; TLS = tumor lysis syndrome.

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] Patients 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. Patients who discontinue study drug prior to completing 12 cycles of therapy should continue to be followed for disease progression per the schedule in Appendix 2.

[b] 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.

[c] 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.

[d] See Appendix 2 for Schedule of PK Assessments.

Schedule of Assessments (Follow-Up Period)

	Follow-Up Visits Duration from Last Study Drug Administration until Disease Progression			Survival (All Patients)
Assessment	+3 months after Treatment Completion/Early Termination [a]	+6, 9, 12, 15 and18 months after Treatment Completion/Early Termination	+24 months after Treatment Completion/Early Termination then every 6 months until 5 years from last patient enrolled	Every year after disease progression until 5 years from last patient enrolled
Complete physical examination	x	x	x	
Weight	x	x	x	
Vital signs [b]	x	x	x	
ECG 12-lead	As clinically indicated	As clinically indicated	As clinically indicated	
LVEF	As clinically indicated	As clinically indicated	As clinically indicated	
Lymphadenopathy during physical examination [c]	x	x	x	
Liver/spleen (by physical examination)	x	x	x	
ECOG performance status	x	x	x	
B symptoms	x	x	x	
CT scan assessment (or MRI if performed at screening)	x			
CT scan of involved nodes at time of PD if determined by physical examination alone	x	x	x	
Concomitant medications	x	x	x	x
Response assessment	x	x	x	
Follow-up for PD/disease transformation	x	x	x	

Schedule of Assessments (Follow-Up Period) (contd..)

	Follow-Up Visits Duration from Last Study Drug Administration until Disease Progression			Survival (All Patients)
Assessment	+3 months after Treatment Completion/Early Termination [a]	+6, 9, 12, 15 and18 months after Treatment Completion/Early Termination	+24 months after Treatment Completion/Early Termination then every 6 months until 5 years from last patient enrolled	Every year after disease progression until 5 years from last patient enrolled
After PD continue to follow-up for NLT	x	x	x	x
PRO questionnaire (MDASI-CLL, EQ-5D-3L, and EORTC-QLQ C30) until NLT [d]	x	x	x	
Collection of NLT				x
Grade 3 and 4 adverse events (until 6 months after the end of treatment)	x	x		
Unrelated SAEs	x	x	x	
Grade 3 and 4 infections (until 2 years after the end of treatment)	x	x	x	
Related SAEs and secondary malignancies, indefinitely	x	x	x	x
Hematology [e]	x	x	x	
Chemistry [f]	x	x	x	
Immunoglobulin (IgA, IgG, IgM)	x	x	x	
Urinalysis [g]	x			

Schedule of Assessments (Follow-Up Period) (contd..)

	Follow-Up Visits Duration from Last Study Drug Administration until Disease Progression			Survival (All Patients)
Assessment	+3 months after Treatment Completion/Early Termination [a]	+6, 9, 12, 15 and18 months after Treatment Completion/Early Termination	+24 months after Treatment Completion/Early Termination then every 6 months until 5 years from last patient enrolled	Every year after disease progression until 5 years from last patient enrolled
GCLLSG biobanking [h]	x (at timepoint of refractory disease or PD only)			
Genetic analysis (IGHV mutation status, Cytogenetics [FISH], gene mutations and resistance markers)	x (at time point of refractory disease or PD only)			
Evaluation of resistance by CD40L stimulation	x (at time point of refractory disease or PD only)			
Flow cytometry (BCL2)	x (at time point of refractory disease or PD only)			
BCL2 family and CLL markers (DNA/RNA)	x (PD only)			
MRD (blood)	x [i]	x [i]	x [j]	
Bone Marrow Aspirate	x [k]			
Bone Marrow Biopsy	x [k]			
Blood for safety monitoring/ B-cell recovery [l]		x (12 and 18 months only)	x	

AE = adverse event; ASO-PCR = allele-specific oligonucleotide polymerase chain reaction; CLL = chronic lymphocytic leukemia; CR = complete response; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic Case Report Form; EORTC = European Organization for Research and Treatment of Cancer; EQ-5D-3L = EuroQol 5-Dimension questionnaire; FISH = fluorescence in situ hybridization; GCLLSG = German CLL Study Group; MDASI-CLL = M.D. Anderson Symptom Inventory-Chronic Lymphocytic Leukemia; MRD = minimal residual disease; MRI = magnetic resonance imaging; NLT = next anti-leukemia treatment; PD = progressive disease; PK = pharmacokinetic; PR = partial response; PRO = patient-reported outcome; RCR = Roche Clinical Repository; SAE = serious adverse event.

Schedule of Assessments (Follow-Up Period) (contd..)

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 (3 months 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-monthly and within a month for 6-monthly assessments of the scheduled visits.

[a] Visit should be performed no earlier than 2 months and no later than 3 months after end of treatment. If the patient is in CR or PR following the CT scan a bone marrow examination should be performed a minimum of 3 months after the end of the treatment. This visit also correlates to 2 months after the Day 28 after Treatment Completion/Early Termination visit.

[b] Includes pulse rate, respiratory rate and systolic and diastolic blood pressure while the patient is in a seated position, and temperature.

[c] 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

[d] 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.

[e] Includes: WBC count, RBC count, hemoglobin, hematocrit, platelet count, differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells.

[f] 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.

[g] Includes: dipstick pH, specific gravity, glucose, protein, ketones, blood) and microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria).

[h] For patients who have signed the additional consent for GCLLSG biobanking, residual sample will be sent to the GCLLSG for analysis.

[i] Blood for MRD assessment will include 10 mL of blood at all timepoints for ASO-PCR; 5 or 6 mL at baseline and 10 mL at other timepoints for analysis by NGS and flow cytometry

[j] Blood for MRD assessment will include 10 mL of blood for ASO-PCR and 10 mL for analysis by NGS at 24 months after treatment completion/early termination and then every 6 months thereafter (until 5 years from last patient enrolled).

[k] A bone marrow aspirate must be taken within 8 weeks from patients who achieve a CR/PR for central assessment of MRD. Bone marrow aspirate (separate sample, assessed at a local laboratory) and biopsy to confirm CR is required.

[l] For 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 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.

Appendix 3
Fallback Test in a Group-Sequential Trial

1. TRIAL DESIGN AND ANALYSIS STRATEGY

A group-sequential trial is proposed for evaluating the efficacy profile of an experimental treatment versus control. The efficacy will be evaluated using the following ordered endpoints:

- Endpoint 1 (Investigator-assessed PFS)
- Endpoint 2 (IRC assessed PFS)
- Endpoint 3 (MRD in bone marrow at EOT assessment)
- Endpoint 4 (CR (investigator assessed) at EOT assessment)
- Endpoint 5 (MRD in peripheral blood at EOT assessment)
- Endpoint 6 (MRD in CR in bone marrow at EOT assessment)
- Endpoint 7 (MRD in CR in peripheral blood at EOT assessment)
- Endpoint 8 (ORR (investigator assessed) at EOT assessment)
- Endpoint 9 (OS)

Let m denote the total number of endpoints (m=9). Also, let k denote the total number of decision points that will be utilized in this trial, which includes the final analysis for Endpoint 9, i.e., k=3.

A multiplicity adjustment strategy that accounts for the two sources of multiplicity in this trial (multiple looks at the data and multiple endpoints) is defined in Section 2 below.

2. MULTIPLICITY ADJUSTMENT STRATEGY

A fallback-based multiplicity adjustment will be employed to control the overall Type I error rate at a two-sided α=0.05 in this trial. The adjustment relies on the following two components:

- An α-spending function is specified for each of the endpoints (Jennison and Turnbull, 2000) to control for multiplicity across the decision points. Using the α-spending function for the ith endpoint, let $c_i(t|\lambda)$ denote the adjusted significance level at the decision point corresponding to the information fraction t ($0<t\leq 1$) which controls the Type I error rate across the decision points at the two-sided level equal to λ; $0<\lambda\leq\alpha$. The endpoint-specific information fractions corresponding to the pre-defined decision points are denoted by t_{ij}. Note that, for Endpoints 3, 4, 5, 6, 7 and 8, the outcomes are available at the interim analysis and thus t_{ij}=1, which implies that $c_i(t_{ij}|\lambda)=\lambda$, i=3, 4, 5, 6, 7, 8.
- A combination of the fixed-sequence and fallback procedures (Dmitrienko and D'Agostino, 2013) will be applied to control for multiplicity across the endpoints, namely, the primary endpoint (Investigator-assessed PFS) and the first secondary endpoint (IRC-assessed PFS) will be tested at the full α level and, if both of these endpoints are significant, a fallback-based multiplicity adjustment will be applied to the other secondary endpoints, starting with MRD. To define

the fallback procedure, the endpoint-specific weights, denoted by $w_3,\ldots, w_m$, need to be pre-specified. The weights are positive and add up to 1.

Finally, let H_i denote the null hypothesis of no treatment effect on the ith endpoint. Let p_{ij} denote the two-sided p-value produced by the appropriate treatment effect test for the ith endpoint at the jth decision point.

The following testing algorithm will be utilized in the trial to protect the overall Type I error rate at a two-sided $\alpha=0.05$. The endpoints where fallback procedure will be implemented are assumed to be equally weighted i.e., $w_i = 1/7$, for i=3, 4, 5, 6, 7, 8, 9. Considering the jth decision point, the treatment effect on the ordered endpoints will be evaluated as follows:

- Step 1. Reject the hypothesis H_1 if $p_{1j} \le c_1(t_{1j}|\alpha_1)$, where $\alpha_1=\alpha$. Proceed to Step 2 if the hypothesis H_1 is rejected. Boundary $c_1(t_{1j}|\alpha_1)$ is obtained using gamma-family α-spending.
- Step 2. Reject the hypothesis H_2 if $p_{2j} \le c_2(t_{2j}|\alpha_2)$, where $\alpha_2=\alpha$. Proceed to Step 3 if the hypothesis H_2 is rejected. Boundary $c_2(t_{2j}|\alpha_2)$ is obtained using gamma-family α--spending.
- Step 3. Reject the hypothesis H_3 if $p_{3j} \le c_3(t_{3j}|\alpha_3)$, where $\alpha_3=w_3\alpha$. Proceed to Step 4 if the the hypothesis H_3 is rejected. Boundary $c_3(t_{3j}|\alpha_3)= \alpha_3$.
- Step 4. Reject the hypothesis H_4 if $p_{4j} \le c_4(t_{4j}|\alpha_4)$, where $\alpha_4=\alpha_3+w_4\alpha$ if the hypothesis H_3 is rejected in Step 3 and $\alpha_4=w_4\alpha$ otherwise. Proceed to Step 5 if the hypothesis H_4 is rejected. Boundary $c_4(t_{4j}|\alpha_4)=\alpha_4$.
- Step 5. Reject the hypothesis H_5 if $p_{5j} \le c_5(t_{5j}|\alpha_5)$, where $\alpha_5=\alpha_4+w_5\alpha$ if the hypothesis H_4 is rejected in Step 4 and $\alpha_5=w_5\alpha$ otherwise. Proceed to Step 6 if the hypothesis H_5 is rejected. Boundary $c_5(t_{5j}|\alpha_5)=\alpha_5$.
- Step 6. Reject the hypothesis H_6 if $p_{6j} \le c_6(t_{6j}|\alpha_6)$, where $\alpha_6=\alpha_5+w_6\alpha$ if the hypothesis H_5 is rejected in Step 5 and $\alpha_6=w_6\alpha$ otherwise. Proceed to Step 7 if the hypothesis H_6 is rejected. Boundary $c_6(t_{6j}|\alpha_6)=\alpha_6$.
- Step 7. Reject the hypothesis H_7 if $p_{7j} \le c_7(t_{7j}|\alpha_7)$, where $\alpha_7=\alpha_6+w_7\alpha$ if the hypothesis H_6 is rejected in Step 6 and $\alpha_7=w_7\alpha$ otherwise. Proceed to Step 7 if the hypothesis H_7 is rejected. Boundary $c_7(t_{7j}|\alpha_7)=\alpha_7$.
- Step 8. Reject the hypothesis H_8 if $p_{8j} \le c_8(t_{8j}|\alpha_8)$, where $\alpha_8=\alpha_7+w_8\alpha$ if the hypothesis H_7 is rejected in Step 7 and $\alpha_8=w_8\alpha$ otherwise. Proceed to Step 9 if the hypothesis H_8 is rejected. Boundary $c_8(t_{8j}|\alpha_8)=\alpha_8$.
- Step 9. Reject the hypothesis H_9 if $p_{9j} \le c_9(t_{9j}|\alpha_9)$, where $\alpha_9=\alpha_8+w_9\alpha$ if the hypothesis H_8 is rejected in Step 8 and $\alpha_9=w_9\alpha$ otherwise. Boundary $c_9(t_{9j}|\alpha_9)$ is obtained using gamma family error spending function with parameter γ=-4.

The decision rules utilized in the resulting multiple testing procedure result in a flexible algorithm, e.g., if the fallback procedure fails to reject a certain secondary null hypothesis, it can still proceed to the null hypotheses placed later in the sequence.

Table 1 Information Fractions for Endpoints 1 through 9

Endpoint	Information fractions
Endpoint 1	t_{11}=0.6471, t_{12}=1, t_{13}=1
Endpoint 2	t_{21}=0.5, t_{22}=0.6471, t_{23}=1
Endpoint 3	t_{31}=t_{32}=t_{33}=1
Endpoint 4	t_{41}=t_{42}=t_{43}=1
Endpoint 5	t_{51}=t_{52}=t_{53}=1
Endpoint 6	t_{61}=t_{62}=t_{63}=1
Endpoint 7	t_{71}=t_{72}=t_{73}=1
Endpoint 8	t_{81}=t_{82}=t_{83}=1
Endpoint 9	t_{91}=0.55, t_{92} =0.70, t_{93}=1.00

Actual information fractions will be re-calculated based on the actual number of PFS events based on Investigator and IRC assessments. We expect to see 170 IRC-assessed PFS events and 188 INV-assessed PFS events at the PFS FA decision point.