Clinical Study Protocol

A Phase 1b Study to Assess Safety, Tolerability and Antitumor Activity of the Combination of BGB-3111 with Obinutuzumab in Subjects with B-Cell Lymphoid Malignancies

Protocol Number:	**BGB-3111_GA101_Study_001**
IND Number:	**125326**
Product:	**Zanubrutinib (BGB-3111 [BTK inhibitor]) and obinutuzumab (glycoengineered, type 2 anti CD20 monoclonal antibody)**
Indication:	**B-Cell Lymphoid Malignancies**
Clinical Phase:	**1b**
Principal Investigator:	[redacted] **Disease Group Lead, Low Grade Lymphoma & CLL** [redacted]
Sponsor:	**BeiGene AUS Pty Ltd.** **1C/528 Compton Road Stretton** **Queensland 4116, Australia**
Sponsor Medical Monitor:	[redacted]
Version:	**6.0**
Date:	**03 January 2019**

Confidentiality Statement

PROTOCOL AMENDMENT, VERSION 6.0: RATIONALE

Protocol BGB-3111_GA101_Study_001 has been updated:

- To introduce the use of the International Nonproprietary Name (INN) of "zanubrutinib" for "BGB-3111."
- To add the Sponsor's address to the Protocol Title Page.
- To change the Sponsor's Medical Monitor.
- To update the Sponsor Medical Monitor's address on the Protocol Title Page.
- To remove the protocol amendment rationales for previous protocol amendments to align with the current BeiGene protocol format to show only the current protocol amendment rationale.
- To update Section 1.2 (Overview of Clinical Pharmacology) with the results of a thorough QT study (BGB-3111-106) that was recently completed in healthy volunteers and has shown that both therapeutic and supratherapeutic doses of zanubrutinib had no clinically relevant effect on electrocardiogram (ECG) parameters, including QTc intervals and other ECG intervals. As a result, drug guidance and ECG monitoring for QT/QTc prolongation were removed from the protocol in Section 7.3 (Medications to be used with Caution), Section 8.4 (Electrocardiogram), and Section 16.5 (Appendix 5).
- To update Section 1.2 (Overview of Clinical Pharmacology) with the results of a drug-drug interaction study (BGB-3111-104) that was recently completed in healthy volunteers and showed that co-administration of zanubrutinib with a strong CYP3A inducer (rifampin) decreased $AUC_{0-\infty}$ of zanubrutinib by 13.5-fold and co-administration of zanubrutinib with a strong CYP3A inhibitor (itraconazole) increased $AUC_{0-\infty}$ of zanubrutinib by 3.8-fold. As a result, Section 7.2 (Prohibited/Restricted Medications) and Section 7.3 (Medications to be used with Caution) were updated, and dose modification guidance for zanubrutinib when co-administered with strong/moderate CYP3A inhibitors and inducers was provided.
- To update Section 1.2 (Overview of Clinical Pharmacology) with the results of a drug-drug interaction study using a cocktail approach (BGB-3111-108) that was recently completed in healthy volunteers and showed that zanubrutinib does not significantly affect drugs metabolized by CYP2C9 (warfarin) or transported by P-gp (digoxin) and BCRP (statins); however, zanubrutinib has a mild induction effect on CYP3A and CYP2C19 enzymes. Section 7.3 (Medications to be used with Caution) was updated accordingly.
- To update Section 1.5 (Benefit and Risk Conclusions for Zanubrutinib) with the number of patients treated with zanubutinib and add a reference to the Investigator's Brochure (IB) for more information.
- To update the zanubrutinib treatment duration so that treatment can continue until disease progression, intolerance, death, subject withdraws from the study, or study closure, whichever occurs first.
- To change tumor imaging frequency after Week 48 from investigator's discretion to every 24 weeks to ensure consistent data are collected to assess response and progression in this study.

- To change the Week 52 assessment/visit to Week 48 in order to align the updated tumor imaging frequency with the assessment/visit schedule. To also reduce the frequency of visits after Week 48 of the study (from every 8 weeks [±7 days] to every 12 weeks [±10 days]).
- To update Section 8.5 (Computed Tomography) to allow more flexibility around the timing of CT scans when a subject's scan may fall outside the specified imaging procedure window (eg, due to out-of-town travel or other unforeseen circumstances).
- To add a new Section 8.7 (Minimal Residual Disease for Subjects with CLL) that outlines samples to be taken for minimal residual disease testing in subjects with Chronic Lymphocytic Leukemia (CLL); all subsequent sections were renumbered. The Study Assessments and Procedures Schedule for Part 1 (Table 1) and Part 2 (Table 2) were updated for this testing as well.
- To clarify procedures for an optional post-progression biomarker assessment sample for all patients at the Safety Follow-up Visit (added in Protocol Amendment, Version 5.0) and to update the associated exploratory endpoint.
- To update the Study Assessments and Procedures Schedule for Part 1 (Table 1) and Part 2 (Table 2) to clarify when response assessments are performed and how response is assessed.
- To update the Study Assessments and Procedures Schedule for Part 1 (Table 1) and Part 2 (Table 2), as well as Appendices 16.1 and 16.2, to remove coagulation testing after screening, and to remove selected hematology and clinical chemstry tests that were deemed unnecessary given the experience with zanubrutinib to date. In addition, the frequency of hematology, clinical chemistry, urine analysis, immunoglobulins, and serum EPG laboratory assessments were reduced after Week 25.
- To update the Study Assessments and Procedures Schedule for Part 1 (Table 1) and Part 2 (Table 2), as well as Section 8.4 (Electrocardiograms), to remove ECGs after screening (post-screening ECGs will be performed at the investigator's discretion if medically indicated).
- To add clarifications in Section 6.2.1 (Dosage and Administration, Zanubrutinib) regarding zanubrutinib dosing and reference to the patient diary and Pharmacy Manual.
- To add language in Section 7.1 (Permitted Medications) about the potential for opportunistic infections, including Pneumocystis jirovecii pneumonia (PJP), in patients with hematologic malignancies, particularly those having received prior lymphodepleting chemotherapy or having prolonged corticosteroid exposure, and guidance to consider prophylaxis treatment per institutional standards.
- To clarify in Section 7.2 (Prohibited/Restricted Medications) that limited duration doses ≤20 mg of prednisone are allowed for malignant indications, not just doses <20 mg.
- To change the collection of adverse events (AEs) and serious adverse events (SAEs) from 120 days after the last dose of obinutuzumab to 90 days after the last dose of obinutuzumab.
- To revise text in Section 10.9 (Prompt Reporting of Serious Adverse Events) to update the serious adverse event reporting process.
- To clarify and reduce redundancy in text regarding the analysis sets.
- To delete text that is included in the Statistical Analysis Plan.
- To clarify that the hematological improvement analysis is for CLL patients only.

- To clarify in Table 9 (Safety Laboratory Assessments) that bands are optional, and to remove selected hematology and clinical chemstry tests that were deemed unnecessary given the experience with zanubrutinib to date.
- To update and align language in Section 12 (Regulatory and Ethical Issues) and Section 13 (Study Management) with current BeiGene protocols.
- To update Section 14 (References) with new references added to the protocol.
- To update the format of Section 15 (Protocol Signatures).
- To clarify the Categorical Waldenström's Macroglobulinemia Response Definition for "very good partial response" in Appendix 16.3. In addition, to align with other BeiGene protocols, the repeat IgM level for determining progressive disease in the case of a drug hold was changed from 6 weeks to 10 weeks after restarting study administration, and "≥ 25% increase in serum IgM" was added for total increase from lowest nadir (to the already specified criterion of "at least 500mg/dL from lowest nadir").
- To incorporate the following updates to the protocol per administrative memos that have been issued since Protocol Amendment Version 5.0:
    - Correction of typo (ie, deletion of stray text) in Appendix 16.3, Response Criteria, Non-Hodgkin Lymphoma (including SLL; excluding WM)
    - Administrative change to Appendix 16.3 Guidelines for specific clinical or laboratory circumstances: Changed any reference of "central" laboratory to "local" laboratory because a central laboratory is not used in this study
    - Clarification change made to footnote 2 under Tables 1 and 2 Study assessments and Procedures Schedule to remove the restriction to perform biopsy at relapse for selected sites only, and this is now open to all sites and subjects who consent to have this procedure done
    - Addition of clarifying text regarding tumor assessments after Week 48

- To note the following changes that were implemented in Protocol Amendment Version 5.0 but were omitted in error in the "Protocol Amendment, Version 5.0: Rationale" section of the previous protocol version:
    - To modify the adverse events and serious adverse events reporting period in Section 10.5.1.
    - To include specific instructions for recording adverse events and serious adverse events in Section 10.5.3.
    - To clarify the Assessment of Severity (previously Assessment of Intensity) in Section 10.7.1.
    - To add guidance for Assessment of Causality in Section 10.7.2.
    - To add Section 10.13 Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards and Ethics Committees.

- To make other minor changes for consistency between protocol sections and clarity

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SYNOPSIS

Name of Sponsor/Company:	BeiGene AUS Pty Ltd.
Name of Finished Product(s):	Zanubrutinib (BGB-3111) and obinutuzumab (GA101, Gazyva®)
Name of Active Ingredient(s):	Zanubrutinib (BGB-3111 [BTK inhibitor]) and obinutuzumab (glycoengineered, type 2 anti CD20 monoclonal antibody)
Title of Study: A Phase 1b Study to Assess Safety, Tolerability and Antitumor Activity of the Combination of BGB-3111 with Obinutuzumab in Subjects with B-Cell Lymphoid Malignancies	
Study Duration:	Screening (up to 28 days); treatment until disease progression, intolerance, death, subject withdraws from the study, or study closure, whichever occurs first; followed by a 28-day safety follow up.
Clinical Phase:	Phase 1b

Objectives:

Part 1

Primary:

- To evaluate the safety and tolerability of zanubrutinib (also known as BGB-3111) in combination with obinutuzumab.
- To determine the maximum tolerated dose (MTD) or recommended Phase 2 dose (RP2D) of zanubrutinib, in combination with obinutuzumab, when given continuously orally.

Secondary:

- To assess the preliminary antitumor activity of zanubrutinib in combination with obinutuzumab.
- To characterize the pharmacokinetics (PK) of zanubrutinib and obinutuzumab when administered in combination.

Exploratory:

- [redacted]
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Part 2

Primary:

- To assess the preliminary antitumor activity of zanubrutinib in combination with obinutuzumab.

Secondary:

- To further evaluate the safety and tolerability of zanubrutinib in combination with obinutuzumab.

- To further characterize the pharmacokinetics (PK) of zanubrutinib and obinutuzumab when administered in combination.

Exploratory:

- [redacted]
- [redacted]

Methodology:

This is a two part, open label Phase 1b clinical trial designed to determine the safety, tolerability and preliminary antitumor activity of zanubrutinib in combination with obinutuzumab: Part 1 (safety evaluation) and Part 2 (indication specific expansion cohorts).

Part 1: Safety Evaluation

Part 1 is designed to evaluate the safety and tolerability of zanubrutinib in combination with obinutuzumab in subjects with relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), R/R non-germinal center B-cell (non-GCB) diffuse large B-cell lymphoma (DLBCL), R/R follicular lymphoma (FL), R/R mantle cell lymphoma (MCL), R/R Waldenström's macroglobulinemia (WM), and R/R marginal zone lymphoma (MZL).

Two dose regimens of zanubrutinib, 320 mg once daily [QD] and 160 mg twice daily [BID] (added per Amendment Version 3.0), will be evaluated in combination with obinutuzumab, consistent with the U.S. label regimen as specified below, in a cohort of 6 subjects for each dose regimen. It is anticipated based on available data that both regimens will be well tolerated. However, if there appear 2 or more dose limiting toxicities (DLTs) in a 6-subject cohort in either regimen, the dose level is considered to have exceeded the MTD and a reduced dose level of zanubrutinib (160 mg QD or 80 mg BID) will be evaluated in combination with obinutuzumab in another cohort of 6 subjects in that regimen. Further reduction of the zanubrutinib dose level will be allowed until a safe dose combination is identified. The period for DLT assessment is 29 days from first administration of zanubrutinib. In the event that a MTD is not exceeded, the Sponsor will select both 320 mg QD and 160 mg BID for the Part 2 of the study.

Zanubrutinib will be administered orally with or without food every day in each cycle (29 days for Cycle 1, and 28 days for Cycle 2 and each cycle thereafter) until disease progression, death, unacceptable toxicity, other reason for treatment discontinuation, or study closure, whichever occurs first.

Obinutuzumab will be administered intravenously for up to 6 cycles consistent with the US label regimen:

- Day 2 Cycle 1: 100 mg obinutuzumab,
- Day 3 Cycle 1: 900 mg obinutuzumab,
- Day 9 and Day 16 Cycle 1: 1000 mg obinutuzumab.
- Day 1 Cycles 2 to 6: 1000 mg obinutuzumab.

The continuous safety evaluation will be performed by a Safety Monitoring Committee (SMC) composed of the Sponsor, the Sponsor's medical delegate, the coordinating investigator, up to 2 additional investigators, and the contract research organization (CRO) medical monitor. The SMC composition and responsibilities will be further detailed in the SMC Charter. The SMC will be responsible for the determination of dose levels and regimens to be administered during the study.

The Sponsor, in consultation with investigators, may decide to explore alternative zanubrutinib and/or obinutuzumab dosing regimens. If this decision is made, the protocol will be appropriately amended.

Part 2: Indication Specific Expansion

In Part 2, the RP2D and the 2 regimens will be investigated in 5 expansion cohorts (revised per Amendment Version 4.0) with histology type of tumor defined as below. Based on the safety, tolerability, pharmacokinetic (PK), and antitumor activity data from the safety evaluation part (Part 1) of the study, additional cohorts may be enrolled:

- Cohort 1: treatment-naïve CLL/SLL subjects (approximately 20 subjects divided by the 2 regimens)
- Cohort 2: R/R CLL/SLL subjects (approximately 20 subjects divided by the 2 regimens)
- Cohort 3: R/R non-GCB DLBCL, defined by Hans algorithm (approximately 20 subjects divided by the 2 regimens)
- Cohort 4: R/R FL, MCL, MZL, and WM (approximately of 20 subjects divided by the 2 regimens)
- Cohort 5: R/R FL (approximately of 40 subjects in 160 mg BID regimen. Among them, 10-15 should meet double-refractory criterion, defined as refractoriness to both rituximab and an alkylating agent, whether administered together or in successive treatment regimens. Refractoriness was defined per protocol as less than a partial response or progression of disease within 6 months after completion of a prior therapy, added per Amendment Version 4.0).

In Part 2, once the SMC confirms that the 6 subjects in 160 mg BID regimen passed Part 1 DLT test, all new eligible subjects will be enrolled into 160 mg BID regimen in each of the 5 cohorts until the total number of that cohort reaches the pre-specified number (revised per Amendment Version 4.0).

Subjects enrolled in zanubrutinib 320 mg QD dose regimen will have the option to switch to 160 mg BID once Amendment 4.0 is active.

Zanubrutinib will be administered orally with or without food every day in each cycle (28 days for each cycle) until disease progression, death, unacceptable toxicity, other reason for treatment discontinuation, or study closure, whichever occurs first.

Obinutuzumab will be administered intravenously for up to 6 cycles consistent with the US label regimen:

- Day 1 Cycle 1: 100 mg obinutuzumab,
- Day 2 Cycle 1: 900 mg obinutuzumab,
- Day 8 and Day 15 Cycle 1: 1000 mg obinutuzumab.
- Day 1 Cycles 2 to 6: 1000 mg obinutuzumab.

The safety evaluation by the SMC will be performed on as needed basis (see the SMC Charter) but at a minimum of every 6 months to review all subjects enrolled, or when there is any significant safety finding. Any treatment-related death will also trigger review by the SMC. The SMC will determine whether it is safe to proceed with the study.

If the frequency of Grade 3 or 4 toxicities or other unacceptable chronic toxicities in the indication expansion cohorts suggests that the MTD of zanubrutinib in combination with obinutuzumab has been exceeded at that dose level, any remaining accrual at that dose level will be halted. Consideration will then be given to enrolling an expansion cohort at a lower dose level or at a different schedule. The protocol will be appropriately amended.

Number of Subjects:

Approximately 132 subjects (revised per Amendment Version 4.0)

Study Population:

Inclusion Criteria:

1. Aged ≥18 years, able and willing to provide written informed consent and to comply with the study protocol.
2. Part 1 (Safety evaluation): R/R CLL/SLL, FL, MCL, MZL, WM, and non-GCB DLBCL.
3. Part 2 (Indication specific expansion):
   - Cohort 1: treatment-naïve CLL/SLL.
   - Cohort 2: R/R CLL/SLL.
   - Cohort 3: R/R non-GCB DLBCL.
   - Cohort 4: R/R FL, MCL, MZL, and WM.
   - Cohort 5: R/R FL. About 10-15 out of 40 subjects should meet double-refractory criterion, defined as refractoriness to both rituximab and an alkylating agent, whether administered together or in successive treatment regimens. Refractoriness was defined per protocol as less than a partial response or progression of disease within 6 months after completion of a prior therapy (added per Amendment Version 4.0).
     - For R/R CLL, FL, MCL, MZL, and WM: Evidence of progression or lack of response following at least 1 prior treatment.
     - For R/R non-GCB DLBCL: Evidence of progression or refractory disease following at least a standard anthracycline/ rituximab based primary treatment regimen (eg, R-CHOP) and not currently appropriate for autologous stem cell transplantation.
4. Laboratory parameters as specified below:
   - Hematologic: Platelet count >$40x10^9$/L (may be post-transfusion); absolute neutrophil count >$1.0x10^9$/L (growth factor use is allowed to bring pre-treatment neutrophils to >$1.0x10^9$ /L if marrow infiltration is involved).
   - Hepatic: Total bilirubin <3 x upper limit normal (ULN); and aspartate aminotransferase (AST) and alanine transaminase (ALT) ≤3xULN.
   - Renal: Creatinine clearance ≥ 30 mL/min (as estimated by the Cockcroft Gault equation or as measured by nuclear medicine scan or 24-hour urine collection); subjects requiring hemodialysis will be excluded.
5. Anticipated survival of at least 6 months.
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.
7. Female subjects of childbearing potential and non-sterile males must agree to practice at least one of the following methods of birth control with partner(s) throughout the study and for ≥3 months after discontinuing zanubrutinib or ≥18 months following treatment with obinutuzumab, whichever is longer: total abstinence from sexual intercourse, double barrier contraception, intra uterine device (IUD) or hormonal contraceptive initiated at least 3 months prior to first administration of study drug.
8. Male subjects must not donate sperm from first study drug administration, until ≥3 months after discontinuing zanubrutinib or ≥18 months following treatment with obinutuzumab, whichever is longer.

Key Exclusion Criteria:

1. Known central nervous system lymphoma or leukemia.
2. Known prolymphocytic leukemia or history of, or currently suspected, Richter's syndrome.
3. Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenia purpura.
4. History of significant cardiovascular disease, define as:
    - congestive heart failure greater than New York Heart Association (NYHA) class II according to the NYHA functional classification
    - unstable angina or myocardial infarction with 6 months of enrollment
    - serious cardiac arrhythmia or clinical significant electrocardiogram (ECG) abnormality: corrected QT wave (QTc) prolongation, defined as a QTc >450 msecs based on the Bazett's formula (Subjects with QTc prolongation due to a cardiac pacemaker may be allowed with approval of the medical monitor), or other ECG abnormalities including 2nd degree atrioventricular (AV) block type II, 3rd degree AV block, or bradycardia (ventricular rate less than 50 beats/min).
5. Severe or debilitating pulmonary disease (dyspnea at rest, significant shortness of breath, chronic obstructive pulmonary disease [COPD]).
6. History of severe allergic or anaphylactic reactions to monoclonal antibody therapy.
7. Prior BTK inhibitor treatment.
8. Use of strong CYP3A inhibitors and strong CYP3A inducers (see Table 6).
9. Vaccination with a live vaccine within 28 days of the initiation of treatment.
10. Allogeneic stem cell transplantation within 6 months, or has active graft versus host disease (GvHD) requiring ongoing immunosuppression.
11. Receipt of the following treatment prior to first administration of zanubrutinib, corticosteroids given with anti-neoplastic intent within 7 days, chemotherapy or radiotherapy within 3 weeks, monoclonal antibody within 4 weeks.
12. Participate in any investigational drug study within 28 days of study entry, or not recovered from non-hematologic toxicity of any prior chemotherapy up to ≤ Grade 1 (except for alopecia).
13. History of other active malignancies within 2 years of study entry, with exception of (1) adequately treated in situ carcinoma of cervix; (2) localized basal cell or squamous cell carcinoma of skin; (3) previous malignancy confined and treated locally (surgery or other modality) with curative intent.
14. Unable to swallow capsules or disease significantly affecting gastrointestinal function such as malabsorption syndrome, resection of the stomach or small bowel, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction (revised per Amendment Version 3.0).
15. Major surgery in the past 4 weeks.
16. Active symptomatic fungal, bacterial and/or viral infection including evidence of infection with human immunodeficiency virus (HIV), human T cell lymphotropic virus (HTLV 1) seropositive status.
17. Subjects with positive serology for hepatitis B defined as positivity for hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (anti-HBc); subjects who are positive for anti-HBc may be considered for inclusion in the study on a case-by-case basis if they are hepatitis B viral deoxyribonucleic acid (DNA) negative and are willing to undergo ongoing

HBV DNA testing by real-time polymerase chain reaction (PCR); subjects with presence of hepatitis B surface antibody (anti-HBs) consistent with prior vaccination (ie, HBsAg negative, anti-HBc negative, anti-HBs positive) may participate; subjects suspected to have false positive serologic studies because of IV immunoglobulin administration are potentially eligible after negative PCR studies for viral DNA/ribonucleic acid (RNA) and discussion with the principal investigator.

18. Evidence of active hepatitis C (HCV): subjects with positive hepatitis C serology and positive HCV RNA test
19. Inability to comply with the study procedures.
20. Pregnant or nursing women.
21. Any illness or condition that in the opinion of the investigator may affect the safety of treatment or evaluation of any study's endpoints.

Test Product, Dose and Route of Administration:

Zanubrutinib 80 mg oral capsules.

Reference Therapy, Dose and Route of Administration:

1000 mg/vial of obinutuzumab (preservative free liquid concentrate) by intravenous infusion.

Duration of Treatment:

Treatment until disease progression, intolerance, death, subject withdraws from the study, or study closure.

Criteria for Evaluation:

Part 1

Primary Endpoints:

- The safety and tolerability of zanubrutinib in combination with obinutuzumab will be evaluated by the incidence, nature, and severity of AEs, clinical laboratory abnormalities, deaths and cause of death, and DLTs.
- The RP2D of zanubrutinib in combination with obinutuzumab will be determined based on the incidence of DLTs in Part 1 of the study according to the MTD/RP2D evaluation process described in Section 4.

Secondary Endpoints:

- Preliminary antitumor activity of zanubrutinib in combination with obinutuzumab will be assessed by the frequency, quality, and durability of objective responses for each of the specified disease cohorts (treatment-naïve CLL, R/R CLL/SLL, R/R non-GCB DLBCL, R/R FL, R/R MCL, R/R MZL and R/R WM)) as per the standard International Working Group (IWG) Criteria for each disease.
- Clinical activity of zanubrutinib in combination with obinutuzumab will be further assessed by the frequency and rate of hematologic improvement for subjects with CLL with anemia and/or thrombocytopenia at baseline (hemoglobin <9 g/dL, platelets <100,000/uL).
- The PK profile of zanubrutinib will be determined, following the Cycle 1 Day 1 and Cycle 2 Day 1, by the area under the plasma concentration-time curve from zero to the last quantifiable concentration (AUC_{last}), area under the plasma concentration-time curve from zero to infinity (AUC), maximum observed plasma concentration (C_{max}), time to maximum

observed plasma concentration (t_{max}), terminal half-life ($t_{1/2}$), apparent clearance (CL/F), and apparent volume of distribution (V_{zd}/F). After steady state: $AUC_{last,ss}$, $C_{max,ss}$, and $t_{max,ss}$.

- The PK profile of obinutuzumab will be determined by plasma concentration prior to start of the infusion, and at 4 hours (end of infusion) on Cycle 1 Day 2, Cycle 1 Day 3, Cycle 1 Day 9, Cycle 1 Day 16, as well as Day 1 Cycles 2, 4, and 6.

Exploratory Endpoints:

- [redacted]

Part 2

Primary Endpoints:

- Preliminary antitumor activity of zanubrutinib in combination with obinutuzumab will be assessed by the frequency and durability of objective responses for each of the specified disease cohorts as per the standard International Working Group (IWG) Criteria for each disease.

Secondary Endpoints:

- The safety and tolerability of zanubrutinib in combination with obinutuzumab will be further evaluated as described for Part 1.
- Activity of zanubrutinib in combination with obinutuzumab will be assessed by the frequency and rate of hematologic improvement for subjects with CLL with anemia and/or thrombocytopenia at baseline (hemoglobin <9 g/dL, platelets <100,000/uL).
- The PK profiles of zanubrutinib and obinutuzumab will be further characterized as described for Part 1.

Exploratory Endpoints:

- [redacted]

Statistical Methods

The number of dose levels in the safety evaluation part and the emerging zanubrutinib in combination with obinutuzumab toxicities will determine the sample size. It is anticipated that approximately 132 (revised per Amendment Version 4.0) subjects (12 subjects in the safety evaluation part and 120 subjects in the indication specific expansion part) will be required to complete the Phase 1b trial of zanubrutinib in combination with obinutuzumab.

Data will be listed and summarized according to the Sponsor agreed reporting standards, where applicable.

All subjects who are exposed to (or started receiving) zanubrutinib in combination with obinutuzumab will be included in the safety analysis set. All subjects for whom valid zanubrutinib PK sample can be estimated and no major protocol deviations affecting PK will be included in the PK analysis set on an as treated basis. Similarly, subjects for whom valid obinutuzumab PK sample can be estimated and no major protocol deviations affecting PK will be included in the PK analysis set on an as treated basis. For other parameters, all evaluable data will be included in the summaries.

No formal statistical hypothesis testing will be performed for safety and tolerability. All safety and tolerability data recorded during the study will be listed and summarized as appropriate. Continuous variables will be summarized using descriptive statistics by treatment and by time points where applicable. Categorical variables will be summarized in frequency tables by treatment.

LIST OF ABBREVIATIONS

Abbreviations	Definition
ABC	activated B-cell-like
ACD	acid citrate dextrose
ADCC	antibody dependent cell-mediated cytotoxicity
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve from zero to infinity
AUC_{last}	area under the plasma concentration-time curve from zero to the last quantifiable concentration
$AUC_{last.ss}$	area under the plasma concentration-time curve from zero to the last quantifiable concentration at steady state
AV	Atrioventricular
BCR	B-cell receptor
BID	twice daily
BMI	body mass index
BQL	below quantifiable limit
BTK	Bruton's tyrosine kinase
CI	confidence interval
CLL	chronic lymphocytic leukemia
CL/F	apparent clearance
C_{max}	maximum observed plasma concentration
$C_{max.ss}$	maximum observed plasma concentration at steady state
COPD	chronic obstructive pulmonary disease
CR	complete response
CrCl	creatinine clearance
CRO	contract research organization
CRR	complete response rate
CT	computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CV%	coefficient of variation
CYP	cytochrome P450
DBP	diastolic blood pressure
DLBCL	diffuse large B-cell lymphoma
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EDTA	ethylenediaminetetra acetic acid
EGFR	epithelial growth factor receptor
EPG	serum electrophoresis
FDA	Food and Drug Administration

Abbreviations	Definition
FL	follicular lymphoma
FRK	Fyn-related kinase (tyrosine protein kinase 5)
FGR	Gardner-Rasheed feline sarcoma viral (v-fgr) oncogene homolog
GA101	Gazyva® (obinutuzumab)
GCB	germinal center B-cell-like
GCP	Good Clinical Practice
GvHD	graft-versus-host disease
HBc	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCL	hairy cell leukemia
HCV	hepatitis C virus
HER2	human epidermal growth factor receptor 2 (erb-b2 receptor kinase 2)
HER4	human epidermal growth factor receptor 4 (erb-b4)
HIV	human immunodeficiency virus
Hgb	Hemoglobin
HTLV-1	human T-cell lymphotropic virus
IB	investigator's brochure
IC_{50}	50% maximal inhibiting concentration
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IND	investigational new drug
IRB	Institutional Review Board
ITK	interleukin-2-inducible T-cell kinase
IUD	intra-uterine device
IWG	International Working Group
JAK3	janus kinase 3
λ_z	terminal rate constant
LCK	lymphocyte-specific protein tyrosine kinase
MCH	mean corpuscular hemoglobin
MCL	mantle cell lymphoma
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MM	multiple myeloma
MRD	minimal residual disease
MRI	magnetic resonance imaging
MTD	maximal tolerated dose
MZL	marginal zone lymphoma
NCI	National Cancer Institute
NHL	non-Hodgkin's lymphoma
NK	natural killer cells
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction

Abbreviations	Definition
PD	Pharmacodynamics
PET	positron emission tomography
PFS	progression free survival
PJP	Pneumocystis jirovecii pneumonia
PK	Pharmacokinetic
PLCγ2	phospholipase gamma 2 (phosphatidylinositol-specific)
PR	partial response
PRR	partial response rate
PT	preferred term
QD	once daily
RBC	red blood cell
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
R/R	relapsed/refractory
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	stable disease
SLL	small lymphocytic lymphoma
SMC	Safety Monitoring Committee
SOC	system organ class
SOP	standard operating procedure
$t_{1/2}$	terminal half-life
TEAE	treatment–emergent adverse events
TEC	tyrosine kinase expressed in hepatocellular carcinoma
TESAE	treatment-emergent serious adverse event
t_{max}	time to maximum observed plasma concentration
$t_{max,ss}$	time to maximum observed plasma concentration at steady state
ULN	upper limit of normal
$V_{d,ss}$	volume of distribution at steady state
V_{zd}/F	volume of distribution
WBC	white blood cell
WHO DD	World Health Organization Drug Dictionary
WM	Waldenström's macroglobulinemia
zanubrutinib	BGB-3111

1 INTRODUCTION

1.1 Background and Pharmacology

Bruton's tyrosine kinase (BTK), a member of the tyrosine kinase expressed in hepatocellular carcinoma (TEC) family kinases, is a critical component of the B-cell receptor (BCR) signalling cascade. Inhibition of BTK has emerged as a promising strategy for targeting B-cell malignancies. Ibrutinib has demonstrated promising anti-tumor activity in several B-cell malignancies, including mantle cell lymphoma (MCL), chronic lymphocytic leukemia (CLL), Waldenström's macroglobulinemia (WM), follicular lymphoma (FL), multiple myeloma (MM), and activated B-cell like (ABC) subtype of diffuse large B-cell lymphoma (DLBCL).[1,2,3,4] It was recently approved by the Food and Drug Administration (FDA) for treatment of subjects with MCL and CLL who had received at least one prior therapy, and subjects with WM and CLL with 17p deletion at any line.

While ibrutinib treatment frequently generates objective responses in these diseases, few of them are complete responses, thus management requires continuous treatment.[5,6] In addition, though ibrutinib is well-tolerated in comparison to traditional chemotherapies, it is associated with adverse reactions that in some cases can be life-threatening or treatment-limiting. These adverse reactions, including but not limited to skin rash, nausea, vomiting, thrombocytopenia, bleeding and atrial fibrillation, are believed to be related to ibrutinib's off-target activities against epithelial growth factor receptor (EGFR)/janus kinase 3 (JAK3)/TEC.

Thus there is a clear medical need for a more potent, more specific, and better-tolerated secondary generation BTK inhibitor.

Zanubrutinib (also known as BGB-3111) is a potent, specific and irreversible BTK inhibitor with a favorable pharmacology/toxicology profile. Preclinical data suggests that zanubrutinib is differentiated from ibrutinib in the following aspects:

1. Zanubrutinib is more selective than ibrutinib in the inhibition of BTK versus epithelial growth factor receptor (EGFR), Gardner-Rasheed feline sarcoma viral (v-fgr) oncogene homolog (FGR), Fyn-related kinase (tyrosine protein kinase 5) (FRK), human epidermal growth factor receptor (HER)2, HER4, interleukin-2-inducible T cell kinase (ITK), JAK3, lymphocyte-specific protein tyrosine kinase (LCK), and TEC. The predicted efficacious dose of zanubrutinib in subjects is much lower than ibrutinib. Accordingly, off-target kinase inhibition potentially associated with common, and occasionally severe, adverse effects seen with ibrutinib therapy, such as thrombocytopenia, bleeding, atrial fibrillation, rash, and gastrointestinal toxicities may be reduced relative to ibrutinib.

2. Zanubrutinib has better oral bioavailability than ibrutinib.

3. Due to its weaker ITK inhibitory activity, zanubrutinib displayed significantly less inhibitory effect on rituximab-induced antibody dependent cell-mediated cytotoxicity (ADCC) than ibrutinib[7,8] in preclinical studies and is therefore unlikely to adversely impact the anti-tumor effects of agents such as obinutuzumab.

In vivo studies demonstrated that zanubrutinib had dose dependent anti-tumor activity against Rec-1 MCL xenografts engrafted either subcutaneously or systemically in mice. Zanubrutinib was significantly more effective than ibrutinib in both models. In pharmacokinetic (PK)/pharmacodynamic (PD) studies, oral administration of zanubrutinib resulted in time dependent occupancy of BTK in both blood and spleen of mice.

Refer to the Investigator's Brochure (IB) for more detailed information on the background of zanubrutinib.[9]

1.2 Overview of Clinical Pharmacology

In the Phase 1, first-in-human trial of zanubrutinib as monotherapy (A Phase 1, open-label, multiple-dose, dose escalation and expansion study to investigate the safety and pharmacokinetics of the BTK inhibitor zanubrutinib in subjects with B-cell lymphoid malignancies; protocol number BGB-3111-AU-003)[10], interim PK data in a limited number of subjects showed that zanubrutinib is rapidly absorbed and eliminated after oral administration. The maximum plasma concentration and the drug exposure (area under the concentration-time curve [AUC]) increased in a nearly dose-proportional manner from 40 mg to 320 mg both after the single dose and at steady state. The terminal half-life ($t_{1/2}$) ranged from 1.8 hours to 3.7 hours. At 320 mg once daily (QD) and 160 mg twice daily (BID), the means for maximum observed plasma concentration (C_{max}) and the area under the concentration-time curve from 0 to 24 hours (AUC_{0-24h}) are around 646 ng/mL and 2,704 ng/mL*h, and 282 ng/mL and 3,006 ng/mL*h, respectively, at the steady state.

In the same Phase 1 trial, the pharmacodynamic activity of zanubrutinib as measured by BTK occupancy in peripheral blood mononuclear cells (PBMCs) was determined in a limited number of subjects. The data indicates that even at the starting dose (40 mg), zanubrutinib achieved rapid, durable, and near complete inhibition of BTK, which is comparable to the reported effect of ibrutinib at 560 mg in clinic[4]. These data suggest that zanubrutinib is a very potent BTK inhibitor.

The QT interval prolongation potential of zanubrutinib was evaluated in healthy subjects in a thorough QT study (BGB-3111-106). Results from this study demonstrated that single oral doses of zanubrutinib at a therapeutic dose of 160 mg and a supratherapeutic dose of 480 mg did not have a clinically relevant effect on ECG parameters, including

QTc intervals and other ECG intervals. Because of the short half-life and no accumulation seen upon multiple-dosing, these results are also applicable for steady-state conditions.

Results from a dedicated drug-drug interaction study (BGB-3111-104) indicate that co-administration of zanubrutinib with the strong CYP3A inducer rifampin (600 mg every day for 8 days) decreased exposure of zanubrutinib by 13.5-fold for $AUC_{0-\infty}$, and 12.6-fold for C_{max}, in healthy subjects. Co-administration of zanubrutinib with the strong CYP3A inhibitor itraconazole (200 mg every day for 4 days) increased exposure of zanubrutinib by 3.8-fold for $AUC_{0-\infty}$, and 2.6-fold for C_{max}. These results are consistent with the role for CYP3A isoenzymes as the principal metabolic pathway for zanubrutinib.

Based on the in vitro study, a clinical drug-drug interaction study (BGB-3111-108) was conducted to assess the effect of zanubrutinib on the PK of substrates of CYP3A (midazolam), CYP2C9 (warfarin), CYP2C19 (omeprazole), P-gp (digoxin), BCRP (rosuvastatin) using a cocktail approach. The results show that zanubrutinib does not significantly affect drugs metabolized by CYP2C9 (warfarin) or transported by P-gp (digoxin) and BCRP (statins). Zanubrutinib has a mild induction effect on CYP3A and CYP2C19 enzymes. AUC_{0-t} and C_{max} values were approximately 47% and 30% lower, respectively, when midazolam was coadministered with zanubrutinib. AUC_{0-t} and C_{max} values were approximately 36% and 20% lower, respectively, when omeprazole was coadministered with zanubrutinib.

1.3 Overview of Efficacy

As of 30 July 2015, the preliminary results from the Phase 1 trial of zanubrutinib demonstrates promising anti-tumor activity in subjects with B-cell malignancies, including CLL, WM, MCL, hairy cell leukemia (HCL), DLBCL, MZL, and FL. Among the twenty-five (25) subjects enrolled in the dose-escalation phase of the study, the best responses are: one (1) subject with MCL achieved complete response/remission (CR); fifteen (15) subjects achieved partial responses/remission (PR), including six (6) subjects with CLL, five (5) subjects with WM, three (3) subjects with MCL, and one (1) subject with HCL; six (6) subjects achieved stable disease (SD), including two (2) subjects with CLL, one (1) subject with MCL, one (1) subject with MZL, one (1) subject with DLBCL, and one (1) subject with FL. Three (3) subjects, including one (1) subject with WM, one (1) subject with MCL, and one (1) subject with DLBCL, presented with progressive disease.

1.4 Overview of Safety of Zanubrutinib

Zanubrutinib has also demonstrated a favorable toxicology and safety pharmacology profile in non-clinical experiments compared to ibrutinib in terms of the overall tolerance and severe toxicities in single and repeat dose toxicity studies.

The preliminary results from the ongoing first-in-human Phase 1 trial demonstrates that zanubrutinib is well tolerated in subjects with advanced B-cell malignancies. As of 30 July 2015, except for 4 subjects who had disease progression, all the other 21 subjects enrolled in the dose-escalation part of the zanubrutinib study have received zanubrutinib treatment for more than 100 days. No dose limiting toxicities (DLT) were encountered, and the maximum tolerated dose (MTD) was not reached. There were no drug-related SAEs, AEs leading to drug discontinuation, or AE-related deaths. Of 21 >grade 3 AEs, 3 were assessed by investigators as potentially drug-related - all were self-limiting neutropenia in CLL subjects, two of whom had neutropenia at baseline. No G3/4 bleeding events were recorded. Four subjects had a baseline history of atrial fibrillation/flutter (AF); no exacerbation or new event of AF was reported. All subjects have received regular electrocardiogram (ECG) monitoring and none has demonstrated any clinically significant cardio-electric changes such as QTc prolongation.

1.5 Benefit and Risk Conclusions for Zanubrutinib

Zanubrutinib has demonstrated a very favorable toxicology and safety pharmacology profile in the ongoing Phase 1 study. The dose escalation portion of the study has been completed. Preliminary data from the current Phase 1 study showed that zanubrutinib has been well tolerated and has demonstrated promising anti-tumor activity in advanced B-cell malignancies, including CLL, MCL, WM, HCL, DLBCL, FL, and MZL. The study is currently ongoing to further evaluate the safety, PK, PD, and efficacy of zanubrutinib.

Zanubrutinib is an investigational drug with safety data in more than 600 patients as of 15 September 2017. Refer to the IB for more detailed information. Subjects enrolled in clinical studies with zanubrutinib must be closely monitored by means of AEs, vital signs, electrocardiograms, and clinical laboratory safety tests of blood and urine.

1.6 Obinutuzumab

Obinutuzumab (Gazyva®)[11,12] is a recombinant monoclonal humanized and glycoengineered Type II anti-CD20 antibody of the IgG1 isotype. It specifically targets the extracellular loop of the CD20 transmembrane antigen on the surface of non-malignant and malignant pre-B and mature B-lymphocytes, but not on hematopoietic stem cells, pro-B-cells, normal plasma cells or other normal tissue. Glycoengineering of the Fc part of obinutuzumab results in higher affinity for FcγRIII receptors on immune effector cells such as natural killer (NK) cells, macrophages and monocytes as compared to non-glycoengineered antibodies. Obinutuzumab in combination with chlorambucil has been approved by the US Food and Drug Administration and the Australia Therapeutic Goods Administration (TGA) to treat patients with previously untreated CLL. Obinutuzumab in combination with bendamustine followed by GAZYVA monotherapy, is indicated for the treatment of patients with follicular lymphoma (FL) who relapsed

after, or are refractory to, a rituximab-containing regimen. Refer to Section 6 for more details.

1.7 Rationale for the Combination of Zanubrutinib and Obinutuzumab

As noted above, signaling via the aberrantly activated B-cell receptor (BCR) has a critical role in the pathogenesis of B-cell tumors by promoting survival and clonal expansion of malignant B-cells. Ibrutinib, a FDA-approved BTK inhibitor, has demonstrated objective responses among different B-cell malignancies in clinical trials, including CLL/SLL, MCL, DLBCL, FL and WM. Zanubrutinib, differentiated from ibrutinib, is a more potent, more specific second-generation BTK inhibitor. An ongoing Phase 1 trial (BGB-3111-AU-003) has shown zanubrutinib to be very well tolerated, safe and active in B-cell malignancies of various histologies.

Anti-CD20 antibodies are widely used in treating B-cell malignancies and their anti-tumor activities are largely dependent on ADCC effect. Ibrutinib was tested in combination with rituximab, an anti-CD20 antibody, in a Phase 2 trial of CLL.[8,13] After a follow-up of 6 months, the overall response rate (ORR) was 83% with a large and rapid reduction in lymph-node and spleen sizes. [13] However, most of the responses were partial responses (PRs). A recent pre-clinical study also showed that ibrutinib could antagonize rituximab induced ADCC by inhibiting ITK.[14] Since zanubrutinib is more selective than ibrutinib against off-target kinases including ITK, zanubrutinib did not show any interference with the ADCC effect induced by anti-CD20 antibodies in the pre-clinical studies. In addition, zanubrutinib has demonstrated good combination activity with rituximab or obinutuzumab in preclinical xenograft models.

Obinutuzumab is a humanized anti-CD20 monoclonal antibody which demonstrated clinical superiority compared with rituximab in a recent Phase 3 study. This is a type II glycoengineered monoclonal antibody, with an enhanced ADCC and direct-cell killing activity, but without complement-dependent cytotoxicity. Obinutuzumab alone or in combination with other chemo-therapy drugs, as well as with other BTK inhibitors, ie, ibrutinib and ACP-196, are being evaluated in different B-cell malignancies.

Based upon these background data and the promising results from the combination of ibrutinib and rituximab, this combination study offers a path to evaluation of the promise of an improved therapy for these subjects.

This trial is designed to evaluate the safety, tolerability, and PK profile as well as preliminary evidence of the anti-tumor activity of zanubrutinib in combination with obinutuzumab in subjects with B-cell malignancies. The starting doses and regimens of zanubrutinib, 160 mg BID and 320 mg QD, are the recommended Phase 2 dose (RP2Ds) for monotherapy that have been determined based on the PK, safety and tolerability, PD

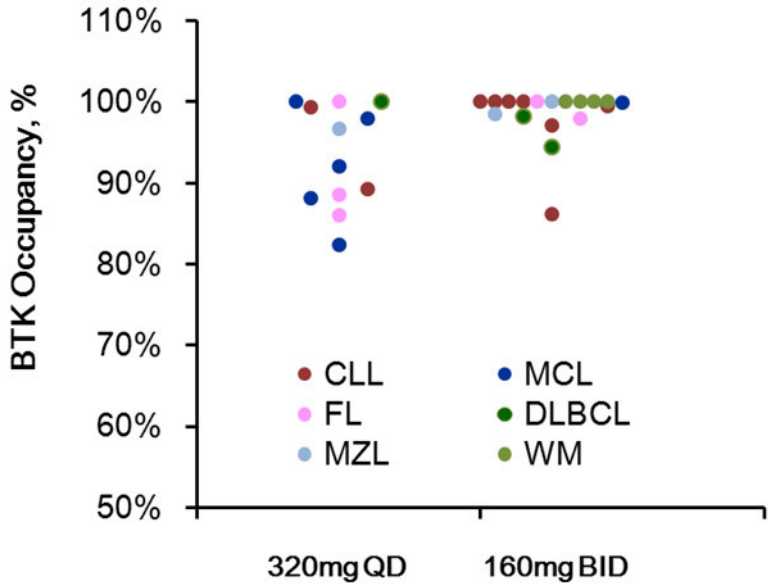
and preliminary efficacy in the ongoing zanubrutinib trial (BGB-3111-AU-003). The dose and regimen of obinutuzumab was selected based on the US label to treat patients with untreated CLL. The Phase 1/2 experiences with ibrutinib in combination with other anti-CD20 antibodies, such as rituximab and ofatumumab, has shown that the combinations are active, lack overlapping toxicity, and can be combined at full monotherapy doses of the respective agents.

The study will be conducted in compliance with the protocol, Good Clinical Practice (GCP) guidelines, the Declaration of Helsinki and any applicable regulatory requirements.

1.8 Rationale to Change Zanubrutinib Dose from 320 mg QD to 160 mg BID (added per Amendment 4.0)

Before Amendment 3.0, zanubrutinib was administrated 320 mg QD. Starting from Amendment 3.0, zanubrutinib will be administrated 160 mg BID for new subjects enrolled. The change is based on lymph node (LN) BTK occupancy findings in study BGB-3111-AU-003. Thirty subjects from the study were evaluated for BTK occupancy in LN tissue using a fluorescent probe assay on paired lymph node biopsies. Median occupancy was 100% in subjects receiving zanubrutinib 160 mg BID (n=18) vs 94% in subjects receiving zanubrutinib 320 mg QD (n=12) (p=0.002, Wilcoxon). The proportion of subjects with $\geq$90% BTK occupancy was 94% (160 mg BID) vs 58% (320 mg QD) (p=0.027, Fisher's exact). Occupancy did not appear to differ amongst histologic subtype. BTK occupancy in LN tissue by dose/schedule is shown in the following Figure 1.

Figure 1 BTK occupancy in LN tissue by dose/schedule



Subjects enrolled in zanubrutinib 320 mg QD dose regimen will have the option to switch to 160 mg BID once Amendment 4.0 is active.

1.9 Rationale to Remove Food Restriction for Zanubrutinib (added per Amendment 4.0)

Before Amendment 4.0, food was restricted 2 hours before and 1 hour after zanubrutinib administration. Starting from Amendment 4.0, this food restriction will be removed for all subjects. This is based on the preliminary result from a dedicated food-effect study, BGB-3111-103, which indicated that zanubrutinib plasma exposure was not affected by a high-fat breakfast and was increased by 37% and 56% for AUC and C_{max}, respectively, by a standard breakfast, as compared to fasting. Since the increase fall within the variability of zanubrutinib clearance (approximately 50% coefficient of variation) and that a wide therapeutic index was observed on zanubrutinib, it is recommended that all food restriction on zanubrutinib administration be removed from this trial, and subjects may take zanubrutinib with or without food.

2 STUDY OBJECTIVES

2.1 Study Objectives in Part 1

2.1.1 Primary Objectives

- To evaluate the safety and tolerability of zanubrutinib in combination with obinutuzumab.
- To determine the MTD and/or the RP2D of zanubrutinib, in combination of with obinutuzumab, when given continuously orally.

2.1.2 Secondary Objectives

- To assess the preliminary antitumor activity of zanubrutinib in combination with obinutuzumab.
- To characterize the PK of zanubrutinib and obinutuzumab when administered in combination.

2.1.3 Exploratory Objectives

- [redacted]

2.2 Study Objectives in Part 2

2.2.1 Primary Objectives

- To assess the preliminary antitumor activity of zanubrutinib in combination with obinutuzumab.

2.2.2 Secondary Objectives

- To further evaluate the safety and tolerability of zanubrutinib in combination with obinutuzumab.
- To further characterize the PK of zanubrutinib and obinutuzumab when administered in combination.

2.2.3 Exploratory Objectives

- [redacted]

- [redacted]

3 STUDY ENDPOINTS

3.1 Study Endpoints in Part 1

3.1.1 Primary Endpoints

- The safety and tolerability of zanubrutinib in combination with obinutuzumab will be evaluated by the incidence, nature, and severity of AEs, clinical laboratory abnormalities, deaths and cause of death, and DLTs.
- The RP2D dose regimens of zanubrutinib in combination with obinutuzumab will be determined based on the incidence of DLTs in the Part 1 of the study according to the MTD/RP2D evaluation process described below.

3.1.2 Secondary Endpoints

- Preliminary antitumor activity of zanubrutinib in combination with obinutuzumab will be assessed by the frequency, quality, and durability of objective responses for each of the specified disease cohorts (treatment-naïve CLL, R/R CLL/SLL, R/R non-GCB DLBCL, R/R FL, R/R MCL, R/R MZL and R/R WM) as per the standard International Working Group (IWG) Criteria for each disease.[15,16,17]
- Clinical activity of zanubrutinib in combination with obinutuzumab will be further assessed by the frequency and rate of hematologic improvement for subjects with CLL with anemia and/or thrombocytopenia at baseline (hemoglobin <9 g/dL, platelets <100,000/uL).
- The PK profile of zanubrutinib will be determined, following the Cycle 1 Day 1 and Cycle 2 Day 1, by the area under the plasma concentration-time curve from zero to the last quantifiable concentration (AUC_{last}), area under the plasma concentration-time curve from zero to infinity (AUC), maximum observed plasma concentration (C_{max}), time to maximum observed plasma concentration (t_{max}), terminal half-life ($t_{1/2}$), apparent clearance (CL/F), and apparent volume of distribution (V_{zd}/F). After steady state: $AUC_{last,ss}$, $C_{max,ss}$, and $t_{max,ss}$.
- The PK profile of obinutuzumab will be determined by plasma concentration prior to start of the infusion, and at 4 hours (end of infusion) on Cycle 1 Day 2, Cycle 1 Day 3, Cycle 1 Day 9, Cycle 1 Day 16, as well as Day 1 Cycles 2, 4, and 6.

3.1.3 Exploratory Endpoints

- [redacted]

- [redacted]
- [redacted]

3.2 Study Endpoints in Part 2

3.2.1 Primary Endpoints

- Preliminary antitumor activity of zanubrutinib in combination with obinutuzumab will be assessed by the frequency and durability of objective responses for each of the specified disease cohorts as per the standard International Working Group (IWG) Criteria for each disease.

3.2.2 Secondary Endpoints

- The safety and tolerability of zanubrutinib in combination with obinutuzumab will be further evaluated as described for the Part 1.
- Activity of zanubrutinib in combination with obinutuzumab will be assessed by the frequency and rate of hematologic improvement for subjects with CLL with anemia and/or thrombocytopenia at baseline (hemoglobin <9 g/dL, platelets <100,000/uL).
- The PK profiles of zanubrutinib and obinutuzumab will be further characterized as described for the Part 1.

3.2.3 Exploratory Endpoints

- [redacted]
- [redacted]
- [redacted]

4 INVESTIGATIONAL PLAN

4.1 Summary of Study Design

This is a two-part, open-label Phase 1b clinical trial designed to determine the safety, tolerability, and clinical activity of zanubrutinib in combination with obinutuzumab: Part 1 (safety evaluation) and Part 2 (indication specific expansion cohorts).

Part 1: Safety Evaluation

Part 1 is designed to evaluate the safety and tolerability of zanubrutinib in combination with obinutuzumab in subjects with R/R CLL/SLL, R/R non-GCB DLBCL, R/R FL, R/R MCL, R/R WM, and R/R MZL.

Two dose regimens of zanubrutinib (320 mg QD and 160 mg BID [added per Amendment Version 3.0]) will be evaluated in combination with obinutuzumab consistent with the US label regimen (as specified below), in a cohort of 6 subjects for each dose regimen. If there appear 2 or more DLTs in a 6-subject cohort in either regimen, the dose level is considered to have exceeded the MTD; and a reduced dose level of zanubrutinib (160 mg QD or 80 mg BID) will be evaluated in combination with obinutuzumab in another cohort of 6 subjects in that regimen. Further reduction of zanubrutinib dose level will be allowed until a safe dose combination is identified. The period for DLT assessment is 29 days from first administration of zanubrutinib. In the event that a MTD is not exceeded, the Sponsor will select both 320 mg QD and 160 mg BID for the Part 2 of the study.

Zanubrutinib will be administered orally with or without food every day in each cycle (29 days for Cycle 1, and 28 days for Cycle 2 and each cycle thereafter) until disease progression, death, unacceptable toxicity, other reason for treatment discontinuation, or study closure, whichever occurs first.

Obinutuzumab will be administered intravenously for up to 6 cycles consistent with the U.S. label regimen:

- Day 2 Cycle 1: 100 mg obinutuzumab
- Day 3 Cycle 1: 900 mg obinutuzumab
- Day 9 and Day 16 Cycle 1: 1000 mg obinutuzumab
- Day 1 Cycles 2 to 6: 1000 mg obinutuzumab

The continuous safety evaluation will be performed by a Safety Monitoring Committee (SMC) composed of the Sponsor, the Sponsor's medical delegate, the coordinating investigator, and up to two (2) additional investigators, and the contract research organization (CRO) medical monitor. The SMC composition and responsibilities will be

further detailed in the SMC Charter. The SMC will be responsible for the determination of dose levels and regimens to be administered during the study.

The Sponsor, in consultation with investigators, may decide to explore alternative zanubrutinib and/or obinutuzumab dosing regimens. If this decision is made, the protocol will be appropriately amended.

Part 2: Indication Specific Expansion Cohorts

In Part 2, the RP2D and the 2 regimens will be investigated in 5 expansion cohorts (revised per Amendment Version 4.0) with histology type of tumor defined as below. Based on the safety, tolerability, PK, and antitumor activity data from the safety evaluation part (Part 1) of the study, additional cohorts may be enrolled:

- Cohort 1: treatment-naïve CLL/SLL subjects (approximately 20 subjects divided by the 2 regimens)
- Cohort 2: R/R CLL/SLL subjects (approximately 20 subjects divided by the 2 regimens)
- Cohort 3: R/R non-GCB DLBCL, defined by Hans algorithm (approximately 20 subjects divided by the 2 regimens)
- Cohort 4: R/R FL, MCL, MZL, and WM (approximately of 20 subjects divided by the 2 regimens)
- Cohort 5: R/R FL (approximately of 40 subjects in 160 mg BID. About 10-15 of them should meet double-refractory criterion, defined as refractoriness to both rituximab and an alkylating agent, whether administered together or in successive treatment regimens. Refractoriness was defined per protocol as less than a partial response or progression of disease within 6 months after completion of a prior therapy, added per Amendment Version 4.0).

In Part 2, once the SMC confirms that the 6 subjects in 160 mg BID regimen passed Part 1 DLT test, all new eligible subjects will be enrolled into 160 mg BID regimen in each of the 5 cohorts until the total number of that cohort reaches the pre-specified number (revised per Amendment Version 4.0).

Subjects enrolled in zanubrutinib 320 mg QD dose regimen will have the option to switch to 160 mg BID once Amendment 4.0 is active.

Zanubrutinib will be administered orally with or without food every day in each cycle (28 days for each cycle) until disease progression, death, unacceptable toxicity, other reason for treatment discontinuation, or study closure, whichever occurs first.

Obinutuzumab will be administered intravenously for up to 6 cycles consistent with the U.S. label regimen:

- Day 1 Cycle 1: 100 mg obinutuzumab
- Day 2 Cycle 1: 900 mg obinutuzumab
- Day 8 and Day 15 Cycle 1: 1000 mg obinutuzumab
- Day 1 Cycles 2 to 6: 1000 mg obinutuzumab

The safety evaluation by the SMC will be performed on as needed basis (see the SMC Charter) but at a minimum of every 6 months to review all subjects enrolled, or when there is any significant safety finding. Any treatment-related death will also trigger review by the SMC. The SMC will determine whether it is safe to proceed with the study.

If the frequency of Grade 3 or 4 toxicities or other unacceptable chronic toxicities in the indication expansion cohorts suggests that the MTD of zanubrutinib in combination with obinutuzumab has been exceeded at that dose level, any remaining accrual at that dose level will be halted. Consideration will then be given to enrolling an expansion cohort at a lower dose level or at a different schedule. The protocol will be appropriately amended.

4.2 Safety Evaluation

Two dose regimens of zanubrutinib will be evaluated, 320 mg QD and 160 mg BID. The plan is to dose 6 subjects in each of the 2 dose regimens with the plan modified as necessary by DLT experience. The DLT assessment period is defined as 29 days from the first administration of zanubrutinib. If 2 or more of the subjects in either of the 6-subject cohorts develop a DLT during the DLT assessment period, the MTD is considered to have been exceeded and no further subjects will be treated in that dose regimen.

In the event that a MTD is not exceeded, the Sponsor will select both 320 mg QD and 160 mg BID for the Part 2 of the study.

If the starting regimen (320 mg QD or 160 mg BID of zanubrutinib in combination with obinutuzumab) is not tolerated, 160 mg QD or 80 mg BID of zanubrutinib in combination with obinutuzumab may be tested (as determined by the SMC and the Sponsor) to define a potential RP2D. The period for DLT assessment is 29 days from the first administration of zanubrutinib.

Depending on the decision of the SMC and on review of available data, an additional intermediate dose level may be explored prior to a final decision on a RP2D.

4.2.1 Safety Monitoring Committee

The continuous safety evaluation will be performed by a SMC composed of the Sponsor, the Sponsor's medical delegate, the coordinating investigator, up to two (2) additional investigators, and the CRO medical monitor. The SMC composition and responsibilities will be further detailed in the SMC Charter. Ad hoc members will be consulted as needed

and may include, but are not restricted to a biostatistician and a pharmacokineticist. The SMC will be responsible for the determination of dose levels and regimens to be administered during the study.

4.2.2 Dose Limiting Toxicity

For Part 1 subjects only. The period for DLT assessment is 29 days from first administration of zanubrutinib.

All toxicities or AEs will be graded according to the NCI CTCAE Version 4.03.[18] Subjects who initiate treatment with an ANC <1000/µl will not be considered evaluable for neutrophil toxicity as outlined in the 2008 IWCLL guidelines.[15]

Dose limiting toxicities are defined as a toxicity or AE occurring during the DLT assessment period (first 29 days of treatment), which is not clearly attributable to a cause other than zanubrutinib and/or obinutuzumab (such as disease progression, underlying illness, concurrent illness or concomitant medication) and meets one of the following criteria:

- Grade 3 or 4 drug-related non-hematologic toxicity (excluding Grade 3 nausea, vomiting, hypertension, and asymptomatic laboratory abnormalities).
- Grade 4 drug-related hematologic toxicity persisting for >14 days.
- Any grade toxicity which in the judgment of the investigator or Sponsor requires removal of the subject from the study.

Resumption of zanubrutinib and obinutuzumab administration for subjects experiencing DLTs is permitted, if clinically appropriate and after discussion with the Sponsor medical monitor, contingent on the return of the DLT to ≤ Grade 1 severity within 14 days and interruption or delay of treatment for no more than 21 days. Resumption of treatment after resolution of a DLT will be at the 50% decreased dose level of zanubrutinib. The administration of obinutuzumab will be resumed at the same dose according to the original schedule.

If a subject could only receive 75% of the expected dose of either component of the combination for reasons other than treatment related toxicity, then an additional subject will be enrolled in the cohort.

4.2.3 Dose Continuation and Dose Reduction

The continuous safety evaluation will be performed by the Sponsor, the CRO medical monitor, the investigators and the SMC (see Section 4.2.1 above). At the conclusion of the dose regimen safety evaluation part (Part 1), the SMC will determine the RP2D to be further investigated.

In the absence of unacceptable toxicity, disease progression, or subject withdrawal, subjects may continue with daily administrations of zanubrutinib at the discretion of the investigator. Subjects with disease progression may continue study drug treatment if they are benefitting from the treatment in the judgment of the investigators and approved by Sponsor medical monitor.

In the event of a DLT, treatment with both investigational drugs will be stopped and supportive therapy administered as required. If the toxicity resolves or subsides to Grade 0 or Grade 1 (or baseline) within 14 days of the onset of the DLT and the subject is showing clinical benefit in the investigator's opinion, treatment of zanubrutinib may be restarted at the 50% decreased dose level (at the investigator's discretion after discussions with the Sponsor's medical monitor). The administration of obinutuzumab will be resumed at the same dose according to the original schedule.

If the toxicity does not resolve to Grade 0 or Grade 1 (or baseline) within 14 days of onset, the subject must be withdrawn from further investigational drug treatment. Any exception to this must be agreed upon by the investigator and the Sponsor's medical monitor.

4.2.4 Dose Interruption and Modification

The continuous safety evaluation will be performed by the Sponsor, the CRO medical monitor, the coordinating investigator, and investigators. When at least 6 or more subjects have been treated with zanubrutinib in an expansion cohort and ≥ 33% of the treated subjects experience a DLT during the first cycle, study accrual will be held pending data review by the SMC.

Dosing of zanubrutinib will be held for individual subjects under any of the following conditions:

- Grade 4 neutropenia related to zanubrutinib lasting > 7 days or Grade ≥ 3 febrile neutropenia
- Grade 4 thrombocytopenia related to zanubrutinib lasting > 7 days or Grade ≥ 3 thrombocytopenia associated with Grade ≥ 2 bleeding
- Any Grade ≥ 3 non-hematologic toxicity related to zanubrutinib except for asymptomatic laboratory abnormalities

After the subject's toxicity improved to Grade ≤ 1 or to baseline values within 14 days, the investigator may elect to have the subject restart the treatment. If the subject's toxicity improves to Grade 1 or baseline within 15 to 28 days of study drug discontinuation and if, in the investigator's opinion, it is in the subject's best interest to restart treatment after more than 14 days, then a written approval must be obtained from the Sponsor Medical Monitor.

The causality of the toxicity should be assessed by the investigator.

If, in the investigator's opinion, the toxicity is unrelated to zanubrutinib, the subject may be restarted at the preceding dose, zanubrutinib 320 mg QD or 160 mg BID. However, if the toxicity recurs, the dose must be reduced to 160 mg QD or 80 mg BID (revised per Amendment Version 3.0). If in the investigator's opinion, the toxicity is related to zanubrutinib, the subject may restart therapy at a reduced dose of 160 mg QD or 80 mg BID (revised per Amendment Version 3.0). A second dose reduction to 80 mg QD for both regimens (revised per Amendment Version 3.0), based on the criteria outlined above, may be considered upon consultation with the Sponsor Medical Monitor. Any subjects, who do not tolerate 80 mg QD (revised per Amendment Version 3.0), must be removed from the study.

If, in the investigator's opinion, the toxicity is related to obinutuzmab, obinutuzmab may be interrupted or discontinued. There will be no dose modification for obinutuzmab.

If a non-disease related surgery is required during the study, zanubrutinib should be interrupted 3 days before and 7 days after the surgery. Obinutuzmab should also be interrupted, if applicable.

4.3 Study Assessments and Procedures

The schedule of assessments is presented in Table 1, Table 2, and Table 3.

Table 1 Study Assessments and Procedures Schedule in Part 1

		Treatment Period										Safety Follow-up[2]	Follow-up Visit[3]
	Screening[1] -28 to -1	Cycle 1 (29 days, DLT period)						Cycle 2 to 6 (28 days)		Weeks 25 to 48	Weeks 48+		
Days Window (days)[4]		1	2	3	9 ±1 day	16 ±1 day	23 ±1 day	1 ±2 days	15 ±2 days	Every 4 weeks ±4 days	Every 12 weeks ±10 days	28 days after last dose ± 7 days	Every 3 months ±7 days
Informed consent[5]	X												
Review inclusion/ exclusion criteria	X												
Demographic data	X												
General medical history & baseline conditions	X												
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete physical examination[7]	X												
Weight (& height at screening)	X	X						X		X	X	X	X
B symptoms[6]	X	X						X		X	X	X	X
Target physical examination[7]		X			X	X	X	X	X	X	X	X	X
ECOG status	X	X						X		X	X	X	
Echocardiogram	X												
12-Lead ECG[8]	X												
Zanubrutinib administration[9,12]		Orally											

Table 1 Study Assessments and Procedures Schedule in Part 1

		Treatment Period										Safety Follow-up[2]	Follow-up Visit[3]
	Screening[1] -28 to -1	Cycle 1 (29 days, DLT period)						Cycle 2 to 6 (28 days)		Weeks 25 to 48	Weeks 48+		
Days Window (days)[4]		1	2	3	9 ±1 day	16 ±1 day	23 ±1 day	1 ±2 days	15 ±2 days	Every 4 weeks ±4 days	Every 12 weeks ±10 days	28 days after last dose ± 7 days	Every 3 months ±7 days
Obinutuzumab administration			100 mg	900 mg	1000 mg	1000 mg		1000 mg					
Review of concomitant medications	X	X			X	X	X	X	X	X	X	X	
AEs (including serious)	X	X	X	X	X	X	X	X	X	X	X	X	
Response Assessment[25]		Every 12 weeks (end of week 12, 24, 36 and 48)									X	X[10]	X[3]
Tumor assessment by CT or MRI[10]	X	Every 12 weeks (end of week 12, 24, 36 and 48)									X[10]	X[10]	X[3]
Bone Marrow evaluation[11]	X	End of Week 12											
Local Laboratory													
Hematology[13]	X	X			X	X	X	X	X	X[26]	X	X	X
Clinical chemistry[14]	X	X			X	X	X	X	X	X[26]	X	X	X
Coagulation	X												
IgA, IgG, IgM level and serum EPG [15]	X							X		X[26]	X[26]	X	X

Table 1 Study Assessments and Procedures Schedule in Part 1

		Treatment Period										Safety Follow-up[2]	Follow-up Visit[3]
	Screening[1] -28 to -1	Cycle 1 (29 days, DLT period)						Cycle 2 to 6 (28 days)		Weeks 25 to 48	Weeks 48+		
Days Window (days)[4]		1	2	3	9 ±1 day	16 ±1 day	23 ±1 day	1 ±2 days	15 ±2 days	Every 4 weeks ±4 days	Every 12 weeks ±10 days	28 days after last dose ± 7 days	Every 3 months ±7 days
Pregnancy test[16]	X	X						X		X	X		
Viral serologies[17]	X												
Urine analysis[18]	X	X			X	X	X	X	X	X[26]	X	X	
CLL prognostic factors[19]	X												
Central Laboratory													
Tumor tissue and/or bone marrow sampling	X[20]											X[23]	
Blood sampling for biomarker analysis												X[24]	
Pharmacokinetic blood sampling[21]		X	X	X	X	X		X[22]					
Pharmacodynamic blood sampling[21]		X	X					X					
MRD sampling (CLL subjects only)											X[27]		

Abbreviations: AE: adverse event, ALT: alanine aminotransferase, AST: aspartate aminotransferase, CLL: chronic lymphoid leukemia, CR: complete response, CT: computed tomography, DLT: dose limiting toxicity, ECG: electrocardiogram, ECOG: Eastern Cooperative Oncology Group, EPG: serum electrophoresis, DLBCL: diffuse

large B-cell lymphoma, GCB: germinal center B-cell-like, HBsAg: hepatitis B surface antigen, HBV: hepatitis B virus, HCV: hepatitis C virus, Ig: immunoglobulin, MCV: mean corpuscular volume, MRD: minimal residual disease, MRI: magnetic resonance imaging, PCR: polymerase chain reaction.

Assessments scheduled on study drug administration days should be performed predose, unless otherwise specified.

1. Perform within 28 days prior to Day 1. Assessments performed as standard of care may be used for screening.
2. Perform 28 days after the last dose of zanubrutinib (± 7 days). Subjects who have disease relapse at any time will be asked to undergo biopsies of representative tumour sites and/or blood collection to obtain samples for studying mechanisms of resistance (see Section 8.14.1).
3. Subjects who discontinue study drug due to reasons other than disease progression will remain on study and be followed every 3 months until subject exhibits first progression, withdraws consent, starts new anti-cancer therapy, death or study closure, whichever occurs first. Once subjects progress or start use of alternative anti-cancer therapy, subjects will not return to the study center but will be contacted every 3 months by telephone, to assess survival until death, withdrawal of consent or study closure, whichever occurs first (see Section 8.10.2).
4. Windows: days allowed for reschedule of an entire visit due to logistic reasons (eg, public holidays). In all cases elements relating to medical assessments may be performed 48 hours prior to the scheduled day. These are: B symptoms, physical examination, ECOG, concomitant medications, AE, hematology, clinical chemistry, coagulation, pregnancy test and urinalysis.
5. Written informed consent form(s) must be signed by the subject before any study specific procedures are performed.
6. Unexplained weight loss >10% over previous 6 months, fever (>38°C), and/or drenching night sweats.
7. Complete physical examination includes all systems described in the body of the protocol. Targeted physical exams should be limited to systems of clinical relevance (ie, cardiovascular, respiratory, lymph nodes, liver, and spleen), and those systems associated with clinical signs/symptoms.
8. Perform a single 12-lead ECG. Subjects should be in the semi-recumbent or supine position. Additional ECGs will be performed at the discretion of the investigator if medically indicated.
9. Administer one dose of zanubrutinib in the study center, review and dispense diary.
10. Tumor assessments must be performed within 7 days of the end of Weeks 12, 24, 36 and 48, every 24 weeks after Week 48, and at disease progression. Computed tomography scans must encompass neck, chest, abdomen and pelvis and use intravenous contrast or follow investigators' decision. A CT scan of diagnostic quality performed as part of positron emission tomography (PET)/CT is acceptable, provided bidimensional nodal and liver/spleen measurements can be made. MRI may be used in place of CT, at investigator discretion. If the subject has no assessable disease by CT/MRI at study entry (eg, Waldenström's macroglobulinemia without

nodal enlargement), repeat scans are not required during the study. For the early termination visit, CT/MRI and response assessment are required if the previous scan was performed more than 3 months ago.

11. A bone marrow examination must be performed at screening for all participants and within 7 days of the end of week 12 for subjects with baseline marrow disease. In those subjects who had evidence of bone marrow disease at the time of enrollment, upon achieving a possible CR (eg, physical examination or CT/MRI scan indicating a possible CR), a bone marrow aspirate and biopsy will be obtained to confirm the CR. Peripheral blood and/or bone marrow aspirate/biopsy with flow cytometry assessment(s) for minimal residual disease should be done at least 3 months after the last dose if there is evidence of CR in all of the response parameters (ie, hematology, CT/MRI scan).

12. Zanubrutinib will be taken at least 30 minutes before obinutuzumab infusion on the day obinutuzumab is administrated.

13. Hematology, including hemoglobin, MCV, WBC count, absolute differential count (neutrophils, eosinophils, lymphocytes, blasts), bands (optional), and platelet count. In the event of neutropenia (absolute neutrophil count $<1000/mm^3$) or thrombocytopenia (platelets of less than $50{,}000/mm^3$), these assessments will be conducted as frequently as the physician feels needed until toxicity resolves to ≤ Grade 2.

14. Clinical chemistry includes sodium, potassium, glucose, urea, creatinine, calcium, magnesium, total and direct bilirubin, total protein, albumin, ALT, AST, lactose dehydrogenase, alkaline phosphatase and uric acid. In the event of ≥ Grade 3 clinical chemistry toxicity, these assessments will be conducted as frequently as the physician feels needed until toxicity resolves to ≤ Grade 2.

15. Serum EPG on first test for WM subjects only, and if a paraprotein is present, repeated on all subsequent immunoglobulin assessments. IgA, IgG and IgM tests should be performed for all subjects at screening and only for those with significant abnormal findings at subsequent visits.

16. All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

17. Viral serology include hepatitis B (HBsAg and total hepatitis B core antibody [anti HBc] as well as HBV DNA by PCR if the subject is HBcAb positive), HCV antibody (as well as HCV RNA by PCR if the subject is HCV antibody positive), and HIV1/2 antibodies.

18. Collect urine dipstick, as well as urine microscopy if dipstick is abnormal. If urine protein is ≥2+ by dipstick, a 24 hour urine for total protein and a random urine for total protein and creatinine will be obtained and evaluated (see Section 8.2).

19. Subjects with CLL should have a blood sample sent at screening for interphase FISH for chromosomal abnormalities including 17p, 11q, 13q, and +12. Other analysis, including IgVH and P53 mutational status, is optional.

20. Subjects with non-GCB DLBCL must have archival tumor tissues or agree to a tumor biopsy for confirmation of the DLBCL subtype and for exploratory biomarker analysis.

21. Serial pharmacokinetic and pharmacodyamic blood samples will be collected at the time points specified in Table 3.

22. PK blood samples will be collected only on Day 1 of Cycle 2, Cycle 4, and Cycle 6.

23. Subjects (except CLL) who have disease relapse at any time will be asked to undergo biopsies of representative tumor sites (bone marrow will be collected for WM patients). These procedures are optional.

24. Subjects who have disease relapse at any time will be asked to undergo blood collection to obtain samples for studying mechanisms of resistance. This procedure is optional.

25. Response should be assessed against baseline per disease relevant instructions in Appendix 16.3. Physical exam should be used at any time points where imaging is not required, but physical exam revealing disease progression or potential progression may require confirmation via imaging. Visits that contain components sufficient to determine a change in overall response in the patient (ie, unscheduled CT scans and labs, IgM-based change response between scheduled efficacy assessments for WM patients) should complete an overall efficacy response assessment as needed.

26. For Weeks 25 through 48, hematology, clinical chemistry, urine analysis, immunoglobulins, and serum EPG assessments will be conducted every 12 weeks. After Week 48, hematology and clinical chemistry assessments and urine analysis, will continue every 12 weeks; however, immunoglobulins and serum EPG assessments will be conducted every 24 weeks until disease progression.

27. Samples will be taken from subjects with CLL to assess MRD at the following time points:

    • Peripheral blood sample at Cycle 18, or at the earliest opportunity after Cycle 18, in all CLL subjects on study; a bone marrow sample is requested if the peripheral blood sample is MRD negative

    • Peripheral blood sample at the time of newly attained CR, and at each CR assessed timepoint thereafter, for continuing CLL subjects; a bone marrow sample is requested if the peripheral blood sample is MRD negative

Table 2 Study Assessments and Procedures Schedule in Part 2

		Treatment Period								Safety Follow-up[2]	Follow-up Visit[3]
	Screening[1] -28 to -1	Cycle 1 (28 days)				Cycle 2 to 6 (28 days)		Weeks 25 to 48	Weeks 48+		
Days Window (days)[4]		1	2	8 ±1 day	15 ±1 day	1 ±2 days	15 ±2 days	Every 4 weeks ±4 days	Every 12 weeks ±10 days	28 days after last dose ± 7 days	Every 3 months ±7 days
Informed consent[5]	X										
Review inclusion/ exclusion criteria	X										
Demographic data	X										
General medical history & baseline conditions	X										
Vital signs	X	X	X	X	X	X	X	X	X	X	X
Complete physical examination[7]	X										
Weight (& height at screening)	X	X				X		X	X	X	X
B symptoms[6]	X	X				X		X	X	X	X
Target physical examination[7]		X		X	X	X	X	X	X	X	X
ECOG status	X	X				X		X	X	X	
Echocardiogram	X										
12-Lead ECG[8]	X										
Zanubrutinib administration[9]		Orally									

Table 2 Study Assessments and Procedures Schedule in Part 2

		Treatment Period								Safety Follow-up[2]	Follow-up Visit[3]
	Screening[1] -28 to -1	Cycle 1 (28 days)				Cycle 2 to 6 (28 days)		Weeks 25 to 48	Weeks 48+		
Days Window (days)[4]		1	2	8 ±1 day	15 ±1 day	1 ±2 days	15 ±2 days	Every 4 weeks ±4 days	Every 12 weeks ±10 days	28 days after last dose ± 7 days	Every 3 months ±7 days
Obinutuzumab administration		100 mg	900 mg	1000 mg	1000 mg	1000 mg					
Review of concomitant medications	X	X		X	X	X	X	X	X	X	
AEs (including serious)	X	X	X	X	X	X	X	X	X	X	
Response Assessment[24]		Every 12 weeks (end of week 12, 24, 36 and 48)							X	X[10]	X[3]
Tumor assessment by CT or MRI[10]	X	Every 12 weeks (end of week 12, 24, 36 and 48)							X[10]	X[10]	X[3]
Bone Marrow evaluation[11]	X	End of Week 12									
Local Laboratory											
Hematology[13]	X	X		X	X	X	X	X[25]	X	X	X
Clinical chemistry[14]	X	X		X	X	X	X	X[25]	X	X	X
Coagulation	X										
IgA, IgG, IgM level and serum EPG [15]	X					X		X[25]	X[25]	X	X
Pregnancy test[16]	X	X				X		X	X		

Table 2 Study Assessments and Procedures Schedule in Part 2

		Treatment Period								Safety Follow-up[2]	Follow-up Visit[3]
	Screening[1] -28 to -1	Cycle 1 (28 days)				Cycle 2 to 6 (28 days)		Weeks 25 to 48	Weeks 48+		
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Viral serologies[17]	X										
Urine analysis[18]	X	X		X	X	X	X	X[25]	X	X	
CLL prognostic factors[19]	X										
Central Laboratory											
Tumor tissue and/or bone marrow sampling	X[20]									X[22]	
Blood sampling for biomarker analysis										X[23]	
Pharmacokinetic blood sampling[21]						X					
MRD sampling (CLL subjects only)									X[26]		

Abbreviations: AE: adverse event, ALT: alanine aminotransferase, AST: aspartate aminotransferase, CLL: chronic lymphoid leukemia, CR: complete response, CT: computed tomography, DLT: dose limiting toxicity, ECG: electrocardiogram, ECOG: Eastern Cooperative Oncology Group, EPG: serum electrophoresis, DLBCL: diffuse large B-cell lymphoma, GCB: germinal center B-cell-like, HBsAg: hepatitis B surface antigen, HBV: hepatitis B virus, HCV: hepatitis C virus, Ig: immunoglobulin, MCV: mean corpuscular volume, MRD: minimal residual disease, MRI: magnetic resonance imaging, PCR: polymerase chain reaction.

Assessments scheduled on study drug administration days should be performed predose, unless otherwise specified.

1. Perform within 28 days prior to Day 1. Assessments performed as standard of care may be used for screening.
2. Perform within 28 days after the last dose of zanubrutinib (± 7 days). Subjects who have disease relapse at any time will be asked to undergo biopsies of representative tumour sites and/or blood collection to obtain samples for studying mechanisms of resistance (see Section 8.14.1).
3. Subjects who discontinue study drug due to reasons other than disease progression will remain on study and be followed every 3 months until subject exhibits first progression, withdraws consent, starts new anti-cancer therapy, death or study closure, whichever occurs first. Once subjects progress or start use of alternative anti-cancer therapy, subjects will not return to the study center but will be contacted every 3 months by telephone, to assess survival until death, withdrawal of consent or study closure, whichever occurs first (see Section 8.10.2).
4. Windows: days allowed for reschedule of an entire visit due to logistic reasons (eg, public holidays). In all cases elements relating to medical assessments may be performed 48 hours prior to the scheduled day. These are: B symptoms, physical examination, ECOG, concomitant medications, AE, hematology, clinical chemistry, coagulation, pregnancy test and urinalysis.
5. Written informed consent form(s) must be signed by the subject before any study specific procedures are performed.
6. Unexplained weight loss >10% over previous 6 months, fever (>38°C), and/or drenching night sweats.
7. Complete physical examination includes all systems described in the body of the protocol. Targeted physical exams should be limited to systems of clinical relevance (ie, cardiovascular, respiratory, lymph nodes, liver, and spleen), and those systems associated with clinical signs/symptoms.
8. Perform a single 12-lead ECG at screening. Subjects should be in the semi-recumbent or supine position. Additional ECGs will be performed at the discretion of the investigator if medically indicated.
9. Administer one dose of zanubrutinib in the study center, review and dispense diary.
10. Tumor assessments must be performed within 7 days of the end of Weeks 12, 24, 36 and 48, every 24 weeks after Week 48, and at disease progression. Computed tomography scans must encompass neck, chest, abdomen and pelvis and use intravenous contrast or follow investigators' decision. A CT scan of diagnostic quality performed as part of positron emission tomography (PET)/CT is acceptable, provided bidimensional nodal and liver/spleen measurements can be made. MRI may be used in place of CT, at investigator discretion. If the subject has no assessable disease by CT/MRI at study entry (eg, Waldenström's macroglobulinemia without nodal enlargement), repeat scans are not required during the study. For the early termination visit, CT/MRI and response assessment are required if the previous scan was performed more than 3 months ago.
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indicating a possible CR), a bone marrow aspirate and biopsy will be obtained to confirm the CR. Peripheral blood and/or bone marrow aspirate/biopsy with flow cytometry assessment(s) for minimal residual disease should be done at least 3 months after the last dose if there is evidence of CR in all of the response parameters (ie, hematology, CT/MRI scan).

12. The study drug will be taken at least 30 minutes before obinutuzumab infusion on the day obinutuzumab is administrated.

13. Hematology, including hemoglobin, MCV, WBC count, absolute differential count (neutrophils, eosinophils, lymphocytes, blasts), bands (optional), and platelet count. In the event of neutropenia (absolute neutrophil count $<1000/mm^3$) or thrombocytopenia (platelets of less than $50,000/mm^3$), these assessments will be conducted as frequently as the physician feels needed until toxicity resolves to ≤ Grade 2.

14. Clinical chemistry includes sodium, potassium, glucose, urea, creatinine, calcium, magnesium, total and direct bilirubin, total protein, albumin, ALT, AST, lactose dehydrogenase, alkaline phosphatase and uric acid. In the event of ≥ Grade 3 clinical chemistry toxicity, these assessments will be conducted as frequently as the physician feels needed until toxicity resolves to ≤ Grade 2.

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16. All women of childbearing potential (including those who have had a tubal ligation) will have a serum pregnancy test at screening. Urine pregnancy tests will be performed at specified subsequent visits. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test.

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18. Collect urine dipstick, as well as urine microscopy if dipstick is abnormal. If urine protein is ≥2+ by dipstick, a 24 hour urine for total protein and a random urine for total protein and creatinine will be obtained and evaluated (see Section 8.2).

19. Subjects with CLL should have a blood sample sent at screening for interphase FISH for chromosomal abnormalities including 17p, 11q, 13q, and +12. Other analysis, including: Ig VH and P53 mutational status, is optional.

20. Subjects with non-GCB DLBCL must have archival tumor tissues or agree to a tumor biopsy for confirmation of the DLBCL subtype and for exploratory biomarker analysis.

21. Serial pharmacokinetic blood samples will be collected at the time points specified in Table 3 on Day 1 of Cycle 2, Cycle 4, and Cycle 6.

22. Subjects (except CLL) who have disease relapse at any time will be asked to undergo biopsies of representative tumor sites (bone marrow will be collected for WM patients). These procedures are optional.

23. Subjects who have disease relapse at any time will be asked to undergo blood collection to obtain samples for studying mechanisms of resistance. This procedure is optional.

24. Response should be assessed against baseline per disease relevant instructions in Appendix 16.3. Physical exam should be used at any time points where imaging is not required, but physical exam revealing disease progression or potential progression may require confirmation via imaging. Visits that contain components sufficient to determine a change in overall response in the patient (ie, unscheduled CT scans and labs, IgM-based change response between scheduled efficacy assessments for WM patients) should complete an overall efficacy response assessment as needed.

25. For Weeks 25 through 48, hematology, clinical chemistry, urine analysis, immunoglobulins, and serum EPG assessments will be conducted every 12 weeks. After Week 48, hematology and clinical chemistry assessments and urine analysis will continue every 12 weeks; however, immunoglobulins and serum EPG assessments will be conducted every 24 weeks until disease progression.

26. Samples will be taken from subjects with CLL to assess MRD at the following time points:

    • Peripheral blood sample at Cycle 18, or at the earliest opportunity after Cycle 18, in all CLL subjects on study; a bone marrow sample is requested if the peripheral blood sample is MRD negative

    • Peripheral blood sample at the time of newly attained CR, and at each CR assessed timepoint thereafter, for continuing CLL subjects; a bone marrow sample is requested if the peripheral blood sample is MRD negative

Table 3 Pharmacokinetic and Pharmacodynamic Sampling

Procedure	Cycle 1 Day 1					Cycle 1 Day 2		Cycle 1 Day 3		Cycle 1 Day 9		Cycle 1 Day 16		Cycle 2 Day 1					Cycle 4 Day 1		Cycle 6 Day 1	
Hours	**Pre-dose**	**1**	**2**	**4**	**7**	**Pre-dose**	**4**	**Pre-dose**	**4**	**Pre-dose**	**4**	**Pre-dose**	**4**	**Pre-dose**	**1**	**2**	**4**	**7**	**Pre-dose**	**4**	**Pre-dose**	**4**
PK blood sampling for zanubrutinib for Part 1	X[4]	X[1]	X[2]	X[2]	X[5]	X[3]								X[3]	X[1]	X[2]	X[2]	X[5]				
PK blood sampling for obinutuzuma for Part 1*						X[3]	X[2]	X[3]	X[2]	X[3]	X[2]	X[3]	X[2]	X[3]			X[2]		X[3]	X[2]	X[3]	X[2]
PD blood sampling for Part 1	X[4]			X[2]		X[3]								X[3]								
PK blood sampling for zanubrutinib for Part 2														X[3]	X[1]	X[2]	X[2]	X[5]				
PK blood sampling for obinutuzumab for Part 2*																			X[3]	X[2]	X[3]	X[2]
Vital signs and 12-lead ECGs	X		X											X		X						

* Four hours post obinutuzumab is in reference to the start of the infusion. As obinutuzumab may generally be infused within 4 hours, 4 hours post obinutuzumab marks the end of obinutuzumab infusion. Should the infusion be interrupted or delayed beyond 4 hours, the 4 hours post obinutuzumab PK samples should be taken at the end of the infusion.

Abbreviations: PD: pharmacodynamics; PK: pharmacokinetics

General note:

If cycle 1 and 2 vital signs and ECGs listed in tables 1 and 2 are performed before GA101 and/or zanubrutinib are administered, the pre-dose vital signs/ECGs may be omitted.

It is important that PK and PD sampling occurs as close as possible to the scheduled time. In order to achieve this, some of the other assessments scheduled at the same time need to be initiated prior to or after the time point to allow for completion of these measurements in enough time for the PK/PD sampling to be taken at the designated time point. Thus, the sequence at a particular time point is: 1) scheduled ECG and vital signs measurements; 2) PK/PD blood samples (to be performed at the precise protocol scheduled time); and 3) any other scheduled or unscheduled measurements at that time point.

1. A window period of ±10 minutes exists.
2. A window period within 30 minutes from the end of infusion.
3. Within 2 hours prior to dosing.
4. Within 3 hours prior to dosing.
5. A window period of ±1 hour exists.

5 STUDY POPULATION

Approximately 132 subjects (12 subjects in the safety evaluation part and 120 subjects in the indication expansion part) will be required to complete the Phase 1b trial of zanubrutinib in combination with obinutuzumab. Subjects with B-cell lymphoid malignancies will be entered into this study provided that they satisfy the inclusion and exclusion criteria.

5.1 Inclusion Criteria

Subjects may be entered in the study only if they meet all of the following criteria

1. Aged ≥18 years, able and willing to provide written informed consent and to comply with the study protocol.
2. Part 1 (Safety evaluation): R/R CLL/SLL, R/R FL, R/R MCL, R/R MZL, R/R WM, and R/R non-GCB DLBCL.
3. Part 2 (Indication specific expansion):
    - Cohort 1: treatment-naïve CLL/SLL.
    - Cohort 2: relapsed/refractory CLL/SLL.
    - Cohort 3: relapsed/refractory non-GCB DLBCL.
    - Cohort 4: relapsed/refractory FL, R/R MCL, R/R MZL, and R/R WM.
    - Cohort 5: relapsed/refractory FL. About 10-15 out of 40 should meet double-refractory criterion, defined as refractoriness to both rituximab and an alkylating agent, whether administered together or in successive treatment regimens. Refractoriness was defined per protocol as less than a partial response or progression of disease within 6 months after completion of a prior therapy (added per Amendment Version 4.0).
        - For R/R CLL, R/R FL, R/R MCL, R/R MZL, and R/R WM: Evidence of progression or lack of response following at least 1 prior treatment.
        - For R/R non-GCB DLBCL: Evidence of progression or refractory disease following at least a standard anthracycline/ rituximab-based primary treatment regimen (eg, R-CHOP), and not currently appropriate for autologous stem cell transplantation.
4. Laboratory parameters as specified below:
    - Hematologic: Platelet count >$40x10^9$/L (may be post-transfusion); absolute neutrophil count >$1.0x10^9$/L (growth factor use is allowed to bring the

pre-treatment neutrophils to >1.0x10^9 /L if marrow infiltration is involved).

- Hepatic: Total bilirubin <3 x upper limit normal (ULN); and aspartate aminotransferase (AST) and alanine transaminase (ALT) ≤3xULN.
- Renal: Creatinine clearance ≥ 30 ml/min (as estimated by the Cockcroft Gault equation or as measured by nuclear medicine scan or 24 hour urine collection); Subjects requiring hemodialysis will be excluded.

5. Anticipated survival of at least 6 months.
6. ECOG performance status of 0 to 2.
7. Female subjects of childbearing potential and non-sterile males must agree to practice at least one of the following methods of birth control with partner(s) throughout the study and for ≥3 months after discontinuing zanubrutinib or ≥ 18 months following treatment with obinutuzumab, whichever is longer: total abstinence from sexual intercourse, double barrier contraception, intrauterine device (IUD) or hormonal contraceptive initiated at least 3 months prior to first dose of study drug.
8. Male subjects must not donate sperm from initial study drug administration, until ≥3 months after discontinuing zanubrutinib or ≥18 months following treatment with obinutuzumab, whichever is longer.

5.2 Exclusion Criteria

1. Known central nervous system lymphoma or leukemia.
2. Known prolymphocytic leukemia or history of, or currently suspected, Richter's syndrome.
3. Uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenia purpura.
4. History of significant cardiovascular disease, define as:
   - congestive heart failure greater than New York Heart Association (NYHA) class II according to the NYHA functional classification
   - unstable angina or myocardial infarction with 6 months of enrollment
   - serious cardiac arrhythmia or clinical significant electrocardiogram (ECG) abnormality: corrected QT wave (QTc) prolongation, defined as a QTc >450 msecs based on the Bazett's formula (Subjects with QTc prolongation due to a cardiac pacemaker may be allowed with approval of the medical monitor), or other ECG abnormalities including 2nd degree atrioventricular (AV) block type II, 3rd degree AV block, or bradycardia (ventricular rate less than 50 beats/min).
5. Severe or debilitating pulmonary disease (dyspnea at rest, significant shortness of breath, chronic obstructive pulmonary disease [COPD]).

6. History of severe allergic or anaphylactic reactions to monoclonal antibody therapy.
7. Prior BTK inhibitor treatment.
8. Use of strong CYP3A inhibitors and strong CYP3A inducers (see Table 6).
9. Vaccination with a live vaccine within 28 days of the initiation of treatment.
10. Allogeneic stem cell transplantation within 6 months, or has active graft versus host disease (GvHD) requiring ongoing immunosuppression.
11. Receipt of the following treatment prior to first administration of zanubrutinib, corticosteroids given with anti-neoplastic intent within 7 days, chemotherapy or radiotherapy within 3 weeks, monoclonal antibody within 4 weeks.
12. Participate in any investigational drug study within 28 days of study entry, or not recovered from non-hematologic toxicity of any prior chemotherapy up to ≤ Grade 1 (except for alopecia).
13. History of other active malignancies within 2 years of study entry, with exception of (1) adequately treated in situ carcinoma of cervix; (2) localized basal cell or squamous cell carcinoma of skin; (3) previous malignancy confined and treated locally (surgery or other modality) with curative intent.
14. Unable to swallow capsules or disease significantly affecting gastrointestinal function such as malabsorption syndrome, resection of the stomach or small bowel, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction (revised per Amendment Version 3.0).
15. Major surgery in the past 4 weeks.
16. Active symptomatic fungal, bacterial and/or viral infection including evidence of infection with human immunodeficiency virus (HIV), human T cell lymphotropic virus (HTLV 1) seropositive status.
17. Subjects with positive serology for hepatitis B defined as positivity for hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (anti-HBc); subjects who are positive for anti-HBc may be considered for inclusion in the study on a case-by-case basis if they are hepatitis B viral deoxyribonucleic acid (DNA) negative and are willing to undergo ongoing HBV DNA testing by real-time polymerase chain reaction (PCR); subjects with presence of hepatitis B surface antibody (anti-HBs) consistent with prior vaccination (ie, HBsAg negative, anti-HBc negative, anti-HBs positive) may participate; subjects suspected to have false positive serologic studies because of IV immunoglobulin administration are potentially eligible after negative PCR studies for viral DNA/ribonucleic acid (RNA) and discussion with the principal investigator.

18. Evidence of active hepatitis C (HCV): subjects with positive hepatitis C serology and positive HCV RNA test.
19. Inability to comply with study procedures.
20. Pregnant or nursing women.
21. Any illness or condition that in the opinion of the investigator may affect safety of treatment or evaluation of any study's endpoints.

5.3 Other Eligibility Criteria Considerations

To assess any potential impact on subject eligibility with regard to safety, the investigator must refer to the IB for detailed information regarding warnings, precautions, contraindications, AEs, and other significant data pertaining to the study drug being used in this study.

5.4 Subject Completions and Withdrawals

5.4.1 Subject Completion

A subject will be considered complete if he/she has completed at least one full cycle of zanubrutinib plus obinutuzumab treatment and has not withdrawn from the study prior to completing the first cycle (29 days for subjects in Part 1 and 28 days for subjects in Part 2).

5.4.2 Subject Withdrawal

A subject may voluntarily discontinue participation in this study at any time. The investigator may also, at his/her discretion, discontinue the subject from participating in this study at any time. If a subject is prematurely discontinued from participation in the study for any reason, the investigator must make every effort to perform the following evaluations 28 days from the last administration of zanubrutinib: physical examination, vital signs, computed tomography (CT) scan (if it has been more than 3 months since the previous CT scan), B symptoms, ECG, laboratory tests (hematology, clinical chemistry, coagulation, urinalysis, and serum protein), and AE assessment. These data will be recorded as they comprise an essential evaluation that needs to be done prior to discharging any subject from the study.

In the event that a subject is prematurely discontinued from the study at any time due to an AE (as defined in Section 10.1), the procedures stated in Section 10 must be followed.

In addition to the post study assessments, if a DLT occurs, the investigator will obtain, when possible, a 4 mL blood sample for analysis of plasma zanubrutinib concentration.

Subjects who drop out or are withdrawn for any reason which does not fall under a DLT will be considered for replacement after due consideration from the Sponsor and safety committee.

Subject Withdrawal from the Investigational Product

Premature discontinuation of zanubrutinib would be any time a subject is discontinued for reasons other than unacceptable toxicity. The reason for discontinuation of zanubrutinib will be recorded in the electronic case report form (eCRF). These reasons include:

- Withdrawal of consent by the subject
- Discontinuation of zanubrutinib by the Sponsor
- Pregnancy
- Any significant AE that compromises the subject's ability to participate in the study (including infusion reactions)
- The investigator or Sponsor determines it is in the best interest of the subject.
- Intercurrent illness
- Progression of disease at any time during the study
- Need for prohibited medication
- Lack of compliance with the study and/or study procedures (eg, study drug administration instructions, study visits)
- Significant deviation from the protocol by the investigator without the consent of the Sponsor

6 STUDY TREATMENT

6.1 Description of Investigational Products

6.1.1 Zanubrutinib

Zanubrutinib is available as 20 mg blue opaque capsules (size 3), or 80 mg white opaque capsules (size 0), depending on the dose level. Zanubrutinib is intended for oral use.

6.1.2 Obinutuzumab

Obinutuzumab is provided as a sterile, clear, colorless to slightly brown, preservative free liquid concentrate for intravenous administration in 1000 mg/40 mL (25 mg/mL) single use vials.

Obinutuzumab is for intravenous use and should be administered as an intravenous infusion through a dedicated line after dilution. The U.S. label indicates a duration of treatment of 6 cycles, each 28 days duration.

6.2 Dosage and Administration

6.2.1 Zanubrutinib

Zanubrutinib (either 320 mg or 160 mg based on QD or BID) will be administered orally, at least 30 minutes before obinutuzumab infusion on the day obinutuzumab is administered, in each cycle (Cycle 1: 29 days for subjects in the Part 1 and 28 days for subjects in the Part 2; Cycle 2 and each cycle thereafter: 28 days). Treatment with zanubrutinib will continue until disease progression, death, unacceptable toxicity, withdrawal from the study, other reason for treatment discontinuation, or study closure, whichever occurs first.

Zanubrutinib will be dispensed by the study center personnel to subjects at scheduled study visits to ensure adequate drug supply for administration at home throughout the treatment phase as detailed in the Pharmacy Manual. The investigator is to instruct the subject to take the study drug exactly as prescribed and at approximately the same time each day of dosing. Subjects will be asked to complete a patient diary that records dates and times of dosing between clinic visits.

If a dose of the study drug is not taken at the scheduled time, the subject should skip the study drug if the time to next dose is 8 hours or less and return to normal dosing with next dose. If a subject vomits after taking the zanubrutinib capsules, that dose should not be repeated.

6.2.2 Obinutuzumab

Obinutuzumab will be administered at a final concentration of 0.4 mg/mL to 4 mg/mL as an intravenous infusion only for up to 6 cycles, see Table 4.

Table 4 Dose of Obinutuzumab to be Administered during the 6 Treatment Cycles

Cycle	Day of Treatment	Dose of Obinutuzumab
Cycle 1	Day 2 (Part 1) Or Day 1 (Part 2)	100 mg Administer at 25 mg/hr over 4 hours. Do not increase the infusion rate
	Day 3 (Part 1) Or Day 2 (Part 2)	900 mg Administer at 50 mg/hr. The rate of the infusion can be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr
	Day 9 (Part 1) Or Day 8 (Part 2)	1000 mg Infusions can be started at a rate of 100 mg/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr
	Day 16 (Part 1) Or Day15 (Part 2)	1000 mg Infusions can be started at a rate of 100 mg/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr
Cycles 2 to 6	Day 1	1000 mg Infusions can be started at a rate of 100 mg/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr

If a planned treatment is missed, the missed treatment should be administered as soon as possible and the treatment schedule adjusted accordingly. If appropriate, subjects who do not complete the Day 2 Cycle 1 treatment may proceed to the Day 3 Cycle 1 treatment.

Preparation of obinutuzumab

The obinutuzumab solution for intravenous solution should be prepared aseptically and diluted into a 0.9% sodium chloride PVC or non PVC polyolefin infusion bag. The prepared solution should be mixed by gentle inversion. It should not be frozen, but be administered immediately after preparation. If not used immediately, the solution may be stored in a refrigerator at 2°C to 8°C (36°F to 46°F) for up to 24 hours. The solution should be inspected visually for any particulate matter and discoloration prior to administration.

6.3 Packaging and Labelling

The zanubrutinib capsules will be provided in a child resistant closure and be open labelled with space to enter the subject number and name of investigator. The label will also include content and quantity of zanubrutinib, protocol number, batch number,

administration instructions, storage conditions, and cautions. The contents of the study treatment labels will be in accordance with all applicable regulatory requirements.

A release document signed by a legally authorized Qualified Person (QP) at the CRO will be placed in the appropriate section of the Trial Master File to document labeling and dispensing of the study drugs to the subject.

6.4 Storage and Handling Procedures

The study drug will be dispatched to a study center only after receipt of the required documents in accordance with applicable regulatory requirements and the Sponsor's procedures.

The study drug must be dispensed or administered according to procedures described herein. Only subjects enrolled in the study may receive study drug, in accordance with all applicable regulatory requirements. Only authorized study center personnel may supply or administer study drug. All study drugs must be stored in a secure area with access limited to the investigator and authorized study center personnel and under physical conditions that are consistent with study drug specific requirements. The study drug must be stored at the condition as specified on the labels, or according to the latest version of the IB.

6.5 Investigational Product Accountability

The investigator is responsible for study drug accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the investigator or designated study center personnel must maintain study drug accountability records throughout the course of the study. This person(s) will document the amount of study drug received from the Sponsor, the amount supplied and/or administered to and returned by subjects, if applicable.

After completion of the study, all unused study drug will be inventoried and packaged for return shipment by the hospital unit pharmacist. The inventoried supplies will be returned to the Sponsor or destroyed on site, after receiving written Sponsor approval.

6.6 Treatment Assignment

Subjects will be identified by a subject number. Each subject enrolled in this study will receive a unique subject number which will be assigned when the subject is screened or enrolled in the study. Each subject receiving zanubrutinib in combination with obinutuzumab will also receive a treatment allocation number. Subject and treatment numbers will be assigned in chronological order starting with the lowest number. Once a subject number and treatment number have been assigned to a subject, it cannot be reassigned to any other subject.

If a subject is replaced, the replacement subject will be assigned the next available subject number.

6.7 Warnings and Precautions

Warnings and precautions to obinutuzumab include the following adverse reactions: HBV reactivation, progressive multifocal leukoencephalopathy, infusion reactions, tumor lysis syndrome, infections, neutropenia, and thrombocytopenia.

- Infusion reactions: Obinutuzumab can cause severe and life-threatening infusion reactions. For subjects with Grade 4 infusion reactions, including but not limited to anaphylaxis, acute life-threatening respiratory symptoms, or other life-threatening infusion reaction, stop and permanently discontinue obinutuzumab therapy. Management of Gazyva-related infusion reactions should be conducted per the Gazyva package insert. It is recommended to closely monitor subjects during the entire infusion. Infusion reactions within 24 hours of receiving obinutuzumab have occurred. For Grade 1, 2, or 3 infusion reactions, interrupt or discontinue the infusion (see Section 6.11 initial management of infusion reaction).
- Tumor Lysis Syndrome (TLS): TLS can occur within 12 to 24 hours after the first infusion. Subjects with high tumor burden and/or high circulating lymphocyte count (> $25x10^9$/L) are at greater risk for TLS and should receive appropriate tumor lysis prophylaxis per the Gazyva package insert. In addition, BTK inhibitor can also induce TLS in subjects with high tumor burden. Even though no incidence of TLS has been observed in the ongoing Phase 1 monotherapy trial (BGB-3111-AU-003), there is a potentially enhanced risk of TLS when obinutuzumab is administered in combination with zanubrutinib (see Section 6.13 for initial management of TLS).
- Infection: Serious bacterial, fungal, and new or reactivated viral infections can occur during and following obinutuzumab therapy. Do not administer obinutuzumab to subjects with an active infection as fatal infections have been reported.
- Neutropenia: Severe neutropenia can occur. Monitor subjects with Grade 3 to 4 neutropenia frequently with regular laboratory tests until resolution. Neutropenia can also be of late onset and/or prolonged.
- Thrombocytopenia: Fatal hemorrhagic events have been reported. Monitor subjects for thrombocytopenia and hemorrhagic events. In subjects with Grade 3 or 4 thrombocytopenia, monitor platelet counts frequently until resolution and consider dose delays of obinutuzumab. [11]

Detailed information regarding warnings, precautions, contraindications, AEs, and other significant data pertaining to the study drugs being used in this study are provided in the Obinutuzumab Prescribing Information, Genentech Gazyva® Safety Information, and the Zanubrutinib IB.[9,11,12] Facilities and staff for resuscitation and the treatment of other medical emergencies will be provided.

6.8 Assessment of Compliance

On all visits to the study center, subjects will be questioned in regard to compliance with study instructions.

6.9 Treatment of Investigational Product Overdose

Since an actual efficacious dose for the zanubrutinib -obinutuzumab combination is unknown, an overdose cannot be defined. Subjects with a suspected overdose should be managed with appropriate supportive therapy as determined by the investigator in consultation with the Sponsor medical monitor. Any adverse effects occurring as a result of an overdose should be reported to the Sponsor medical monitor.

6.10 Occupational Safety

The investigational product is not expected to pose significant occupational safety risk to the study center personnel under normal conditions of use and administration. A material safety data sheet describing occupational hazards and recommended handling precautions will be provided to the investigator, where this is required by local laws, or is available upon request from the Sponsor.

6.11 Infusion-Related Reactions with Obinutuzumab

Symptoms of infusion-related reactions with obinutuzumab include fever, chills, rigors, diaphoresis, and headache (Table 5).

Table 5 Treatment Modification for Symptoms of Infusion-Related Reactions Caused by Obinutuzumab

NCI-CTCAE Grade	Treatment Modification for Obinutuzumab
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease the obinutuzumab infusion rate by 50% and monitor closely for any worsening.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hr.	Stop obinutuzumab infusion. Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening.
Grade 3 or Grade 4 – severe or life-threatening **Grade 3**: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. **Grade 4**: Life-threatening consequences; urgent intervention indicated.	Stop the obinutuzumab infusion immediately and disconnect infusion tubing from the subject. Subjects have to be withdrawn immediately from obinutuzumab treatment and must not receive any further obinutuzumab treatment.

Abbreviations: IV: intravenous, NCI-CTCAE: National Cancer Institute-Common Terminology Criteria for Adverse Event, NSAIDs: non-steroidal anti-inflammatory drugs.

6.12 Severe Hypersensitivity Reactions and Flu-like Symptoms

If a hypersensitivity reaction occurs, the subject must be treated according to the best available medical practice. A complete guideline for the emergency treatment of anaphylactic reactions according to the Working Group of the Resuscitation Council (United Kingdom) can be found at https://www.resus.org.uk/pages/reaction.pdf. Subjects should be instructed to report any delayed reactions to the Investigator immediately.

Symptoms:

- Impaired airway
- Decreased oxygen saturation (<92%)

- Confusion
- Lethargy
- Hypotension
- Pale/clammy skin
- Cyanosis

Management:

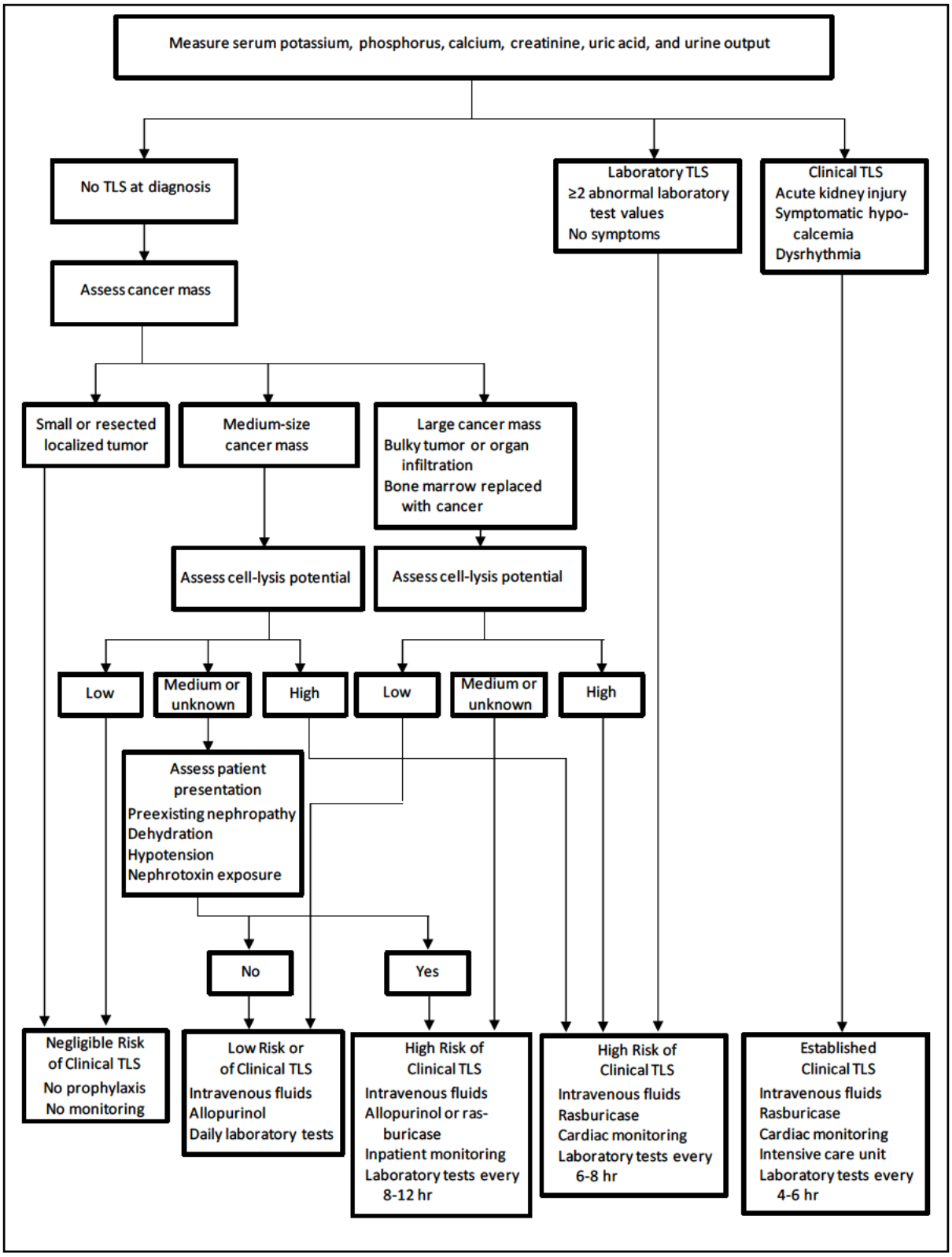
1. Epinephrine injection and intravenous dexamethasone
2. Subject should be placed on cardiac, blood pressure, heart rate, and oxygen saturation monitor immediately
3. Alert intensive care unit for possible transfer if required

For prophylaxis of flu-like symptoms, follow the premedication instructions in Section 6.7.

6.13 Tumor Lysis Syndrome

Since obinutuzumab can induce ADCC, there is a potential risk of TLS. In addition, zanubrutinib can also induce TLS in subjects with high tumor burden although no incidence of TLS has been observed in the ongoing Phase 1 monotherapy trial (BGB-3111-AU-003). There is a potentially enhanced risk of TLS when obinutuzumab is administered in combination with zanubrutinib. Should this occur, subjects should be treated per the local guidelines and the management algorithm stipulated in Figure 2.[19]

Figure 2 Assessment and Initial management of Tumor Lysis Syndrome



7 CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

7.1 Permitted Medications

All concomitant medications taken during the study will be recorded in the eCRF with indication, dose information, and dates of administration.

As vomiting and nausea are the known side effects of obinutuzumab, prophylaxis of emesis would be allowed as per institutional standard at the physician's discretion (added per Amendment Version 3.0).

Patients with hematologic malignancies, particularly those having received prior lymphodepleting chemotherapy or having prolonged corticosteroid exposure, are pre-disposed to opportunistic infections as a result of disease and treatment-related factors. In patients with a high risk for opportunistic infections, including Pneumocystis jirovecii pneumonia (PJP), prophylaxis should be considered as per institutional standards.

7.2 Prohibited/Restricted Medications

Subjects should not receive other anticancer therapy (cytotoxic, biologic, or hormone other than for replacement) while on treatment in this study.

- Other anticancer therapy should not be administered until disease progression (as per clinical practice standards at the study center), unmanageable toxicity, or no further clinical benefit occurs which requires permanent discontinuation of the study drug.
- Bisphosphonate use is permitted if the subject has already been on it for 3 or more months and on a stable dose.
- Corticosteroid courses of limited duration (2 weeks or less) and dose (≤20 mg prednisone per day, or equivalent) are permitted, if used to treat a concomitant (non-cancer) medical condition, with the exception of glucocorticoids used for management of Gazyva-related infusion reaction (see Section 6.7).

7.3 Medications to be used with Caution

Administration of zanubrutinib with strong/moderate CYP3A inhibitors or CYP3A inducers (refer to Table 6 for a list of these medications) and grapefruit juice and Seville oranges should be used with caution as they may affect the metabolism of zanubrutinib (Section 1.2). If at all possible, patients are encouraged not to use strong/moderate CYP3A inhibitors and inducers and consider using alternative agents. If these agents will be used, follow the dose modification in Table 7. The Medical Monitor should be

consulted in these situations. Please refer to http://medicine.iupui.edu/clinpharm/ddis/main-table/ for a more complete list.

Table 6 CYP3A Inhibitors and Inducers

Strong CYP3A Inhibitors
Antibiotics: clarithromycin, telithromycin, troleandomycin
Antifungals: itraconazole, ketoconazole, posaconazole, voriconazole
Antivirals: boceprevir, telaprevir
Other: cobicistat, conivaptan, elvitegravir, mibefradil, nefazodone
Protease inhibitors: indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir
Moderate CYP3A Inhibitors
Antibiotics: ciprofloxacin, erythromycin
Antifungals: fluconazole, clotrimazole
Protease inhibitors: amprenavir, atazanavir, darunavir/ritonavir, fosamprenavir
Calcium channel blockers: diltiazem, verapamil
Tyrosine kinase inhibitors (anticancer)： imatinib, crizotinib
Food products: grapefruit juice（*citrus paradisi* juice）
Herbal medications: Schisandra sphenanthera
Others: amiodarone, aprepitant, casopitant, cimetidine, cyclosporine, dronedarone, tofisopam
Strong/Moderate CYP3A Inducers
Avasimibe, carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), St. John's wort (hypericum perforatum), enzalutamide, mitotane, bosentan, efavirenz, etravirine, modafinil

Source: Food and Drug Administration Drug Development and Drug Interactions: Table of Substrates, Drug Development and Drug Interactions and Inducers. Note: The list of drugs in this table is not exhaustive. Please refer to the prescribing information of concomitant medication to check for CYP3A inhibition or induction risks or contact the medical monitor of the protocol.

For a more complete list, please refer to http://medicine.iupui.edu/clinpharm/ddis/main-table/ or

Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine. http://medicine.iupui.edu/flockhart/table.htm

Abbreviation: CYP: cytochrome P450.

Table 7 Dose Modification for Zanubrutinib when Co-Administered with Strong/Moderate CYP3A Inhibitors or Inducers

CYP3A	Co-administered Drug	Recommended use
Inhibition	Strong CYP3A inhibitor (eg, ketoconazole, conivaptan, clarithromycin, indinavir, itraconazole, lopinavir, ritonavir, telaprevir, posaconazole, voriconazole)	80 mg once daily
	Moderate CYP3A inhibitor (eg, erythromycin, ciprofloxacin, diltiazem, dronedarone, fluconazole, verapamil, aprepitant, imatinib, grapefruit products)	80 mg twice daily
Induction	Strong CYP3A inducer (eg, carbamazepine, phenytoin, rifampin, St. John's wort)	Avoid concomitant use; Consider alternative agents with less induction potential.
	Moderate CYP3A inducer (eg, bosentan, efavirenz, etravirine, modafinil, nafcillin)	160 mg twice daily, use with caution; Monitor for potential lack of efficacy.

Clinical drug-drug interaction study indicated that zanubrutinib is a mild inducer of CYP3A4 and CYP2C19 (Section 1.2). Narrow therapeutic index drugs that are metabolized by CYP3A4 (alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus), and CYP2C19 (eg, S-mephenytoin) should be used with caution, as zanubrutinib may decrease the plasma exposures of these drugs. For subjects using hormonal contraceptives such as birth control pills or devices, a second barrier method of contraception (eg, condoms) must be used.

In the interests of subject safety and acceptable standards of medical care the investigator will be permitted to prescribe treatment(s) at his/her discretion. All treatments must be recorded in the subjects' eCRF (medication, dose, treatment duration and indication).

8 STUDY ASSESSMENTS

A signed, written informed consent must be obtained prior to screening assessments and before any study specific assessments are initiated. The study specific assessments and procedures are shown in the study assessments and procedures schedule in Table 1 and Table 2. The PK and PD sampling time points are presented in Table 3.

8.1 Demographic and Baseline Safety Assessments

Demographic data will include date of birth, race, height (in cm), body weight (in kg), and body mass index (BMI; in kg/m^2). For height and weight measurements, the subject will be allowed to wear indoor daytime clothing with no shoes. This data will be captured in the eCRF and database.

Having given consent, subjects will be required to undergo a medical screen to determine whether they are eligible to participate in the study according to the criteria listed in Section 5. Screening assessments will be completed within 28 days prior to the first treatment. Screening assessments completed within 72 hours of administration can be used as Day 1 assessments as indicated in Table 1 and Table 2.

The screening assessments will include:

- Demographic data
- General medical history & baseline conditions
- Vital signs (systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse rate, temperature, and respiratory rate)
- B symptoms (unexplained weight loss >10% over previous 6 months, fever [>38°C], and/or drenching night sweats)
- Complete physical examination
- ECOG performance status
- Echocardiogram
- 12 lead ECG
- Review of concurrent medication
- Recording of AEs and serious adverse events (SAEs)
- Tumor assessment by CT/ MRI scan (neck, chest, abdomen and pelvis)
- Bone marrow evaluation (aspirate or biopsy)
- Hematology
- Clinical chemistry

- Coagulation
- Immunoglobulin (Ig) A, IgG, IgM level and serum electrophoresis
- Pregnancy test for women of childbearing potential
- Viral serology (HBV, HCV, HIV)
- Urinalysis

The aforementioned data will be captured in the source documents. Any results falling outside the normal range will be repeated at the discretion of the investigator.

Safety assessments should be performed at all visits to the study center and throughout the study. The list of events and the time when they will be performed are presented in Table 1 and Table 2.

Measurements used to evaluate safety will include vital signs, B symptoms, clinical laboratory tests (hematology, clinical chemistry, coagulation, urinalysis, and immunoglobulin assessment and serum EPG), 12 lead ECG, and physical examinations. Throughout the study, the study center personnel will be monitoring AEs. Adverse events and toxicities will be graded according to NCI CTCAE, Version 4.03.[18] Subjects who initiate treatment with an ANC <1000/µl will not be considered evaluable for neutrophil toxicity as outlined in the 2008 IWCLL guidelines.[15]

8.2 Laboratory Evaluations

Laboratory assessments should be performed at a local certified laboratory on Day 1 before the study drug administration. Laboratory assessments need not be repeated on Day 1 if these assessments were completed for screening within 72 hours of the first administration. Other laboratory assessments will be sent to central laboratory for the required procedures. Required assessments are listed in Table 9.

Clinical chemistry, hematology, coagulation, urinalysis, and immunoglobulin assessment and serum EPG will be performed at the time points specified in Table 1 and Table 2.

All subjects, who have any Grade 3 or Grade 4 laboratory abnormalities at withdrawal from the study, must be followed up until they have returned to Grade 1 or Grade 2, unless these are not likely to improve due to the underlying disease.

On routine urinalysis, if urine protein is ≥2+ by dipstick, a 24 hour urine sample for total protein and a random urine sample for total protein and creatinine will be obtained. If urine protein is >2 g/24 hours, the study drug administration will be interrupted until it returns to ≤2 g/24 hours. If urine protein is ≤2 g/24 hours, further clinical evaluation and/or more frequent testing may be performed as clinically indicated. A random urine protein to creatinine ratio can serve as a reliable surrogate for the 24 hour urine protein when following subjects with urine protein of ≤2 g, documented by a 24 hour urine

collection. In such cases, the 24 hour urine for total protein should be repeated only if a clinically significant increase is observed in the random urine protein to creatinine ratio.

Serum electrophoresis should be tested during screening for all subjects, and if a paraprotein is present, it should be repeated on all subsequent immunoglobulin assessments.

8.3 Physical Examination, Vital Signs, and B Symptoms

A complete or targeted physical examination, vital signs (SBP, DBP, pulse rate, temperature, and respiratory rate), weight, and B symptoms assessment will be performed at the time points specified in Table 1 and Table 2.

Complete physical examination includes assessment of cardiovascular, respiratory, abdominal and neurological systems as well as lymph nodes, spleen, skin, oropharynx and extremities. Targeted physical exams should be limited to systems of clinical relevance (ie, cardiovascular, respiratory, lymph nodes, liver, and spleen) and those systems associated with clinical signs/symptoms. B symptoms include unexplained weight loss >10% over previous 6 months, fever (>38°C), and/or drenching night sweats.

8.4 Electrocardiogram

Perform a single 12 lead ECG at screening and as medically indicated. Subjects should be in the semi recumbent or supine position. Electrocardiograms will be obtained at the time points specified in Table 1 and Table 2.

8.5 Computed Tomography

Tumor assessments must be performed within 7 days of the end of Weeks 12, 24, 36 and 48, every 24 weeks after Week 48, and at disease progression. In rare instances the timing of a subject's scan may fall outside this specified imaging procedure window – for example, due to out-of-town travel or other unforeseen circumstances. Rare occurrences of missing scans or scans outside the procedure window will not necessarily be considered as a protocol deviation; the Sponsor will make the final determination. Subjects continue treatment and undergo additional tumor assessments until disease progression or intolerance, death, subject withdraws from the study, or at the discretion of the investigators, or study closure, whichever occurs first. Computed tomography scans must encompass neck, chest, abdomen and pelvis and use intravenous contrast or investigators' decision. A CT scan of diagnostic quality performed as part of positron emission tomography (PET)/CT is acceptable, provided bidimensional nodal and liver/spleen measurements can be made. For lesions not amenable to measurement by CT, MRI may be utilized after consultation with the Sponsor Medical Monitor. If the subject has no assessable disease by CT at study entry (eg, WM without nodal enlargement), repeat scans are not required during the study. The CT scan will be used for disease assessment by the investigator at each study center. For subjects who discontinue early, a

CT scan will be performed at the discontinuation visit if the previous scan was more than 3 months ago.

8.6 Bone Marrow Evaluation

A bone marrow examination must be performed at screening for all participants and within 7 days of the end of Week 12 for subjects with baseline marrow disease. In those subjects who had evidence of bone marrow disease at the time of enrollment, upon achieving a possible complete response (CR) (eg, physical exam or CT scan indicating a possible CR), based on the response criteria of NHL, repeated bone marrow aspirations and biopsies are required to confirm CR.

Peripheral blood and/or bone marrow aspirate/biopsy with flow cytometry assessment(s) for minimal residual disease should be done at least 3 months after the last dose if there is evidence of CR in all of the response parameters (ie, hematology, CT scan).

8.7 Minimal Residual Disease for Subjects with CLL

Chemo-immunotherapy combinations are standard treatments for many patients with CLL. Novel targeted agents are being used in front-line and relapsed settings. Minimal residual disease (MRD) status has been shown to be a predictor of both progression-free survival (PFS) and overall survival (OS) following chemo-immunotherapy.[20,21] In this study, samples will be requested from subjects with CLL to assess MRD at the following timepoints:

- Peripheral blood sample at Cycle 18, or at the earliest opportunity after Cycle 18, in all CLL subjects on study; a bone marrow sample is requested if the peripheral blood sample is MRD negative
- Peripheral blood sample at the time of newly attained CR, and at each CR assessed timepoint thereafter, for continuing CLL subjects; a bone marrow sample is requested if the peripheral blood sample is MRD negative

CLL subjects who do not achieve CR will not have the second set of peripheral blood and bone marrow samples taken.

Samples will be analyzed at a central laboratory.

8.8 Adverse Events

After informed consent has been signed, but prior to the administration of the study drug, only SAEs should be reported. After initiation of study drug, all AEs and SAEs, regardless of the relationship to the study drug, will be collected until 30 days after the last zanubrutinib treatment or 90 days after the last dose of obinutuzumab, and until resolution of all treatment related AEs.

8.9 Pregnancy

8.9.1 Pregnancy Testing

A serum pregnancy test will be performed at screening and a urine pregnancy test at the time points specified in Table 1 and Table 2 in women of childbearing potential. Any female subject who is pregnant will not be eligible for the study. A subject who has a positive pregnancy test result at any time after the study drug administration will be immediately withdrawn from participation in the study. The results of pregnancy tests will not be recorded in the database.

8.9.2 Action to be taken if a Pregnancy Occurs

A subject who has a positive pregnancy test result at any time after the study drug administration will be immediately withdrawn from participation in the study. All post study assessments will be collected at the time of discontinuation as described in Section 5.4.1.

The investigator, or his/her designee, will collect pregnancy information on any female subject of childbearing potential or a female partner of a male subject who becomes pregnant while participating in this study. The investigator, or his/her designee, will record pregnancy information on the appropriate form and submit it to the Sponsor within 2 weeks of learning of a subject's pregnancy. The subject will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, follow up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE, as described in Section 10.6 and will be followed as described in Section 10.8.

A spontaneous abortion is always considered to be an SAE and will be reported as described in Section 10. Furthermore, any SAE occurring as a result of a post study pregnancy and is considered reasonably related to the study drug (zanubrutinib in combination with obinutuzumab) by the investigator, will be reported to the Sponsor as described in Section 10.11. While the investigator is not obligated to actively seek this information in former subjects, he/she may learn of an SAE through spontaneous reporting.

8.10 Follow-up Assessments

8.10.1 Safety Follow-up

Approximately 28 days after the last administration of the study drug, all subjects should return for a final evaluation. Assessments to be performed are presented in Table 1 and Table 2.

Any abnormal finding of clinical consequence and not related to the disease progression will be monitored until resolution or baseline status.

8.10.2 Progression and Survival Follow up

Subjects who discontinue study drug due to reasons other than disease progression will remain in the study and be followed every 3 months until the subject exhibits first progression, withdraws consent, starts new anti-cancer therapy, death or study closure, whichever occurs first. Once a subject progresses or starts use of alternative anti-cancer therapy, he/she will not return to the study center, but will be contacted every 3 months by telephone, to assess survival until death, withdrawal of consent or study closure, whichever occurs first.

8.11 Efficacy

The following efficacy endpoints will be assessed:

- The number and proportion of subjects who achieve objective tumor response (CR, PR, PR-L, and CR+PR) or SD.
- Minimal residual disease (MRD) clearance rate.
- Hematological improvement.
- Progression free survival (PFS). It is the responsibility of the investigator to determine the date of disease progression.
- Overall survival.
- Duration of response for responders (CR or PR). Duration: time from date of first occurrence of CR or PR to date of progression.

Efficacy assessments will use the applicable response criteria (IWCLL for CLL[15,22], NCI WG for NHL[16], and IWWM for WM[17], as shown in Section 16.3) with CT (or PET if applicable) scans after Weeks 12, 24, 36 and 48, every 24 weeks after Week 48, and bone marrow aspirate and trephine after 12 weeks (and repeated subsequently if the subject attains criteria for complete remission in every other respect beyond 12 weeks).

8.12 Pharmacokinetic Assessments

Blood will be collected to describe the PK profiles of zanubrutinib and obinutuzumab and may be used for a preliminary analysis of major metabolites.

The maximum total amount of blood taken for the PK analysis will be approximately 150 mL. These samples will be collected at the time points presented in Table 3. Frozen plasma samples should be shipped as soon as possible after collection since exposure will be monitored while the study is ongoing.

8.12.1 Pharmacokinetic Blood Samples for Zanubrutinib and Obinutuzumab

Cannulation for blood sampling for PK will be performed. Blood will be collected via the intravenous cannula predose and at the time points specified in Table 3. A 1 mL blood sample will be taken (for flush of the cannula) and discarded prior to each blood sample. The actual time each sample was collected will be captured to the nearest minute in the eCRF and recorded in the database.

Blood samples (4 mL and 5 mL) for zanubrutinib and obinutuzumab PK analysis, respectively, will be collected according to the Lab Manual. Plasma (for zanubrutinib) and serum (for obinutuzumab) will be separated and immediately frozen. Samples must remain frozen in a freezer set at or below -70°C and in a box with dry ice during shipping.

Prior to collection, the collection tube and serum or plasma storage tube must be labelled with the corresponding labels provided by the Sponsor. The labels must be placed along the length of the tube so they can be read easily. Tape must not be used to secure the labels as the tube will not fit into the autoanalyzer test tube rack. The labels are of high quality and will not peel off of the tube even under extreme conditions.

Samples will be shipped to the central laboratory where all samples will be analyzed for plasma zanubrutinib and obinutuzumab concentrations using a validated method.

8.13 Pharmacodynamic Assessments

Pharmacodynamics is not a primary objective of this study. BTK occupancy in PBMCs will be determined and used as direct PD biomarker for BTK inhibition. This is for the subjects enrolled in Part 1 only.

8.13.1 PBMC Preparation

Blood samples (8 mL) for PD analysis will be collected into plastic potassium EDTA collection tubes immediately following PK blood sampling at the time points specified in Table 3. PBMCs will be prepared using the peripheral blood mononuclear cell preparation kit provided by the Sponsor. PBMC samples will be immediately frozen in a freezer at or below -70°C.

8.13.2 Sample Shipment and Analysis

Samples must remain frozen in a box with dry ice during shipping. Samples will be shipped to the central laboratory where all samples will be analysed for BTK occupancy using a validated method.

8.14 Other Assessments

8.14.1 Subject Tissue Analysis

Subjects who have DLBCL must have archival tumor tissues or agree to a tumor biopsy for confirmation of the DLBCL subtype and further genetic analysis, either prior to enrollment or during/after the study treatment. Either a formalin fixed, paraffin embedded block with tumor tissue (preferred) or 10 to 15 unstained slides must be sent to the central laboratory to confirm the DLBCL subtype and conduct exploratory biomarker analysis.

Subjects who have disease relapse at any time will be asked for a blood sample and asked to undergo biopsies of representative tumor sites (or BM) to obtain samples for studying mechanisms of resistance. These studies may include phosphoprotein analysis of relevant pathways, whole exome or genome sequencing, and assessments of RNA expression. To achieve these goals, at disease progression, subjects who have CLL will be asked to provide a peripheral blood sample, subjects who have WM will be asked to provide a bone marrow aspirate, and subjects from other indications will be asked to undergo tissue biopsies of representative tumor sites. If feasible, samples collected for disease progression confirmation may be used for biomarker testing in lieu of requesting additional marrow and biopsy samples from patients. For non-CLL subjects, while bone marrow collection or tumor tissue re-biopsy is preferred, peripheral blood samples are acceptable if bone marrow or biopsies are not accessible.

8.15 Appropriateness of Measurements

All safety and PK assessments used in this study are standard, ie, widely used and generally recognized as reliable, accurate, and relevant.

9 QUALITY CONTROL AND QUALITY ASSURANCE

According to the GCP guidelines, the Sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written Standard Operating Procedures (SOPs).

Quality control will be applied to each stage of data handling.

The following steps will be taken to ensure the accuracy, consistency, completeness, and reliability of the data:

- Investigator meeting(s)
- Certified local laboratories for laboratory measurements and ECGs
- Study center initiation visit
- Early study center visits after enrollment
- Routine study center monitoring
- Ongoing study center communication and training
- Data management quality control checks
- Continuous data acquisition and cleaning
- Internal review of data
- Quality control check of the final clinical study report

In addition, the Sponsor and/or the CRO clinical quality assurance department may conduct periodic audits of the study processes, including, but not limited to the study center, study center visits, central laboratories, vendors, clinical database, and the final clinical study report. When audits are conducted, access must be authorized for all study related documents including medical history and concomitant medication documentation to authorized Sponsor's representatives and regulatory authorities.

9.1 Monitoring

In accordance with applicable regulations, GCP, and Sponsor procedures, the Sponsor and/or CRO monitors will contact the study center prior to the subject enrollment to review the protocol and data collection procedures with the study center personnel. In addition, the monitor will periodically contact the study center, including conducting on site visits. The extent, nature and frequency of onsite visits will be based on such considerations as the study objective and/or endpoints, the purpose of the study, study design complexity, and enrollment rate.

During these contacts, the monitor will:

- Check the progress of the study
- Review study data collected
- Conduct source document verification
- Identify any issues and address their resolution

This will be done in order to verify that the:

- Data are authentic, accurate, and complete
- Safety and rights of subjects are being protected
- Study is conducted in accordance with the currently approved protocol (and any amendments), GCP, and all applicable regulatory requirements

The investigator agrees to allow the monitor direct access to all relevant documents and to allocate his/her time and the time of his/her personnel to the monitor to discuss findings and any relevant issues.

At study closure, monitors will also conduct all activities described in Section 13.1.

9.2 Data Management/Coding

Data generated within this clinical study will be handled according to the relevant SOPs of the data management and biostatistics departments of the CRO.

An electronic data capture (EDC) system will be used for this study, meaning that all eCRF data will be entered in electronic forms at the study center. Data collection will be completed by authorized study center personnel designated by the investigator. Appropriate training and security measures will be completed with the investigator and all authorized study center personnel prior to the study being initiated and any data being entered into the system for any subjects.

The eCRFs should always reflect the latest observations of the subjects participating in the study. Therefore, the eCRFs are to be completed as soon as possible during or after the subject's visit. To avoid inter observer variability, every effort should be made to ensure that the same individual who made the initial baseline determinations completes all safety evaluations. The investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available or not applicable or unknown, the investigator should indicate this in the eCRF. The investigator will be required to electronically sign off on the clinical data once complete.

The monitor will review the eCRFs and evaluate them for completeness and consistency. The eCRF will be compared with the source documents to ensure that there are no

discrepancies between critical data. All entries, corrections, and alterations are to be made by the responsible investigator or his/her designee. The monitor cannot enter data in the eCRFs. Once clinical data has been entered into the eCRF, any corrections or alterations to the data fields will be traceable via an audit trail, meaning that the reason for change, the name of the person who performed the change, together with time and date will be logged. Roles and rights of the study center personnel responsible for entering the clinical data into the eCRF will be determined in advance. If additional corrections are needed, the responsible monitor or data manager will raise a query in the EDC application. The appropriate study center personnel will respond to any queries raised.

The eCRF is essentially considered a data entry form and should not constitute the original (or source) medical records unless otherwise specified. Source documents are all documents used by the investigator or hospital that relate to the subject's medical history, that verify the existence of the subject, the inclusion and exclusion criteria and all records covering the subject's participation in the study. They include laboratory notes, ECG results, memoranda, pharmacy dispensing records, subject files, etc.

The investigator is responsible for maintaining source documents. These will be made available for inspection by the study monitor at each monitoring visit. The investigator must submit a completed eCRF for each subject who receives the study drug, regardless of the duration. All supportive documentation submitted with the eCRF, such as laboratory or hospital records, should be clearly identified with the study and subject number. Any personal information, including subject name, should be removed or rendered illegible to preserve individual confidentiality.

Electronic CRF records will be automatically appended with the identification of the creator, by means of their unique User ID. Specified records will be electronically signed by the investigator to document his/her review of the data and acknowledgement that the data are accurate. This will be facilitated by means of the investigators unique User ID and password; date and time stamps will be added automatically at the time of the electronic signature. If an entry on an eCRF requires change, the correction should be made in accordance with the relevant software procedures. All changes will be fully recorded in a protected audit trail, and a reason for the change will be required.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 17.0 or higher. Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO DD). Concomitant diseases/medical history will be coded using MedDRA Version 17.0 or higher.

9.3 Quality Assurance Audit

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit. Regulatory agencies may also conduct a

regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to the facilities used for this trial and all relevant documents and to allocate his/her time and the time of his/her personnel to the auditor/inspector to discuss findings and any relevant issues.

10 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE as provided in this protocol. During the study, when there is a safety evaluation, the investigator or study center personnel will be responsible for detecting AEs and SAEs, as detailed in this section of the protocol. Adverse event and SAE collection is to begin from subject consenting, and continued until 30 days after the last zanubrutinib treatment, and until resolution of all treatment related AEs.

10.1 Definition of an Adverse Event

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (zanubrutinib in combination with obinutuzumab).

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study drug.

Examples of an AE include:

- Worsening of a chronic or intermittent pre-existing condition including an increase in severity, frequency, duration, and/or has an association with a significantly worse outcome.
- New conditions detected or diagnosed after study drug administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concurrent medication.
- Significant failure of expected pharmacological or biological action. See Section 10.3 for additional information.

10.2 Definition of a Serious Adverse Event

An SAE is any untoward medical occurrence that, at any dose:

- Results in death.
- Is life threatening.

NOTE: The term "life threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

- Requires hospitalization or prolongation of existing hospitalization.

  NOTE: In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

  Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an SAE.

- Results in disability/incapacity.

  NOTE: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere or prevent everyday life functions, but do not constitute a substantial disruption.

- Is a congenital anomaly/birth defect.

- Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition.

10.3 Lack of Efficacy

"Lack of efficacy" will not be reported as an AE. The signs and symptoms or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the AE or SAE definition (including clarifications).

10.4 Abnormal Assessments as AEs or SAEs

Abnormal laboratory findings (eg, clinical chemistry, hematology, coagulation, urinalysis) or other abnormal assessments (eg, ECGs, chest X rays, vital signs, etc.) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs if they meet the definition of an AE, as defined in Section 10.1, or an SAE, as defined in

Section 10.2. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs. They should be reported as AEs or SAEs if they induce clinical signs or symptoms, need active intervention, need dose interruption or discontinuation or are clinically significant in the opinion of the investigator.

The investigator will exercise his/her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

10.5 Time Period, Frequency, and Method of Detecting AEs and SAEs

10.5.1 Adverse Event Reporting Period

After informed consent has been signed but prior to the administration of the study drug, only SAEs should be reported.

After initiation of study drug, all AEs and SAEs, regardless of relationship to study drug, will be reported until 30 days after the last study treatment of zanubrutinib or 90 days after the last dose of obinutuzumab. After this period, the investigator should report any SAEs that are believed to be related to prior study drug treatment.

10.5.2 Eliciting Adverse Events

The investigator or designee will ask about AEs by asking the following standard questions:

- How are you feeling?
- Have you had any medical problems since your last visit?
- Have you taken any new medicines since your last visit?

All AEs and SAEs will be recorded in the source documents. All AEs and SAEs will be reported in the eCRF.

10.5.3 Specific Instructions for Recording Adverse Events and Serious Adverse Events

10.5.3.1 Diagnosis versus Signs and Symptoms

If a diagnosis is known at the time of reporting, this should be recorded in the eCRF (and SAE report, as applicable), rather than the individual signs and symptoms (eg, record only hepatitis rather than elevated transaminases, bilirubin or jaundice). However, if a

constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual AE should be recorded as an SAE or AE on the eCRF (and SAE report, if applicable). If a diagnosis is subsequently established, it should replace the individual signs and/or symptoms as the AE term on the eCRF (and SAE report, if applicable), unless the signs/symptoms are clinically significant.

10.5.3.2 Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other AEs (eg, clinical sequelae or a cascade of AEs) should be identified by their primary cause. For example, if severe vomiting is known to result in dehydration, it is sufficient to record only vomiting as the SAE or AE on the eCRF (and SAE report, if applicable). However, if a subject initially has a non-serious AE, and it subsequently becomes an SAE, both AEs should be reported separately on the eCRF. The onset date of the non-serious AE should be recorded as the start date of the non-serious AE. The onset date of the SAE should be recorded as the start date when the non-serious AE becomes an SAE.

10.5.3.3 Persistent or Recurring Adverse Events

A persistent AE is one that extends continuously, without resolution, between subject evaluation time points. Such AEs should only be recorded once on the AE eCRF (and SAE report, if applicable). If a persistent AE worsens in grade, it should be recorded as a new AE on the eCRF (and a stop date should be recorded in the previous AE).

A recurrent AE is one that occurs and resolves between subject evaluation time points, and subsequently recurs. All recurrent AEs should be recorded separately on the eCRF (and SAE report, if applicable).

10.5.3.4 Disease Progression

Disease progression is expected in this study population, and the term “disease progression” should not be reported as an AE term. When disease progression is identified, the AE that identifies the disease progression should be reported as the AE term. For instance, a subject with pleural effusion presents with shortness of breath. The cause of the shortness of breath is a pleural effusion resulting from disease progression. The AE term should be reported as “pleural effusion” instead of disease progression or metastasis to lungs. If a subject has a seizure that is determined to be associated with a brain metastasis, the term “seizure” should be recorded as the AE instead of disease progression or brain metastasis. If a subject experienced multi-organ failure due to disease progression, the term “multi-organ failure” should be reported as the AE instead of disease progression. Deaths that are assessed by the investigator as solely due to disease progression should be recorded on Study Completion or Early Discontinuation eCRF as efficacy data. They should not be reported as an SAE. If deaths are attributed by

the investigator not solely due to disease progression, whether they are assessed as related or not related to the study drug, they should be reported as SAE immediately.

If there is any uncertainty regarding whether an AE is due to disease progression, it should be reported as an AE.

10.5.3.5 Death

When recording a death as an SAE, the AE that caused or contributed to fatal outcome should be recorded as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, record "unexplained death".

10.6 Recording of Adverse Events and Serious Adverse Events

When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE or SAE in the eCRF. It is not acceptable for the investigator to send photocopies of the subject's medical records to the Sponsor in lieu of completion of the appropriate AE or SAE eCRF pages. However, there may be instances when copies of medical records for certain cases are requested by the Sponsor. In this instance, all subject identifiers will be blinded on the copies of the medical records prior to submission to the Sponsor.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE or SAE and not the individual signs/symptoms. Adverse events are independent components of the study.

10.7 Evaluating Adverse Events and Serious Adverse Events

10.7.1 Assessment of Severity

The investigator will make an assessment of intensity for each AE and SAE reported during the study. When applicable, AEs and SAEs should be assessed and graded based upon the NCI CTCAE Version 4.03.[18] Subjects who initiate treatment with an ANC <1000/µl will not be considered evaluable for neutrophil toxicity as outlined in the 2008 IWCLL guidelines. [15]

Toxicities that are not specified in the NCI-CTCAE will be defined as follows:

- Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Grade 2: Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)
- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL

- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

NOTE: The terms "severe" and "serious" are not synonymous. Severity is a measure of intensity (for example, grade of a specific AE, mild [Grade 1], moderate [Grade 2], severe [Grade 3], or life-threatening [Grade 4]), whereas seriousness is classified by the criteria based on the regulatory definitions. Seriousness serves as the guide for defining regulatory reporting obligations from the Sponsor to applicable regulatory authorities as described in Section 10.2.

10.7.2 Assessment of Causality

The investigator is obligated to assess the relationship between the study drug and the occurrence of each AE or SAE. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study drug will be considered and investigated. The investigator will also consult the IB and/or Product Information, for marketed products, in the determination of his/her assessment.

There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always makes an assessment of causality for every event prior to transmission of the SAE report to the Sponsor. The investigator may change his/her opinion of causality in light of follow up information, amending the SAE report accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

The investigator will provide the assessment of causality (zanubrutinib in combination with obinutuzumab) as per instructions on the SAE form.

The causality of each AE should be assessed and classified by the Investigator as "related" or "not related". An AE is considered related if there is "a reasonable possibility" that the AE may have been caused by the study drug (ie, there are facts, evidence, or arguments to suggest possible causation). A number of factors should be considered in making this assessment, including:

- Temporal relationship of the AE to the administration of study treatment/study procedure
- Whether an alternative etiology has been identified
- Mechanism of action of the study drug
- Biological plausibility

An AE should be considered 'related' to study drug if any of the following are met:

- There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
- There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.
- There is some evidence to suggest a causal relationship (eg, the AE occurred within a reasonable time after administration of the study drug). However, the influence of other factors may have contributed to the AE (eg, the subject's clinical condition or other concomitant AEs).

An AE should be considered 'unrelated' to study drug if any of the following are met:

- An unreasonable temporal relationship between administration of the study drug and the onset of the AE (eg, the AE occurred either before or too long after administration of the product for it to be considered product-related)
- A causal relationship between the study drug and the AE is biologically implausible (eg, death as a passenger in an automobile accident)
- A clearly more likely alternative explanation for the AE is present (eg, typical adverse reaction to a concomitant drug and/or typical disease-related AE)

10.8 Follow Up of Adverse Events and Serious Adverse Events

After the initial AE or SAE report, the investigator is required to proactively follow each subject and provide further information to the Sponsor on the subject's condition.

All AEs and SAEs documented at a previous visit/contact and are designated as ongoing, will be reviewed at subsequent visits/contacts.

All AEs and SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow up. Once resolved, the appropriate AE or SAE eCRF page(s) will be updated. The investigator will ensure that follow up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

The Sponsor may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obligated to assist. If a subject dies during participation in the study or during a recognized follow up period, the Sponsor will be provided with a copy of any post mortem findings, including histopathology.

New or updated information will be recorded on the originally completed SAE form. The updated SAE form should be resent to the Sponsor within the time frames outlined in Section 10.9.

10.9 Prompt Reporting of Serious Adverse Events

10.9.1 Timeframes for Submitting Serious Adverse Events

As soon as the investigator determines that an AE meets the protocol definition of an SAE, the event must be reported promptly (within 24 hours) to the Sponsor or designee as described in Table 8.

Table 8 Timeframes and Documentation for Reporting Serious Adverse Events to the Sponsor or Designee

	Timeframe for Making Initial Report	Documentation Method	Timeframe for Making Follow-up Report	Documentation Method	Reporting Method
All SAEs	Within 24 hours of first knowledge the AE	SAE Report	As expeditiously as possible	SAE Report	Email or fax SAE form

Abbreviations: SAE: serious adverse event

10.9.2 Completion and Transmission of the Serious Adverse Event Report

Once an investigator becomes aware that an SAE has occurred in a subject, he/she will report the information to the Sponsor within 24 hours as outlined in Section 10.9.1. The SAE report will always be completed as thoroughly as possible with all available details of the event, and forwarded to the Sponsor within the designated timeframes. If the investigator does not have all information regarding an SAE, he/she will not wait to receive additional information before notifying the Sponsor of the event and completing the form. The form will be updated when additional information is received.

The investigator will always provide an assessment of causality at the time of the initial report as described in Section 10.7.2.

The Sponsor will provide a list of project contacts for SAE receipt, fax numbers, telephone numbers, and mailing addresses.

10.10 Regulatory Reporting Requirements for Serious Adverse Events

The investigator will promptly report all SAEs to the Sponsor in accordance with the procedures detailed in Section 10.9.1. The Sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the appropriate project contact for SAE receipt is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met.

The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to regulatory

authorities and the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

This protocol is being filed under an Investigational New Drug (IND) application with the FDA. A given SAE may qualify as an IND safety report if the SAE is both attributable to the study drug and unexpected. In this case, all investigators filed to the IND (and associated INDs for the same compound) will receive an expedited investigator safety report, identical in content to the IND safety report submitted to the FDA.

Expedited investigator safety reports are prepared according to the Sponsor's policy and are forwarded to investigators as necessary. Such a report is prepared for an SAE that is both attributable to study drug and unexpected. The purpose of the report is to fulfill specific regulatory and GCP requirements regarding the product under investigation.

When a study center receives an initial or follow up report or other safety information (eg, revised IB) from the Sponsor, the responsible person according to local requirements is required to promptly notify his/her IRB or IEC.

10.11 Post Study Adverse Events and Serious Adverse Events

A post study AE or SAE is defined as any event that occurs outside of the AE/SAE reporting period, defined in Section 10.5.

Investigators are not obligated to actively seek AEs or SAEs in former subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study drug (zanubrutinib in combination with obinutuzumab), the investigator will promptly notify the Sponsor.

10.12 Serious Adverse Events Related to Study Participation

An SAE considered related to study participation (eg, procedures, invasive tests), even if it occurs during the post treatment period, will be reported promptly to the Sponsor (see Section 10.9).

10.13 Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards and Ethics Committees

The sponsor will promptly assess all SAEs against cumulative study drug experience to identify and expeditiously communicate new safety findings to regulatory authorities, investigators, IRBs and IECs based on applicable legislation.

To determine the reporting requirements for individual SAEs, the sponsor will assess the expectedness of the SAEs using the following reference documents:

- Zanubrutinib Investigator's Brochure
- Obinutuzumab Investigator's Brochure

11 DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

11.1 Sample Size Considerations

The number of dose regimens in the safety evaluation part and the emerging zanubrutinib and obinutuzumab toxicities will determine the sample size. It is anticipated that approximately 12 subjects will be required to establish the selected treatment regimen of zanubrutinib when administered in combination with obinutuzumab in the safety evaluation part.

Approximately 120 subjects will be enrolled during the indication expansion period. Enrollment in certain arms may be closed prematurely due to safety intolerability to zanubrutinib at the discretion of Sponsor or SMC.

11.2 General Considerations for Data Analysis

The following descriptive statistics will be used to summarize the trial data on the basis of their nature unless otherwise specified:

- Continuous variables: number of non-missing observations, mean, standard deviation, coefficient of variation (CV%) as appropriate, median, minimum, and maximum.
- Categorical variables: frequencies and percentages.
- Time to event variables: number of non-missing observations (N), median, minimum and maximum. Kaplan Meier median times, 25th and 75th percentiles and associated 95% confidence intervals (CIs) will also be provided for specific time to event variables.

Further description of the statistical methods and analyses will be provided in the SAP.

11.2.1 Analysis Populations

All Subjects Enrolled Set:

The all subjects enrolled set will include all subjects who provide informed consent for this study. The all subjects enrolled set will be used to summarize and describe the analysis set.

Safety Analysis Set:

The safety analysis set will include all subjects in the all subjects enrolled set who receive at least 1 administration of zanubrutinib and/or obinutuzumab. The safety analysis set will be used for all summaries, including efficacy analyses (except DLTs and PK/PD analyses).

DLT Analysis Set:

The DLT analysis set includes all subjects who experienced a DLT during Cycle 1 or subjects who received at least 80% of the planned doses of zanubrutinib and missed no more than one administration of obinutuzumab during the DLT observation period (Cycle 1). DLT summary will be performed for Part 1 only.

PK Analysis Set:

The PK analysis set will include subjects who have received at least the first administration of zanubrutinib and provided PK samples as per protocol (without significant protocol deviation affecting the PK blood sample) following the first treatment on Day 1 Cycle 1.

PD Analysis Set:

The PD analysis set will include subjects who have received at least the first administration of zanubrutinib and provided PD samples as per protocol (without any significant protocol deviation affecting the PD blood sample) following the first treatment on Day 1 Cycle 1.

11.2.2 Interim Analysis

No interim analysis is planned for this study. Since this is a dose regimen safety evaluation study, safety, PK and PD data will be evaluated on an ongoing basis.

11.2.3 Withdrawal

Subjects who drop out or are withdrawn for any reason which does not fall under DLT will be considered for replacement after due consideration from Sponsor and safety committee and will be replaced whenever possible.

11.3 Pharmacokinetic Analysis

Nominal sampling times will be used for interim PK parameter calculations, while actual sampling times will be used in the final PK parameter calculations.

Plasma samples will be collected at the time points detailed in Table 3.

Where possible, the following plasma PK parameters will be determined for zanubrutinib (Cycle 1 Day 1 and Cycle 2 Day 1) and obinutuzumab:

AUC	Area under the plasma concentration-time curve from zero extrapolated to infinity calculated using the linear up/log down trapezoidal method
AUC_{last} and $AUC_{last,ss}$	Area under the plasma concentration time-curve from zero to the last quantifiable concentration

C_{max} and $C_{max,ss}$	Maximum observed plasma concentration
t_{max} and $t_{max,ss}$	Time to maximum observed plasma concentration
λ_z	Terminal rate constant
$t_{1/2}$	Terminal half life
CL/F	Apparent systemic plasma clearance
V_{zd}/F	Apparent volume of distribution during the terminal phase

Where possible, the following diagnostic parameters of the plasma PK analysis will be calculated and listed, but not summarized:

Interval	The time interval (hours) of the log linear regression used to determine λ_z
N	Number of data points included in the log linear regression analysis to determine λ_z (a minimum of 3 points will be used)
Rsq	Rsquare; coefficient of determination for calculation of λ_z. If Rsq is less than 0.800, then λ_z and related parameters will not be reported
%AUCex	Percentage of AUC obtained by extrapolation; if greater than 30% then AUC and related parameters will not be reported

Additional PK parameters may be calculated if deemed appropriate.

Plasma zanubrutinib concentration time data will be summarized and displayed in both tabular and graphical form. Predose samples that are below quantifiable limits (BQL) or missing will be assigned a numerical value of zero for the calculation of PK parameters. The BQL concentrations will be treated as zero for summary statistics. Concentration time data will be analyzed with standard non compartmental PK methods. The PK parameters for a single dose profile (AUC_{last}, AUC, C_{max}, t_{max}, $t_{1/2}$, CL/F, and V_d/F) and after steady state ($AUC_{last,ss}$, $C_{max,ss}$, $t_{max,ss}$), will be calculated, if there are sufficient data. Individual subject parameter values, as well as a descriptive summary (N, mean, standard deviation, median, minimum, maximum, and the standard deviation, CV%, and geometric mean of log transformed parameters) by treatment group will be reported. Individual subject parameter values will be plotted against dose.

Plasma obinutuzumab concentrations will be measured as detailed at the times in Table 3. Plasma obinutuzumab concentration time data will be summarized and displayed in tabular form. Limited PK parameters [AUC_{last}, C_{max}, and t_{max}) will be reported for

obinutuzumab during Cycle 1 treatment. This is due to the long elimination half-life (about 29.7 hours) and sparse PK blood sampling schedule in this study. A pop-PK approach may be used for this analysis.

11.4 Pharmacodynamic Analyses

Pharmacodynamics is not a primary objective of this study. BTK occupancy in PBMCs will be summarized and listed if possible.

11.5 Efficacy Analysis

Response assessment will be performed per the standard International Working Group (IWG) Criteria for each disease as described in Appendix 16.3.

ORR, MRD clearance rate, hematological improvement:

The number and percentage of subject along with 95% exact binomial CIs will be presented for overall response (ORR defined as CR or PR [CR+PR]]), CR, PR, SD, progressive disease, MRD clearance rate and, for subjects with CLL, hematological improvement (HI).

HI for subjects with CLL will be described by the frequency and number of subjects with:

1. Erythroid response (HI-E)

   Major response: For subjects with pretreatment hemoglobin less than 9 g/dL, greater than 2 g/dL increase in hemoglobin; for RBC transfusion-dependent subjects, transfusion independence. The defined improvement in haemoglobin levels must be maintained for at least 2 months while on study treatment.

   Minor response: For subjects with pretreatment hemoglobin less than 9 g/dL, 1 to 2 g/dL increase in hemoglobin; for RBC transfusion-dependent subjects, 50% decrease in transfusion requirements. The defined improvement in haemoglobin levels must be maintained for at least 2 months while on study treatment.

2. Platelet response (HI-P)

   Major response: For subjects with pretreatment platelet count less than 100,000/mm^3, an absolute increase of 30,000/mm^3 or more; for platelet transfusion-dependent patients, stabilization of platelet counts and transfusion independence. The defined improvement in platelet levels must be maintained for at least 2 months while on study treatment.

   Minor response: For subjects with pretreatment platelet count less than 100,000/mm^3, a 50% or more increase in platelet count with a net increase greater than 10,000/mm^3 but less than 30,000/mm^3. The defined improvement in platelet levels must be maintained for at least 2 months while on study treatment.

3. Neutrophil response (HI-N)

   Major response: For absolute neutrophil count (ANC) less than 1500/mm^3 before therapy, at least a 100% increase or an absolute increase of more than 500/mm^3, whichever is greater. The defined improvement in neutrophil levels must be maintained for at least 2 months while on study treatment.

   Minor response: For ANC less than 1500/mm^3 before therapy, ANC increase of at least 100%, but absolute increase less than 500/mm^3. The defined improvement in neutrophil levels must be maintained for at least 2 months while on study treatment.

RBC and platelet transfusion dependence and independence are defined in Section 16.4.

PFS and OS:

Progression-free survival and OS will be analyzed by Kaplan Meier methodology to estimate median PFS and OS, and 95% CI. Kaplan Meier curves will be constructed to provide a visual description of the PFS and OS change with time.

PFS is defined as the time from the date of first study treatment to disease progression or death whichever occurs first in subjects. As noted previously, it is the investigator's responsibility to define the date of progression. Subjects without event (no disease progression or death) will be censored at the date of 'last tumor assessment'. Subjects for whom no post baseline tumor assessments are available are censored at the time of first treatment.

OS is defined as the time from the date of first study treatment to death (any cause). Subjects without death will be censored at the final known date of survival.

Duration of Response:

Duration of response for responders (CR or PR) is defined as the time interval between the date of the earliest qualifying response and the date of progressive disease or death for any cause, whichever occurs earlier. For subjects who are alive without progression following the qualifying response, duration of response will be censored on the date of last evaluable tumor assessment or last follow up for progression of disease.

Duration of response will be analysed by Kaplan-Meier methodology to estimate median durations and 95% CI.

This analysis is planned for the statistical analysis plan.

11.6 Safety Data Analysis

11.6.1 Dose Limiting Toxicity

The number and proportion of subjects experiencing DLTs will be reported by dose level/regimen, based on DLT observations during the first cycle. The DLT analysis set will be used for this analysis.

11.6.2 Adverse Event

Adverse events will be coded and grouped using MedDRA Version 17.0 or higher. Adverse events and toxicities will be graded according to NCI CTCAE, Version 4.03.[18] Subjects who initiate treatment with an ANC <1000/µl will not be considered evaluable for neutrophil toxicity as outlined in the 2008 IWCLL guidelines.[15] Adverse events representing clear evidence of disease progression will not be considered relevant to the assessment of toxicity.
Analyses will include but may not be restricted to:

- All AEs
- SAEs
- AEs related to study treatment (zanubrutinib in combination with obinutuzumab)
- AEs leading to withdrawal of study treatment
- AEs leading to death
- AEs with toxicity Grade ≥3
- AEs of special interest: summarize by cycle (Cycles 1, 2, 3, 4, 5, 6 and Cycles >6)

The number and percent of subjects will be summarized for above items, and also summarized according to MedDRA system organ classes (SOCs) and preferred terms (PTs). The toxicities and causality of AEs will be summarized.

11.6.3 Laboratory Assessments

Hematology, clinical chemistry, coagulation, and urinalysis values will be listed for each subject and flagged as high or low relative to the normal range, where applicable. Predose values will be used to assess laboratory shifts occurring at postdose. A comparison of pre-study and post-study values will be performed to identify any parameters that have not returned to pre study levels.

Table 9 Safety Laboratory Assessments

Clinical Chemistry	Hematology	Coagulation	Urinalysis	Immunoglobulin Assessment and Serum Electrophoresis
Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Albumin Calcium Creatinine Glucose Lactate dehydrogenase Magnesium Total protein Potassium Sodium Total and direct bilirubin Urea Uric Acid	Hemoglobin MCV Platelet counts WBC count with differential Neutrophil count Bands (optional) Lymphocyte count Eosinophil count Blasts	Prothrombin time Partial thromboplastin time International normalized ratio	pH Specific gravity Glucose Protein Ketones Blood 24 hour protein[1] Random urine protein to creatinine ratio[1]	IgA IgG IgM Serum EPG [2]

Abbreviations: EPG: serum electrophoresis; Ig: Immunoglobulin; MCV: mean corpuscular volume.

1. On routine urinalysis, if urine protein is ≥2+ by dipstick, then obtain a 24 hour urine sample for total protein and a random urine sample for total protein and creatinine to determine a protein to creatinine ratio.
2. Serum EPG on 1st test for WM subjects only, and if a paraprotein is present, repeated on all subsequent immunoglobulin assessments.

11.6.4 Electrocardiogram

All ECG parameters, including the QT interval corrected for heart rate (QTc), will be listed for each subject and summarized by dose level and assessment time. Change from baseline will also be summarized. The clinical markedly abnormalities will be summarized. Relationship between dose level and QTc changes will be explored by graphs. QTc will be calculated using Bazett's formula.

11.6.5 Vital Signs

Blood pressure (SBP and DBP), pulse, respiratory, body temperature, and weight will be summarized and listed. The change from baseline will also be displayed.

11.6.6 Extent of Exposure

Extent of exposure to zanubrutinib in combination with obinutuzumab will be calculated for each subject. Overall exposure will also be summarized by treatment arms, as well as dose adjustment information.

11.6.7 Physical Examination

Physical examination results will be listed and summarized.

11.6.8 Other Safety Endpoints

B symptoms, including unexplained weight loss >10% over the previous 6 months, fever (>38°C), and/or drenching night sweats will be listed and summarized.

Eastern Cooperative Oncology Group status, pregnancy test and viral serology will be listed.

11.7 Other Explorative Endpoints

Correlative blood samples will be collected as per Table 1 and Table 2. Clinical response to the zanubrutinib and obinutuzumab combination will be correlated with established prognostic and biological markers for the specific histology (eg, International Prognostic Index for DLBCL, adverse cytogenetics for CLL, and genomic alterations in non-GCB DLBCL).

12 REGULATORY AND ETHICAL ISSUES

12.1 Regulatory Authority Approval

The Sponsor will obtain approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country specific regulatory requirements before the study is initiated at a study center in that country.

12.2 Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the "Declaration of Helsinki" International Conference of Harmonisation (ICH) guidelines, and that the basic principles of "Good Clinical Practice," as outlined in 21 Code of Federal Regulations (CFR) 312, Subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, Part 50, and 21 CFR, Part 56, are adhered to.

Investigators and all subinvestigators must provide documentation of their financial interest or arrangements with BeiGene, or proprietary interests in the drug being studied. This documentation must be provided before participation of the investigator and any subinvestigator. The investigator and subinvestigator agree to notify BeiGene or its authorized representative of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date that the last patient has completed the protocol defined activities.

12.3 Ethical Conduct of the Study and Ethics Approval

This study will be conducted by the principal investigator and the study center in accordance with GCP and all applicable regulatory requirements, including, where applicable, current version of the Declaration of Helsinki.

The investigator (or Sponsor, where applicable) is responsible for ensuring that this protocol, the study center's informed consent form, and any other information that will be presented to potential subjects (eg, advertisements or information that supports or supplements the informed consent) are reviewed and approved by the appropriate IEC/IRB. The investigator agrees to allow the IEC/IRB direct access to all relevant documents. The IEC/IRB must be constituted in accordance with all applicable regulatory requirements. The Sponsor will provide the investigator with relevant document(s)/data that are needed for IEC/IRB review and approval of the study. Before the study drug(s) can be shipped to the study center, the Sponsor must receive copies of the IEC/IRB approval, the approved informed consent form, and any other information that the IEC/IRB has approved for presentation to potential subjects.

If the protocol, the informed consent form, or any other information that the IEC/IRB has approved for presentation to potential subjects is amended during the study, the investigator (or Sponsor, where applicable) is responsible for ensuring the IEC/IRB

reviews and approves, where applicable, these amended documents. The investigator must follow all applicable regulatory requirements pertaining to the use of an amended informed consent form including obtaining IEC/IRB approval of the amended form before new subjects consent to take part in the study using this version of the form. Copies of the IEC/IRB approval of the amended informed consent form/other information and the approved amended informed consent form/other information must be forwarded to the Sponsor promptly.

12.4 Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must utilize an IRB/IEC-approved ICF for documenting written informed consent. Each ICF will be appropriately signed and dated by the patient or the patient's legally authorized representative and the person obtaining consent.

Informed consent will be obtained before the subject can participate in the study. The contents and process of obtaining informed consent will be in accordance with all applicable regulatory requirements.

12.5 Investigator Reporting Requirements

As indicated in Section 10.10, the investigator (or Sponsor, where applicable) is responsible for reporting SAEs to the IEC/IRB, in accordance with all applicable regulations. Furthermore, the investigator may be required to provide periodic safety updates on the conduct of the study at his/her study center and notification of study closure to the IEC/IRB. Such periodic safety updates and notifications are the responsibility of the investigator and not of the Sponsor.

12.6 Confidentiality

Information on maintaining patient confidentiality in accordance to individual local and national patient privacy regulations must be provided to each patient as part of the informed consent process, either as part of the ICF or as a separate signed document (for example, in the US, a study-center specific HIPAA consent may be used). The investigator must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only patient initials, date of birth, and an identification code (ie, not names) should be recorded on any form or biological sample submitted to the sponsor, IRB, or laboratory. The investigator must keep a screening log showing codes, names, and addresses for all patients screened and for all patients enrolled in the study.

The investigator agrees that all information received from BeiGene, including but not limited to the IB, this protocol, eCRFs, the IND, and any other study information, remain

the sole and exclusive property of BeiGene during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from BeiGene. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

If a written contract for the conduct of the study includes confidentiality provisions inconsistent with this section is executed, that contract's provisions shall apply to the extent they are inconsistent with this section.

12.7 Indemnity and Compensation

In accordance with Statutory Instrument 1031 and amendments section 15 (5i, j) and the EU Clinical Trials Directive 2000/20/EC Article 3 (2f), provision is to be made for:

- The indemnity or compensation in the event of injury or death attributable to the clinical trial; and
- Insurance or indemnity to cover the liability of the investigator or Sponsor.

Therefore the Sponsor will indemnify the Investigators from all and any claims arising out of this study except for their negligence or malpractice and providing that the study is conducted according to the standards established by the protocol.

In the event that it can be demonstrated that a subject suffers any significant deterioration in health or wellbeing or any harmful susceptibility or toxicity as a direct result of their participation in this study then the Sponsor will agree to abide by the current ABPI/FDA/Swedish Guidelines with regard to compensation payable to the subject. The amount of compensation will be calculated by reference to the level of damages commonly awarded in law for similar injuries at the time when such injury occurred.

The investigators declare to having insurance cover for the malpractice and/or negligence of their employees and agents.

12.8 Electronic Case Report Forms

For each patient enrolled, an eCRF must be completed and signed by the principal investigator or subinvestigator within a reasonable time period after data collection. This also applies to records for those patients who discontinue the study early. If a patient withdraws from the study, the reason must be noted on the eCRF. If a patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

The eCRFs exist within an EDC system with controlled access managed by BeiGene or its authorized representative for this study. Study staff will be appropriately trained in the

use of eCRFs and applications of electronic signatures before the study start and before being given access to the EDC system. Original data and any changes of data will be recorded using the EDC system, with all changes tracked by the system and recorded in an electronic audit trail. The investigator attests that the information contained in the eCRFs is true by providing an electronic signature within the EDC system. After final database lock, the investigator will receive a copy of the patient data on CD ROMs for archiving the data at the study center.

12.9 Drug Accountability

The investigator or designee (ie, pharmacist) is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgment of receipt of each shipment of study product (quantity and condition), patient dispensing records and returned or destroyed study product. Dispensing records will document quantities received from BeiGene, quantities dispensed to patients, and quantities destroyed or returned to BeiGene, including lot number, date dispensed, patient identifier number, patient initials, and the initials of the person dispensing the medication.

At study initiation, the monitor will evaluate the study center's standard operating procedure for study drug disposal/destruction in order to ensure that it complies with BeiGene requirements. At the end of the study, following final drug inventory reconciliation by the monitor, the study center will dispose of and/or destroy all unused study drug supplies, including empty containers, according to these procedures. If the study center cannot meet BeiGene's requirements for disposal, arrangements will be made between the study center and BeiGene or its representative for destruction or return of unused study drug supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

12.10 Inspections

The investigator should understand that the facilities used for this trial and all source documents for this study should be made available to appropriately qualified personnel from BeiGene or its representatives, to IRBs/IECs, or to regulatory authority or health authority inspectors.

12.11 Protocol Adherence

The investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol. Investigators assert they will apply due diligence to avoid protocol deviations and shall report all protocol deviations to sponsor.

12.12 Protocol Modifications

Protocol modifications, except those intended to reduce immediate risk to study patients, may be initiated only by BeiGene. All protocol modifications must be submitted to regulatory authorities and the IRB/IEC together with, if applicable, a revised model ICF in accordance with local requirements. As applicable by local requirements, written documentation of regulatory authorities, IRB/IEC and required study center approval must be obtained by the sponsor before changes can be implemented.

Information on any change in risk and /or change in scope must be provided to patients already actively participating in the study, and they must read, understand and sign each revised ICF confirming his/her willingness to remain in the study.

12.13 Access to Information for Monitoring

In accordance with ICH GCP guidelines, the study monitor must have direct access to the investigator's source documentation in order to verify the data recorded in the eCRFs for consistency.

The monitor is responsible for routine review of the CRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The monitor should have access to any patient records needed to verify the entries on the eCRFs. The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

12.14 Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of BeiGene may conduct inspections or audits any time during or after completion of this clinical study. If the investigator is notified of an inspection by a regulatory authority the investigator agrees to notify the sponsor or its designee immediately. The investigator agrees to provide to representatives of a regulatory agency or BeiGene access to records, facilities, and personnel for the effective conduct of any inspection or audit.

13 STUDY MANAGEMENT

13.1 Study and Study Center Closure

Upon completion of the study, the monitor will conduct the following activities in conjunction with the investigator or study center personnel, as appropriate:

- Return of all study data to the Sponsor
- Data queries
- Accountability, reconciliation, and arrangements for unused study drug(s)
- Review of study records for completeness
- Return of treatment codes to the Sponsor
- Shipment of PK and PD samples to assay laboratories

In addition, the Sponsor reserves the right to temporarily suspend or prematurely discontinue this study either at a single study center or at all study centers at any time for reasons including, but not limited to, safety or ethical issues or severe non compliance with this protocol, GCP, the clinical study agreement, or applicable laws and regulations. If the Sponsor determines such action is needed, the Sponsor will discuss this with the investigator (including the reasons for taking such action) at that time. When feasible, the Sponsor will provide advance notification to the investigator of the impending action prior to it taking effect.

The Sponsor will promptly inform all other investigators and/or institutions conducting the study if the study is suspended or terminated for safety reasons, and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the IEC/IRB promptly and provide the reason for the suspension or termination.

If the study is prematurely discontinued, all study data must still be provided to the Sponsor. In addition, arrangements will be made for all unused study drug(s) in accordance with the applicable Sponsor procedures for the study.

Financial compensation to investigators and/or institutions will be in accordance with the agreement established between the investigator and the Sponsor.

13.2 Records Retention and Study Files

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following 2 categories: (1) investigator’s study file, and (2) patient clinical source documents.

The investigator's study file will contain the protocol/amendments, eCRF and query forms, IRB/IEC, and governmental approval with correspondence, ICF, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Patient clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the eCRFs) would include (although not be limited to) the following: patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, electroencephalogram, X-ray, pathology and special assessment reports, consultant letters, screening and enrollment log, etc.

Following closure of the study, the investigator must maintain all study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (eg, audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and personnel. Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (eg, microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must assure that all reproductions are legible, are a true and accurate copy of the original, and meet accessibility and retrieval standards, including re generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back up of these reproductions and that an acceptable quality control process exists for making these reproductions.

The Sponsor will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that study center for the study, as dictated by any institutional requirements or local laws or regulations, or the Sponsor's standards/procedures; otherwise, the retention period will default to 15 years.

The investigator must notify the Sponsor of any changes in the archival arrangements, including, but not limited to, the following: archival at an off site facility, transfer of ownership or responsibility for of the records in the event the investigator leaves the study center.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, arrangements must be made between the investigator and BeiGene to store these in secure containers outside of the study center so that they can be returned to the investigator in case of a regulatory audit. When source documents are required for the continued care of the patient, appropriate copies should be made for storage outside of the study center.

Biological samples at the conclusion of this study may be retained as outlined in the agreement with the CRO managing the biological samples, for the shorter of: a period of up to 10 years or as allowed by your IRB/IEC.

13.3 Provision of Study Results and Information to Investigators

When the clinical study report is completed, the Sponsor will provide the major findings of the study to the investigator.

In addition, details of the study treatment assignment will be provided to the investigator to enable him/her to review the data to determine the outcome of the study for his/her subjects.

The Sponsor will not routinely inform the investigator or subject of the test results, because the information generated from this study will be preliminary in nature, and the significance and scientific validity of the results will be undetermined at such an early stage of research.

13.4 Information Disclosure and Inventions

All information provided by the Sponsor and all data and information generated by the study center as part of the study (other than a subject's medical records) is the sole property of the Sponsor.

All rights, title, and interests in any inventions, know how or other intellectual or industrial property rights which are conceived or reduced to practice by the study center personnel during the course of or as a result of the study are the sole property of the Sponsor, and are hereby assigned to the Sponsor.

If a written contract for the conduct of the study which includes ownership provisions inconsistent with this statement is executed between the Sponsor and the study center, that contract's ownership provisions shall apply rather than this statement.

All information provided by the Sponsor and all data and information generated by the study center as part of the study (other than a subject's medical records) will be kept by the investigator and other study center personnel. This information and data will not be used by the investigator or other study center personnel for any purpose other than conducting the study.

These restrictions do not apply to:

- Information which becomes publicly available through no fault of the investigator or study center personnel.
- Information which is necessary to disclose in confidence to an IEC/IRB solely for the evaluation of the study.

- Information which is necessary to disclose in order to provide appropriate medical care to a subject.
- Study results which may be published as described in Section 13.4.1.

If a written contract for the conduct of the study which includes provisions inconsistent with this statement is executed, that contract's provisions shall apply rather than this statement.

13.4.1 Publication Policy

The results of this study will be published or presented at scientific meetings in a timely, objective, and clinically meaningful manner that is consistent with good science, industry and regulatory guidance, and the need to protect the intellectual property of BeiGene (sponsor), regardless of the outcome of the study. The data generated in this clinical study are the exclusive property of the sponsor and are confidential. As this is a multicenter study, the first publication or disclosure of study results shall be a complete, joint multicenter publication or disclosure coordinated by the sponsor. Thereafter, any secondary publications will reference the original publication(s). Authorship will be determined by mutual agreement and all authors must meet the criteria for authorship established by the International Committee of Medical Journal Editors Uniform Requirements for Manuscripts or stricter local criteria (International Committee of Medical Journal Editors 2016[23]).

Each investigator agrees to submit all manuscripts, abstracts, posters, publications, and presentations (both oral and written) to the sponsor prior to submission or presentation in accordance with the clinical study agreement. This allows the sponsors to protect proprietary information, provide comments based on information from other studies that may not yet be available to the investigator, and ensure scientific and clinical accuracy. Each investigator agrees that, in accordance with the terms of clinical study agreement, a further delay of the publication/presentation may be requested by the sponsor to allow for patent filings and/or protection in advance of the publication/presentation.

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15 PROTOCOL SIGNATURES

INVESTIGATOR SIGNATURE

PROTOCOL TITLE: A Phase 1b Study to Assess Safety, Tolerability and Antitumor Activity of the Combination of BGB-3111 with Obinutuzumab in Subjects with B-Cell Lymphoid Malignancies

PROTOCOL NO: BGB-3111_GA101_Study_001

I agree with the content of this protocol and the confidential nature of the documentation made as part of this study. I also acknowledge that the Sponsor of the study has the right to discontinue the study at any time. I have read the protocol and understand it and will work according to it and according to the principles of Good Clinical Practices, applicable laws and regulations, and the Declaration of Helsinki.

_____ _____

Signature of Investigator Date

_____

Printed Name

SPONSOR SIGNATURE

PROTOCOL TITLE: A Phase 1b Study to Assess Safety, Tolerability and Antitumor Activity of the Combination of BGB-3111 with Obinutuzumab in Subjects with B-Cell Lymphoid Malignancies

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_____ _____

[redacted]

Date

16 APPENDIX

16.1 Appendix 1: Blood Volume Requirements for the Subjects in Part 1

Time point	Assessment	Total blood volume (mL)
Screening **Day -28 to Day -1**	Clinical chemistry Hematology Coagulation IgA, IgG, IgM level and serum EPG Pregnancy test Virology	5 2.5 3 5 3.5 5
	Total	24 mL
Cycle 1 Day 1	Clinical chemistry Hematology PK sampling for zanubrutinib (5 samples x 4 mL) PD sampling (2 samples x 8 mL)	5 2.5 20 16
	Total	43.5 mL
Cycle 1 Day 2	PK sampling for zanubrutinib (1 sample x 4 mL) PK sampling for obinutuzumab (2 samples x 5 mL) PD sampling (1 sample x 8 mL)	4 10 8
	Total	22 mL
Cycle 1 Day 3	PK sampling for obinutuzumab (2 samples x 5 mL)	10
	Total	10 mL
Cycle 1 Day 9	Clinical chemistry Hematology PK sampling for obinutuzumab (2 samples x 5 mL)	5 2.5 10
	Total	17.5 mL
Cycle 1 Day 16	Clinical chemistry Hematology PK sampling for obinutuzumab (2 samples x 5 mL)	5 2.5 10
	Total	17.5 mL

Time point	Assessment	Total blood volume (mL)
Cycle 1 Day 23		
	Clinical chemistry	5
	Hematology	2.5
	Total	7.5 mL
Cycle 2 to Cycle 6 Day 1		
	Clinical chemistry	5
	Hematology	2.5
	IgA, IgG, IgM level and serum EPG (where required as per Footnote 15 of Table 1 and 2)	5
	PK sampling for zanubrutinib (only on Day 1 of Cycle 2; 5 samples x 4 mL)	20
	PK sampling for obinutuzumab (only on Day 1 of Cycle 2, Cycle 4 and Cycle 6; 2 samples x 5 mL)	10
	PD sampling (only on Day 1 of Cycle 2; 1 sample x 8 mL)	8
	Total	50.5 mL
Cycle 2 to Cycle 6 Day 15		
	Clinical chemistry	5
	Hematology	2.5
	Total	7.5 mL
Week 25 to Week 48 (Every 12 weeks)		
	Clinical chemistry	5
	Hematology	2.5
	IgA, IgG, IgM level and serum EPG (where required as per Footnote 15 of Table 1 and 2)	5
	Total	12.5 mL
Week 48+ (Every 12 weeks[1])		
	Clinical chemistry	5
	Hematology	2.5
	IgA, IgG, IgM level and serum EPG (where required as per Footnote 15 of Table 1 and 2)	5
	Total	12.5 mL

Time point	Assessment	Total blood volume (mL)
Safety Follow-up		
	Clinical chemistry	5
	Hematology	2.5
	IgA, IgG, IgM level and serum EPG (where required as per Footnote 15 of Table 1 and 2)	5
	Post-progression Biomarker testing (optional)	10
	Total	22.5 mL
Follow-up Visit		
	Clinical chemistry	5
	Hematology	2.5
	IgA, IgG, IgM level and serum EPG (where required as per Footnote 15 of Table 1 and 2)	5
	Total	12.5 mL

1. Immunoglobulins and serum EPG assessments will be conducted every 24 weeks until disease progression.

Notes:

Unscheduled blood samples for pharmacokinetic analysis may also be collected whenever any notable safety is seen, to evaluate if the observation is exposure related.

Cannulation for blood sampling for PK and pharmacodynamics will be performed. Blood will be collected via the intravenous cannula predose and at the time points specified in Table 1 and Table 3. A 1 mL blood sample will be taken and discarded prior to each blood sample.

Blood samples (4 mL) should be obtained, when possible, for analysis of plasma zanubrutinib in the event of a DLT.

Should a drug-drug interaction between zanubrutinib and a concomitant medication be suspected, further blood samples for PK analyses may be taken to characterize the extent of the interaction.

Additional blood PK samples will be taken to determine the plasma concentration of zanubrutinib if there is an intra-subject dose escalation. The investigator must record the time points for PK sampling and the time of dose administration before PK sampling in eCRFs.

16.2 Appendix 2: Blood Volume Requirements for the Subjects in Part 2

Time point	Assessment	Total blood volume (mL)
Screening **Day -28 to Day -1**		
	Clinical chemistry	5
	Hematology	2.5
	Coagulation	3
	IgA, IgG, IgM level and serum EPG	5
	Pregnancy test	3.5
	Virology	5
	Total	24 mL
Cycle 1 Day 1		
	Clinical chemistry	5
	Hematology	2.5
	Total	7.5 mL
Cycle 1 Day 8		
	Clinical chemistry	5
	Hematology	2.5
	Total	7.5 mL
Cycle 1 Day 15		
	Clinical chemistry	5
	Hematology	2.5
	Total	7.5 mL
Cycle 2 to Cycle 6 Day 1		
	Clinical chemistry	5
	Hematology	2.5
	IgA, IgG, IgM level and serum EPG	5
	PK sampling for zanubrutinib (only on Day 1 of Cycle 2; 5 samples x 4 mL)	20
	PK sampling for obinutuzumab (only on Day 1Cycle 4 and Cycle 6; 2 samples x 5 mL)	10
	Total	42.5 mL
Cycle 2 to Cycle 6 Day 15		
	Clinical chemistry	5
	Hematology	2.5
	Total	7.5 mL

Time point	Assessment	Total blood volume (mL)
Week 25 to Week 48 (Every 4 weeks)	Clinical chemistry Hematology IgA, IgG, IgM level and serum EPG	5 2.5 5
	Total	12.5 mL
Week 48+ (Every 12 weeks[1])	Clinical chemistry Hematology IgA, IgG, IgM level and serum EPG	5 2.5 5
	Total	12.5 mL
Safety Follow-up	Clinical chemistry Hematology IgA, IgG, IgM level and serum EPG Post-progression Biomarker testing (optional)	5 2.5 5 10
	Total	22.5 mL
Follow-up Visit	Clinical chemistry Hematology IgA, IgG, IgM level and serum EPG	5 2.5 5
	Total	12.5 mL

1. Immunoglobulins and serum EPG assessments will be conducted every 24 weeks until disease progression.

Notes:

Unscheduled blood samples for pharmacokinetic analysis may also be collected whenever any notable safety is seen, to evaluate if the observation is exposure related.

Cannulation for blood sampling for PK and pharmacodynamics will be performed. Blood will be collected via the intravenous cannula predose and at the time points specified in Table 2 and Table 3. A 1 mL blood sample will be taken and discarded prior to each blood sample.

Blood samples (4 mL) should be obtained, when possible, for analysis of plasma zanubrutinib in the event of a DLT.

Should a drug-drug interaction between zanubrutinib and a concomitant medication be suspected, further blood samples for PK analyses may be taken to characterize the extent of the interaction.

Additional blood PK samples will be taken to determine the plasma concentration of zanubrutinib if there is an intra-subject dose escalation. The investigator must record the time points for PK sampling and the time of dose administration before PK sampling in eCRFs.

16.3 Appendix 3: Response Criteria

Response Definition after Treatment for Patients with CLL

Parameter	CR*	PR*	PR-L:	PD*
Group A				
Lymphadenopathy†	None > 1.5 cm	Decrease ≥ 50%	Decrease ≥ 50%	Increase ≥ 50% or new lesion
Hepatomegaly	None	Decrease ≥ 50%	Decrease ≥ 50%	Increase ≥ 50%
Splenomegaly	None	Decrease ≥ 50%	Decrease ≥ 50%	Increase ≥ 50%
Blood lymphocytes	< 4000/µL	Decrease ≥ 50% from baseline	Decrease < 50% or increase from baseline	**
Marrow‡	Normocellular, < 30% lymphocytes, no B-lymphoid nodules. Hypocellular marrow defines CRi (5.1.6).	50% reduction in marrow infiltrate, or B-lymphoid nodules	50% reduction in marrow infiltrate, or B-lymphoid nodules	
Group B				
Platelet count	> 100,000/µL	> 100,000/µL or increase ≥ 50% over baseline	> 100,000/µL or increase ≥ 50% over baseline	Decrease of ≥ 50% from baseline secondary to CLL
Hemoglobin	> 11.0 g/dL	> 11 g/dL or increase ≥ 50% over baseline	> 11 g/dL or increase ≥ 50% over baseline	Decrease of > 2 g/dL from baseline secondary to CLL
Neutrophils‡	> 1500/µL	> 1,500/µL or > 50% improvement over baseline	> 1,500/µL or > 50% improvement over baseline	

CLL = chronic lymphocytic leukemia; CR = complete remission (response); CRi = CR with incomplete bone marrow recovery; PD = progressive disease; PR = partial remission (response); PR-L = partial remission (response) with lymphocytosis; SD = stable disease.

Group A criteria define the tumor load, Group B criteria define the function of the hematopoietic system (or marrow).

CR*: all of the criteria have to be met, and patients have to lack disease-related constitutional symptoms; PR*: at least two of the criteria of group A (lymphadenopathy, splenomegaly, hepatomegaly, or lymphocytes) plus one of the criteria of Group B (platelets, hemoglobin, or neutrophils) have to be met (with the exception of patients who

have only one abnormal group A criteria at baseline, who have to meet one of the criteria of group A plus one of the criteria of Group B); PR-L: presence of lymphocytosis, plus ≥ 50% reduction in lymphadenopathy and/or in spleen or liver enlargement, plus one of the criteria for platelets, hemoglobin, or neutrophils have to be met; SD: is absence of progressive disease (PD) and failure to achieve at least a PR; PD: at least one of the above PD criteria has to be met.

** Note: In the absence of other objective evidence of PD, lymphocytosis alone should not be considered an indicator of PD (Cheson, 2012).

† Sum of the products of multiple lymph nodes (as evaluated by CT scans, or by physical examination)

‡ These parameters are irrelevant for some response categories

Non-Hodgkin Lymphoma (including SLL; excluding WM)

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measurable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identified node > 1 cm in short axis. Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Categorical Waldenström's Macroglobulinemia Response Definitions (Modified Owen 2013)

Response category	Definition
Complete response (CR)	• Normal serum IgM values • Disappearance of monoclonal protein by immunofixation • No histological evidence of bone marrow involvement • Complete resolution of lymphadenopathy/splenomegaly (if present at baseline) [a]
Very good partial response (VGPR)	• Monoclonal IgM protein is detectable • ≥90% reduction in serum IgM level from baseline (or normal serum IgM level)[a] • Improvement in extramedullary disease, lymphadenopathy/splenomegaly if present at baseline • No new signs or symptoms of active disease
Partial response (PR)	• ≥50% reduction of serum IgM from baseline • Reduction in lymphadenopathy/splenomegaly (if present at baseline) [a]
Minor response (MR)	• At least 25% but <50% reduction of serum IgM from baseline
Stable disease (SD)	• Not meeting criteria for CR, VGPR, PR, MR, or progressive disease
Progressive disease (PD)	At least one of the following: • Confirmed ≥25% increase in serum IgM and total increase of ≥500 mg/dL from nadir (on treatment)[b,c] • New lymph nodes >1.5 cm, or ≥50% increase from nadir in SPD of >1 node, or ≥50% increase in longest diameter of a previously identified node >1 cm in short axis

	• New splenomegaly or ≥50% increase from nadir in enlargement • New extranodal disease • New or recurrent involvement in bone marrow • New symptomatic disease

[a] For response assessments that occur during cycles where a CT scan is not required then results from prior scans (up to 12 weeks during the first 48 weeks and up to 24 weeks thereafter) can be carried forward in those subjects with extramedullary disease at baseline

[b] Sequential changes (separated by at least 4 weeks) in IgM levels should be determined by the IgM value from the quantitative serum immunoglobulin assay, unless for assay limitations this is not possible, in which case the M protein level by densitometry (SPEP) will be used

[c] Isolated increase in serum IgM levels during periods of study drug withholding will not be considered as progressive disease unless confirmed by a repeat serum IgM level at least 6 weeks after restarting study drug administration and accompanied by a total increase of at least 500mg/dL from lowest nadir. Please see Guidelines for specific clinical or laboratory circumstances below.

Guidelines for specific clinical or laboratory circumstances:

1. *Baseline serum total IgM value above the local laboratory limit of quantitation.*
   If the baseline local laboratory serum total IgM value exceeds the upper limit of quantitation, the M-protein value, by local assessment, will be used for response determination throughout the study.

2. *Baseline serum total IgM value, by local assessment, is not interpretable due to technical reasons.*
   If the baseline local laboratory serum total IgM value is not interpretable due to technical reasons, the local laboratory serum M-protein value will be used of response determination throughout the study. In cases where both the local laboratory total serum IgM and M-protein values are not interpretable due to technical reasons, the local serum total IgM (or local M-protein value, in cases where the local serum total IgM value exceeds the upper level of quantitation) will be used for response assessment throughout the study.

3. *Subjects with documented cryoglobulinemia.*
   For these subjects, serum quantitative immunoglobulin and serum immunoelectrophoresis assays should be conducted under warm conditions in the local laboratory. The local serum total IgM (or local M-protein value, in cases where the local serum total IgM value exceeds the upper level of quantitation) will be used for response assessment throughout the study.

4. *Plasmapheresis*
   Subjects may undergo plasmapheresis, when clinically indicated, during the first two cycles of study treatment. A pre-plasmapheresis serum total IgM and M-protein must be obtained during the screening period, and will serve as the baseline value for response assessment throughout the study. Response determination will commence 4 weeks following the last plasmapheresis procedure and will be based upon the baseline pre-plasmapheresis serum total IgM or M-protein value (according to the guidelines above). Subjects requiring plasmapheresis after cycle 2 will be adjudged to have progressive disease.

5. *Assigning Response in the Case of Drug Hold*
   Isolated increase in serum IgM levels during periods of study drug withholding will not be considered as progressive disease unless confirmed by a repeat serum IgM level at least 10 weeks after restarting study drug administration and accompanied by a total increase of ≥ 25% increase in serum IgM and at least 500mg/dL from lowest nadir. Instead a response of "IgM Flare" (IgM-rise of undetermined significance) should be selected. As IgM levels fall, response should be in comparison to the IgM at baseline

6. *Missing CT Scans*
   During treatment cycles where CT scans are required for subjects with extramedullary disease at baseline that has not resolved, if a CT scan is missed it should be performed as soon as possible. In cases where a single CT scan is missed and the findings remain the same or improved from the prior scan, response can be assessed for the intervening cycles using the CT scan obtained prior to the missed CT scan. If 2 consecutive CT scans are missed, then the best response that can be assessed during those cycles is an MR (minor response).

16.4 Appendix 4: Transfusion Dependence and Independence

Appendix a Definitions of Red Blood Cell Transfusion Dependence and Independence

	RBC Transfusions
RBC transfusion dependence	≥2 units/month
RBC transfusion independence	None
Reduced RBC transfusion dependence	50% decrease

Abbreviation: RBC = red blood cell.

Source: Gale RP, Barosi G, Barbui T, et al. What are RBC-transfusion-dependence and –independence? Leuk Res. 2011;35:8-11.

Appendix b Definitions of Platelet Transfusion Dependence and Independence

	Platelet Transfusions
Platelet transfusion dependence	Any episode of platelet transfusion during the past month
Platelet transfusion independence	No platelet transfusion during the past month