Official Title: **PHASE II TRIAL TO EVALUATE THE EFFICACY OF OBINUTUZUMAB (RO5072759) + BENDAMUSTINE TREATMENT IN PATIENTS WITH REFRACTORY OR RELAPSED CHRONIC LYMPHOCYTIC LEUKEMIA**

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PROTOCOL APPROVAL FORM

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MEDICAL MONITOR:	[redacted]
SPONSOR:	Roche Farma, S.A.

I agree to conduct the trial in accordance with the current Protocol.

_____

Name of the Principal Investigator (printed)

_____ _____

Signature of the Principal Investigator Date

Please return the signed original of this form as indicated by the Trial Monitor. Please keep a copy for your trial files.

PROTOCOL SYNOPSIS

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PHASE:	II
INDICATION:	REFRACTORY/RELAPSED CHRONIC LYMPHOCYTIC LEUKEMIA
SPONSOR:	Roche Farma, S.A.

Objectives

Objectives

Primary Objective

- To evaluate the overall response rate (ORR) after treatment with obinutuzumab and bendamustine, in patients with refractory or relapsed chronic lymphocytic leukemia (CLL).

  The results will be placed in perspective respect other studies like the GREEN study (MO28543).

Secondary Objectives

- To evaluate the best response rate during study treatment and until 6-8 months after end of study treatment, according IWCLL2008 criteria
- To evaluate progression free survival (PFS).
- To evaluate overall survival (OS) and event free survival (EFS).
- To evaluate disease free survival (DFS) among patients with complete response (CRi or CR).
- To evaluate duration of response (DR) among patients with complete (CRi or CR) or partial response.
- To evaluate time to re-treatment/new anti-leukemia therapy.
- To evaluate remission using multi-parametric flow cytometry.
- To evaluate the safety profile of the study treatment.

Exploratory Objectives

- To evaluate the association between overall response rate (ORR) and the following prognostic markers: p53 (17p13.1), ATM (11q22.3), NOTCH1, SF3B1, BIRC3, mutations in the immunoglobulin heavy chain variable region (IGHV) and expression of ZAP70, CD38, CD49D.
- To evaluate the association between the response rate and the DNA sequencing in a sample of saliva, through the study of the following 26 genes: ATM, BIRC3, BRAF, CHD2, CSMD3, DDX3X, FBXW7, KLHL6, KRAS, LRP1B, MAPK1, MUC2, MYD88, NFKBIE, NOTCH1, PLEKHG5, POT1, SAMHD1, SF3B1, SI, SMARCA2, TGM7, TP53, XPO1, ZMYM3, EGR.

Study Design

Description of Study

Multicentre, non-comparative, phase II clinical trial

Number of Patients

72 patients will be included in a two-stage Simon´s design.

Target Population

Patients must meet the following criteria for study entry:

1. Age 18 years or older
2. Have documented CD20+ B-CLL according to NCI criteria (see Appendix 2)
3. Active disease meeting at least 1 of the following IWCLL 2008 criteria for requiring treatment:
    a) Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia (Hgb < 10 g/dL) and/or thrombocytopenia (platelets < 100,000/µL)
    b) Massive (i.e. at least 6 cm bellow the left costal margin), progressive or symptomatic splenomegaly
    c) Massive nodes (i.e. at least 10 cm in the longest diameter), progressive or symptomatic lymphadenopathy
    d) Progressive lymphocytosis with an increase of more than 50% over a 2-month period or a lymphocyte doubling time (LDT) of less than 6 months. LDT may be obtained by linear regression extrapolation of absolute lymphocyte counts (ALC) obtained at intervals of 2 weeks over an observation period of 2-3 months. In patients with initial blood lymphocyte counts of less than 30 x 10^9/L (30,000/µL), LDT should not be used as a single parameter to define indication for the treatment. In addition, factors contributing to lymphocytosis or lymphadenopathy other than CLL (eg, infections) should be excluded,
    e) Autoimmune anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy
    f) Constitutional symptoms documented in the patient´s chart with supportive objective measures, as appropriate, defined as one or more of the following disease-related symptoms or signs:
        i. Unintentional weight loss > 10% within the previous 6 months prior to Screening
        ii. Fever higher than 38.0ºC for 2 or more weeks prior to Screening without evidence of infection
        iii. Night sweats for more than 1 month prior to Screening without evidence of infection.

4. Refractory CLL (i.e. treatment failure or progression during treatment or within 6 months after the last treatment) or relapse CLL (i.e. patient who met criteria for CR or PR, but progressed beyond 6 months post-treatment).
5. At least 1 prior purine analogue or bendamustine containing therapy
6. Creatinine clearance ≥30ml/min or both
7. Hemoglobin ≥ 9 g/dL; absolute neutrophil count (ANC) ⩾ 1.5 x 109/L, platelets (Plt) ⩾ 75 x 109/L and leukocyte count > 3,000/µL, unless cytopenia is caused by the underlying disease, i.e. no evidence of additional bone marrow dysfunction (e.g. myelodysplastic syndrome [MDS])
8. Life expectancy >6-8 months
9. Able and willing to provide written informed consent and to comply with the study protocol procedures

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

1. Prior Alogenic Bone Marrow Transplant
2. ≥ 3 previous lines of chemotherapy and/or immunotherapy for the CLL.
3. Previous obinutuzumab-containing regimen.
4. Refractory CLL to bendamustine treatment (i.e. treatment failure or progression within 6 months of bendamustine-containing regimen).
5. Transformation of CLL to aggressive NHL (Richter's transformation). Patients with prolymphocytic transformation cannot be enrolled in the study either.
6. Active haemolytic anaemia
7. Inadequate liver function: NCICTC Grade 3 liver function tests (AST, ALT >5 x ULN for >2 weeks; Bilirubin >3 x ULN) unless due to underlying disease.
8. History of other malignancy which could affect compliance with the protocol or interpretation of results. Patients with a history of malignancy that has been treated but not with curative intent will be excluded, unless the malignancy has been in remission without treatment for ⩾ 2 years prior to enrolment. Patients with a history of adequately treated carcinoma in situ of the cervix; basal or squamous cell skin cancer; low grade, early stage localized prostate cancer treated surgically with curative intent; good prognosis DCIS of the breast treated with lumpectomy alone with curative intent are eligible.
9. Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results, including significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, severe arrhythmia, myocardial infarction within the previous 6 months, unstable arrhythmias, or unstable angina) or pulmonary disease (including obstructive pulmonary disease and history of bronchospasm).
10. Recent major surgery (within 4 weeks prior to the start of Cycle 1), other than for diagnosis.
11. Regular treatment with corticosteroids during the 4 weeks prior to the start of Cycle 1, unless administered for indications other than CLL at a dose equivalent to ⩽ 30 mg/day prednisone
12. Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) or any major episode of infection requiring treatment with IV antibiotics or hospitalization (relating to the completion of the course of antibiotics, except if for tumor fever) within 4 weeks prior to the start of Cycle 1.
13. Patients with known infection with Human immunodeficiency virus (HIV) or Human T Cell Leukemia Virus 1 (HTLV-1).
14. Positive hepatitis serology:

a) Hepatitis B (HBV): Patients with positive serology for Hepatitis B defined as positivity for Hepatitis B surface antigen (HBsAg) or anti Hepatitis B core antibody (anti-HBc). Patients positive for anti-HBc may be included if Hepatitis B viral DNA is not detectable.

b) Hepatitis C (HCV): Patients with positive Hepatitis C serology unless HCV (RNA) is confirmed negative.

15. History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies.
16. Known sensitivity or allergy to murine products.
17. Known hypersensitivity to any of the study drugs
18. Women who are pregnant or lactating
19. Fertile men or women of childbearing potential unless: (1) surgically sterile or ⩾ 2 years after the onset of menopause (2) willing to use a highly effective contraceptive method (Pearl Index <1) such as oral contraceptives, intrauterine device, sexual abstinence or barrier method of contraception in conjunction with spermicidal jelly during study treatment and in female patients for 18 months after end of antibody treatment and male patients for 6 months after end of bendamustine treatment.
20. Vaccination with a live vaccine a minimum of 28 days prior to baseline visit.
21. Participation in another clinical trial with drug intervention within 28 days prior to start of Cycle 1.

Length of Study

- Study recruitment: 18 months, in competitive recruitment
- Study treatment: 6 months (i.e. 6 cycles of 28 days)
- Study follow up: Until 30 months after the last patient has been enrolled

End of Study

The end of study will be defined as 2.5 years after the last patient first visit (unless all patients have died or withdrawn from the study before that).

Efficacy Outcome Measures

- Treatment response will be assessed by the investigators using the IWCLL criteria (7) (See Appendix 3):
  - Overall response rate (ORR) [i.e. Complete Response (CR), CR incomplete (CRi) or Partial Response (PR)] after 2-3 months after last dose of study treatment (In the visit of evaluation of response).
  - Best response (CR/CRi and PR) up to 6 months after treatment.
- Time to event efficacy measures:

- PFS is defined as the time from the start of Cycle 1 to the first occurrence of progression, relapse or death from any cause as assessed by the investigator.
- OS is defined as the time from the start of Cycle 1 to the date of death due to any cause.
- EFSis defined as the time from the start of Cycle 1 to the date of disease progression/relapse, death or start of a new anti-leukemic therapy.
- DFS is defined for all patients with complete response. Complete response lasts from the date the complete response was first recorded to the date on which progressive disease is first noted or the date of death due to any cause
- DR is defined similarly for complete and partial responders. Response starts at the date the response (either complete or partial) was first recorded to the date on which progressive disease is first noted or the date of death due to any cause.
- Time to re-treatment/new leukemic therapy is defined as time between the start of Cycle 1 and the date of first intake of re-treatment or new leukemic therapy.

- Molecular remission measure:
  - Proportion of patients without minimal residual disease (MRD-negative).

Safety Outcome Measures

- Proportion of patients with adverse events, serious adverse events and AEs of special interest Proportion of patients with infusion related reactions
- Proportion of patients abnormal laboratory values.
- Proportion of patients with abnormal vital signs.
- Proportion of premature withdrawals and reasons.
- Proportion of patients with previous/concomitant diseases.
- Proportion of patients taking concomitant medications.

Investigational Medicinal Products

Test Product

Obinutuzumab and bendamustine will be the Investigational Medicinal Products in this study.

Patients will be enrolled to receive a maximum of 6 cycles of obinutuzumab and bendamustine. A treatment Cycle will be defined as lasting 28 days.

- **Obinutuzumab** will be administered by IV infusion at a dose of 1000 mg. Subjects will receive obinutuzumab infusions on Day 1* (please see below details), Day 8, and Day 15 of the first treatment Cycle (Cycle 1) and on Day 1 of Cycles 2, 3, 4, 5, and 6.

  C1- Day1*- It will be necessary to prepare two bags (100mg and 900mg) for the first infusion, and allow the treating physician to administer - depending on the patient's status -, the two 2 bags within 1 or 2 day(s). The patients for whom the first bag (100mg) is completed without modifications of the infusion rate or interruptions (i.e. in the current SmPC any IRR would warrant rate reduction), the second bag can be administered on the same day provided that appropriate conditions and medical supervision are available throughout the infusion.

- **Bendamustine** will be administered by IV infusion at dose 70 mg/m2, on days 2 and 3 of cycle 1 and days 1 and 2 of cycles 2 - 6.

The dose of obinutuzumab will not be modified. Decision for treatment delays will be based on the dose modification recommendation of the bendamustine. If obinutuzumab is discontinued, the patient should be followed for disease progression, survival, and new anti-lymphoma treatment.

Bendamustine dose modification decisions for patients with cytopenia (below the lower limit of the normal range) will be based on the NCI-sponsored Working Group (NCI-WG) grading scale for hematologic toxicity in CLL studies (7). For patients with a normal neutrophil count, platelet count, and or hemoglobin value the NCI-CTCAE, v4.0, will be used.

Statistical Methods

Efficacy Analysis

All recruited patients who receive at least one dose of the study medication will be included in the efficacy analysis. For the primary analysis, the overall response rate (ORR) will be calculated. In addition the best response rate (CR/CRi and PR) up to 6-8 months after treatment will also be estimated. Response rates will be provided together with 95% confidence limits. Patients with no response assessments (due to whatever reason) will be considered non-responders.

In case of Stage 1 would not be exceeded, all the outcomes recorded and features of the initial population of 24 patients will be analyzed thoroughly in order to identify the reasons of that very low response rate observed.

The effect of prognostic markers in peripheral blood [i.e. p53 (17p13.1), ATM (11q22.3), ZAP70, CD38, CD49D, NOTHC1, SF3B1, BIRC3, IGHV] and from samples of saliva [ATM, BIRC3, BRAF, CHD2, CSMD3, DDX3X, FBXW7, KLHL6, KRAS, LRP1B, MAPK1, MUC2, MYD88, NFKBIE, NOTCH1, PLEKHG5, POT1, SAMHD1, SF3B1, SI, SMARCA2, TGM7, TP53, XPO1, ZMYM3, EGR] will be assessed using stratified exploratory analyses. In addition, the effect of those prognostic markers that show a significant association with treatment response will be further analyzed in an exploratory analysis using multivariate exact logistic regression..

Time to event endpoints such as progression free survival, event-free survival, disease-free survival, re-treatment/new ant-leukemic therapy, overall survival and duration of response will be analyzed using the Kaplan-Meier method.

Secondary Safety Analysis

All subjects who received at least one dose of treatment will be included in the safety evaluation. Safety of the treatment will be evaluated by: adverse events, laboratory tests and vital signs.

Adverse and serious adverse events will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.0. Laboratory safety assessments will include regular routine monitoring of hematology and blood chemistry

Interim analyses

An interim analysis will be performed once the evaluation of treatment response of all patients enrolled is available.

Determination of Sample Size

For a power of 90.0% to detect differences in the null hypothesis significance testing (H_0: p1=p2) using a unilateral binomial exact test for given sample in a two-stage Simon´s design (8), considering a significance level of 5.0%, assuming that ORR will not be less than 50 % and an expected ORR with the experimental treatment of 70 %, it will be necessary to apply the decision criteria: 13/24 and 36/61, respectively for each stage. This implies that 24 subjects will be initially analyzed in the first stage of the study. If treatment response is achieved by more than 13 subjects, then up to 61 subjects need to be analyzed.

Those patients who discontinue treatment and are not evaluable for efficacy will be considered as non-responders. In addition, we expect a 15% of missing data due to loss to follow-up or protocol non-compliance. This 15% will need to be replaced. Therefore, 72 patients will need to be enrolled.

GLOSSARY OF ABBREVIATIONS

µl	*Microliter*
AE	*Adverse Event*
AESI	*Adverse Events of Special Interest*
SAE	*Serious Adverse Event*
DNA	*Deoxyribonucleic acid*
AIHA	*Autoimmune Hemolytic Anemia*
ALT	*Alanine aminotransferase*
Anti-HBc	*Hepatitis B Virus Core Antibody*
RNA	*Ribonucleic acid*
AST	*Aspartate aminotransferase*
EDC	*Electronic Data Capture*
CREC	*Clinical Research Ethics Committee*
CHOP	*Cyclophosphamide, Hydroxydaunorubicin, Oncovin (vincristine) and Prednisone*
DCIS	*Ductal carcinoma in situ*
CIRS	*Cumulative Illness Rating Scale*
MFC	*Multiparametric Flow Cytometry*
eCRF	*Electronic Case Report Form*
CTCAE	*Common Terminology Criteria for AE*
RD	*Response duration*
ECG	*Electrocardiogram*
ECOG	*Eastern Cooperative Oncology Group*
EDTA	*Ethylenediaminetetraacetic acid*
SD	*Stable Disease*
USA	*United States*
EEA	*European Economic Area*
EEG	*Electroencephalogram*
PS	*Performance Status*
EORTC	*European Organization for Research and Treatment of Cancer*
DP	*Disease Progression*
MRD	*Minimal Residual Disease*
Fc	*Fragment crystallizable region*

FcλRIIIa	*Fc-gamma receptor IIIa*
FCR	*Fludarabine, cyclophosphamide, rituximab*
FISH	*Fluorescence in situ hybridization*
H0	*Null hypothesis*
H1	*Alternative hypothesis*
HAHA	*Human Anti-Human Antibody*
Hb	*Hemoglobin*
HBsAg	*Hepatitis B surface Antigen*
ICH	*International Conference on Harmonisation*
Ig	*Immunoglobulin*
Igs	*Surface immunoglobulin*
IGHV	*Immunoglobulin Heavy Chain Variable region*
IND	*Investigational New Drug*
IWCLL	*International Workshop on CLL*
LDH	*Lactate dehydrogenase*
CLL	*Chronic lymphocytic leukemia*
PML	*Progressive multifocal leukoencephalopathy*
NHL	*Non-Hodgkin's Lymphoma*
ULN	*Upper Limit of Normal*
mAb	*Monoclonal Antibody*
BMI	*Body Mass Index*
IMP	*Investigational Medicinal Product*
mg	*Milligram*
IB	*Investigator's Brochure*
ml	*Milliliter*
NCI	*National Cancer Institute of the United States*
NK	*Natural Killer cells*
PCR	*Polymerase Chain Reaction*
PMN	*Polymorphonuclear neutrophils*
SOP	*Standard Operating Procedure*
ALC	*Absolute Lymphocyte Count*
ANC	*Absolute Neutrophil Count*
CR	*Complete response or remission*

CRi	*Complete response with incomplete bone marrow recovery*
MRI	*Magnetic Resonance Imaging*
PR	*Partial Response*
nPR	*Nodular Partial Response (CR with histologically-defined nodules in bone marrow)*
IRR	*Infusion-Related Reactions*
BSA	*Body Surface Area*
OS	*Overall Survival*
TLS	*Tumor lysis syndrome*
DFS	*Disease-Free Survival*
EFS	*Event-Free Survival*
PFS	*Progression-Free Survival*
MDS	*Myelodysplastic Syndrome*
PFS	*Progression-Free Survival*
CAT	*Computerized Axial Tomography*
LDT	*Lymphocyte Doubling Time*
DLT	*Dose-Limiting Toxicity*
PT	*Prothrombin Time*
ORR	*Overall Response Rate*
aPTT	*Activated Partial Thromboplastin Time*
EU	*European Union*
VEGF	*Vascular Endothelial Growth Factor*
HBV	*Hepatitis B Virus*
HCV	*Hepatitis C Virus*
HIV	*Human Immunodeficiency Virus*
JCV	*John Cunningham Virus*
HTLV-1	*Human T-cell leukemia virus, type 1*
ZAP-70	*Zeta-chain associated protein*

1. INTRODUCTION

1.1 CHRONIC LYMPHOCYTIC LEUKEMIA

Chronic lymphocytic leukemia (CLL) is the most common leukemia in Western countries with an incidence of 4.2/100,000 year (1, 3). The median age at the time of diagnosis is 72 years and only 10% of patients are under 55 years of age(3).

The prognosis varies, with a median survival that can range between 18 months and over 10 years (3). There are two CLL staging classification systems, the Binet et al. system, used in Europe (4) and the American system of Rai et al. (5). Both classify patients according to their prognosis (good, intermediate and poor). In addition, in the last decade, additional prognostic markers have been identified that enable a more precise prediction of the prognosis for patients with CLL(6). Of them, the mutations/deletions of the genes p53 (17p13.1) and ATM (11q22.3) are known markers of poor prognosis (3). Indirect prognosis markers have also been identified, as is the case of the proteins CD38 and ZAP70. The expression of CD38 and ZAP70 correlate with the mutational status of the genes of the Immunoglobulin Heavy Chain Variable region (IgHV) which, in turn, have been associated with a lower overall survival and treatment duration (3). Then, the prognostic value of the expression of CD49D was recognized in patients with CLL(7). Recently, new mutations have been identified in genes SF3B1, NOTCH1 and BIRC3, which also seem to play an important role in the survival and resistance to the apoptosis of the B-cells of CLL (8).

For the initial phases of CLL (Binet A or B, Rai 0-II) without active disease, it has been shown that early treatment does not increase survival and, therefore, for those stages, starting pharmacological therapy is not recommended. Instead, the "watch and wait" principle should be applied (3).

The choice of the first-line treatment for the treatment of advanced or active disease is made based on the comorbidity of the patients. The FCR chemotherapy-immunotherapy combination based on the administration of fludarabine and cyclophosphamide together with the anti-CD20 monoclonal antibody, rituximab, is the treatment recommended as the first option for patients with previously untreated active CLL with an adequate physical status and no renal alteration or other serious

concomitant diseases (3). For those patients with CLL and more serious comorbidities, the standard first-line treatment is less defined. In this case, chlorambucil has been classically recommended, though more recently, other alternatives based on purine analogues (fludarabine+cyclophosphamide or pentostatin+cyclophosphamide+rituximab) or bendamustine have also been considered recently(3). The primary limitation of the extensive use of fludarabine for CLL is the mutation of (17p) that is expressed in 5-10% of patients with CLL and that is associated with an insufficient response to fludarabine (3).

For refractory patients (those who do not response to the standard first-line treatment) or relapsed patients (those who relapse shortly after the finalization of the first line of treatment), the level of evidence for the treatment recommendations is inferior and, at the present time, there is no standard treatment for this indication. In this case, the treatment selection depends largely on the patient's physical condition. In general, the first-line treatment can be repeated 24 months after the immunochemotherapy and, in the case of early relapse or refractory disease, the initial therapy must be changed (1). The most frequently studied alternatives, in addition to allogeneic bone marrow transplant, include FCR for patients who received first-line therapy based on an alkylating agent or therapy based on alentuzumab or bendamustine for patients with poor prognosis (relevant comorbidities) and who are not candidates to receive fludarabine due to the expression of the mutation of (17p) (3).

1.2 OBINUTUZUMAB (RO5072759)

Obinutuzumab (which is also known as GA101 and RO5072759) is a new glycomodified, humanized, type 2 anti-CD20, immunoglobulin G1 (IgG1) isotope monoclonal antibody. The antibody was designed to strengthen the direct and immunoeffector cell-mediated cell death with respect to the type 1 CD20 antibody, rituximab, which is the current standard treatment for lymphoma and CLL. Obinutuzumab is obtained through the humanization of the original B- Ly1 mouse antibody. It is bound to CD20 with a low affinity, with a single-digit nM. In comparison with rituximab, the molecule presents the following characteristics in cell-based trials:

- Strengthened capacity to induce direct cell death, accompanied by a reduction of the complement-dependent cytotoxicity as it is a type II antibody. Obinutuzumab-

induced cell death is related to the homotypical aggregation and represents a new type of actin-dependent, lysosome-induced cell death.

- Strengthened capacity to induce the cytotoxicity of antibody-dependent cells and the phagocytosis of antibody-dependent cells, as a result of the glycomodification of the Fragment crystallizable region (Fc) that gives way to a strengthened affinity for the Fc gamma receptor IIIa (FcλRIIIa) in immunoeffector cells (natural killer [NK] cells, macrophages/monocytes and neutrophils/polymorphonuclear neutrophils [PMN]). As a result of these characteristics, obinutuzumab was shown to be significantly more potent and effective in causing the depletion of normal and malignant B-cells, as compared to rituximab, in B-cell depletion trials in whole blood of healthy donors and patients with CLL. In preclinical studies, these characteristics translated into a strengthened anti-tumor activity of obinutuzumab, in direct comparison with rituximab, versus various models of aggressive lymphoma xenografts.

- Cases of GI perforation have been reported in patients receiving obinutuzumab, mainly in NHL. Patients with GI involvement should be monitored for signs of GI perforation.

Moreover, in xenograft studies, obinutuzumab's activity was proven in combination with classic chemotherapy agents, like cyclophosphamide, vincristine, bendamustine, chlorambucil and fludarabine or targeted agents, such as inhibitors of the B cell lymphoma 2 (Bcl-2) family proteins, of the double minute 2 murine gene or of the mammalian target of rapamycin. It is important to point out that obinutuzumab in combination with chemotherapy was superior to the respective chemotherapy agents when administered in combination with rituximab. The properties of obinutuzumab have recently been described in detail in several original expert-reviewed publications (9-19).

The preclinical pharmacology, pharmacokinetic (PK) and toxicity studies performed on adequate animal models, in line with the guidelines of the International Conference on Harmonisation, which back the clinical development of obinutuzumab, are summarized below. (For more information, please see the Investigator's Brochure for obinutuzumab).

1.2.1 Clinical development program

As of 2 July 2012 (deadline for the collection of safety data; please refer to the most recent obinutuzumab Investigator's Brochure for updated information), clinical data was available on obinutuzumab from 11 clinical trials including approximately 1310 patients with malignant CD20+ disease. These clinical trials include four Phase I and/or II studies on obinutuzumab in monotherapy (GAUGUIN [BO20999], GAUSS [BO21003], GAGE [GAO4768g] and JO21900), two phase Ib studies on obinutuzumab in combination with chemotherapy (GAUDI [BO21000] and GALTON [GAO4779g]), one phase II study in combination with chemotherapy with a single treatment group (GATHER [GAO4915g]) and four phase III studies (CLL11 [BO21004] in patients with previously untreated CLL, with comorbidities, GADOLIN [GAO4753g] in patients with indolent CD20+ lymphoma refractory to rituximab, GALLIUM [BO21223] in advanced indolent lymphoma not treated previously and GOYA [BO21005] in CD20+ diffuse large B-cell lymphoma not treated previously).

All studies remain ongoing, with the exception of the phase I study BO21003 and JO21900. The preliminary data of the ongoing studies is provided.

Please refer to the most recent obinutuzumab Investigator's Brochure for updated information.

1.2.1.1 Pharmacokinetics

In the phase I studies in which obinutuzumab is researched in monotherapy (BO20999 and BO21003), the serum concentrations peaked at the end of the infusion and then decreased slowly. In the range of doses researched in those studies, the serum concentration of obinutuzumab increased as the dose increased (with doses between 50 and 2000 mg in each infusion). The levels of obinutuzumab exposure in Japanese patients obtained in the JO21900 study were comparable to those observed in non-Japanese patients. The results indicated that, in order to attain adequate serum concentrations of obinutuzumab (> 400 µg/ml) in patients with lymphoma or CLL, doses of at least 800 mg are needed.

A bicompartimental PK model, which included a linear elimination pathway and a non-linear elimination pathway variable with time, was adapted to the data of the BO20999 and BO21003 studies. The elimination appeared to be dependent on time, starting with a

standard value of 594 ml/day, followed by a gradual decrease until values of approximately 112 ml/day were achieved in steady state. The PK data available indicate that obinutuzumab clearance may be faster in patients with a higher disease burden. The clearance decreased over time and with repeat administration; this was considered to be due to a reduction in the number CD20+ tumor cells. These findings are consistent with the previous assumptions established for other anti-CD20 antibodies, according to which elimination is primarily a function of the target antigen.

In general, the clinical data available to date back the dose selected for the currently ongoing phase III studies of obinutuzumab, which is a fixed dose of 1000 mg administered every 3 weeks or every 4 weeks (depending on the chemotherapy administration regimen). In order to attain and maintain adequate exposure levels quickly, the additional infusions of obinutuzumab are administered on Days 8 and 15 of the first treatment cycle.

1.2.1.2 Efficacy

Efficacy data is available from phase I/II studies on 38 patients with CLL who received obinutuzumab in monotherapy (see Table 1). No complete remissions (CR) were achieved, but in the phase I/II study BO20999, 8/13 patients (62%) and 4/20 patients (20%) achieved partial remission (PR) at the end of treatment.

Table 1 Summary of response achieved at the end of treatment in patients with CLL who received obinutuzumab in monotherapy (results from the phase I/II studies)

	Number of patients (%)					
	Response (CR + PR)	**CR**	**PR**	**SD**	**DP**	**No data**
BO20999 Phase I (N=13)	8 (62)	–	8 (62)	4 (31)	1 (8)	–
BO20999 Phase II [a] (N=20)	4 (20)	–	4 (20)	5 (25)	7 (35)	4 (20)
BO21003 Phase I (N=5)	–	–	–	3 (60)	1 (20)	1 (20)

CR, complete response; PR, partial response; SD, stable disease; DP, disease progression. This table presents the results of the primary efficacy analysis performed at the end of the main treatment period (BO20999) or of the induction treatment period (BO21003). The results include the combined data of all the dose groups.

a. Includes confirmed and unconfirmed response.

1.2.1.3 Safety

please refer to the most recent obinutuzumab Investigator's Brochure for updated information). The adverse events (AE) observed most commonly in the clinical trials performed to date in patients with lymphoma and CLL were infusion-related reactions (IRR). These AEs were, most of the time, associated with the first infusion and generally occurred at the start of the infusion, shortly after it was finished or, in some cases, up to 24 hours after completing the infusion of obinutuzumab. The incidence and severity of the IRRs decreased in the subsequent infusions of obinutuzumab. In some patients, concomitant signs of tumor lysis syndrome (TLS) were observed. Other AEs commonly observed were infections and neutropenia. These events appeared to be more common in patients with CLL than in patients with lymphoma. In studies in which obinutuzumab was researched in combination with cyclophosphamide, hydroxydaunorubicin, Oncovin

(vincristine), prednisone (prednisolone; CHOP), fludarabine/cyclophosphamide (FC), chlorambucil or bendamustine, the incidence of AEs registered in the combination treatment groups was consistent with the known safety profiles of the respective drugs in the studies.

Rarely, cases of progressive multifocal leukoencephalopathy (PML) could occur. More detailed information in that regard is provided in Section 5.

To date, no maximum tolerated dose, dose-limiting toxicities or evident dose-related trends with respect to the incidence of AEs have been determined.

1.2.1.4 Adverse Events of Special Interest

The following types of adverse events are considered by the Sponsor to be "Adverse Events of Special Interest" (AESI) due to the frequency with which they are observed and/or their clinical significance:

- SAEs associated with the infusion of obinutuzumab Obinutuzumab infusion-related reaction (which are defined as AEs occurring during or within 24 hours following the administration of an infusion of obinutuzumab and considered related to obinutuzumab) fulfilling the criteria of seriousness (protocol Section 5.2.2).

- Serious infection fulfilling the criteria of seriousness (protocol Section 5.2.2)
- Serious neutropenia Neutropenia fulfilling the criteria of seriousness (protocol Section 5.2.2)
- Any TLS (regardless if serious or not)

- Second malignancies

Other events considered of particular interest such as hepatitis B reactivation and PML will also be followed (reference section 5.1)

In the two studies in which obinutuzumab was assessed in monotherapy, BO20999 and BO21003, the patients with CLL appeared to have a higher risk of presenting AESI than patients with lymphoma. With respect to the incidence of these events, the major differences are observed in the cases of neutropenia (47% of patients with CLL [18/38]

versus 8% of patients with aggressive lymphoma [4/49] and 8% of patients with indolent lymphoma [13/156]) and infusion-related AEs (100% [38/38] versus 80% (39/49 patients and 8% [129/156]).

As of 2 July 2012 (cut-off date for safety data), six patients have presented TLS, including four patients from the aggressive lymphoma population (which also included patients with mantle-cell lymphoma) and one case each in the populations of patients with CLL and indolent lymphoma. Please refer to the most recent obinutuzumab Investigator's Brochure for updated information on additional cases.

Infections have been reported in 20/49 patients with aggressive lymphoma (41%), 74/156 patients with indolent lymphoma (47%) and 21/38 patients with CLL (55%). One of the patients with indolent lymphoma was removed from the study due to an infection. Moreover, one patient with CLL and another with indolent lymphoma died from infection (septic shock in both cases) during the survival monitoring, respectively, 671 and 494 days after receiving the last dose of treatment.

The study treatment needed to be suspended in 3 patients with CLL and in another three with indolent lymphoma due to an AESI, which consisted of an IRR in all cases. The treatment had to be discontinued in another patient in the indolent lymphoma group due to an infection. These results indicate that those events were generally manageable.

Most of the IRR were associated with the first infusion of obinutuzumab. The frequency and severity of these reactions decreased with subsequent infusions.

1.3 BENDAMUSTINE

Bendamustine hydrochloride is an antineoplastic agent whose mechanism of action is based on the cross-linking of the double and simple-strands of DNA by alkylation, which results in the alteration of DNA synthesis and repair.

Based on the results obtained in a phase III clinical trial comparing bendamustine with chlorambucil (20), bendamustine in monotherapy was authorized as first-line treatment for patients with CLL (Binet stage B or C) who are not candidates to receive chemotherapy with fludarabine (See Summary of Product Characteristics for

Bendamustine). The indicated dose in monotherapy for CLL is 100 mg/m^2, on Days 1 and 2, every 28 days.

The clinical experience obtained up until the date of bendamustine treatment in combination with chemotherapy and with immunotherapy is drawn from clinical trials. Specifically, the combination with the anti-CD20 monoclonal antibody, rituximab, has shown promising results in patients with CLL refractory to standard chemotherapy (21-23). Based on the results obtained in phase I/II, the recommended dose in combination with rituximab in patients with refractory CLL is 70 mg/m^2, on Days 1 and 2 every 28 days (21).

Moreover, bendamustine has presented a favorable toxicity profile for use in elderly patients (24), which is the stratum of the population to which a significant percentage of patients with CLL pertain(3). The most common adverse reactions are hematological reactions (leukopenia and thrombopenia), dermatological reactions, fever, nausea and vomiting (See Summary of Product Characteristics for Bendamustine).

1.4 RATIONALE FOR THE STUDY

As mentioned above, the "gold standard" for first-line treatment in patients with CLL without relevant comorbidities is the combination of the anti-CD20 monoclonal antibody (rituximab) with fludarabine and cyclophosphamide (FCR) (1, 3). However, a given percentage of patients will relapse or be refractory to fludarabine(25). In this scenario, bendamustine, a bifunctional alkylating agent, appears to be a good treatment for second-line therapy due to the absence of relevant cross-resistance with other alkylating agents or fludarabine (21, 22). Moreover, rituximab has also shown promising results when used in combination with chemotherapy in patients with CLL refractory to fludarabine (21, 23, 25, 26). Specifically, the combination of bendamustine and rituximab achieved an overall response rate (ORR) of 59.0% (95% CI: 47.3% to 70.0%), a median progression-free survival of 15.2 months (95% CI: 12.5 to 17.9 months) and a median overall survival of 34 months (95% CI: 25.5 to 42.1 months) in patients with relapsed or refractory CLL (23). Even in patients previously treated with bendamustine, the combination of bendamustine, rituximab and mitoxantrone reached an ORR of 76%

and a median overall survival from the first treatment with bendamustine of 33 months (27).

Obinutuzumab (RO5072759) is a new anti-CD20 monoclonal antibody with an increased antibody-dependent cell-mediated cytotoxicity and capacity for direct induction of cell death. These properties could provide a greater efficacy than rituximab, particularly in 80%-85% of patients who are carriers of the polymorphism of the low-affinity receptor FcγRIIIa (see the Investigator's Brochure for Obinutuzumab-RO5072759).

Considering the limited treatment opportunities for patients with refractory or relapsed CLL and given the promising results obtained to date with the rituximab-bendamustine combination in this indication, (23) we propose conducting this phase II clinical trial to explore the efficacy and safety of the combination of obinutuzumab and bendamustine in patients with relapsed or refractory CLL.

1.5 RISK-BENEFIT ASSESSMENT

Obinutuzumab shares a therapeutic target with rituximab (CD20), whose safety profile is manageable and well-established. However, the efficacy of obinutuzumab is believed to be greater and, therefore, a greater obinutuzumab-associated toxicity is also to be expected, specifically in terms of adverse events related to the faster, more extensive depletion of both malignant and normal CD20+ lymphocytes, caused by obinutuzumab (See Investigator's Brochure for obinutuzumab).

The clinical experience obtained to date with rituximab suggests that its use in combination with bendamustine could be beneficial for patients with refractory CLL (21, 22). Moreover, bendamustine has presented a favorable toxicity profile for use in elderly patients (24), which is the stratum of the population to which a significant percentage of patients with CLL pertain (3).

Given the good results obtained with rituximab in combination with bendamustine in refractory CLL, we believe that the combination of obinutuzumab with bendamustine could optimize the potential beneficial effect resulting from the more complete depletion of CD20+ lymphocytes caused by obinutuzumab, thus obtaining a greater tumor response and slower disease progression. On the other hand, the low toxicity profile of bendamustine, together with the experience obtained in recent years in the

management of anti-CD20 monoclonal antibody-associated toxicities, could, in turn, compensate for the expected increase in obinutuzumab-associated toxicity.

Considering the scarcity of therapeutic alternatives for patients with refractory or relapsed CLL, we believe that the potential risks associated with participation in the trial would be offset by the expected benefits.

2. OBJECTIVES

2.1 PRIMARY OBJECTIVE

- To evaluate the overall response rate (ORR) after treatment with obinutuzumab and bendamustine, in patients with refractory or relapsed chronic lymphocytic leukemia (CLL).

  The results will be placed in perspective respect other studies like the GREEN study (MO28643, EudraCT No. 2013-000087-29).

2.2 SECONDARY OBJECTIVES

- To evaluate the best response rate during study treatment and until 6-8 months after end of study treatment, according IWCLL2008 criteria
- To evaluate progression free survival (PFS).
- To evaluate overall survival (OS) and event free survival (EFS).
- To evaluate disease free survival (DFS) among patients with complete response (CRi or CR).
- To evaluate duration of response (DR) among patients with complete (CRi or CR) or partial response.
- To evaluate time to re-treatment/new anti-leukemia therapy.
- To evaluate remission using multi-parametric flow cytometry.
- To evaluate the safety profile of the study treatment.

2.3 EXPLORATORY OBJECTIVE

- To evaluate the association between overall response rate (ORR) and the following prognostic markers: p53 (17p13.1), ATM (11q22.3), NOTCH1, SF3B1, BIRC3, mutations in the immunoglobulin heavy chain variable region (IGHV) and expression of ZAP70, CD38, CD49D.

- To evaluate the association between the response rate and the DNA sequencing in a sample of saliva, through the study of the following 26 genes: ATM, BIRC3, BRAF, CHD2, CSMD3, DDX3X, FBXW7, KLHL6, KRAS, LRP1B, MAPK1, MUC2, MYD88, NFKBIE, NOTCH1, PLEKHG5, POT1, SAMHD1, SF3B1, SI, SMARCA2, TGM7, TP53, XPO1, ZMYM3, EGR.

3. STUDY DESIGN

3.1 STUDY DESCRIPTION

Multicentre, non-comparative, phase II clinical trial

Figure 1. Overall study description

Pre-selection	Selection	Treatment	Post-treatment	Follow-up
• Age ≥ 18 Relapsed or refractory CLL • Review of selection criteria • Informed consent	• Review of selection criteria • Sending samples: Immunophenotype and mutations; MRD (PB);	• Obinituzumab + Bendamustine (6 cycles) • Safety assessment	• Assessment of the Response • Sending samples: MRD (PB and BM)	• Every 6 months*

EMR=Minimum Residual Disease BM=Bone Marrow; PS=Peripheral Blood

(*) Follow-up every 6 months to death, loss of follow-up or study finalization (2.5 years after last patient's first visit)

The assessment calendar is presented in Appendix 1.

3.2 STUDY FINALIZATION

Study finalization is defined as the date of the last patient's last visit (LPLV). The LPLV is expected to take place 2.5 years after the first visit of the last patient (unless all patients have died or left the study beforehand).

3.3 RATIONALE FOR THE STUDY DESIGN

The experience available to date on the combination of an anti-CD20 monoclonal antibody in combination with bendamustine for the treatment of refractory CLL originates from phase I/II clinical trials in which rituximab and bendamustine are used (21, 23). Keeping in mind the analogous nature of the mechanism of action of rituximab and obinutuzumab, we believe it is appropriate to propose a clinical trial to assess the efficacy of obinutuzumab in combination with bendamustine in patients with relapsed or refractory CLL. Given that the clinical experience is incipient, we believe the most appropriate design to study the potential beneficial effect of the combination of obinutuzumab and bendamustine in this indication is a phase II trial due to its

exploratory nature. Since there is no standard treatment for patients with relapsed or refractory CLL, no comparator group has been included.

3.3.1 Justification of the dose of the investigational treatment

According to the results of the clinical trials conducted to date with obinutuzumab, the recommended dose is 1000 mg (fixed dose) every 3 or 4 weeks, depending on the frequency of the dose of chemotherapy against which it is compared. Given that, in this case, the antineoplastic agent with which it is combined, bendamustine, is administered every 4 weeks, the obinutuzumab will likewise be administered every 4 weeks. According to the experience obtained to date in patients with CLL, administering extra doses of obinutuzumab on Days 8 and 15 of Cycle 1 is recommended. Moreover, the first infusion of Cycle 1 will be administered fragmented in 2 steps (first 100 mg and then 900 mg) on Day 1 of Cycle 1 or on Days 1 and 2 of Cycle 1 (Section 4.2.2.1. The dose of obinutuzumab for use in this trial as described in Section 4.2.2.1. has been established in line with those recommendations. (For more information, please see the Investigator's Brochure for Obinutuzumab).

The indicated dose of bendamustine in monotherapy for CLL is 100mg/m^2, Days 1 and 2, every 28 days. However, based on the results obtained in phase I/II, the recommended dose of bendamustine in combination with rituximab in patients with refractory CLL is 70 mg/m^2, on Days 1 and 2 every 28 days (21). Given those results, bendamustine will be administered in this trial as described in Section 4.2.2.2.

3.4 ENDPOINTS

3.4.1 Efficacy Endpoints

The following variables will be used for the assessment of the efficacy outcomes:

- Treatment response will be assessed by the investigators using the IWCLL criteria (Appendix 3):
  - Overall response rate (ORR) [i.e. Complete Response (CR), incomplete CR (CRi) or Partial Response (PR)] after 2-3 months after last dose of the study treatment (In the visit of evaluation of response).
  - Best response (CR/CRi and PR) up to 6 months post-treatment.

- Efficacy endpoints "Time to event":
  - PFS is defined as the time from the start of Cycle 1 to disease progression, relapse or death from any cause, whichever occurs first, as assessed by the investigator.
  - OS is defined as the time from the start of Cycle 1 to death from any cause.
  - EFS is defined as the time from the start of Cycle 1 to disease progression/relapse, death from any cause or start of a new anti-leukemia therapy.
  - DFS is defined for all patients who achieve complete response. DFS lasts from the date on which complete response is recorded until the date on which the first disease progression or death from any cause occurs.
  - RD is defined in a similar manner for patients with complete and partial response. RD spans from the date on which response is recorded (regardless of whether it is complete or partial), until the date on which disease progression or death from any cause occurs.
  - Time to re-treatment/new leukemia therapy is defined as the time between the start of Cycle 1 and the date of the first administration of re-treatment or new leukemia therapy.
- Variable for determining molecular remission:
  - Percentage of patients with minimal residual disease (MRD) negativity, which is defined as the presence of less than 1 cell of CLL per 10,000 leukocytes, assessed by flow cytometry in a laboratory accredited by EuroFlow at the end of the treatment (in the final response assessment)(6).

3.4.2 Safety Endpoints

The following variables will be used for the assessment of the safety outcomes:

- Percentage of patients with adverse events, serious adverse events and adverse events of special interest.
- Percentage of patients with infusion-related reactions.
- Percentage of patients with altered laboratory values.

- Percentage of patients with abnormal vital signs.
- Percentage of patients who discontinue the treatment prematurely and their reasons.
- Percentage of patients with previous/concomitant diseases.
- Percentage of patients with concomitant medication.

4. MATERIAL AND METHODS

4.1 PATIENTS

The study population will be made up of patients over 18 years of age with relapsed or refractory CLL.

4.1.1 Inclusion criteria

The patients must must meet the following criteria for study entry:

1. Age 18 years or older
2. Have documented CD20+ B-CLL according to NCI criteria (see Appendix 2)
3. Active disease meeting at least 1 of the following IWCLL 2008 criteria for requiring treatment:
    a) Evidence of progressive marrow failure as manifested by the development of, or worsening of, anemia (Hgb < 10 g/dL) and/or thrombocytopenia (platelets < 100,000/µL)
    b) Massive (i.e. at least 6 cm bellow the left costal margin), progressive or symptomatic splenomegaly
    c) Massive nodes (i.e. at least 10 cm in the longest diameter), progressive or symptomatic lymphadenopathy

d) Progressive lymphocytosis with an increase of more than 50% over a 2-month period or a lymphocyte doubling time (LDT) of less than 6 months. LDT may be obtained by linear regression extrapolation of absolute lymphocyte counts (ALC) obtained at intervals of 2 weeks over an observation period of 2-3 months. In patients with initial blood lymphocyte counts of less than 30 x 10^9/L (30,000/µL), LDT should not be used as a single parameter to define indication for the treatment. In addition, factors contributing to lymphocytosis or lymphadenopathy other than CLL (eg, infections) should be excluded,

e) Autoimmune anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy

f) Constitutional symptoms documented in the patient´s chart with supportive objective measures, as appropriate, defined as one or more of the following disease-related symptoms or signs:

i. Unintentional weight loss > 10% within the previous 6 months prior to Screening

ii. Fever higher than 38.0ºC for 2 or more weeks prior to Screening without evidence of infection

iii. Night sweats for more than 1 month prior to Screening without evidence of infection.

4. Refractory CLL (i.e. treatment failure or progression during treatment or within 6 months after the last treatment) or relapse CLL (i.e. patient who met criteria for CR or PR, but progressed beyond 6 months post-treatment).
5. At least 1 prior purine analogue or bendamustine containing therapy
6. Creatinine clearance ≥30ml/min or both
7. Hemoglobin ≥ 9 g/dL; absolute neutrophil count (ANC) ≥ 1.5 x 109/L and platelets (Plt) ≥ 75 x 109/L and leukocyte count > 3,000/µL unless cytopenia is caused by the underlying disease, i.e. no evidence of additional bone marrow dysfunction (e.g. myelodysplastic syndrome [MDS])
8. Life expectancy >6-8 months

9. Able and willing to provide written informed consent and to comply with the study protocol procedures

4.1.2 Exclusion criteria

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

1. Prior Alogenic Bone Marrow Transplant
2. ≥ 3 previous lines of chemotherapy and/or immunotherapy for the CLL.
3. Previous obinutuzumab-containing regimen.
4. Refractory CLL to bendamustine treatment (i.e. treatment failure or progression within 6 months of bendamustine-containing regimen).
5. Transformation of CLL to aggressive NHL (Richter's transformation). Patients with prolymphocytic transformation cannot entry the study either.
6. Active haemolytic anaemia
7. Inadequate liver function: NCICTC Grade 3 liver function tests (AST, ALT >5 x ULN for >2 weeks; Bilirubin >3 x ULN) unless due to underlying disease.
8. History of other malignancy which could affect compliance with the protocol or interpretation of results. Patients with a history of malignancy that has been treated but not with curative intent will be excluded, unless the malignancy has been in remission without treatment for ≥ 2 years prior to enrolment. Patients with a history of adequately treated carcinoma in situ of the cervix; basal or squamous cell skin cancer; low grade, early stage localized prostate cancer treated surgically with curative intent; good prognosis DCIS of the breast treated with lumpectomy alone with curative intent are eligible.
9. Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results, including significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, severe arrhythmia, myocardial infarction within the previous 6 months, unstable arrhythmias, or unstable angina) or pulmonary disease (including obstructive pulmonary disease and history of bronchospasm).

10. Recent major surgery (within 4 weeks prior to the start of Cycle 1), other than for diagnosis.
11. Regular treatment with corticosteroids during the 4 weeks prior to the start of Cycle 1, unless administered for indications other than CLL at a dose equivalent to ≤ 30 mg/day prednisone
12. Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) or any major episode of infection requiring treatment with IV antibiotics or hospitalization (relating to the completion of the course of antibiotics, except if for tumor fever) within 4 weeks prior to the start of Cycle 1.
13. Patients with known infection with Human immunodeficiency virus (HIV) or Human T Cell Leukemia Virus 1 (HTLV-1).
14. Positive hepatitis serology:
    a) Hepatitis B (HBV): Patients with positive serology for Hepatitis B defined as positivity for Hepatitis B surface antigen (HBsAg) or anti Hepatitis B core antibody (anti-HBc). Patients positive for anti-HBc may be included if Hepatitis B viral DNA is not detectable.
    b) Hepatitis C (HCV): Patients with positive Hepatitis C serology unless HCV (RNA) is confirmed negative.
15. History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies.
16. Known sensitivity or allergy to murine products.
17. Known hypersensitivity to any of the study drugs
18. Women who are pregnant or lactating

19. Fertile men or women of childbearing potential unless: (1) surgically sterile or ≥ 2 years after the onset of menopause (2) willing to use a highly effective contraceptive method (Pearl Index <1) such as oral contraceptives, intrauterine device, sexual abstinence or barrier method of contraception in conjunction with spermicidal jelly during study treatment and in female patients for 18 months after end of antibody treatment and male patients for 6 months after end of bendamustine treatment.
20. Vaccination with a live vaccine a minimum of 28 days prior to baseline visit.
21. Participation in another clinical trial with drug intervention within 28 days prior to start of Cycle 1.

4.2 STUDY TREATMENT

Obinutuzumab and bendamustine are considered the IMPs in this trial.

4.2.1 Formulation, packaging, preparation and handling

4.2.1.1 Obinutuzumab

Obinutuzumab will be supplied by Roche to the research sites on a regular basis. The packaging of the investigational medicinal products shall be supervised by the Roche Global Clinical Trial Supply Department. The containers shall be packaged in such a way that they bear the labels with the identification required by local legislation and in accordance with Roche's standards.

Obinutuzumab is supplied as a concentrated liquid containing 1000 mg, for administration in a single dose as an infusion, containing 25 mg/ml of obinutuzumab. The 1000 mg dose is supplied in 50 ml glass vials containing 40 ml of concentrated liquid at 25 mg/ml. In addition to the active ingredient, the formulation also contains histidine, trehalose and poloxamer 188. Obinutuzumab must be prepared by a healthcare professional using aseptic techniques. The amount of concentrated liquid required is extracted from the vial and diluted in PVC or PVC-free polyolefin bags containing a sterile, nonpyrogenic aqueous sodium chloride (NaCl) solution at 0.9%. No other diluents, such as 5% dextrose solution, should be used.

The recommended storage conditions for obinutuzumab are at a temperature between 2°C and 8°C (36-46°F), protected from light.

The chemical and physical stability of obinutuzumab in NaCl at 0.9% in the concentration range of 0.4 to 20 mg/ml, has been shown to be 24 hours between 2°C and 8°C and another 24 hours at room temperature (≤30ºC).

From the microbiological point of view, the product must be used immediately. Otherwise, the time and storage conditions until use will be the responsibility of the user and normally should not exceed 24 hours between 2°C and 8°C, unless the reconstitution/dilution is performed under controlled, validated aseptic conditions.

The vials of obinutuzumab do not contain antimicrobial preservatives. Therefore, caution must be exercised to ensure that the solution for infusion is not microbiologically contaminated during preparation.

The vials of obinutuzumab must not be frozen or shaken. The mixing process must be gentle. All drug transfer procedures must be performed under strict aseptic conditions. Do not use obinutuzumab after the expiry date printed on the package.

Administration sets with PVC, PUR or PE can be used for obinutuzumab infusion preparation. Also 0.22 µm inline-filters with PES, stopcocks with PVC, catheters with PEU and IV bags with PVC, PP, PE or PO can be used.

For more information, please see the Investigator's Brochure.

4.2.1.2 Bendamustine

Bendamustine is supplied in single-use vials containing 55 or 220 mg of powder for the preparation of a solution for infusion containing 25 or 100 mg of bendamustine HCl respectively. The Sponsor will supply bendamustine to the study sites as an investigational medicinal product (IMP).

The powder must be reconstituted immediately after opening the vial . First dissolve the contents of the bendamustine hydrochloride vial with water for injection and diluted afterwards with 0.9% NaCl solution. After reconstitution and dilution, the product has been shown to remain physically and chemically stable for 3.5 hours at 25ºC/relative

humidity of 60% and for 2 days at 2ºC-8ºC in polyethylene bags. The vial must be stored in the cardboard outer box to protect the bendamustine from light.

From a microbiological point of view, the solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. Bendamustine preparation instructions are provided in Appendix 9.

For more information, see the Summary of Product Characteristics for bendamustine.

4.2.2 Dosage, administration and treatment compliance

4.2.2.1 Obinutuzumab

Obinutuzumab dosage

Obinutuzumab will be administered as an IV infusion at a 1000 mg fixed dose. Each treatment cycle will last 28 days.

Patients will receive the first infusion of obinutuzumab on Day 1* of Cycle 1 (see details below) and the subsequent infusions on Days 8 and 15 of the first treatment cycle (Cycle 1) and on Day 1 of Cycles 2, 3, 4, 5 and 6 (Table 2).

(*) N.B. On Day 1 of Cycle 1, 2 bags (100 mg and 900 mg) will have to be prepared for the first infusion. At the physician's discretion, based on the patient's status, the 2 bags can be administered in 1 day or in 2 consecutive days. In the patients for whom the first bag (100 mg) is completed without modifications in the infusion rate or discontinuations (see Investigator's Brochure for Obinutuzumab - Any IRR will require a reduction of the infusion rate), the second bag (900 mg) may be administered on the same day as the first, provided the adequate conditions are in place and there is medical supervision available during the infusion.

The dose of obinutuzumab will not be modified. The decision to postpone the treatment shall be based on the dose-modification recommendations for bendamustine (see Section 4.2.2.2), but all infusions of obinutuzumab must be administered. If the administration of obinutuzumab is discontinued, the patient will be monitored until disease progression occurs or until he/she starts a new treatment for leukemia or to assess survival. In the event the treatment is delayed, it shall be resumed as soon as possible following the same regimen; the complete dose shall be administered as indicated in the Protocol.

For Grade 3 or 4 adverse events occurring on obinutuzumab administration Days 1, 2, 8 and 15, up to a 2-week delay of infusions is allowed during Cycle 1. For subsequent obinutuzumab cycles, a maximum dose delay of 4 weeks is permitted per cycle. A maximum of 8 weeks of cumulative delay due to toxicity is allowed in total per patient. If either obinutuzumab or chemotherapy administration is delayed, the entire treatment cycle will be delayed (e.g. if the obinutuzumab dose at Cycle 1 / Day 15 is delayed by 1 week, the Cycle 2 / Day 1 dose of both obinutuzumab and chemotherapy will be delayed by 1 week).

Obinutuzumab administration

Prior to the treatment, all patients should be assessed in accordance with the guidance issued in Appendix 7 and must receive premedication in accordance with the guidelines explained below, in the section on premedication for obinutuzumab.

Obinutuzumab **MUST** be administered in a hospital setting with complete resuscitation equipment available that can be accessed immediately in case of emergency, and the patients must be closely monitored by the investigator at all times. Obinutuzumab will be administered as a slow IV infusion through a single line. Infusion pumps will be used to control the infusion rate for obinutuzumab. It must not be administered as a pulse or bolus IV. Once the first infusion has been finalized, the IV line must be left *in situ* for at least 2 hours to be able to administer other drugs by IV, if necessary should AEs appear. If no AEs appear after 2 hours, the line can be removed. In subsequent infusions, the IV line must be left *in situ* for at least 1 hour from the end of the infusion. If no AEs appear after 1 hour, it can be removed.

For information on the guidelines for managing IRRs and anaphylactic reactions, see Section 5.1.1.

Infusion rate and dose used in the first infusion (Days 1 and 2 of Cycle 1) (Appendix 8)

The standard administration scheme used in previous clinical trials is as follows:

- On Day 1 of Cycle 1, 2 bags (100 mg and 900 mg) will have to be prepared for the first infusion. At the physician's discretion, based on the patient's status, the 2 bags can be administered in 1 day or in 2 consecutive days. In the patients for whom the first bag (100 mg) is completed without modifications in the infusion rate or discontinuations (see Investigator's Brochure for Obinutuzumab - Any IRR

will require a reduction of the infusion rate), the second bag (900 mg) may be administered on the same day as the first, provided the adequate conditions are in place and there is medical supervision available during the infusion.

- The bag of 100 mg obinutuzumab shall be administered at a rate of 25 mg/h for 4 hours (Table 2). The 900 mg bag shall be administered at an initial rate of 50 mg/h:
    - If no IRR/hypersensitivity reactions appear, the infusion rate shall be increased in 50 mg/h increments every 30 minutes, up to a maximum of 400 mg/h.
    - If IRR/hypersensitivity reactions do appear, the infusion shall be suspended (if the reaction severity is Grade 4), temporarily discontinued (if the reactions are Grade 3), or the infusion rate should be slowed (if they are Grade 1-2), and concomitant medication can be administered if the investigator believes it to be appropriate. Once the symptoms are resolved, if the IRR intensity was grade 1-3, the infusion can be resumed at half of the previous rate (that used at the time at which the hypersensitivity or infusion-related reaction occurred) and the rate can continue to be increased using the increments and intervals established above. If a patient presents an IRR on Day 1, the infusion will be resumed at the rate previously tolerated by the patient (Table 2).

<u>Infusion rate and dose used in subsequent infusions (Appendix 8)</u>

If the first infusion of obinutuzumab was well-tolerated (it is considered to be well-tolerated if no IRRs occur with a final infusion rate of ≥100 mg/h), the following infusions of 1000 mg shall be administered at an initial rate of 100 mg/h, with increments of 100 mg/h at 30-minute intervals, based on tolerance, up to a maximum of 400 mg/h.

If hypersensitivity/IRR reactions occur, the infusion shall be temporarily discontinued or the rate slowed, and concomitant medications can be administered if the investigator believes it to be appropriate.

Once the symptoms are resolved, the infusion can be resumed at half of the previous rate (that used at the time at which the hypersensitivity or infusion-related reaction

occurred) and the rate can continue to be increased using the increments and intervals established above (see Table 3).

If the previous infusion was not well-tolerated at the rate used, according to the definition provided above, the instructions for adjusting the rate of the first infusion shall be applied.

Table 2 Standard administration of obinutuzumab

Cycle and day of treatment		**Dose of obinutuzumab**	**Infusion rate (if no infusion-related/hypersensitivity reactions have occurred during the previous infusions)**
Cycle 1	Day 1	100 mg	Administer at a rate of 25 mg/h for 4 hours. Do not increase the infusion rate.
	Day 1 or 2 ¥	900 mg	Administer at a rate of 50 mg/h. The infusion rate can be increased in 50 mg/h increments every 30 minutes, up to a maximum of 400 mg/h.
	Day 8	1000 mg	The infusions can be started at a rate of 100 mg/h and increased in 100 mg/h increments every 30 minutes, up to a maximum of 400 mg/h.
	Day 15	1000 mg	
Cycles 2 – 6	Day 1	1000 mg	

In the event of a reaction to the infusion, adjust the infusion as indicated in *Table 6* below.

¥ *On Day 1 of Cycle 1, 2 bags (100 mg and 900 mg) will have to be prepared for the first infusion. At the physician's discretion, based on the patient's status, the 2 bags can be administered in 1 day or in 2 consecutive days. In the patients for whom the first bag (100 mg) is completed without modifications in the infusion rate or discontinuations (see Investigator's Brochure for Obinutuzumab - Any IRR will require a reduction of the infusion rate), the second bag (900 mg) may be administered on the same day as the first, provided the adequate conditions are in place and there is medical supervision available during the infusion.*

Table 3 Guidelines for modifying the infusion rate in the event of infusion-related reactions

Grade 4. (life-threatening)	Stop the infusion and discontinue the treatment.
Grade 3 (severe)	Temporarily stop the infusion and administer symptomatic treatment. Once the symptoms are resolved, the infusion can be resumed at a maximum of half of the previous rate (that used at the time at which the IRR occurred), and if the patient does not present symptoms of IRR, the rate can continue to be increased using the increments and intervals appropriate for the dose of the treatment (see Table 2).
Grade 1-2 (mild and moderate)	Reduce the infusion rate (to the previous rate which was well tolerated) and administer symptomatic treatment. Once the symptoms are resolved, continue infusion and, if the patient does not present symptoms of IRR, the rate can continue to be increased using the increments and intervals appropriate for the dose of the treatment (see Table 2).

Modification Delays of the obinutuzumab treatment

The dose of obinutuzumab will not be modified. The decision to postpone the treatment shall be based on the recommendations for the modification of the dose of bendamustine (see Section 4.2.2.2). If the administration of obinutuzumab is discontinued, the patient will be monitored until disease progression occurs or until he/she starts a new treatment for leukemia, and then until death (to assess overall survival).

For Grade 3 or 4 adverse events occurring on obinutuzumab administration Days 1, 2, 8 and 15, up to a 2-week delay of infusions is allowed during Cycle 1. For subsequent obinutuzumab cycles, a maximum dose delay of 4 weeks is

permitted per cycle. A maximum of 8 weeks of cumulative delay due to toxicity is allowed in total per patient. If either obinutuzumab or chemotherapy administration is delayed, the entire treatment cycle will be delayed (e.g. if the obinutuzumab dose at Cycle 1 / Day 15 is delayed by 1 week, the Cycle 2 / Day 1 dose of both obinutuzumab and chemotherapy will be delayed by 1 week).

Premedication for obinutuzumab

Any premedication used for obinutuzumab must be reported to the investigator and recorded in the eCRF.

Infusion-Related Reactions

Since hypotension may be experienced as a result of an IRR, withdrawing any anti-hypertensive medications 12 hours prior to the administration of the infusion shall be considered.

Since some patients may present hypersensitivity reactions or other IRRs to obinutuzumab, a premedication regimen consisting of acetaminophen/paracetamol (p.o. or i.v. 650-1000 mg) and an antihistamine, such as diphenhydramine (50-100mg), must be administered approximately 30 minutes prior to starting obinutuzumab infusions (unless it is contraindicated). In infusions of obinutuzumab subsequent to Cycle 1 Day 1 and Day 2, the anti-histamine premedication may be omitted if the previous infusion did not cause CTCAE grade > 1 IRRs (i.e. no medications were needed to treat the IRR and the infusion did not have to be discontinued).

In the first infusion of obinutuzumab (on Day 1 or Days 1 and 2), patients must obligatorily receive premedication with 100 mg of prednisolone or prednisone, which will be administered intravenously at least 1 hour prior to the infusion of the antibody. An equivalent dose of dexamethasone (20 mg) or methylprednisolone (80 mg) is allowed, but hydrocortisone must not be used. It is necessary to note that the administration regimen of the premedication with 100 mg of corticosteroids can be changed from 1 hour to 12 hours prior to the first infusion of obinutuzumab (i.e. administer them the night before), according to the alternative strategies for the administration of the first infusion of obinutuzumab in terms of the IRRs described previously.

In subsequent infusions, premedication with corticosteroids will be administered in the following cases:

- Patients who have presented a grade ≥ 3 IRR with the previous infusion
- Patients with lymphocyte counts > 25 x 10^9/L
- According to the investigator's criteria

In patients with a high lymphocyte count and voluminous lymphadenopathy, the infusion can be administered extremely slowly over a longer period of time or the dose can be divided and administered on two consecutive days. It must be noted that the risk factors that could predict the onset of an IRR in the first infusion have not yet been confirmed and that no clear correlation has been established between the tumor mass (circulating disease or lymph nodes) and the incidence of IRRs.

Tumor lysis syndrome

Patients with a high tumor burden (white blood cell count ≥ 25 x 10^9/L or bulky lymphadenopathy) must receive prophylaxis for TLS prior to the initiation of treatment. This includes appropriate hydration, consisting of a fluid intake of approximately 3 L/day, starting 1–2 days before the first dose of obinutuzumab. All such patients with high tumor burden must be treated with allopurinol or a suitable alternative treatment (i.e. rasburicase) starting at least 72 hours prior to the first infusion of obinutuzumab (Cycle 1, Day 1). Note that allopurinol should not be given on the same day than bendamustine. These measures may also be extended to other patients considered at risk of TLS in the judgement of the investigator.

Patients still considered at risk for TLS because of persistently high tumor burden (i.e., peripheral blood lymphocyte counts ≥ 25 × 10^9/L) before the second and subsequent infusions of obinutuzumab should continue to receive TLS prophylaxis with allopurinol or a suitable alternative (i.e., rasburicase) and adequate hydration until the risk is abated, as determined by the investigator.

All patients considered at risk by the investigator should be carefully monitored during the initial days of study treatment with a special focus on renal function, potassium, and uric acid values. Hematology and biochemistry assessments must be performed as per the Schedule of Assessments (Appendix 2) at every study visit, including both Day 1 and 2 of Cycle 1. Chemotherapy should not be resumed before all symptoms (clinical or laboratory) of TLS have disappeared.

Any additional guidelines according to institutional practice should be followed (Cairo et al, 2010; Howard et al, 2011, Table 4).

Table 4 Definition of Laboratory and Clinical Tumor Lysis Syndrome *

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

*In laboratory tumor lysis syndrome, two or more metabolic abnormalities must be present during the same 24-hour period within 3 days before the start of therapy or up to 7 days afterward. Clinical tumor lysis syndrome requires the presence of laboratory tumor lysis syndrome plus an increased creatinine level, seizures, cardiac dysrhythmia, or death.
¥The corrected calcium level in miligrams per deciliter=measured calcium level in miligrams per deciliter + 0.8 x (4-albumin in grams per deciliter)
^Acute kidney injury is defined as an increase in the creatinine level of at least 0.3 mg per deciliter (26.5 µmol per liter) or a period of oliguria lasting 6 hours or more. By definition, if acute kidney injury is present, the patient has clinical tumor lysis syndrome. Administration of G-CSF

Patients with neutropenia must receive G-CSF, which will be administered according to the guidelines of the American Society of Clinical Oncology (ASCO) or of the site.

4.2.2.2 Bendamustine

All patients in this study will receive obinutuzumab in combination with bendamustine, which will be administered in 28-day cycles for 6 cycles.

All patients will receive 70 mg/m^2 doses of bendamustine as an IV infusion on Days 2 and 3 of Cycle 1 and Days 1 and 2 in Cycles 2-6.

Modification of the bendamustine treatment

Dose-modification decisions in patients presenting cytopenia at the start of the cycle (values below the lower limit of normal) shall be based on the Grading Scale for Hematological Toxicity in CLL Studies of the NCI-Sponsored Working Group (NCI-WG) (See Appendix 6)(6). In patients with normal neutrophil, platelet and/or hemoglobin values at baseline, the NCI-CTCAE, v4.0 will be used (see Appendix 7).

In patients who presented an AE during the antibody infusion, the administration of obinutuzumab and of bendamustine can be delayed to the next day, if clinically required, which will then be Day 1 of that cycle. An empirical adjustment of the chemotherapy dose can be performed in obese patients (defined as those with a body mass index ≥ 30, measured in kg/m^2), according to the site's guidelines.

Bendamustine is an IMP in the trial. A total of six 28-day cycles of bendamustine must be administered. If the administration of bendamustine is suspended for reasons other than toxicity, the patients will stop receiving the study treatment and will pass directly on to the monitoring phase.

Bendamustine shall be administered at least 30 minutes after obinutuzumab. No body surface area limit has been established for the determination of the bendamustine dose.

For more information on the modification of the bendamustine dose, please see Appendix 7.

4.2.2.3 Investigational Medicinal Product Accounting

The Sponsor will supply the IMPs (obinutuzumab and bendamustine) necessary to conduct this study. The research sites shall confirm receipt of the IMPs, as well as of the status and contents of the shipment. Any damaged supplies shall be replaced.

The IMPs shall be destroyed at the study sites in accordance with their respective standard operating procedures or shall be returned to the Sponsor together with the appropriate documentation. The method used at the site for IMP destruction must be

agreed upon with the Sponsor. The site must obtain written authorization from the Sponsor prior to destroying any IMP, and the destruction must be documented in the appropriate form.

The medicinal product inventory must include an adequate record of all IMPs received, dispensed, returned and destroyed by the study site.

4.2.2.4 Access to obinutuzumab and bendamustine after the study

The Sponsor has no intention of supplying obinutuzumab or bendamustine to patients once the study has been concluded or after a patient's early withdrawal.

4.3 CONCOMITANT TREATMENT

4.3.1 Permitted treatments

The permitted concomitant therapies include any medication (for example, prescription medication, over-the-counter medications, herbal/homeopathic remedies, nutritional supplements) used by the patients in the 7 days prior to screening until the end of treatment/early treatment discontinuation visit. All concomitant medications must be reported to the investigator and must be recorded in the eCRF under concomitant medications.

4.3.2 Prohibited treatments

The use of the following treatments is not permitted during the study treatment period:

- Investigational or unauthorized or unapproved medicinal products
- Immunotherapy or radioimmunotherapy (other than the trial immunotherapy, obinutuzumab).
- Chemotherapy (other than the trial chemotherapy, bendamustine).
- Radiotherapy

If any of the aforementioned treatments is administered, the patient will be considered to present a treatment failure and will be removed from the study.

Patients may not receive treatment with systemic corticosteroids, except intermittently to control or prevent infusion reactions.

4.4 TRIAL PROCEDURES

4.4.1 Description of the trial procedures

The obligatory trial assessments are summarized in the Assessment Calendar (Appendix 1).

For details regarding the time at which each assessment indicated in this section should be performed, please see Section 4.4.2.

4.4.1.1 Medical history and demographic data

The medical history includes clinically-significant disease, cancer history (including previous therapies and cancer procedures) experienced by the patient in the 28 days prior to the Screening Visit, as well as his/her fertility potential.

In order to assess patient comorbidity, the following scales will be used at the baseline/Screening visit:

- CLL Comorbidity Scale (COLLECT) [Appendix 4]
- Cumulative Illness Rating Scale (CIRS) [Appendix 5]

Concomitant therapy includes any medication (for example, prescription medication, over-the-counter medications, herbal/homeopathic remedies, nutritional supplements) taken by the patient in the 7 days prior to Screening until the end of treatment/early treatment discontinuation visit.

The demographic data will include age, sex and race.

4.4.1.2 Physical examination

The complete physical examination at the baseline visit must include an assessment of the head, eyes, ears, nose and throat and of the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary and neurological systems. Any abnormality identified at the Screening/baseline visit must be recorded in the eCRF. Limited, symptoms-focused physical examinations must be performed at the subsequent trial visits. The changes in the baseline abnormalities must be recorded in the patient's

clinical history. The new abnormalities or worsening of existing abnormalities must be recorded as an AE in the Adverse Event form of the eCRF.

As part of the tumor assessment, a full physical examination should be performed to assess the extent of disease involvement. The exam should also include the evaluation of presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly. Up to a maximum of 6 largest palpable lymph nodes, hepatomegaly, and splenomegaly should be reported in the eCRF.

4.4.1.3 Vital signs

The determination of vital signs shall include pulse, systolic and diastolic blood pressure with the patient in the seated position and body temperature.

4.4.1.4 Eastern Cooperative Oncology Group Performance Status

The performance status will be assessed at the baseline visit and at each study visit using the ECOG scale. When possible, we recommend the performance status assessment of each patient be performed by the same person throughout the entire study.

4.4.1.5 B Symptoms

The B symptoms will be assessed at the baseline visit and at each study visit. They include unjustified fever (> 38°C), night sweats or weight loss (> 10% of body mass in the previous 6 months). B symptoms shall not be reported as AEs. Exacerbation is generally considered a symptom (but is not an objective criterion) of disease progression.

4.4.1.6 12-Lead Electrocardiograms

A 12-lead electrocardiogram must be performed on all patients at the Screening visit, and after that when clinically indicated. The ECGs for each patient must be performed with the same machine, when possible.

4.4.1.7 Clinical stage assessment (Binet and Rai)

At the baseline visit, the disease stage will be assessed according to the Binet and Rai criteria.

Binet Classification:

The staging classification is based on the number of affected areas, defined by the presence of lymph nodes > 1 cm in diameter (only in the physical examination) or organomegaly, as well as anemia or thrombocytopenia.

The affected areas considered for the staging classification are as follows:

- Head and neck, including the Waldeyer's ring (this is counted as a single area, even if there is more than one group of nodes affected)
- Axillae (involvement of both axillae is counted as a single area)
- Inguinal, including superficial femoral arteries (the involvement of both groin sides counts as a single area)
- Palpable spleen
- Palpable liver (clinically enlarged)

Binet Stage A

- Hemoglobin ≥ 100 g/L (10 g/dL) and platelets ≥ 100 x 10^9/L and up to 2 affected areas

Binet Stage B

- Hemoglobin ≥ 100 g/L (10 g/dL) and platelets ≥ 100 x 10^9/L and 3-5 affected areas

Binet Stage C

- Hemoglobin < 100 g/L (10 g/dL) and/or platelets < 100 x 10^9/L, regardless of the presence of lymphadenopathy and organomegaly

Rai Staging System

Stage 0

Stage 0 CLL is characterized by absolute lymphocytosis (>15,000/mm3) without adenopathy, hepatosplenomegaly, anemia, or thrombocytopenia.

Stage I

Stage I CLL is characterized by absolute lymphocytosis with lymphadenopathy without hepatosplenomegaly, anemia, or thrombocytopenia.

Stage II

Stage II CLL is characterized by absolute lymphocytosis with either hepatomegaly or splenomegaly with or without lymphadenopathy.

Stage III

Stage III CLL is characterized by absolute lymphocytosis and anemia (hemoglobin <11 g/dL) with or without lymphadenopathy, hepatomegaly, or splenomegaly.

Stage IV

Stage IV CLL is characterized by absolute lymphocytosis and thrombocytopenia (<100,000/mm3) with or without lymphadenopathy, hepatomegaly, splenomegaly, or anemia.

4.4.1.8 Tumor and response assessments

The tumor assessment will be made according to the assessment calendar of the Protocol (Appendix 1) based on imaging tests carried out in line with the clinical practice of the participating sites.

28 days prior to Day 1 and Cycle 1. The results of the computerized tomography scans (CAT) with contrast medium that were performed prior to the Screening visit as part of the patient's routine clinical assessment can be recorded in the eCRF up to 6 weeks prior to inclusion (in order to prevent patients who have recently undergone a CAT from being re-exposed to radiation). However, a CAT scan must be performed in the 4 weeks prior to inclusion in those patients with signs of rapid disease progression at the Screening Visit. Up to a maximum of six largest bi-dimensional lesions should be reported in the eCRF. Target lesions should measure at least 10 mm in their longest diameter. Note these may be different to those lesions assessed by physical examination. A repeat CT scan of involved sites at baseline will be performed in patients who satisfy the clinical criteria for partial or complete response 2-3 months after the last dose of study treatment. When PD is detected by physical examination in the absence of any objective hematological progression, a CT scan of the involved nodes will be

performed. In addition, CT scans may be performed at any time at the investigator discretion, if clinically indicated.

The response assessments carried out 2-3 months after the last dose of study treatment will be based on the investigator's assessment, completed following the response criteria of the NCI-WG for CLL (Appendix 3).

In patients with severe renal insufficiency at screening use CT contrast according to local practice. If necessary use MRI scan. CT without contrast is not recommended except for patients who develop renal insufficiency during treatment and have previously been assessed by CT scan. It is obligatory to use the same imaging technique for all tumor evaluations.

4.4.1.9 Laboratory tests

The presence of CLL must be documented in all patients (see Appendix 1).

Consult the laboratory assessment scheme required and the laboratory manual to ascertain the times at which the samples are collected and how they are processed.

4.4.1.9.1 Central laboratory

The tests detailed below will be performed at the central laboratory:

- **Confirmation of the CLL diagnosis**. At the Screening visit, a sample of peripheral blood will be sent to the central laboratory to confirm the CLL diagnosis. In the event of absence of lymphocytosis in blood, the determination will have to be performed in bone marrow in the central laboratory. In the case of suspected Richter's Syndrome, we recommend it be ruled out by lymph node biopsy at the site. A biopsy which has been performed as part of standard clinical care up to 6 weeks prior to the first dose of study medication (but prior to obtaining the patient's informed consent for the study) can be used for study purposes.

- **Determination of Minimal Residual Disease.** At the visit 2-3 months after the trial treatment is finalized, MRD will be determined in peripheral blood and in bone marrow aspirate, only for those patients in which CR/CRi/PR has been observed. The eradication of MRD is becoming a desired endpoint in the treatment of B-lymphocyte CLL. The data indicates that patients achieving

remission and who are MRD-negative have a significantly lower rate of relapse, a longer progression-free survival and, in some cases, a better overall survival.

- **Determination of the prognosis markers**

  A sample of peripheral blood will be obtained at the baseline/Screening visit and sent to the central laboratory for the determination of the following prognostic markers:

  - Expression of ZAP70, CD38 and CD49D, by multiparametric flow cytometry.
  - Mutation analysis
    - Mutations in the immunoglobulin heavy chain variable region (IGHV), by direct sequencing
    - p53 (17p13.1), ATM (11q22.3), by FISH
    - NOTCH 1, by quantitative PCR.
    - SF3B1, by quantitative PCR.
    - BIRC3, by quantitative PCR (fusion curve analysis).

At the Screening/baseline visit, a sample of peripheral blood will be collected with EDTA/heparin (See Sample Manual).

At the visit completed 2-3 months after the finalization of the study treatment, a sample of peripheral blood with EDTA and a sample of bone marrow aspirate with EDTA will be collected, only for patients with CR/CRi/PR (See Sample Manual).

Additionally, at the screening/baseline visit a sample of saliva will be obtained for the study of the following 26 genes: ATM, BIRC3, BRAF, CHD2, CSMD3, DDX3X, FBXW7, KLHL6, KRAS, LRP1B, MAPK1, MUC2, MYD88, NFKBIE, NOTCH1, PLEKHG5, POT1, SAMHD1, SF3B1, SI, SMARCA2, TGM7, TP53, XPO1, ZMYM3, EGR.

Annotation: For subjects included in the study prior to Protocol Amendment 4, this sample of saliva will be obtained as soon as possible, provided that informed consent form amendment has been previously signed.

4.4.1.9.2 Local laboratory

The laboratory tests detailed below will be performed at the participating sites. The results of the laboratory safety assessments must be available on the days of treatment, prior to the administration of the study treatment.

These laboratory tests will be carried out locally, according to local standards. Roche must be provided the normal values of the laboratory parameters for the trial prior to trial start.

- The hematological parameters will include: hemoglobin, hematocrit, red blood cell count, white blood cell count, absolute differential count (neutrophils, eosinophils, lymphocytes, monocytes, basophils, other cells). and platelet count.
    - The biochemistry parameters will include sodium, potassium, chloride, bicarbonate, fasting glucose, blood urea nitrogen (BUN), creatinine, calcium, total and direct bilirubin, total proteins, albumin, ALT, AST, alkaline phosphatase, phosphorus, magnesium, LDH, creatinine phosphokinase, uric acid.
- The coagulation tests will include: International Normalized Ratio (INR), Prothrombin Time (PT), activated Partial Thromboplastin Time (aPTT).
- Pregnancy test: women of childbearing potential (defined as premenopausal women for whom < 2 years have passed since the onset of menopause and who are not surgically sterilized) must undergo a pregnancy test in blood in the 7 days prior to the start of the administration of the study drug, or else in the 14 days prior if a confirming pregnancy test in urine in the 7 days prior to the administration of the trial drug is done. If the pregnancy test in urine is positive, it must be confirmed with a pregnancy test in blood.
- Quantitative immunoglobulin: IgA, IgG, and IgM
- β2 microglobulin

- The serology and viral detection must be conducted prior to the first administration of the trial drug according to the clinical criteria and must include the following tests:

- HBV: Hepatitis B surface antigen and total Hepatitis virus core antibodies. Additional serology for HBsAb is required prior to Cycle 1, Day 1 for patients who are HBsAg-negative and HBcAb-positive at screening.
- HCV: HCV antibody. HCV RNA is required for patients who are HCV antibody positive.
- Test for the detection of HIV antibodies.

Patients with a known or detected active HIV, HCV or HBV infection must not be included in the trial. The provisions of local legislation must be adhered to with respect to consent when conducting viral tests.

4.4.2 Trial assessment calendar

4.4.2.1 Screening and pre-treatment assessments

Written informed consent for participation in the trial must be obtained prior to performing any trial-specific screening assessment or test. The informed consent forms for patients recruited and for patients who undergo the screening process but were not recruited shall be kept at the site where the trial is conducted.

In order to avoid repetition of irradiation and invasive procedures, CT scans and biopsies performed in the previous 6 weeks will be accepted, except for patients in whom signs of rapid disease progression are observed, in which case, the imaging tests must be performed in the 4 weeks prior to inclusion (see Section 4.4.1.8). All known foci of the presence of the disease must be documented at the Screening/baseline visit to provide an accurate basis for future assessments.

All screening assessments must be completed and reviewed to confirm that the patients comply with the eligibility criteria prior to being selected for the trial.

The investigator shall keep a screening form in line with the local requirements regarding the trial files to record details on all patients assessed and to confirm their eligibility or to record the reasons why they do not fulfill the screening criteria.

The samples required for the laboratory tests performed centrally will be collected and submitted at the Screening visit. At the Screening visit, a sample of peripheral blood will be sent to the central laboratory to confirm the CLL diagnosis. In the event of absence of lymphocytosis in blood, the determination will have to be performed in bone marrow in

the central laboratory. In the case of suspected Richter's Syndrome, we recommend it be ruled out by lymph node biopsy at the site (Section 4.4.1.9.1.).

Additionally, a sample of saliva will be submitted for the study of DNA sequencing.

See Appendix 1 for the screening and pre-treatment assessment calendar.

4.4.2.2 Assessments during treatment

With the exception of Days 1 and 2 in Cycle 1, all assessments must be performed (± 3 days of the planned calculated visit date. For all other cycles, all assessments must be performed within a window of ± 5 days with respect to the planned visit date, with the exception of delays resulting from toxicities [See Appendix 1].

During the treatment, the physical examination, ECOG and B symptoms assessment, local laboratory tests (complete blood count and biochemistry), and the assessment and monitoring of adverse events will be performed, and all concomitant diseases and treatments shall be recorded. The assessments scheduled for the day of the trial treatment administration must be performed prior to the administration of the trial treatment.

Please see Appendix 1 for the Assessment Calendar for assessments carried out during the treatment period.

4.4.2.3 Assessments at the End of Treatment/Early Termination Visit

Patients who complete treatment (defined as 6 cycles of obinutuzumab therapy either alone or in combination with chemotherapy) or discontinue from study treatment early will be asked to return to the clinic 28 (± 5) days after the last dose of study drug for a visit.

If obinutuzumab is discontinued, the patient should be followed for disease progression, new anti-leukemia treatment and survival.

Please see Appendice 1 for the assessments to be performed at the EOT/ET visit.

4.4.2.4 End-of-treatment assessments Assessments at the Final Response Assessment Visit .

Patients who complete the study treatment in accordance with the Protocol (6 treatment

cycles) or who discontinue the study treatment early will be asked to return to the site after 2-3 months after the last dose of the study treatment for the Final Response Assessment visit. The response assessment will be performed at this visit. For patients in whom disease progression was observed, the visit at which disease progression is assessed will be considered the end-of-treatment visit.

Moreover, at the Final Response Assessment visit, samples of peripheral blood and bone marrow will be obtained to be sent to the central laboratory for the MRD study, only for patients in whom CR/CRi/PR is observed (Section 4.5.1.5.1.).

Please see Appendix 1 for the assessments performed at the end-of-treatment visit.

4.4.2.5 Monitoring Assessments during the Follow-Up Visits

Every patient must report to the site for the monitoring visits performed every 6 months (±14 days) from the End of Treatment Visit until the trial finalization (i.e. 2.5 years after the first visit of the last patient), unless the patient has died or left the study prior to trial finalization.

If obinutuzumab is discontinued, the patient should be followed for disease progression, new anti-leukemia treatment and survival.

Once the patient has presented disease progression or started a new leukemia treatment, the monitoring visits will be completed annually to collect survival-related data.

After study finalization, all adverse events must be monitored as indicated in Section 5.5.

See Appendix 1 for the assessment calendar during monitoring.

4.4.2.6 Assessments at unscheduled visits

At unscheduled visits, all tests required according to clinical criteria shall be performed. The tests detailed in the Assessment Calendar (See Appendix 1) shall only be performed in the event the Principal Investigator deems them necessary, with the exception of the review of the patient's overall health and the safety assessment, which must be performed in all cases.

4.5 DISCONTINUATION OF STUDY PATIENTS AND PARTICIPATING SITES

4.5.1 Discontinuation of patients

The investigator has the right to suspend the participation of a patient in the trial treatment or to withdraw a patient from the trial at any time. Moreover, patients have the right to voluntarily discontinue the trial treatment or to withdraw from the trial at any time and for any reason. The reasons for trial discontinuation may include, but are not limited to:

- Any medical condition that the investigator or Sponsor believes could endanger the safety of the patient if he/she were to remain in the trial treatment.
- Pregnancy.
- Serious Protocol deviation.
- Patient's withdrawal of consent at any time. In the cases in which consent is withdrawn, the investigator must clarify and document if the patient is willing to continue to be monitored (for example, for survival).
- The investigator or Sponsor decides what is in the best interest of the patient.
- Loss to follow-up.
- Finalization of the trial by the Sponsor or regulatory authorities.
- Finalization of the trial at the site by the investigator or CREC.

4.5.1.1 Discontinuation of the trial treatment

The trial treatment must be discontinued in any of the following circumstances:

- Pregnancy
- PML
- Grade 4 IRR: the patient will be immediately withdrawn from the study and the treatment will be definitively discontinued
- Grade 3 IRR after re-exposure to the drug, despite having been administered adequate premedication. The patient will be immediately withdrawn from the study and the treatment will be definitively discontinued

- Grade 3 or 4 neutropenia or thrombocytopenia that does not subside to grade ≤ 2 and requires the start of the next treatment cycle to be delayed by 4 weeks.
- Grade ≥ 2 non-hematological toxicity that does not subside to grade ≤ 1/baseline and requires the start of the next treatment cycle to be delayed by 4 weeks.

Patients whose administration of the trial treatment has been discontinued early will be asked to return to the site for the end-of-treatment/early finalization visit (see Section 4.5.2.3). The primary reason for the early treatment discontinuation must be documented in the eCRF.

4.5.1.2 Withdrawal from the trial

All possible efforts must be made to obtain information about the patients removed from the trial. The primary reason for trial withdrawal must be documented in the eCRF. If patients withdraw from study treatment due to PD and have started new anti-leukemia therapy, they should still be followed up for survival–according to the Schedule of Required Assessments (Appendix 1). No patient monitoring for any reason shall be performed after the patient withdraws his/her informed consent. The patients withdrawn from the trial will not be replaced.

4.5.2 Suspension of the trial and of the participating site

The Sponsor has the right to end this trial at any time. The reasons for trial discontinuation may include, but are not limited to:

- When the incidence or severity of the AEs observed in this or other studies indicate a potential risk to the health of the patients.
- If patient inclusion is unsatisfactory.

The Sponsor shall inform the investigator in the event the study is temporarily interrupted, or if a decision was made to cancel the trial or development program.

The Sponsor has the right to replace a site at any time. The reasons for replacing a site may include, but are not limited to:

- Excessively slow patient recruitment.
- Protocol breach and/or repeated protocol deviations.

- Repeated delays/inaccuracies in the data registry or inability to resolve questions regarding data in the eCRFs.
- Breach of the Good Clinical Practices of the International Conference on Harmonization (ICH).
- In the interest of patient safety.

5. SAFETY ASSESSMENT

5.1 SAFETY PLAN

Patients will be assessed based on their previous medical history, vital signs (including blood pressure, pulse and body temperature at rest), physical examination, AEs and concomitant medications. A complete medical history (including previous cancer treatments) will be documented at the Screening/baseline visit. A complete physical examination will be conducted including an assessment of infections at the Screening/baseline visit and at each treatment and post-treatment monitoring visit (see Appendix 1, Assessment Calendar). All patients will be subject to routine laboratory analyses for safety.

All AEs will be monitored and documented continuously throughout the trial (at each treatment visit and during the post-treatment monitoring, as detailed in Section 5.3.1). Please see Sections 5.4.2 and 5.5 for information on the requirements for reporting SAEs and their monitoring, respectively. All AEs and SAEs (including the patients' signs and symptoms of toxicity and hematological and biochemical parameters of clinical significance) will be graded according to the NCI CTCAE version 4.0 (see Appendix 6).

Any changes to concomitant medication will be recorded at each trial visit. The record of concomitant treatments and therapies shall include any new CLL treatment started after the baseline visit.

Please see section 4.5.1.1 for information on treatment discontinuation guidelines.

5.1.1 Infusion-related and hypersensitivity reactions, including anaphylactic reactions

The adverse drug reactions observed most commonly in patients treated with obinutuzumab were IRR, which appeared in the majority of patients primarily during the first infusion. The incidence of the infusion-related symptoms decreased substantially with subsequent infusions.

In most patients, the IRRs were mild to moderate and could be managed by lowering the infusion rate or temporarily discontinuing the first infusion. Some IRRs required treatment. The common symptoms associated with IRRs were hypotension, fever, chills, hot flashes, nausea, vomiting, hypertension and fatigue. Respiratory symptoms related to the infusion, such as hypoxia, dyspnea, bronchospasm, irritation of the larynx and throat and laryngeal edema have also been reported. IRRs may not be clinically distinguishable from IgE-mediated allergic reactions (e.g. anaphylaxis). Patients with a high tumor load (that is, with an elevated peripheral lymphocyte count in CLL [> 25 x 10^9/L]) may have a greater risk of experiencing severe IRRs.

5.1.1.1 Prophylaxis for infusion-related reactions

Hypotension may occur as a result of an IRR; therefore, consideration should be given with respect to withholding antihypertensive medications for 12 hours prior to the infusion.

Since some patients may develop hypersensitivity or other IRRs to obinutuzumab, premedication with acetaminophen/paracetamol (p.o.or i.v. 650–1000 mg) and an anti-histamine such as diphenhydramine (50–100 mg) must be administered approximately 30 minutes prior to the start of obinutuzumab infusions (unless contraindicated). For obinutuzumab infusions subsequent to Cycle 1 Day 1 and Day 2, the anti-histamine premedication may be omitted if the previously administered obinutuzumab infusion did not result in an IRR > CTCAE Grade 1 (i.e., no medication was required to treat the IRR and there was no interruption to the infusion).

For the first infusion (Day 1 / Day 2), premedication with prednisolone or prednisone, 100 mg given i.v. at least 1 hour before the antibody infusion, is mandatory for obinutuzumab patients. An equivalent dose of dexamethasone (20 mg) or methylprednisolone (80 mg) is permitted, but hydrocortisone should not be used. In subsequent infusions, premedication with corticosteroids will be administered in the following cases:

- Patients who have presented a grade ≥ 3 IRR with the previous infusion
- Patients with lymphocyte counts > 25 x 10^9/L

- At the investigator's discretion

In patients with a high lymphocyte count and voluminous lymphadenopathy, the infusion can be administered extremely slowly over a longer period of time or the dose can be divided and administered on two consecutive days. We recommend always administering the first infusion on two consecutive days in these patients.

5.1.1.2 Treatment of IRRs

If an IRR is presented during the infusion, the infusion must be discontinued or the administration rate must be decreased until the IRR is resolved. Then, the infusion can be resumed at half the rate used in the previous infusion. Patients must not receive more infusions of obinutuzumab if they present a grade 4 IRR (i.e. life-threatening) or a second episode of a grade 3 IRR (prolonged/recurrent) (after resuming the first infusion or in a subsequent infusion) despite having been administered proper premedication.

Patients with concurrent cardiac or pulmonary pathologies must be closely monitored during the infusion and in the period following the administration of the infusion. Hypotension is expected to present during IV infusions of obinutuzumab. Therefore, the withdrawal of anti-hypertensive medications 12 hours prior to and during the entire infusion, as well as up to one hour after the administration of the infusion, must be considered. The benefit-risk ratio of this measure must be assessed in patients with severe hypertension.

5.1.2 Tumor lysis syndrome

Patients with a high tumor burden (white blood cell count ≥ 25 x 10^9/L or bulky lymphadenopathy) must receive prophylaxis for TLS prior to the initiation of treatment. This includes appropriate hydration, consisting of a fluid intake of approximately 3 liters per day, starting 1–2 days before the first dose of obinutuzumab. All such patients with high tumor burden must be treated with allopurinol or a suitable alternative treatment (i.e. rasburicase) starting at least 72 hours prior to the first infusion of obinutuzumab (Cycle 1, Day 1. These measures may also be extended to other patients considered at risk of TLS in the judgment of the investigator.

Patients still considered at risk for TLS because of persistently high tumor burden (i.e., peripheral blood lymphocyte counts ≥ 25 × 10^9/L) before the second and subsequent infusions of obinutuzumab should continue to receive TLS prophylaxis with allopurinol or a suitable alternative (i.e., rasburicase) and adequate hydration until the risk is abated, as determined by the investigator.

All patients considered at risk by the investigator should be carefully monitored during the initial days of study treatment with a special focus on renal function, potassium, and uric acid values. Hematology and biochemistry assessments must be performed as per the Schedule of Assessments (Appendix 2) at every study visit, including both Day 1 and 2 of Cycle 1. Chemotherapy should not be resumed before all symptoms (clinical or laboratory) of TLS have disappeared (30-31, Table 4).

Patients fulfilling the criteria described below, who will receive treatment with obinutuzumab in combination with bendamustine, should be treated and monitored more carefully as these patients are at increased risk of TLS:

- Any measurable lymph node ⩾10 cm
- Any measurable lymph node ⩾5 cm and <10 cm AND
  - ⩾25 × 109/L ALC
- Any measurable lymph node ⩾5 cm and <10 cm AND
  - Renal impairment defined as creatinine clearance <70 mL/min
- ⩾25 × 109/L ALC AND renal impairment defined as creatinine clearance <70 mL/min.

These patients must be treated and monitored as follows:

- Patients should receive oral hydration (recommended intake: approximately 3 L per day) for 3 days prior to first dose of obinutuzumab, and should receive i.v. hydration on Day 1 and Day 2 of Cycle 1 (recommended intake: approximately 3 L per day). Oral hydration should restart on Day 3 and continue up until and including Day 8 (recommended intake: approximately 3 L per day)
- Patients should be treated with uricostatics (such as allopurinol) or urate oxidase (such as rasburicase) in accordance with the label or local guidance. Treatment with allopurinol should start 3 days prior to Day 1 of Cycle 1 and continue at least until and including Day 8 of Cycle 1. Due to a potential interaction between allopurinol and bendamustine, which may lead to severe skin reactions, allopurinol treatment should be paused during the days of bendamustine administration and re-started from the day after the second bendamustine treatment. If rasburicase is available it should be considered, especially in patients with elevated pre-treatment urate levels despite allopurinol use, as it has been shown to be more efficacious than allopurinol (Cortes et al. 2010).
- Patients should undergo laboratory assessments for TLS (uric acid, calcium, phosphorus, potassium, and creatinine) and the results should be known on the same day the sample was taken. On the day of study treatment, the results should be known before starting the infusion of obinutuzumab and bendamustine:
  - Day 1 of Cycle 1 (sample taken and results known before starting the infusion)

- Day 2 of Cycle 1 (sample taken and results known before starting the infusion)
- Day 3 of Cycle 1 (sample taken and results known on the same day)
- Day 5 of Cycle 1 (sample taken and results known on the same day)
- Day 8 of Cycle 1 (sample taken and results known before starting the infusion).

• If the Howard criteria for TLS (Howard et al. 2011; Table 7) are fulfilled (two or more electrolyte laboratory abnormalities present simultaneously) or if a medically relevant laboratory abnormality in TLS-related parameters or a sign of clinical TLS (e.g. increased serum creatinine or cardiac dysrhythmia) are noted, study drugs should be withheld and patients should be hospitalized and adequately treated until normalization of laboratory abnormalities. After normalization, treatment may be restarted

• Patients must be informed about symptoms or signs of TLS (e.g., fever, chills, dysrhythmias, nausea, vomiting, diarrhea, diaphoresis, hypotension, muscle aches, weakness, paresthesias, mental status changes, confusion, and seizures) and advised to contact the investigator immediately if any such symptoms occur. If any clinical features are observed, potassium, phosphorus, uric acid, calcium, and creatinine levels must be rechecked within 1 hour.

• For patients who are not considered at risk but have impaired renal function, nephrology findings should be discussed and the laboratory monitoring outlined above must be followed.

5.1.3 Neutropenia

Cases of Grade 3 or 4 neutropenia, including febrile neutropenia, have been reported with GA101 administration. Grade 3 or 4 neutropenia has predominantly been observed in patients with CLL. Patients who experience Grade 3 or 4 neutropenia should be monitored until neutrophil values return to at least Grade 2. Use of granulocyte colony-stimulating factors (G-CSF) has been found to result in a rapid normalization of neutrophils, similar to what has been observed in patients treated with rituximab. The use of G-CSF is allowed for treatment of neutropenia in this study. Primary prophylaxis with G-CSF is recommended according to the American Society of Clinical Oncology (ASCO), EORTC, and European Society for Medical Oncology (ESMO) guidelines, namely for patients who are $\geqslant$ 60 years old and/or with co-morbidities (28).

5.1.4 Thrombocytopenia

Severe and life threatening thrombocytopenia including acute thrombocytopenia (occurring within 24 hours after the infusion) has been observed during treatment with GA101. Fatal haemorrhagic events have also been reported in patients treated with GA101. It seems that the first cycle is the greatest risk of haemorrhage in GA101-treated patients. A clear relationship between thrombocytopenia and haemorrhagic

events has not been established. Patients treated with concomitant medication, which could possibly worsen thrombocytopenia related events such as platelet inhibitors and anticoagulants, may be at greater risk of bleeding. Patients should be closely monitored for thrombocytopenia, especially during the first cycle; regular laboratory tests should be performed until the event resolves, and dose delays should be considered in case of severe or life-threatening thrombocytopenia. Transfusion of blood products (i.e. platelet transfusion) according to institutional practice is at the discretion of the treating physician.

5.1.5 Progressive multifocal leukoencephalopathy

Cases of John Cunningham virus infection resulting in PML (an infection that causes the destruction of the oligodendrocytes of the white matter of the central nervous system) have been reported in patients receiving anti-CD20 treatments, including rituximab and obinutuzumab.

The PML diagnosis must be considered in all patients presenting new-onset neurological manifestations. The symptoms of PML are very unspecific and may vary depending on the region of the brain affected. Motor involvement with findings in the corticospinal tract, sensorial involvement, cerebellous deficits and visual field defects are commonly observed. Some syndromes considered "cortical" (e.g. aphasia or spatial-visual disorientation) may also occur.

The assessment for PML includes, but is not limited to, a consultation with a neurologist, brain MRI and lumbar puncture to quantify the DNA of the John Cunningham virus in cerebrospinal fluid.

The treatment with obinutuzumab must be discontinued while assessing for a potential case of PML, and if the diagnosis is confirmed, it will be discontinued definitively. The suspension or reduction of the dose of any chemotherapeutic agent or concomitant immunosuppressive therapy agent should also be considered. The patients must be referred to a neurologist for PML treatment.

5.1.6 Cardiac disorders

In patients with underlying cardiopathy, arrhythmia, such as atrial fibrillation and tachyarrhythmia, angina of the chest, acute coronary syndrome, myocardial infarction and heart failure have been observed during the treatment with obinutuzumab. These

events may occur as part of an IRR and can be fatal. Therefore, patients with a history of cardiopathy must be closely monitored. In addition, these patients must be hydrated with caution to prevent a possible fluid overload.

5.1.7 Gastrointestinal Perforation

Cases of gastrointestinal (GI) perforation have been reported in patients receiving obinutuzumab, mainly in patients with non-Hodgkin's lymphoma (NHL). Patients with GI involvement should be monitored for signs of GI perforation.

5.1.8 Infection

Obinutuzumab must not be administered in the presence of severe infections and caution must be exercised when considering the use of obinutuzumab in patients with a history of recurrent or chronic infection.

5.1.9 Reactivation of Hepatitis B

Cases of reactivation of hepatitis B have been reported in patients receiving anti-CD20 treatments, including obinutuzumab. These events may be severe and potentially fatal. HBV detection tests must always be performed prior to starting the treatment with obinutuzumab. Patients with positive serology (which is defined as testing positive for the hepatitis B virus surface antigen [HBsAg]) must not be included in the study (however, patients presenting protective HBsAg titers following vaccination will be eligible for the study).

Immunization

The safety of immunization with live virus vaccines after treatment with obinutuzumab has not been assessed; therefore, the use of said vaccines is not recommended.

To improve the traceability of the biological medicinal products, the commercial name of the vaccine administered must be recorded (or indicated) clearly in the patient's file.

5.1.10 Fertile males and potentially fertile females

Males of fertile age and potentially fertile women, unless they have been surgically sterilized or, in the case of women, ≥ 2 years have passed since the onset of menopause, must be willing to use a highly effective contraceptive method (Pearl index < 1), such as oral contraceptives, intrauterine devices, sexual abstinence or a barrier

method, together with a spermicide gel during the study treatment and, in female patients, for 12 months after the treatment with the antibody is finalized, and in males, for 6 months after the treatment with chemotherapy is finalized.

5.1.11 Pregnancy

No studies have been conducted on pregnant women. One reproduction study conducted on cynomolgus monkeys showed no indications of teratogenic effects. However, the number of B cells in lymphoid tissue fell in the offspring of treated females. The B cell counts returned to normal levels and immune function was re-established 6 months after birth.

Using obinutuzumab during pregnancy should be avoided, unless the possible benefit for the mother outweighs the potential risk for the fetus.

5.1.12 Breastfeeding

It is unknown whether obinutuzumab is excreted in human breast milk. Animal studies have shown that obinutuzumab is excreted in breast milk. Given that the human IgG is excreted in human breast milk and that the potential for absorption and damage to the fetus is unknown, women must be warned to stop breastfeeding during treatment with obinutuzumab and up to 18 months after receiving the last dose of this drug.

5.1.13 Fertility

There are no data on the effects of obinutuzumab on human fertility. The effects on male and female fertility have not been assessed in animal studies.

5.1.14 Management of adverse events with bendamustine

Dose-modification decisions in patients presenting cytopenia (values below the lower limit of normal) at baseline shall be based on the Grading Scale for Hematological Toxicity in CLL Studies of the NCI-Sponsored Working Group (NCI-WG) (6) (see Appendix 67).

5.2 SAFETY PARAMETERS AND DEFINITIONS

The safety assessments will consist of the recording and follow-up of AEs, including SAEs and non-serious adverse events of special interest; determination of laboratory parameters or other clinical tests specified by the Protocol, determination of vital signs

specified by the Protocol; and other tests specified by the Protocol that are considered key to the safety assessment of the trial.

Section 5.4 presents the specific types of events that must be immediately reported to the Sponsor.

5.2.1 Adverse Events

According to the ICH Good Clinical Practice guidelines, an AE is an untoward medical event experienced by a clinical trial subject who has been administered a pharmaceutical product, regardless of the causal relationship. Therefore, an AE may be any of the following:

- Any unfavorable or unintentional sign (including the detection of laboratory abnormalities), symptom or disease temporally associated with the use of a medicinal product, regardless of whether it is related to the product in question.
- Any new disease or exacerbation of an existing disease (worsening of the nature, frequency or seriousness of a known disease), except as described in Section 5.3.5.9.
- Reappearance of an intermittent medical condition (e.g. headache) not present at the baseline visit.
- Any worsening of a laboratory value or other clinical test value (for example, ECG, X-rays) associated with symptoms that lead to a change in the trial treatment or concomitant treatment or to the discontinuation of the trial drug.
- AEs related to procedures required by the Protocol, including those occurring prior to the administration of the trial treatment (for example, invasive procedures performed for Screening, such as biopsies).

5.2.2 Serious Adverse Events (for immediate reporting to the Sponsor)

An SAE is any AE that meets any of the following criteria:

- Fatal (that is, the AE caused or led to death)

- Life-threatening (that is, the AE, in the investigator's opinion, put the patient at immediate risk of dying).
- The term "life-threatening" in the definition of "serious" refers to an event in which the patient runs the risk of dying at the time the event occurred; it does not refer to an event that could have hypothetically been fatal had it been more severe.
- Requires or extends the patient's hospitalization (see Section 5.3.5.10).
- Results in a permanent disability/incapacity (that is, the AE results in a substantial change in the patient's capacity to lead a normal life).
- Congenital birth defect/anomaly.
- A significant medical event in the investigator's opinion (for example, that puts the patient's life at risk or that could require medical/surgical intervention to prevent any of the results described above).

For obinutuzumab, the following events are considered serious and immediately reportable to the Sponsor:

- Grade 4 IRR defined as any AE occurring during or within 24 hours of an obinutuzumab infusion and considered related to obinutuzumab (refer also to Table 3 and Section 4.5.1.1)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (classified as mild, moderate or severe according to the NCI CTCAE; see Section 5.3.3 and Appendix 6); the event in itself may be of relatively lower medical significance (such as severe headache with no other findings).

Severity and seriousness must be assessed independently for each AE included in the eCRF.

The investigator must inform the Sponsor of the SAEs (including Adverse Events of Special Interest, AESI, see Appendix 1.2.1.4.) within 24 hours of becoming aware of the event (see Section 5.4 for instructions on the reporting procedure).

5.2.3 Non-Serious Adverse Events of Special Interest (for immediate reporting to the Sponsor)

AEs of special interest (see Appendix 1.2.1.4.) with 24 hours of becoming aware of the event (see Section 5.4 for instructions on the reporting procedure).

5.3 METHODS AND TIMELINES FOR RECORDING AND ASSESSING THE SAFETY PARAMETERS

The investigator is responsible for ensuring that all AEs are recorded (see Section 5.2.1 for definition) in the AE form of the eCRF and that the Sponsor is informed of them according to the instructions provided in this section and Sections 5.4–5.5.

For every AE recorded in the AE form of the eCRF, the investigator must perform an assessment of its seriousness (see Section 5.2.1 for criteria on seriousness, severity (Section 5.3.3), and causal relationship (see Section 5.3.4).

5.3.1 Adverse Event reporting period

The investigators shall seek information on AEs with every contact with the patient. All AEs, regardless of whether they are indicated by the patient or discovered by the trial personnel, must be recorded in the patient's medical history and in the AE form of the eCRF.

After obtaining informed consent but **before starting the trial treatment,** only SAEs occurring due to a Protocol-indicated procedure (e.g. SAEs related to invasive procedures like biopsies) will be reported.

After starting the trial treatment, all AEs, regardless of their relationship with the trial medicinal product, occurring up until the final response assessment is performed shall be reported. Grade 3-4 infections up to 24 months after the end of treatment must be reported. All SAEs, non-serious AESIs and late onset neutropenia that is believed to be related to prior study drug treatment will be reported indefinitely.

Second malignancies will be reported indefinitely, regardless of relationship to study treatment (even if the study has been closed).

After this reporting period, the investigator is not required to actively monitor patients for adverse events; however, the Sponsor should be notified ~~if the investigator becomes aware of any post study serious adverse events~~ if the investigator become aware of the development of cancer (see Section 5.6) after the trial is finalized.

5.3.2 Obtaining information on Adverse Events

A methodology consisting of open-ended questions must be adopted to obtain information on AEs at all times during patient assessment. Examples of open-ended questions include:

- "How have you felt since your last visit to the clinic?"
- "Have you had any new health problems or has there been any change since the last time you were here?"

5.3.3 Assessment of adverse event severity

The NCI CTCAE (version .4; see Appendix 6) will be used to assess AE severity. Table 5 will be used to evaluate the severity of the AEs not specifically indicated in the NCI CTCAE.

Table 5: Adverse Events grading scale

Grade	Severity
1	Mild; asymptomatic or mild symptoms; only clinical or diagnostic observations; or do not indicate intervention
2	Moderate; indication of minimal, local or non-invasive intervention; or that limit the age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant but not life-threatening; indicates hospitalization or extension of existing hospitalization; incapacity or limitation of activities of daily living for self-care [b,c]
4	Fatal consequences or indication of emergency intervention [d]
5	Adverse Event-related death [d]

a. Instrumental activities of daily living refer to preparing meals, shopping for food or clothing, using the phone, managing money, etc.

b. Examples of activities of daily living for self care include bathing, getting dressed and undressed, feeding oneself, using the bathroom and taking medication like patients who are not bedridden.

c. If an event is evaluated as a "medically significant event", it must be reported as an SAE (see Section5.4 for instructions on how it should be reported), according to the definition of SAE in Section 5.2.2.

d. If an event is evaluated as a "medically significant event", it must be reported as an SAE (see Section 5.4 for instructions on how it should be reported), according to the definition of SAE in Section 5.2.2.

5.3.4 Assessment of the causal relationship of the adverse events

The investigators must use their knowledge of the patient, the circumstances of the event and an assessment of any potential alternative cause to decide if an AE is considered to be related to the trial medication, and indicate "yes" or "no" as applicable. The following guidelines should be considered:

- Temporal relationship of the onset of the event with the start of the treatment with the trial medication.
- Course of the event, especially considering the effects of dose reduction, suspension of the administration of the trial medication or re-challenge of the trial medication (if applicable).
- Known association of the event with the trial medication or with similar treatments.
- Known association of the event with the disease studied.
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event.
- Presence of factors not related to the treatment that are known to be associated with the occurrence of the event.

For patients receiving combination therapy, which is the case of the treatment in this trial, the causal relationship will be assessed individually for each therapy indicated by the Protocol.

5.3.5 Procedures for recording Adverse Events

The investigators must use the medically-appropriate terminology/concepts when recording the AE in the Adverse Events form of the eCRF. Colloquial expressions and abbreviations must be avoided.

Only one AE term should be recorded in the event field in the Adverse Events form of the eCRF.

5.3.5.1 Diagnosis versus signs and symptoms

The diagnosis (if known) should be recorded in the Adverse Events form of the eCRF before the individual signs and symptoms (for example, record only liver failure or hepatitis before jaundice, asterixis or elevated transaminases). However, if a constellation of signs and symptoms cannot be medically characterized as a single diagnosis or syndrome at the time the report is made, each individual event must be recorded in the Adverse Events form of the eCRF. If a diagnosis is made at a later time, all AEs that had previously been reported based on signs and symptoms must be voided and replaced by an AE report based on the single diagnosis, with a date of onset corresponding to the date of onset of the first symptom of the possible or temporal diagnosis.

5.3.5.2 Adverse events occurring as a result of other events

In general, AEs occurring secondarily with respect to other events (for example, cascade events or clinical sequelae) must be identified by their primary cause, with the exception of severe or serious secondary events. However, medically significant AEs occurring secondarily with respect to an initial event and that are separated in time must be recorded as independent events in the Adverse Events form of the eCRF. For example:

- If vomiting causes mild dehydration with no need for an additional treatment. Only the vomiting should be reported in the eCRF.
- If the vomiting causes severe dehydration, the two events should be reported separately in the eCRF.
- If a gastrointestinal hemorrhage causes kidney failure, the two events should be reported separately in the eCRF.
- If dizziness causes a fall and fracture, the three events should be reported separately in the eCRF.
- If neutropenia is accompanied by a mild, non-serious, infection, only the neutropenia should be reported in the eCRF.
- If neutropenia is accompanied by a severe or serious infection, the two events should be reported separately in the eCRF.

All AEs must be reported separately in the Adverse Events form of the eCRF if it is unclear whether or not the events are related.

5.3.5.3 Persistent or recurrent adverse events

A persistent AE is one that continuously remains unresolved between patient evaluation time points. This type of event should only be recorded once in the Adverse Events form of the eCRF. The initial severity of the event must be recorded, and the severity should be updated to reflect the maximum severity at any time in which the event worsens. If the event becomes a serious event, the Adverse Event form of the eCRF should be updated to reflect it.

A recurrent AE is that which is resolved between patient assessment points and then reappears. Every reappearance of an AE must be recorded separately in the Adverse Event form of the eCRF.

5.3.5.4 Laboratory test abnormalities

Not all laboratory abnormalities qualify as AEs. A laboratory analysis result must be reported if it meets any of the following criteria:

- It is accompanied by clinical symptoms.
- It results in a change in the trial treatment (for example, dose modification, treatment interruption or treatment discontinuation).
- It results in a medical intervention (for example, potassium supplements for hypokalemia) or a change in the concomitant therapy.
- It is clinically significant in the investigator's opinion.

It is the investigator's responsibility to review all results of laboratory analyses. Medical and scientific discretion should be exercised to decide if an isolated laboratory abnormality should be classified as an AE.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (for example, alkaline phosphatase and bilirubin five times higher than the ULN associated with cholecystitis), it should only be recorded at diagnosis (that is, as cholecystitis) in the Adverse Events form of the eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself must be recorded in the Adverse Events form of the eCRF,

together with a descriptive term that indicates whether the analysis result is above or below normal values (for example, "high potassium", instead of "abnormal potassium"). If the laboratory abnormality can be characterized using an accurate clinical term within the standard definitions, the clinical term should be recorded as the AE. For example, elevated blood potassium of 7.0 mEq/L should be recorded as "hyperkalemia".

The observations of a single laboratory abnormality from one visit to the next must not be recorded repeatedly in the Adverse Events form of the eCRF, unless the etiology has changed. The initial severity of the event must be recorded, and the severity and seriousness should be updated if at any time the event worsens.

5.3.5.5 Vital sign abnormalities

Not all vital sign abnormalities qualify as AEs. A vital sign abnormality must be reported as an AE if it meets any of the following criteria:

- It is accompanied by clinical symptoms.
- It results in a change in the trial treatment (for example, dose modification, treatment interruption or treatment discontinuation).
- It results in a medical intervention or change in the concomitant therapy.
- It is clinically significant in the investigator's opinion.

It is the investigator's responsibility to review all vital sign results. Medical and scientific discretion should be exercised to decide whether an isolated vital sign abnormality should be classified as an AE.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (for example, high blood pressure), it should only be recorded at diagnosis (i.e. as hypertension) in the Adverse Events form of the eCRF.

The observations of a single vital sign abnormality from one visit to the next must not be recorded repeatedly in the Adverse Events form of the eCRF, unless the etiology has changed. The initial severity of the event must be recorded, and the severity and seriousness should be updated if at any time the event worsens.

5.3.5.6 Liver function test abnormalities

The finding of an elevated ALT or AST (> 3 × baseline value) in combination with either elevated total bilirubin (> 2 × ULN) or clinical jaundice, in the absence of cholestasis or other causes of hyperbilirubinemia, is considered an indicator of severe liver lesion. Therefore, the investigator should record the onset of any of the following as an AE:

- ALT or AST > 3 × baseline value appearing during treatment in combination with a total bilirubin > 2 × ULN (35% of which is direct bilirubin)
- ALT or AST > 3 × baseline value appearing during treatment in combination with clinical jaundice.

The most appropriate diagnosis or the abnormal laboratory values (if no diagnosis can be made) should be recorded in the Adverse Events form of the eCRF (see Section 5.3.5.1) and the Sponsor must be informed of the matter immediately (i.e. within 24 hours of becoming aware of the event).

5.3.5.7 Death

In this Protocol, mortality is an efficacy variable. Any deaths that the investigator attributes exclusively to CLL progression alone should be recorded in the eCRF page for early study finalization. Any other deaths occurring during the study, regardless of their relationship with the study drug, must be recorded (as an outcome) in the AE form of the eCRF and should be immediately reported to the Sponsor (see Section 5.4.2).

Death should be considered an outcome and not an event "per se". The event or situation that caused or contributed to the fatal outcome should be recorded as a single medical concept in the AE form of the eCRF. In general, only one of those events will be reported. The term **"sudden death"** will only be used when the death is sudden and unexpected, due to possible cardiac causes in a patient with or without pre-existing cardiopathy and that occurs within one hour of the onset of acute symptoms, or in the case the death has not be witnessed, within 24 hours of the time at which the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, it should be recorded as **"death from an unknown cause"** in the AE form of the eCRF. If the cause of death is determined later (e.g. after the autopsy), the term "death with an unknown cause" should be replaced with the established cause of death.

5.3.5.8 Pre-existing medical conditions

A pre-existing medical condition is that which was already present at the Screening/baseline visit for this trial. These conditions must be recorded in the "*General Medical History and Baseline Conditions*" form of the eCRF.

A pre-existing medical condition should only be recorded as an AE if the frequency, severity or nature of the condition worsens during the trial. When recording this type of event in the Adverse Events form of the eCRF, it is important to communicate the concept that the pre-existing condition had changed by including the corresponding descriptors (for example "*more frequent headaches*").

5.3.5.9 Lack of efficacy or worsening of the CLL

Any events clearly consistent with the expected pattern of progression of the underlying condition (CLL) should not be recorded as AEs. This data will only be recorded as efficacy assessment data. In most cases, the expected pattern of progression will be based on the IWCLL criteria for the response assessment for CLL (See Appendix 3). In very few cases will clinical progression be determined based on symptomatic impairment. However, every effort possible must be made to document progression using objective criteria. If there is any doubt regarding whether an event is due to disease progression, it should be reported as an AE.

5.3.5.10 Hospitalization or prolonged hospitalization

Any AE that results in hospitalization or the extension of a pre-existing hospitalization must be documented and reported as an SAE (according to the definition of an SAE in Section 5.2.2), with the exceptions detailed below.

The following hospitalization scenarios should not be considered SAEs:

- Hospitalization for respite care.
- Scheduled hospitalization required by the Protocol (for example, for the administration of the trial drug or insertion of the access device for the administration of the trial drug)
- Hospitalization for a pre-existing condition, provided it meets all of the following criteria:

- The hospitalization was planned prior to the trial or was scheduled during the trial when the elective surgery became necessary due to the expected normal progression of the disease.
- The patient has not suffered an AE.

- Hospitalization due exclusively to progression of the underlying condition (CLL).

5.3.5.11 Overdose due to medication error, abuse or misuse

An overdose of the trial drug is the accidental or intentional use of the medicinal product in a quantity larger than the dose being studied. An overdose or the incorrect administration of a trial drug is not an AE in itself, but it may result in or lead to the onset of an AE. Any overdose or incorrect administration of the medicinal product of the trial must be recorded in the "*Trial medicinal product administration*" form of the eCRF.

Any AEs associated with an overdose or incorrect administration of the medicinal product in the trial must be recorded in the Adverse Events form of the eCRF. If the associated AE satisfies seriousness criteria, the event must be reported to the Sponsor immediately (i.e. within 24 hours of becoming aware of the event; see Section 5.4.2 for instructions on how to report this matter).

5.4 IMMEDIATE REPORTING BY THE INVESTIGATOR TO THE SPONSOR

Certain events require immediate reporting to enable the Sponsor to take the proper measures to address new potential risks in a clinical trial. The Investigator must report these events to the Sponsor immediately; under no circumstance should the reporting take place more than 24 hours after the Investigator becomes aware of the event. Below is a list of events that the Investigator must report to the Sponsor within 24 hours of becoming aware of the event, regardless of their relationship with the trial medicinal product:

- SAEs (including Adverse Events of Special Interest)
- Non-serious AEs of Special Interest
- Pregnancy

- Suspected transmission of an infectious agent through the medicinal products of the study

The Investigator must report any new information arising from the monitoring of those events to the Sponsor within 24 hours of becoming aware of said new information. Significant new information includes:

- New signs or symptoms or a change in the diagnosis.
- New significant analytical results.
- Change in the causal relationship based on new information
- Change in the outcome of the event, including recovery
- Additional narrative information on the clinical course of the event.

5.4.1 Emergency medical contact

Medical Monitor (Roche's Medical Supervisor) - Contact information

In the event you need to urgently contact any medical supervisor from Roche Farma, S.A. outside of business hours, the Medical Emergency Call Center phone number is: 91-324.81.00.

5.4.2 Requirements for reporting Serious Adverse Events and Non-Serious Adverse Events of Special Interest

For SAE and non-serious AEs of special interest reporting, the Investigator must record all case information he/she can collect **within 24 hours** in the Serious Adverse Event/Non-Serious Adverse Event of Special Interest form. This form, together with a Fax cover sheet, must be completed and sent by fax to Roche Safety Risk Management (Welwyn) or to the designated person within 24 hours of becoming aware of the event, using the fax numbers given to the Investigators (contact the Trial Monitor for more information).

5.4.3 Requirements for reporting pregnancies

5.4.3.1 Pregnancy in female patients

Patients of fertile age shall be instructed to immediately notify the Investigator if they become pregnant during the trial or in the 6 months after the last dose of the trial treatment. The Investigator must complete a pregnancy form within 24 hours of becoming aware of the pregnancy and must send it by fax Roche Safety Risk Management or to the designated person within 24 hours of becoming aware of the event, using the fax numbers given to the Investigators (contact the Trial Monitor - See Section 5.4.2.) A pregnancy must not be recorded in the Adverse Event form. The Investigator must discontinue the administration of the trial medicinal product, consult with the patient, and review all the risks of the pregnancy and possible effects for the fetus with her. The patient must be monitored until the end of the pregnancy.

5.4.3.2 Pregnancies of the partners of male patients

Patients shall be instructed, in the Informed Consent Form, to immediately notify the Investigator if their partner becomes pregnant during the trial or in the 12 months after the last dose of the trial treatment. The Investigator must complete a pregnancy form within 24 hours of becoming aware of the pregnancy and submit it in accordance with the instructions provided in Section 5.4.3.1. Efforts should be made to collect and report the details of the course and outcome of any pregnancy of the partner of a patient receiving the trial medication. The pregnant partner will have to sign an *Authorization for the Use and Disclosure of Health Information on Pregnancy* for her pregnancy to be monitored. Once the authorization has been signed, the Investigator shall update the pregnancy form with additional information on the course and outcome of the pregnancy. An Investigator who has been contacted by the patient or his pregnant partner may provide them information on the risks of the pregnancy and the possible effects on the fetus, in order to back an informed decision in collaboration with the physician or obstetrician treating the pregnant partner.

5.4.3.3 Miscarriage

Any miscarriage must be classified as an SAE (since the Sponsor considers miscarriages to be medically-significant events), recorded in the Adverse Events form

and reported to the Sponsor within 24 hours of becoming aware of the event (see Section 5.4.2).

5.4.3.4 Congenital anomalies/Birth defects

Any congenital abnormality/birth defect in a child of a patient or partner of a patient exposed to the trial medication must be classified as an SAE, recorded in the Adverse Events form, and reported to the Sponsor within 24 hours of becoming aware of the event (see Section 5.4.2).

5.5 PATIENT MONITORING AFTER AN ADVERSE EVENT

5.5.1 Monitoring by the Investigator

The Investigator must monitor every AE until the event has resolved or the Investigator considers it to have stabilized, the patient is lost to follow-up, or the patient withdraws his/her consent. Every possible effort must be made to monitor all SAEs until a final outcome can be reported.

During the trial period, the resolution of the AE (with dates) must be documented in the Adverse Events form of the eCRF and in the patient's medical history to facilitate data verification. If its resolution or stabilization cannot be confirmed, an explanation should be recorded in the Adverse Events form of the eCRF.

If medically-important abnormal laboratory values appear for which there is no explanation, the analyses should be repeated, and they must be monitored until normal values or baseline status has been recovered and/or until a valid explanation of the abnormality is found. If a clearer explanation is established, it must be recorded in the eCRF.

Any pregnancies reported during the trial must be monitored until they are finalized (see Section 5.4.3).

5.5.2 Monitoring by the Sponsor

For SAEs, non-serious AEs of Special Interest and pregnancies, the Sponsor or somebody it appoints may follow-up on them by phone, fax, email and/or a monitoring visit to obtain more details on the case and information on the outcomes (for example, from the hospital discharge report, consultation reports, autopsy reports) to be able to carry out an independent medical assessment of the case in question.

5.6 POST-TRIAL ADVERSE EVENTS

After the end of the adverse event reporting period (defined at section 5.3.1), second malignancies will be reported indefinitely, regardless of relationship to study treatment (even if the study has been closed).~~all deaths, regardless of cause, should be reported through use of the Long-Term Survival Follow-Up eCRF~~. In addition, if the investigator becomes aware of a Serious Adverse Event, Non-serious AE of Special Interest, late neutropenia ~~or secondary malignancy~~ that is believed to be related to prior study drug treatment, the event should be reported through use of the Adverse Event eCRF.

The Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined at section 5.3.1) if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to investigators.

5.7 EXPEDITED REPORTING TO THE HEALTH AUTHORITIES, INVESTIGATORS AND ETHICS COMMITTEES

For the purposes of expedited reporting, the Sponsor shall assess whether or not the adverse events are expected by using:

- The Investigator's Brochure for Obinutuzumab
- The Summary of Product Characteristics for bendamustine

The Sponsor shall compare the severity of each event and the cumulative frequency of the event recorded in the trial with the severity and frequency recorded in the corresponding reference document.

The reporting requirements shall also be based on the assessment of the causal relationship and seriousness performed by the Investigator, leaving room for the Sponsor to increase its classification if necessary.

All investigators participating in the trial and their corresponding CRECs will be notified of any SUSARs reported during the trial. An AE is only considered a SUSAR if it meets all of the following conditions:

- The event is serious (SAE);

- The event is considered to be related to the trial medication, according to the criteria presented in Section 5.3.4. (N.B. any suspected causal relationship should result in an assessment of "related");
- When it is assessed by comparing it with the known safety profile of the study treatment (as described in the Investigator's Brochure for obinutuzumab and in the Summary of Product Characteristics for bendamustine), the event is considered unexpected (that is, it was not expected in the Investigator's Brochure).

The individual Suspected Unexpected Serious Adverse Reaction (SUSAR) reports arising from this trial, including SUSARs regarding an important safety question and/or that result in a recommendation by Roche for a change in the ICF (Informed Consent Form), shall be sent in an expedited manner to the Health Authorities, all participating investigators and to the CREC associated to the site in question in accordance with the applicable legislation. The SUSAR reports arising from other trials using the same IB will be provided in half-year SUSAR reports to all investigators and CRECs.

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 SAMPLE SIZE DETERMINATION

In order to have a power of 90.0% to determine differences in the null hypothesis of the significance test (H0: p1=p2) using an exact one-tailed binomial test for a Simon two-stage study design (2), considering a 5.0% significance level, assuming that ORR will not be lower than 50.0% and an expected ORR with the experimental treatment of 70.00%, the following decision criteria will need to be applied: 13/24 and 36/61, respectively for each phase. This implies that 24 subjects will be analyzed initially in the first phase of the study. If treatment response is observed in more than 13 subjects, it will then be necessary to analyze up to a total of 61 subjects.

Finally, taking into consideration an estimated percentage of losses of 20%, 30 patients would need to be recruited in the first phase and up to 77 patients would have to be recruited in the second phase.

Patients who discontinue treatment and are not evaluable for efficacy will be considered non-responders. In addition, we expect 15% of missing data due to loss to

follow-up or breach of Protocol. This 15% will need to be replaced. Therefore, 72 patients need to be recruited.

6.2 SUMMARY OF THE TRIAL PROCEDURE

This is a phase II, open-label, non-comparative clinical trial whose primary objective is to assess the overall response rate achieved after treatment with obinutuzumab and bendamustine in patients with relapsed or refractory chronic lymphocytic leukemia (CLL). To do so, 6 cycles of treatment will be administered and the response obtained two months after the last dose of the study treatment will be assessed. Moreover, monitoring will continue until the study is finalized to study the time-dependent efficacy endpoints. The safety profile of the treatment will also be studied through the assessment and monitoring of adverse events during the treatment and the subsequent trial observation period.

6.3 EFFICACY ANALYSIS

All patients recruited who receive at least one dose of the study drug will be included in the efficacy analysis.

6.3.1 Primary efficacy endpoint analysis

For the primary analysis, the overall response rate (ORR) will be estimated. In addition, the best response rate (CR/CRi and PR) in the 6-8 months post-treatment will also be estimated. The response rates will be provided with a 95% confidence interval. Any patients for whom no response assessment is available (regardless of the reason) shall be considered non-responders.

If the first phase of the trial is not completed, all variables will be collected for the initial 24-patient population, which will be analyzed in depth to identify the reasons for the low percentage of response observed.

6.3.2 Secondary efficacy endpoint analysis

The "time to event" variables (i.e. progression-free survival, event-free survival, disease-free survival, time to re-treatment/new anti-leukemia therapy, overall survival and duration of response) will be analyzed using the Kaplan-Meier method.

6.4 SAFETY ANALYSIS

All patients who receive at least one dose of the study treatment will be included in the safety analysis. The safety of the treatment will be studied by assessing: adverse events, laboratory determinations and vital signs.

Safety will be assessed by monitoring all adverse events, serious adverse events and adverse events of special interest. They will be scored according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), version 4.0. The analytical safety assessments will consist of a periodic hematology and biochemistry control in blood.

6.5 EXPLORATORY ANALYSES

The effect of prognostic markers in peripheral blood [p53 (17p13.1), ATM (11q22.3), ZAP70, CD38, CD49D, NOTCH1, SF3B1, BIRC3, IGHV] and in a sample of saliva [ATM, BIRC3, BRAF, CHD2, CSMD3, DDX3X, FBXW7, KLHL6, KRAS, LRP1B, MAPK1, MUC2, MYD88, NFKBIE, NOTCH1, PLEKHG5, POT1, SAMHD1, SF3B1, SI, SMARCA2, TGM7, TP53, XPO1, ZMYM3, EGR], on response to treatment will be assessed using stratified exploratory analyses. In addition, the effect of those prognostic markers in which a significant association with the treatment response is observed will be analyzed in an additional exploratory analysis using multivariate logistic regression.

6.6 INTERIM ANALYSIS

We expect to perform an interim analysis as soon as the response assessment at the end of the treatment is available for all patients.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will provide electronic specifications for the eCRF for this trial. A CRO will be responsible for the data management in this trial, which includes verifying the data quality. The data entered manually will be collected through the EDC system using eCRF. The participating sites will be responsible for entering data into the EDC system. In the case of discrepancies in the data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The CRO will create a Data Quality Plan explaining the quality checks that must be carried out for the data.

The Sponsor shall supervise the data management of this trial, including the approval of the data management plans and specifications from the CRO. The data will be transferred periodically from the CRO to the Sponsor, and the Sponsor's Standard Operating Procedures shall be followed in the handling and processing of the electronic transfer of that data.

The eCRF and corrective documentation shall be stored in the audit records of the EDC system. The copies of the system for data stored at Roche and the storage of trial data files shall be consistent with Roche's Standard Operating Procedures.

7.2 ELECTRONIC CASE REPORT FORMS

The eCRFs must be completed using an EDC system designed by the Sponsor. The sites will receive training and have access to a manual for correctly completing the eCRFs. The eCRFs shall be submitted electronically to the Sponsor and must be managed in line with the Sponsor's instructions.

All eCRFs must be completed by the designated, trained site personnel. The eCRFs must be reviewed and signed and dated electronically by the Investigator or person designated to that effect.

At the end of the trial, the Investigator will receive the data from the patients at his/her site in a legible format on CD which must be stored together with all trial records. An acknowledgement of receipt of the compact disc will be required.

7.3 SOURCE DOCUMENTATION

The Trial Monitors will continuously verify the source data to confirm that the data critical to the Protocol (i.e. the source data) entered into the eCRF by the authorized personnel is accurate, complete and verifiable against the original documents.

The source documentation (in hardcopy or electronic format) is that in which patient data is first recorded and documented. This documentation includes, but is not limited to, hospital charts, clinical and office tables, laboratory notes, memorandums, assessment checklists, pharmacy dispensing records, data collected from automated instruments, copies of transcriptions that are certified (after verification) as accurate and completed, microfiles, photographic negatives, microfilms or magnetic media, x-rays, patient files and records stored at pharmacies, laboratories and medical-technical departments involved in a clinical trial.

The type of source documents that will be generated will be clearly defined in the Trial Monitoring Plan prior to Trial start. This includes any Protocol data recorded directly in the eCRFs (i.e. that there is no previous written or electronic record of that data), and shall be considered original data.

The source documentation needed to verify the validity and completion of the data entered in the eCRFs must not be erased or destroyed and must be stored in accordance with the file storage policy explained in Section 7.5.

In order to facilitate the verification of the original data, the investigators and institutions must grant the Sponsor direct access to the pertinent original documents and reports for the monitoring corresponding to the trial, Sponsor audits and review by the Ethics Committee. The site where the research is being conducted must also allow inspection by the corresponding health authorities.

7.4 USE OF IT SYSTEMS

When the clinical observations are directly entered into computerized medical history systems at the site where the research is being conducted (i.e. instead of in physical original records), the electronic record can serve as source documentation if the system

has been validated in accordance with the requirements of the health authorities for IT systems for use in clinical research. An acceptable computerized data collection system enables the original entry of data to be conserved. If the original data is modified, the system must maintain a visible, auditable trace presenting the original data as well as the reasons for the change, the name of the person making the change and the date of the change.

7.5 STORAGE OF ARCHIVES

The Principal Investigator must keep all archives and documents pertaining to the execution of this trial and the distribution of the IMP, including the eCRFs, Informed Consent Forms, results of laboratory tests, and any medicinal product inventory record, for at least 15 years after the finalization or discontinuation of the trial, or for the time required by the relevant national or local health authorities, whichever is longer. After this period, the documents can be destroyed, according to local legislation.

Records cannot be discarded without the written permission of the Sponsor. The Sponsor must be informed in writing before any records are transferred to a third party or moved to a different site.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LEGISLATION AND REGULATIONS

This trial shall be conducted in full compliance with the ICH E6 guidelines on Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever provides the individual with the highest degree of protection. The trial shall comply with the requirements of the ICH E2A guidelines (Clinical Safety Data Management: Definitions and standards for expedited reporting) and the EU directive on Clinical Trials (2001/20/EC).

This trial will be conducted in the European Union (EU)/European Economic Area, and shall thus comply with the EU directive on Clinical Trials (2001/20/EC), in addition to Royal Decree 1090/2015, of 4 December regulating clinical trials with medicinal products and subsequent orders SCO/256/2007 and SCO/362/2008.

Roche Farma, S.A. has taken out a civil liability insurance with the Spanish branch of the company Zurich Insurance PLC, which is in agreement with Royal Decree 223/2004 of 6 February 2004 establishing the requirements to conduct Clinical Trials with medicinal products and to cover any damage that could be experienced as a result of the clinical trial.

8.2 INFORMED CONSENT

The Sponsor shall provide the Informed Consent Form (and any other applicable complementary form, for example, the consent of the pregnant partner) to each participating site. It shall provide a certified translation into the local language, as applicable. The Sponsor or the person designated by the Sponsor must review and approve any proposed deviation from the Informed Consent Form or any alternative consent form proposed by the site (in general, the "Consent Forms") prior to their presentation to the CREC. The final Consent Forms approved by the CREC must be delivered to the Sponsor for presentation before the health authorities in compliance with local requirements.

The patient or his/her legal representative must sign and date the Consent Forms prior to his/her participation in the trial. The clinical history of every patient shall document the informed consent process and the fact that written informed consent was obtained prior to participation in the trial.

The patients shall be informed about his/her right to withdraw his/her consent at any time and for any reason.

The Consent Forms must be reviewed whenever there are changes to the study procedures and when new information that could affect the patient's willingness to participate in the trial becomes available. The final Consent Forms reviewed by the CREC must be delivered to the Sponsor for presentation before the health authorities.

During their participation in the trial, the patients must sign the new version of the Consent Forms approved by the CREC (or an addendum with the new significant information/findings in compliance with the corresponding laws and policy of the CREC).

For any updated or reviewed Consent Form, the case history or clinical history of every patient shall document the informed consent process and the fact that written informed consent to continue participating in the trial was obtained.

The patient or his/her legal representative must be given a copy of every Informed Consent Form. All signed and dated Consent Forms must remain in each patient's trial file and be available for verification by Trial Monitors at any time.

8.3 HEALTH AUTHORITIES, CLINICAL RESEARCH ETHICS COMMITTEE

This Protocol, the Consent Forms, any information given to the patient and relevant supporting information must be submitted to the CREC and to the Spanish Agency for Medicinal Products and Medical Devices (AEMPS), and be reviewed and approved by both parties prior to starting the trial. Moreover, any material related to patient screening must be approved by the CREC and the AEMPS.

The CREC and the AEMPS will be provided reports on the status of the trial on an annual basis or more frequently in compliance with the requirements, policies and procedures established by the CREC and the AEMPS. The investigators or, when applicable, the Trial Monitor, are responsible for informing the CREC without delay of any amendment to the Protocol (see Section 9.5).

In addition to the AE reporting requirements established by the Sponsor, the investigators must comply with the requirements established for SAE reporting to the regulatory authorities and to the CREC. The investigators may receive written safety reports or other types of safety-related memorandums from Roche. The Sponsor is responsible for guaranteeing that said reports are processed in compliance with the requirements of health authorities and the policies and procedures established by its CREC and ensuring that they are stored in the trial file.

8.4 CONFIDENTIALITY

Roche complies with confidentiality standards by encoding each patient selected for the trial by assigning a unique patient identification number. This means that the names and initials of the patients are not included in the data series transferred to any Roche location.

Moreover, the trial will be conducted in compliance with *Ley Orgánica 15/1999* (Personal Data Protection Act 15/1999) of 13 December 1999 and its implementation through Royal Decree 1720/2007.

The patients' medical information obtained through this trial is confidential and can only be provided to third parties as permitted in the Informed Consent (or separate authorization for the use and disclosure of personal medical information) signed by the patient, unless it is permitted or required by law.
Medical information can be provided to the patient's personal doctor or to other medical personnel responsible for the patient's wellbeing with intent to treat.
The data generated for this trial must be available for inspection upon request by representatives of the US drug agency and other national and local health authorities, monitors from Roche, representatives and collaborators and the CREC of each site where the research is being conducted, as applicable.

8.5 CONFLICT OF INTEREST STATEMENT

The investigators shall provide the Sponsor with sufficient financial information adjusted in compliance with local legislation to enable the Sponsor to send an accurate and complete financial certification or confidentiality statements to the corresponding health authorities. The investigators are responsible for providing information on their financial interests during the course of the trial and one year after it has been finalized.

9. TRIAL DOCUMENTATION, MONITORING AND ADMINISTRATION

9.1 TRIAL DOCUMENTATION

The investigator must keep adequate, accurate records that enable the trial to be fully documented, including, but not limited to: the Protocol, the amendments to the Protocol, Consent Forms and CREC documentation and governmental approval. Moreover, at the end of the trial the Investigator will receive the data from the patients which will include an audit tracing with a complete record of all changes made to the data.

9.2 PROTOCOL VIOLATIONS

The Investigator must document and explain any Protocol violation. The Investigator must immediately report to the Sponsor any violation that could affect the integrity and safety of the patient data. Roche will report the information to the AEMPS.

9.3 INSPECTIONS

Roche or a representative authorized by the company will carry out visits to audit trial data, patient medical histories and eCRFs. The Investigator shall permit the local and national health authorities, monitors from Roche, representatives and collaborators and the CRECs to inspect the facilities and files relevant to this trial.

9.4 ADMINISTRATIVE STRUCTURE

The Reference CREC will be the Ethics Committee of Hospital Universitario Puerta de Hierro.

9.5 DATA PUBLICATION AND PROTECTION OF TRADE SECRETS

The results of this trial may be published or presented at scientific meetings. If this is planned, the Investigator agrees to submit all manuscripts and abstracts to the Sponsor prior to presenting them. This will allow the Sponsor to protect all of its commercial information and to provide comments based on information from other trials that may not yet be available to the Investigator.

The Sponsor shall comply with the requirements for the publication of trial results. In compliance with standard editorial ethics practices, in general, the Sponsor shall support the publication of multicenter trials only as a whole and not as individual data from each site. In this case, mutual agreement must be reached to appoint the Coordinating Investigator.

The authorship shall be decided by mutual agreement and in line with the requirements of the International Committee of Medical Journal Editors. Any formal trial publication in

which the contribution of the Sponsor's personnel goes beyond conventional monitoring shall be considered a joint publication by the Investigator and the corresponding Sponsor personnel.

Any resulting invention or patent, improvements and/or knowledge arising from the use of data from this trial shall become the exclusive property, without charge, of the Sponsor, except where otherwise agreed.

9.6 AMENDMENTS TO THE PROTOCOL

Any amendment to the Protocol shall be prepared by the Sponsor. Amendments to the Protocol shall be presented before the CREC and the regulatory authorities in compliance with the legal regulatory requirements.

Approval must be obtained from the CREC and regulatory authorities (according to the local requirements) prior to implementing any change, except those necessary to eliminate an immediate danger for patients or changes that only involve logistical or administrative aspects (for example, change of Medical Monitor or change to the information in the contract).

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APPENDIX 1
ASSESSMENT CALENDAR

	Screening		Treatment Period [a]																					EOT/ET Visit [b]	Final Response Assessment [c]	Follow-Up [d]
			Cycle 1						Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6					
Day	–28 to –1	–7 to –1	1	2	3	5	8	15	1	2	18	1	2	18	1	2	18	1	2	18	1	2	18	**28 days (±5 days) after last study drug**	**2-3 months after last study drug**	Every 6 months (±14 days) after last study drug
Informed Consent	X																									
Demographic data	X																									
General medical history and baseline conditions (see Section 4.4.)	X																									
HIV, HBV, HCV, and HTLV-1 serology [e]	X																									
COLLECT and CIRS*	X																									
Staging (Binet and Rai)	X																									
12-lead ECG	X																							X		
Vital signs [f]	X		x						x			x			x			x			x			x	x	x
Weight	X		x						x			x			x			x			x			x	x	

Appendix 1
Assessment Calendar (cont.)

Height, Pregnancy test in women of childbearing potential	X																							
Physical examination, ECOG, B Symptoms [g]	X		x						x			x			x			x			x			x			x	x	x
Liver/spleen examination and lymphadenopathy (by physical exam) [h]	X														X									X	X	X
Hematology [i]		x	x					x	x		x	x		X	x		x	x		x	x		X	x	x	x
Coagulation Blood tests (INR, TP, aPTT)		x																								
Biochemistry [j]		x	x	x^n	x^n	x^n	x^n	x	x		x	x		X	x		x	x		x	x		X	x	x	x
Immunoglobulin (IgA, IgG, IgM)	x																							x	x	X (during 12 months)
ß2 microglobulin	x																									
Inmunophenotype and mutations [k]	X																									
Study drug administration			x	X	x		x	x	x	x		x	x		x	x		x	x		x	x				
Response assessment [l]	X																								x	x
Confirmation of CLL and MRD [m]	X																								x	

Appendix 1
Assessment Calendar (cont.)

Concomitant Medication		x	x	X	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	X	x	x	
Adverse Events	X	x	x	X	x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	X	x	x	x

*COLLECT = Comorbidity scale for LLC; CIRS = *Cumulative Illness Rating Scale*.

Notes:

a On treatment days, all assessments should be performed prior to dosing, unless otherwise noted. The C1, D1 visit should be scheduled to allow subsequent visits to occur without delay. With the exception of Days 1 and 2 in Cycle 1, all assessments must be performed (± 3 days of the planned calculated visit date. For all other cycles, assessments must be performed within ± 4 days of the planned calculated visit date, with the exception of delays resulting from toxicities. The baseline assessments will be the ones collected before C1D1. If a test is repeated several times during the Screening Period, the baseline value will be the one taken just before C1D1.

Lab assessments where no time window is applicable for (1) patients with CLL at risk of TLS and treated with obinutuzumab in combination with bendamustine, and (2) patients with CLL not considered at risk but with impaired renal function. In these instances, results of hematology and serum chemistry must be checked by the investigator on the same day the samples are taken.

All assessments should be performed within

b The End of Treatment Visit should occur within 28 days (±5 days) after the last administration of study medication, including patients who withdraw early

c All patients will be asked to return to the clinic 2-3 months after the last dose of study drug for the Final Response Assessment visit.

d Follow-up information will be collected at clinic visits every 6 months (± 14 days) after the End of Treatment Visit until death, loss to follow-up, or study termination by the Sponsor.

e HIV, hepatitis B surface antigen (HBsAg), Hepatitis B core antibodies (HBcAb), and HCV antibody serology are required for all patients. HCV RNA required for patients who are HCV antibody positive.

f Pulse rate, systolic and diastolic blood pressure while the patient is in a seated position and body temperature.

Appendix 1
Assessment Calendar (cont.)

g Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. New or worsening abnormalities should be recorded on the Adverse Event eCRF

h As part of the tumor assessment, a full physical examination should be performed to assess the extent of disease involvement. The exam should also include the evaluation of presence and degree of enlarged lymph nodes, hepatomegaly, and splenomegaly.

i Includes hemoglobin, hematocrit, platelet count, RBC count, WBC count, absolute differential count (neutrophils, eosinophils, lymphocytes, monocytes, basophils, other cells).

j Includes sodium, potassium, chloride, bicarbonate, fasting glucose, BUN or urea, creatinine, calcium, total and direct bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, phosphorus, magnesium, LDH, creatinine phosphokinase, uric acid.

k Inmunophenotype (ZAP70, CD38 , CD49D) and mutations´ testing [FISH - p53 (17p13.1), ATM (11q22.3); NOTCH 1, SF3B1; BIRC3, IGHV] will be done at the Central Laboratory. . A sample of saliva will also be submitted for DNA sequencing. For subjects included in the study prior to Protocol Amendment 4, this sample of saliva will be obtained as soon as possible, provided that informed consent form amendment has been previously signed.

l A CT scan (which should include cervical, axillary, mediastinal, paraaortic, mesenteric, inguinal, extranodal, other) will be performed at screening, which can occur up to a maximum of 28 days prior to Day 1 and Cycle 1. The results of the computerized tomography scans (CAT) with contrast medium that were performed prior to the Screening visit as part of the patient's routine clinical assessment can be recorded in the eCRF up to 6 weeks prior to inclusion (in order to prevent patients who have recently undergone a CAT from being re-exposed to radiation). However, a CAT scan must be performed in the 4 weeks prior to inclusion in those patients with signs of rapid disease progression at the Screening Visit. A repeat CT scan of involved sites at baseline will be performed in patients who satisfy the clinical criteria for partial or complete response 2-3 months after the last dose of study treatment. When PD is detected by physical examination in the absence of any objective hematological progression, a CT scan of the involved nodes will be performed. In addition, CT scans may be performed at any time at the investigator discretion, if clinically indicated. In patients with severe renal insufficiency at screening use CT contrast according to local practice. If necessary use MRI scan. CT without contrast is not recommended except for patients who develop renal insufficiency during treatment and have previously been assessed by CT scan. It is obligatory to use the same imaging technique for all tumor evaluations. The response assessments carried out 2-3 months after the last dose of study treatment will be based on the investigator's assessment, completed following the response criteria of the NCI-WG for CLL (Appendix 3).

Appendix 1
Assessment Calendar (cont.)

m A peripheral blood sample would be sent to the Central Laboratory to confirm CLL at the screening (if absence of lymphocytosis in blood, a determination in bone marrow would be done in the Central Laboratory; if Richter´s Syndrome is suspected, a ganglionic biopsy at the participating site is recommended to discard Richter´s Syndrome). MRD should be assessed 2 months after the end of study treatment in peripheral blood sample and bone marrow aspirates, only for those patients with CR/CRi/PR

n Applies to patients with CLL at risk of TLS and treated with obinutuzumab in combination with bendamustine and to patients with CLL not considered at risk but with impaired renal function. Results of hematology and serum chemistry must be checked by the investigator on the same day the samples are taken.

APPENDIX 2
NCI DIAGNOSTIC CRITERIA FOR CLL

Variable	NCI
Diagnosis	
Lymphocytes	>5; ≥ 1 B-Cell marker (CD19, CD20, CD23) + CD5
Atypical cells (%) (for example, prolymphocytes)	<55
Duration of lymphocytosis	Not required
Lymphocytes in BM (%)	≥30
Stage	Modified Rai, BINET
Clinical Trial Eligibility	Active disease (see Protocol)

APPENDIX 3
NCI-WG RESPONSE CRITERIA FOR CLL

Below is an abridged version of the complete tumor response criteria (29).

Complete Response (CR)

CR requires all of the following criteria, assessed at least 2 months after treatment has been finalized:

- Lymphocytes in peripheral blood (assessed through blood count with differential) below 4 x 10^9/L (4,000/µl).
- Absence of significant lymphadenopathy (lymph nodes ≤ 15 mm in the longest diameter or any extranodal manifestation) by physical examination and CAT.
- Absence of hepatomegaly, determined by the measurement below the costal margin. Hepatomegaly that is considered to be due to CLL is defined as > 3 cm below the costal margin.
- Absence of splenomegaly in the physical examination, determined by the measurement below the costal margin. A palpable spleen of any size is considered to be related to the CLL.
- Absence of disease or constitutional symptoms (B symptoms).
- Blood counts above the following values:
    - Neutrophils > 1.5 x 10^9/L [1500/µl] (without growth factors).
    - Platelets > 100 x 10^9/L [100,000/µl] (without transfusion of platelets or growth factors).
    - Hemoglobin > 110 g/L [11 g/dL] (without transfusions of blood or erythropoietin)
- Bone marrow at least normocellular for age, <30% of nucleated cells are lymphocytes. The lymphoid nodules must be absent. The bone marrow aspirate and biopsy must be performed 3 months after the last treatment, when the aforementioned clinical and laboratory results show that CR/cytopenic CR has been achieved. If the bone marrow is hypocellular, the determination must be repeated over the course of 4 weeks and when the peripheral blood counts have recovered. However, this time interval must not exceed 6 months. The bone marrow biopsy must be compared with that performed prior to treatment, if available. Patients who, in all other terms, are in complete remission, though they present nodules in the bone marrow that are histologically identifiable,

should be considered patients in PR (nPR). Immunohistochemistry must be performed to define if those nodules are made up primarily of T-cells, non CLL-cell lymphocytes, or CLL cells.

CR with incomplete bone marrow recovery (CRi)

This criterion applies to patients satisfying the criteria for CR (including bone marrow) but with persistent cytopenia, i.e. anemia, thrombocytopenia and/or neutropenia. The bone marrow examination described above must be performed in detail and not show any clonal infiltrate.

Partial Response (PR)

In order to be considered to have achieved PR, the patients must present the following characteristics for at least 2 months after finishing treatment:

- Reduction ≥ 50% of the lymphocyte count in peripheral blood with respect to the pre-treatment value.

AND

- Reduction ≥ 50% of the lymphadenopathy (sum of the longest diameter of a maximum of the six [6] largest lymph nodes upon physical examination and 50% reduction of the sum of the product of the diameters [SPD] for a maximum of six [6] of the largest lymph nodes, assessed with CAT). No lymph nodes may have increased in size and no new areas of lymphadenopathy may be observed. In small lymph nodes (< 2 cm in diameter), an increase of less than 25% is not considered significant.

OR

- Reduction ≥ 50% of the size of the liver if it is enlarged at the physical examination performed at baseline.

OR

- Reduction ≥ 50% of the size of the spleen if it is enlarged at the physical examination performed at baseline.

Plus, at least, one of the following values:

- Neutrophils > 1.5 x 10^9/L [1500/µl] (without growth factors) or increase ≥ 50% with respect to the pre-treatment value.
- Platelets > 100 x 10^9/L [100,000/µl] (without transfusion of platelets or growth factors) or increase ≥ 50% with respect to the pre-treatment value.

- Hemoglobin > 110 g/L [11 g/dL] (without transfusions of blood or erythropoietin) or increase ≥ 50% with respect to the pre-treatment value.

Disease Progression (DP)

Disease progression (DP) during or after treatment will be defined by at least one of the following characteristics:

- Increase ≥ 50% of the absolute number of circulating lymphocytes up to at least 5 x 10^9/L. During the treatment, the increase must be assessed by comparing it with the baseline value, using a lymphocyte count nadir on Day 1 (before the cycle) and not the counts obtained between cycles, which may not be stable. After the treatment, the increases must be assessed with respect to the assessment of the response at the end of treatment.

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

- Increase ≥ 50% of the longest diameter of any previous area of clinically significant lymphadenopathy (i.e. any lesion > 10 mm at baseline). During the treatment, the increase must be assessed with respect to baseline. After the treatment, the increases must be assessed with respect to the assessment of the response at the end of treatment.

- Increase ≥ 50% of the size of the liver and/or spleen, determined by the measurement under the corresponding costal margin or the appearance of palpable hepatomegaly or splenomegaly that were not previously present. During the treatment, the increase must be assessed with respect to baseline. After the treatment, the increases must be assessed with respect to the assessment of the response at the end of treatment.

- Transformation to a more aggressive histology (e.g. Richter's syndrome or plasmacytoid lymphocytic lymphoma [PLL] with > 55% of prolymphocytes). When possible, this diagnosis must be corroborated by lymph node biopsy.

- After treatment, progression of any cytopenia (unrelated to the autoimmune cytopenia), documented by at least one of the following characteristics:

    - Decrease of hemoglobin levels of more than 20 g/L (2 g/dL) or to below 100 g/L (10 g/dL).

    - Decrease of platelet counts by more than 50% or to below 100 x 10^9/L(100.000 /µl).

    - Decrease in the neutrophil counts by more than 50% or to below 1.0 x 10^9/L occurring after no fewer than 3 months after ending the treatment, if the bone marrow biopsy also shows infiltration of clonal CLL cells.

Stabilization of the disease (SD)

Patients who have not achieved CR or PR, or who have not presented DP, will be considered to present stabilization of the disease.

APPENDIX 4
COLLECT SCALE

Available at: https://imshealth.heor-clinicalstudies.com/escalallc/

APPENDIX 5
CIRS SCALE

CUMULATIVE ILLNESS RATING SCALE

Modified Cumulative Illness Rating Scale

Name:_____

Each system is scored as indicated below:

0 = NONE:	No impairment in that organ or system
1 = MILD:	The impairment does not interfere in normal activities; it may not require treatment; the prognosis is excellent (examples: cutaneous lesions, hernias, hemorrhoids)
2 = MODERATE:	The impairment interferes with normal activities; treatment is needed; the prognosis is good (examples: gallstones, diabetes, fractures)
3 = SEVERE:	The impairment is incapacitating; emergency treatment is needed; the prognosis is reserved (examples: resectable carcinoma, pulmonary emphysema, congestive heart failure)
4 = EXTREMELY SEVERE:	The impairment is life-threatening; the treatment is urgent or ineffective; the prognosis is grave (examples: myocardial infarction, cerebrovascular accident, gastrointestinal hemorrhage, embolism)

Score 0-4

a. Cardiac (heart only) _____

b. Hypertension (scored based on severity; the systems affected are scored separately) _____

c. Vascular (blood, blood vessels and cells, marrow, spleen, lymph nodes) _____

d. Respiratory (lungs, bronchi, trachea below the larynx) _____

e. Eyes, larynx, throat, nose and ears _____

f. Upper GI (esophagus, stomach, duodenum, biliary and pancreatic trees; does not include diabetes) _____

g. Lower GI (intestines, hernias) _____

h. Hepatic (liver only) _____

i. Renal (kidneys only) _____

j. Other GU (ureters, bladder, urethra, prostate, genitals) _____

k. Musculoskeletal integumentary (muscles, bone, skin) _____

l. Neurologic (brain, spinal cord, nerves; does not include dementia) _____

m. Endocrine-metabolic (includes diabetes, diffuse infections, infections, toxicity) _____

n. Psychiatric/behavioral (includes depression, anxiety, agitation, psychosis; not dementia) _____

APPENDIX 6
NATIONAL CANCER INSTITUTE COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (NCI-CTCAE)

Enclosed separately

APPENDIX 7
MODIFICATIONS TO THE CHEMOTHERAPY DOSE, ACCORDING TO THE GRADING SCALE FOR HEMATOLOGICAL TOXICITY IN CLL FROM THE INTERNATIONAL WORKSHOP ON CHRONIC LYMPHOCYTIC LEUKEMIA

Hematological toxicity assessment

The assessment of potential treatment-induced toxicity in patients with advanced CLL can be fairly difficult and require meticulous consideration of both the underlying disease and of the adverse reactions to the study treatment. Some conventional toxicity criteria are not applicable, especially under circumstances of progressive bone marrow failure due to the CLL.

Dose modifications due to hematological toxicity in patients with CLL must be made considering the increase of the frequency of the hematological compromise at treatment start. Therefore, the standard criteria used for solid tumors are difficult to apply directly; many patients could be considered to have grade 2-4 hematological toxicity at the start of the clinical presentation.

Therefore, the dose modification decisions in patients with cytopenia (below the lower limit of normal) at baseline shall be based on the Grading Scale for Hematological Toxicity in CLL Studies of the NCI-Sponsored Working Group (NCI-WG) (29). In patients with normal neutrophil, platelet and/or hemoglobin values at baseline, the NCI-CTCAE, v4.0 criteria will be used.

Grade	Decreased platelet count[a] or Hb[b] (nadir) with respect to the pre-treatment value, %	Absolute Neutrophil Count/μL[c] (nadir)
0	No changes up to 10%	≥2000
1	11-24%	≥1500 and <2000
2	25-49%	≥1000 and <1500
3	50-74%	≥500 and <1000
4	≥75%	<500

Grade 1, mild; 2, moderate; 3, severe; 4, life-threatening; 5, fatal. Death caused by toxicity at any level of decrease with respect to the pre-treatment value shall be recorded as Grade 5.

a. The platelet counts must be below the normal levels for grades 1 to 4. If, at any level of decrease, the platelet count is <20 x 10^9L (20,000/μL), this should be considered grade 4 toxicity,

unless a severe or life-threatening decrease in the initial platelet count was already observed prior to treatment (for example, 20 x 10^9L [20,000/µL]), in which case the patient will not be evaluable for toxicity with respect to the platelet counts.

b. The Hb levels must be below the normal levels for grades 1 to 4. The baseline and subsequent Hb determinations must be performed prior to administering a transfusion. The use of erythropoietin is irrelevant to the toxicity classification, but must be documented.

c. If the absolute neutrophil count (ANC) reaches values <1 x 10 ^{9}L (1000/µL), this will be considered grade 3 toxicity. Other decreases in the circulating neutrophil or leukocyte count will not be considered, since a reduction in the leukocyte count is a desired therapeutic objective. A gradual decrease in the number of granulocytes is not a reliable indication in CLL for the toxicity grading. If the ANC was <1 x 10^9L (1000/µL) prior to treatment, the patient will not be evaluable for toxicity in terms of ANC. The use of growth factors, like G-CSF, is irrelevant to the toxicity classification, but must be documented.

Thrombocytopenia: Special Considerations

Severe and life threatening thrombocytopenia including acute thrombocytopenia (occurring within 24 hours after the infusion) has been observed during treatment with obinutuzumab. Fatal haemorrhagic events have also been reported in patients treated with obinutuzumab. It seems that the first cycle is the greatest risk of haemorrhage in obinutuzumab-treated patients. A clear relationship between thrombocytopenia and haemorrhagic events has not been established. Patients treated with concomitant medication, which could possibly worsen thrombocytopenia related events such as platelet inhibitors and anticoagulants, may be at greater risk of bleeding. Patients should be closely monitored for thrombocytopenia, especially during the first cycle; regular laboratory tests should be performed until the event resolves, and dose delays should be considered in case of severe or life-threatening thrombocytopenia. Transfusion of blood products (i.e. platelet transfusion) according to institutional practice is at the discretion of the treating physician.

Table A: Dose Delays in Case of Severe or Life-Threatening Thrombocytopenia

Severe thrombocytopenia (platelets < 10.000/µL) and/or symptomatic bleeding in patients who are not receiving concomitant anticoagulants or	Hold the administration of obinutuzumab in case of severe thrombocytopenia (platelets obinutuzumab. If either obinutuzumab or chemotherapy administration is delayed, the entire treatment cycle will be delayed.

platelet inhibitors	
Thrombocytopenia with platelets < 20.000/µL and/or symptomatic bleeding in patients who are receiving concomitant anticoagulants or platelet inhibitors [a,b]	Hold obinutuzumab in case of platelets < 20.000/µL or symptomatic bleeding (irrespective of platelet count) until it resolves, but do not skip any doses of obinutuzumab for sake of maintaining the chemo schedule. For patients who are on LMWH, when thrombocytopenia with platelets < 20.000/µL develops, reduce the dose of LMWH used. [b] For patients who are on platelet inhibitors, when thrombocytopenia with platelets < 20.000/µL develops, consideration should be given to temporarily pause their use.[b]
a If the clinical condition of the patient requires the use of concomitant anticoagulants, patients are at increased risk of bleeding when thrombocytopenia with platelets < 20.000/µL develops. When possible, replace prior therapy with vitamin K antagonists with low molecular weight heparins (LMWH) before C1D1. b Clinical decision making may be adjusted depending on the patient-specific assessment of benefit and risk.	

Treatment Delay

For Grade 3 or 4 adverse events occurring on obinutuzumab administration Days 1, 2, 8 and 15, up to a 2-week delay of infusions is allowed during Cycle 1. For subsequent obinutuzumab cycles, a maximum dose delay of 4 weeks is permitted per cycle. A maximum of 8 weeks of cumulative delay due to toxicity is allowed in total per patient. If either obinutuzumab or chemotherapy administration is delayed, the entire treatment cycle will be delayed (e.g. if the obinutuzumab dose at Cycle / 1 Day 15 is delayed by 1 week, the Cycle 2 / Day 1 dose of both obinutuzumab and chemotherapy will be delayed by 1 week).

If either obinutuzumab or chemotherapy administration is delayed, the entire treatment cycle will be delayed.

The dose of obinutuzumab will not be modified.

A decision for treatment delays will be based on the dose modification recommendation for bendamustine (see below).

Modifications to the doses of obinutuzumab-bendamustine

Modifications to the doses of obinutuzumab-bendamustine in the event of hematological toxicity

For more information on dose modifications due to hematological toxicity, see Table B (if the baseline values of the laboratory hematology tests are abnormal) and Table C (if said values are within the normal limits).

Table B: Dose modification in the event the baseline values of the laboratory hematology tests are abnormal (according to the NCI-WB grading for CLL)

Dose modification for obinutuzumab + bendamustine	
Platelets (% decrease from the pre-treatment value)	
11%-49%	No dose modification
≥ 50%	First episode: If on Day 28[a] (or on the day before each study treatment administration) of any cycle grade 3/4 cytopenia is observed, the treatment must be delayed. If the cytopenia subsides to grade ≤ 2, reduce the dose of bendamustine to 60 mg/m^2 in all subsequent cycles. The dose of obinutuzumab will not be reduced. If the cytopenia does not subside to grade ≤ 2 after 4 weeks, all treatment must be discontinued. A maximum dose delay of 4 weeks is permitted per cycle.[b] Second episode: If on Day 28[a] (or on the day before each study treatment administration) of any cycle grade 4 cytopenia is observed, all treatment must be discontinued (obinutuzumab + bendamustine). In the event of a second episode of grade 3 cytopenia, the treatment must be delayed. If the cytopenia subsides to grade ≤ 2, reduce the dose of bendamustine to 50 mg/m^2 in all subsequent cycles. The dose of obinutuzumab will not be reduced. If the cytopenia does not subside to grade ≤ 2 after 4 weeks, all treatment must be discontinued. A maximum dose delay of 4 weeks is permitted per cycle.[b] Third episode: If on Day 28[a] (or on the day before each study treatment administration) of any cycle a third episode of grade 3/4 cytopenia is observed, all treatment must be discontinued. No more than two dose reductions of bendamustine are permitted.
Hemoglobin (% decrease from the pre-treatment value)	
11%-49%	No dose modification
≥ 50%	First episode: If on Day 28[a] (or on the day before each study treatment administration) of any cycle grade 3/4 cytopenia is observed, the treatment must be delayed. If the cytopenia subsides to grade ≤ 2, reduce the dose of bendamustine to 60 mg/m^2 in all subsequent cycles. The dose of obinutuzumab will not be reduced. If the cytopenia does not subside to grade ≤ 2 after 4 weeks, all treatment must be discontinued. A maximum

	dose delay of 4 weeks is permitted per cycle.[b] s. Second episode: If on Day 28[a] (or on the day before each study treatment administration) of any cycle a second episode of grade 3/4 cytopenia is observed, the treatment must be delayed. If the cytopenia subsides to grade ≤ 2, reduce the dose of bendamustine to 50 mg/m^2 in all subsequent cycles. The dose of obinutuzumab will not be reduced. If the cytopenia does not subside to grade ≤ 2 after 4 weeks, all treatment must be discontinued. A maximum dose delay of 4 weeks is permitted per cycle.[b]. Third episode: If on Day 28[a] (or on the day before each study treatment administration) of any cycle a third episode of grade 3/4 cytopenia is observed, the treatment must be delayed. If the cytopenia is not resolved after 4 weeks, all treatment must be discontinued. No more than two dose reductions of bendamustine are permitted.
Neutrophils (cells/mm^3)	
11%-49%	No dose modification
≥ 50%	First episode: If on Day 28[a] (or on the day before each study treatment administration) of any cycle grade 3/4 cytopenia is observed, the treatment must be delayed. If the cytopenia subsides to grade ≤ 2, reduce the dose of bendamustine to 60 mg/m^2 in all subsequent cycles. The dose of obinutuzumab will not be reduced. If the cytopenia does not subside to grade ≤ 2 after 4 weeks, all treatment must be discontinued. A maximum dose delay of 4 weeks is permitted per cycle.[b]. Second episode: If on Day 28[a] (or on the day before each study treatment administration) of any cycle grade 4 cytopenia is observed, all treatment must be discontinued (obinutuzumab + bendamustine). In the event of a second episode of grade 3 cytopenia, the treatment must be delayed. If the cytopenia subsides to grade ≤ 2, reduce the dose of bendamustine to 50 mg/m^2 in all subsequent cycles. The dose of obinutuzumab will not be reduced. If the cytopenia does not subside to grade ≤ 2 after 4 weeks, all treatment must be discontinued. A maximum dose delay of 4 weeks is permitted per cycle.[b] Third episode: If on Day 28[a] (or on the day before each study treatment administration) of any cycle a third episode of grade 3/4 cytopenia is observed, all treatment must be discontinued.

	No more than two dose reductions of bendamustine are permitted.

NCI-WG CLL = National Cancer Institute Working Group Chronic Lymphocytic Leukemia.

[a] Day 28 = laboratory values prior to the cycle, for Day 1 of any cycle.

[b] A maximum of 8 weeks cumulative delay due to toxicity is allowed in total per patient. If toxicity appears before D2, D8 or D15 treatment, a maximum of 2 weeks delay for obinutuzumab treatment is allowed, obinutuzumab dose will not be modified.

Table C: Dose modification in the event the baseline values of the laboratory hematology tests are within the normal range (according to the NCI-CTCAE criteria)

Grade [a]	Dose modification for obinutuzumab + bendamustine
Platelets	
Grade 1 or 2	No dose modification
Grade 3 or 4	First episode: If on Day 28[b] (or on the day before each study treatment administration) of any cycle grade 3/4 cytopenia is observed, the treatment must be delayed. If the cytopenia is resolved to grade ≤ 2, reduce the dose of bendamustine to 60 mg/m^2 in all subsequent cycles. The dose of obinutuzumab will not be reduced. If the cytopenia does not subside to grade ≤ 2 after 4 weeks, all treatment must be discontinued. A maximum dose delay of 4 weeks is permitted per cycle.[c] Second episode: If on Day 28[b] (or on the day before each study treatment administration) of any cycle grade 4 cytopenia is observed, all treatment must be discontinued (obinutuzumab + bendamustine). In the event of a second episode of grade 3 cytopenia, the treatment must be delayed. If the cytopenia subsides to grade ≤ 2, reduce the dose of bendamustine to 50 mg/m^2 in all subsequent cycles. The dose of obinutuzumab will not be reduced. If the cytopenia is not resolved to grade ≤ 2 after 4 weeks, all treatment must be discontinued. A maximum dose delay of 4 weeks is permitted per cycle.[c] Third episode: If on Day 28[a] (or on the day before each study treatment administration) of any cycle a third episode of grade 3/4 cytopenia is observed, all treatment must be discontinued. No more than two dose reductions of bendamustine are permitted.

Hemoglobin	
Grade 1 or 2	No dose modification
Grade 3 or 4	First episode: If on Day 28[b] (or on the day before each study treatment administration) of any cycle grade 3/4 cytopenia is observed, the treatment must be delayed. If the cytopenia subsides to grade ≤ 2, reduce the dose of bendamustine to 60 mg/m^2 in all subsequent cycles. The dose of obinutuzumab will not be reduced. If the cytopenia is not resolved to grade ≤ 2 after 4 weeks, all treatment must be discontinued. A maximum dose delay of 4 weeks is permitted per cycle.[c] . Second episode: If on Day 28[b] (or on the day before each study treatment administration) of any cycle a second episode of grade 3/4 cytopenia is observed, the treatment must be delayed. If the cytopenia improves to grade ≤ 2, reduce the dose of bendamustine to 50 mg/m^2 in all subsequent cycles. The dose of obinutuzumab will not be reduced. If the cytopenia is not resolved to grade ≤ 2 after 4 weeks, all treatment must be discontinued. A maximum dose delay of 4 weeks is permitted per cycle.[c] Third episode: If on Day 28[b] (or on the day before each study treatment administration) of any cycle a third episode of grade 3/4 cytopenia is observed, the treatment must be delayed. If the cytopenia is not resolved in the course of 4 weeks, all treatment must be discontinued. No more than two dose reductions of bendamustine are permitted.
Neutrophils	
Grade 1 or 2	No dose modification

Grade 3 or 4	First episode: If on Day 28[b] (or on the day before each study treatment administration) of any cycle grade 3/4 cytopenia is observed, the treatment must be delayed. If the cytopenia improves to grade ≤ 2, reduce the dose of bendamustine to 60 mg/m^2 in all subsequent cycles. The dose of obinutuzumab will not be reduced. If the cytopenia does not subside to grade ≤ 2 after 4 weeks, all treatment must be discontinued. A maximum dose delay of 4 weeks is permitted per cycle.[c] . Second episode: If on Day 28[b] (or on the day before each study treatment administration) of any cycle grade 4 cytopenia is observed, all treatment must be discontinued (obinutuzumab + bendamustine). In the event of a second episode of grade 3 cytopenia, the treatment must be delayed. If the cytopenia subsides to grade ≤ 2, reduce the dose of bendamustine to 50 mg/m^2 in all subsequent cycles. The dose of obinutuzumab will not be reduced. If the cytopenia is not resolved to grade ≤ 2 after 4 weeks, all treatment must be discontinued. A maximum dose delay of 4 weeks is permitted per cycle.[c] . Third episode: If on Day 28[b] (or on the day before each study treatment administration) of any cycle a third episode of grade 3/4 cytopenia is observed, all treatment must be discontinued. No more than two dose reductions of bendamustine are permitted.
NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events	
[a] According to the NCI CTCAE v4.0 criteria	
[b] Day 28 = laboratory values prior to the cycle, for Day 1 of any cycle. [c] A maximum of 8 weeks cumulative delay due to toxicity is allowed in total per patient. If toxicity appears before D2, D8 or D15 treatment, a maximum of 2 weeks delay for obinutuzumab treatment is allowed, obinutuzumab dose will not be modified.	

Dose modifications due to infectious complications

If a grade 2-4 infection occurs after the administration of the chemotherapy, the next cycle can be delayed up to 4 weeks, until the infection is resolved. If the infection has not been resolved after 4 weeks, the study treatment must be discontinued. If a grade 3/4 infection associated with cytopenia occurs (for example, neutropenia), the guidelines for dose reduction in the event of hematological toxicity described above (in the section "Dose modifications due to hematological toxicity") must be applied.

Administration of granulocyte colony-stimulating factors

G-CSF can be administered as primary prophylaxis in every cycle of treatment, in accordance with the ASCO guidelines or the institutional standards of every site.

Dose modifications due to non-hematological toxicity

For more information on dose modifications due to non-hematological toxicity, see Table D.

Table D: Dose modifications for obinutuzumab + bendamustine due to non-hematological toxicity

Toxicity event	Obinutuzumab + bendamustine
Grade 4 non-hematological	All treatment (obinutuzumab + bendamustine) must be discontinued
Grade 3 non-hematological	First episode: If a grade 3 toxicity is observed any time during any cycle, bendamustine dose should be reduces to 60 mg/m^2 in all subsequent cycles. If on Day 28[a] of any cycle (or on the day before each study treatment administration) grade 3 toxicity is observed, the treatment must be delayed. If the toxicity subsides to grade ≤ 2, reduce the dose of bendamustine to 60 mg/m^2 in all subsequent cycles. 4 weeks, all treatment must be discontinued. . A maximum dose delay of 4 weeks is permitted per cycle.[b] Second episode: : If a second episode of a grade 3 toxicity is observed any time during any cycle, bendamustine dose should be reduces to 50 mg/m^2 in all subsequent cycles. If on Day 28[a] of any cycle (or on the day before each study treatment administration) a second episode of grade 3 toxicity is observed, the treatment must be delayed. If the toxicity subsides to grade ≤ 2, reduce the dose of bendamustine to 50 mg/m^2 in all subsequent cycles. grade ≤ 2 after 4 weeks, all treatment must be discontinued. . A maximum dose delay of 4 weeks is permitted per cycle.[b] Third episode: If a third episode of grade 3 toxicity is observed any time during any cycle, all treatment must be discontinued.

	No more than two dose reductions of bendamustine are permitted.
Grade 1/2 non-hematological	No dose reduction

[a] Day 28 = laboratory values prior to the cycle, for Day 1 of any cycle.

[b] A maximum of 8 weeks cumulative delay due to toxicity is allowed in total per patient. If toxicity appears before D2, D8 or D15 treatment, a maximum of 2 weeks delay for obinutuzumab treatment is allowed, obinutuzumab dose will not be modified.

APPENDIX 8
OBINUTUZUMAB INFUSION RATES

Obinutuzumab Infusion Rates:

First Infusion (Cycle 1 Day 1): 100 mg GA101

Remove 4 mL of saline from a 250 mL bag and add 4 mL of GA101 and administer over 4 hour

Infusion Start Time	
Infusion End Time	
Cumulative time (hh:mm)	**04:00**
Rate mg/hr Rate mL/hr using a 250 mL bag	25 62.5
Administered dose mg	**100**

First Infusion (Cycle 1 Day 1 or Day 2): 900 mg GA101

Remove 36 mL of saline from the **250 mL bag** and add 36 mL of GA101

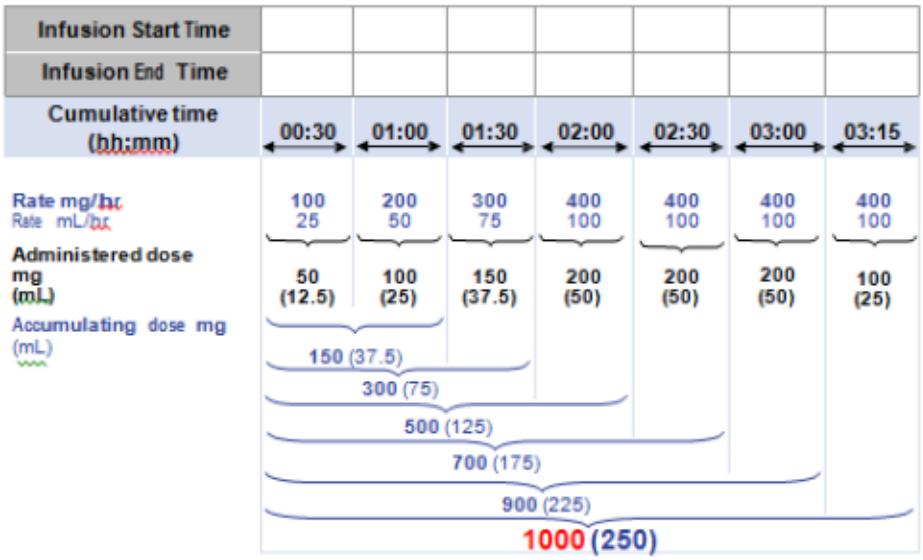
Infusion Start Time								
Infusion End Time								
Cumulative time (hh:mm)	**00:30**	**01:00**	**01:30**	**02:00**	**02:30**	**03:00**	**03:30**	**04:00**
Rate mg/hr Rate mL/hr	50 13.9	100 27.8	150 41.7	200 55.6	250 69.4	300 83.3	350 97.2	400 111.1
Administered dose mg (mL)	**25 (7)**	**50 (13.9)**	**75 (20.8)**	**100 (27.7)**	**125 (34.7)**	**150 (41.6)**	**175 (48.6)**	**200 (55.5)**
Accumulating dose mg (mL)	75 (20.8)							
	150 (41.7)							
	250 (69.4)							
	375 (104.2)							
	525 (145.8)							
	700 (194.4)							
	900 (250)							

All rates are given assuming no Infusion-Related Reactions (IRRs) was observed. In case of an IRR the patient should be managed according to protocol section 4.2.21. Table 2 (Infusion Rate Modification Guidelines for IRRs)

Obinutuzumab Infusion Rates 1000 mg:

Subsequent Infusions, C1D8, C1D15, C2-6

Remove 40 mL of saline from the 250 mL bag and add 40 mL of GA10



Cumulative Time (hh:mm)	00:30	01:00	01:30	02:00	02:30	03:00	03:15
Rate (mg/hr)	100	200	300	400	400	400	400
Rate (ml/hr)	25	50	75	100	100	100	100
Administered dose (mg) at this time	50	100	150	200	200	200	100
Accumulating dose (mg) at this time	50	150	300	500	700	900	1000
Administered dose (mL) at this time	12.5	25	37.5	50	50	50	25
Accumulating dose (mL) at this time	12.5	37.5	75	125	175	225	250

All rates are given assuming no Infusion-Related Reactions (IRRs) was observed. In case of an IRR the patient should be managed according to protocol section 4.2.21. Table 2 (Infusion Rate Modification Guidelines for IRRs)

Appendix 9 Bendamustine Preparation Instructions

For preparation of the ready-for-use solution, the contents of one bendamustine vial are dissolved in water for injection as follows:

Bendamustine powder should be reconstituted immediately after opening of the vial. First dissolve the contents of the bendamustine vial containing 100 mg of bendamustine hydrochloride in 40 mL of water for injection by shaking. Once a clear solution has been obtained (usually after 5–10 minutes), the total recommended bendamustine dose is diluted immediately with 0.9% NaCl solution to a final volume of 500 mL. Bendamustine must be diluted with 0.9% NaCl solution and not with any other injection solution.

Incompatibilities

Bendamustine must not be mixed with other substances in an infusion. The powder must be dissolved only in water and further diluted with 0.9% NaCl solution.

Storage of Diluted Solution for Infusion

After reconstitution and dilution, chemical and physical stability has been demonstrated for 3.5 hours at 25ºC / 60% relative humidity and for 2 days at 2ºC to 8ºC in polyethylene bags. The vial should be kept in the outer carton in order to protect bendamustine from light.

From a microbiological perspective, the ready-for-use preparation should be used immediately. If the ready-for-use preparation is not used immediately, the user is responsible for the duration and conditions of storage.