Official Title: A Multicentric, Open-Label, Single arm Study of Obinutuzumab Short Duration Infusion (SDI) in Patients With Previously Untreated Advanced Follicular Lymphoma

NCT Number: NCT03817853

Document Dates: Protocol Version 5: 30-June-2021

PROTOCOL

TITLE:	**A MULTICENTRIC, OPEN-LABEL, SINGLE ARM STUDY OF OBINUTUZUMAB SHORT DURATION INFUSION (SDI) IN PATIENTS WITH PREVIOUSLY UNTREATED ADVANCED FOLLICULAR LYMPHOMA**
PROTOCOL NUMBER:	MO40597
VERSION NUMBER:	5
EUDRACT NUMBER:	2018-003255-38
IND NUMBER:	104405
TEST PRODUCT:	Obinutuzumab (GA101, RO5072759)
MEDICAL MONITOR:	[redacted]
SPONSOR:	F. Hoffmann-La Roche Ltd
APPROVAL DATE:	See electronic date stamp below

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
30-Jun-2021 07:42:13	Company Signatory	[redacted]

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
5	See electronic date stamp on title page
4	21 September 2019
3	18 December 2018
2	06 December 2018
1	17 October 2018

PROTOCOL AMENDMENT, VERSION 5:
RATIONALE

Protocol MO40597 has been amended to provide guidance on the use of COVID-19 vaccines in study patients and to add in the time windows allowed for completing the regular infusion and short duration infusion. Changes to the protocol, along with a rationale for each change, are summarized below:

- Section 4.4.1 (Permitted Therapy) has been updated to indicate that patients are permitted to use COVID-19 vaccines that have been granted emergency use authorization or equivalent. The vaccine should be captured in the eCRF as a concomitant medication and the brand/trade name or company manufacturer should be reported, if available.
- Section 5.1.1.7 (Risks Associated with Obinutuzumab: Immunizations) has also been updated accordingly to describe the anticipated risk that the efficacy of COVID-19 vaccines may be diminished in patients receiving obinutuzumab.
- Table 1 (Obinutuzumab Infusion Rates at Induction and Maintenance) has been updated to include the time windows allowed for completing the short duration infusion (93 [± 5] minutes) and regular rate infusion (195 [± 10] minutes).
- An error in Figure 1 has been corrected: Patients with stable disease or progressive disease as best response after induction therapy will discontinue study treatment (and not discontinue the study); these patients have a safety follow-up visit 90 days (± 10 days) from the time of the last dose of study treatment.

Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

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

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by the Sponsor.

PROTOCOL SYNOPSIS

TITLE:	**A MULTICENTRIC, OPEN-LABEL, SINGLE ARM STUDY OF OBINUTUZUMAB SHORT DURATION INFUSION (SDI) IN PATIENTS WITH PREVIOUSLY UNTREATED ADVANCED FOLLICULAR LYMPHOMA**
PROTOCOL NUMBER:	MO40597
VERSION NUMBER:	5
EUDRACT NUMBER:	2018-003255-38
IND NUMBER:	104405
TEST PRODUCT:	Obinutuzumab (GA101, RO5072759)
PHASE:	Phase IV
INDICATION:	Follicular lymphoma
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

The primary objective of this study is to evaluate the safety of administering obinutuzumab as a short duration infusion (SDI; target 90-minute infusion) during cycle 2 and from cycle 2 onwards in combination with chemotherapy in patients with previously untreated advanced follicular lymphoma (FL) on the basis of the following endpoints:

Primary endpoint:

- The incidence of Grade ≥3 infusion-related reactions (IRRs*) during cycle 2 in patients who had previously received obinutuzumab at the standard infusion rate during cycle 1 without experiencing a Grade 3 or 4 IRR, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0.

* *IRRs are defined as all adverse events (AEs) that occur during or within 24 hours from the end of study treatment infusion and are judged as related to infusion of study treatment components (obinutuzumab and chemotherapy during induction and obinutuzumab alone during maintenance) by the investigator.*

Secondary safety endpoints:

- Incidence, nature, and severity of all AEs during cycle 1 and from cycle 1 onwards (including maintenance)
- Incidence of IRRs regardless of grade by cycle (separately)
- Time to IRR (in hours) from infusion to onset of the IRR during cycle 2
- Duration (in minutes) of obinutuzumab administration by cycle (all cycles including maintenance)
- Type and duration of Grade ≥3 IRRs, during all cycles, where obinutuzumab was administered as an SDI.

Secondary efficacy objective:

The secondary efficacy objective for this study is to evaluate the efficacy of obinutuzumab administered as an SDI from cycle 2 in patients with previously untreated advanced FL on the basis of the following endpoints:

- Objective response rate at the end of induction (EOI) therapy as determined by the investigator and according to the guidelines used at the site (Lugano [Cheson et al 2014], Cheson et al 2007, or Cheson et al 1999)
- Progression-free survival rate at the end of the study
- Overall survival at the end of the study
- Complete response (CR) rate at 30 months (CR30), as assessed by the investigator and according to the guidelines used at the site.

Exploratory objectives:

The exploratory safety objectives for this study are to further evaluate the safety of obinutuzumab administered in patients with previously untreated advanced FL on the basis of the following endpoints to evaluate the impact of time to IRR:

- The incidence of Grade ≥3 IRRs* (with severity determined according to NCI CTCAE Version 5.0) during the first SDI cycle:
    - cycle 2 in patients who received obinutuzumab at the standard infusion rate without experiencing a Grade 3 IRR in cycle 1
    - cycle 3 in patients who experienced a Grade 3 IRR when administered obinutuzumab at the standard infusion rate in cycle 1 and subsequently received obinutuzumab at the standard infusion rate in cycle 2 without experiencing a Grade 3 IRR
- Time to IRR (in hours) from infusion to onset of the IRR in cycle 1 or cycle 3

* *IRRs are defined as all adverse events (AEs) that occur during or within 24 hours from the end of study treatment infusion and are judged as related to infusion of study treatment components (obinutuzumab and chemotherapy during induction and obinutuzumab alone during maintenance) by the investigator.*

The exploratory efficacy objectives for this study are to evaluate patients with a partial response (PR) at the end of induction treatment who convert to CR during maintenance treatment and to evaluate and compare the objective response and CR rate after the end of induction treatment with and without 18F-fluorodeoxyglucose positron emission tomography (FDG-PET):

- Proportion of patients with a PR at the end of induction treatment who convert to CR during maintenance treatment, as assessed by the investigator and according to the guidelines used at the site (see above)
- Objective response rate and CR rate after the end of induction treatment, as assessed by the investigator and according to the guidelines used at the site (see above), for those with and those without 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) separately.

The exploratory patient-reported objective for this study is to evaluate the severity and interference of disease- and treatment-related symptoms in patients with previously untreated advanced FL treated with obinutuzumab administered as an SDI from cycle 2.

- Severity of disease symptoms experienced by patients and the interference with daily living caused by these symptoms, as assessed through use of the MD Anderson Symptom Inventory (MDASI; Appendix 2).

The exploratory provider-reported objective is to evaluate the site experience with the SDI, specifically:

- Physician / nurse experience on time savings with obinutuzumab SDI compared with obinutuzumab at the regular infusion rate
- Physician / nurse experience on the convenience of and preference for obinutuzumab SDI compared with obinutuzumab at the regular infusion rate.

Study Design

Description of Study

This is an open-label, international, multicenter, single arm Phase IV study to investigate the safety and efficacy of the short duration infusion (SDI; target 90-minute infusion) obinutuzumab in patients with previously untreated advanced FL.

The study has two phases: in the first phase patients will receive the first cycle of obinutuzumab-based chemotherapy (G-chemo) induction therapy as usual with the first three infusions of obinutuzumab (1000 mg) administered at the regular infusion rate (Table 1) on Day 1, 8, and 15 of cycle 1. The investigator is free to choose the chemotherapy for each patient (bendamustine, CHOP [cyclophosphamide, doxorubicin, vincristine, prednisone/prednisolone/methylprednisolone], or CVP [cyclophosphamide, vincristine, and prednisone/prednisolone/methylprednisolone]). The total number of cycles of G-chemo induction therapy and the cycles length depends on the chemotherapy chosen for each patient (see Section 4.3.1).

Study treatment in this protocol refers to obinutuzumab and chemotherapy during the induction phase and obinutuzumab monotherapy during the maintenance phase.

For the purpose of this study IRRs are defined as all AEs that occur during or within 24 hours from the end of study treatment infusion and are judged as related to infusion of study treatment components (obinutuzumab and chemotherapy during induction and obinutuzumab alone during maintenance) by the investigator.

Patients who do not experience any Grade ≥3 IRRs during the first cycle will enter into the second, faster infusion, phase from Cycle 2 onwards. These patients will receive obinutuzumab at the SDI rate, starting on Cycle 2, Day 1 (Table 1).

Patients who experience a Grade 3 IRR during the first cycle will remain on the study but cycle 2 of obinutuzumab must be administered at the regular infusion rate. If these patients do not experience a Grade ≥3 IRR during cycle 2 at the regular infusion rate, then they will be eligible to receive SDI dosing from cycle 3 onwards, according to investigator judgement.

Patients who experience a first occurrence of a Grade 3 IRR during any SDI administration of obinutuzumab may continue to receive SDI dosing during the current infusion, and in the next cycle, as long as the Grade 3 IRR resolves after the infusion is interrupted and symptoms are treated, and no further IRR symptoms reoccur after restarting the SDI. Guidance on IRR management during both regular and SDI infusions is given in Appendix 6.

The obinutuzumab infusion must be stopped, and obinutuzumab must be permanently discontinued, in any patient who experiences a second occurrence of any Grade 3 IRR, regardless of the rate of infusion.

Patients who experience a Grade 4 IRR at any time during the study will permanently discontinue obinutuzumab treatment.

Table 1 Obinutuzumab Infusion Rates at Induction and Maintenance

Regular infusion rate [a]		SDI (approximately 90 minutes) [a]
First Infusion (Cycle 1, Day 1)	**Second and Third Infusions (Cycle 1, Days 8 and 15)**	**Cycle 2, Day 1 and All Other following Infusions (including maintenance) [b]**
50 mg/hr Rate increased by **50 mg/hr** every 30 min **400 mg/hr** max rate **Refer to Appendix 6a for guidance on management of IRRs during regular infusion**	If no IRR, or an IRR of Grade 1 occurred during the previous infusion and the final infusion rate was 100 mg/hr or faster: Start at a rate of **100 mg/hr** Increase rate by **100 mg/hr** every 30 min **400 mg/hr** max rate If an IRR of Grade 2–3 occurred during the previous infusion, start at **50 mg/hr**. The rate of the infusion can be escalated in increments of **50 mg/hr** every 30 min to a maximum rate of **400 mg/hr** **Refer to Appendix 6b for guidance on management of IRRs during regular infusion**	**100 mg/hr** for 30 min, then **900 mg/hr** for 60 min **Refer to Appendix 6c for guidance on management of IRRs during SDI infusion** If an IRR of Grade 1–2, or a first occurrence of Grade 3, occurred during the previous SDI infusion and the patient has **ongoing symptoms** until the time of the next cycle, then the next administration of obinutuzumab should be given at the **regular infusion rate** as per Cycle 1, Days 8 and 15. If the IRR in the previous infusion resolved, then the next cycle can be administered at the SDI rate.

IRR=infusion-related reaction; Max=maximum; SDI=short duration infusion

a. To deliver the full dose of 1000 mg, the whole contents of the bag should be administered *in 195 (± 10) minutes for the regular infusion rate and 93 (± 5) minutes for the SDI.*

b. Patients should only start the SDI infusion in Cycle 2 if they did not experience any Grade ≥3 IRRs during Cycle 1 (on Day 1, 8, or 15). If they did experience a Grade ≥3 IRR during Cycle 1 (on Day 1, 8, or 15), then the infusion on Day 1 of Cycle 2 should be given at the regular infusion rate.

All patients will be assessed for disease response by the investigator at the end of induction therapy and end of maintenance therapy according to local practice and according to the guidelines used at the site (Lugano [Cheson et al 2014], Cheson et al 2007, or Cheson et al 1999). No central confirmation of disease response will be conducted.

Patients who achieve at least a partial response following the completion of induction therapy will receive obinutuzumab maintenance therapy (1000 mg as single agent administered as an SDI every 8 weeks (± 10 days) for 2 years or until disease progression).

The first administration of obinutuzumab maintenance therapy is expected to start 8 weeks ± 10 days from Day 1 of the last induction cycle.

Patients with stable disease or progressive disease as best response after induction therapy will discontinue study treatment and undergo a safety follow-up visit at 3 months (90 days (± 10 days)).

All patients will be followed up at 3 months (90 days (± 10 days)) from the time of the last dose of study treatment.

The first scheduled Internal Monitoring committee (IMC) data review will take place after the first 10 patients have completed the first SDI infusion (i.e. cycle 2). The second IMC data review will happen after 50 patients have completed the first SDI infusion (i.e. cycle 2) or at 6 months after the first IMC, whichever occurs first. Furthermore, the IMC will review results obtained for the primary analysis, end of induction analysis, and final analysis. Further meetings will be scheduled as deemed necessary. Further details will be specified in the IMC charter.

Safety will be evaluated by monitoring dose delays and dose intensity, adverse events, serious adverse events, and deaths. These will be graded using the NCI CTCAE, Version 5.0. Laboratory safety assessments will include regular monitoring of hematology and blood chemistry.

Provider and patient-reported outcome data will be collected via questionnaires to document the severity of disease and treatment-related symptoms experienced by patients and the interference with daily living caused by these symptoms, as assessed through use of the MD Anderson Symptom Inventory (MDASI; Appendix 2); and to evaluate the site experience with the SDI and standard infusions of obinutuzumab.

Number of Patients

A total of 100 patients is needed in the SDI population. Allowing for drop-outs this means that approximately 112 patients will be enrolled in this study.

Target Population

Inclusion Criteria

Patients must meet the following criteria for study entry:

1. Signed Informed Consent Form
2. Age ≥ 18 years at time of signing Informed Consent Form
3. Able and willing to comply with all study related procedures including completion of patient-reported outcome (PRO) endpoints
4. Ability to comply with the study protocol, in the investigator's judgment
5. Patients with previously untreated Stage III or IV FL or Stage II bulky disease scheduled to receive obinutuzumab and chemotherapy due to at least one of the following criteria:
    a. Bulky disease, defined as a nodal or extranodal (except spleen) mass ≥ 7 cm in the greatest diameter
    b. Local symptoms or compromise of normal organ function due to progressive nodal disease or extranodal tumor mass
    c. Presence of B symptoms (fever [> 38ºC], drenching night sweats, or unintentional weight loss of > 10% of normal body weight over a period of 6 months or less)
    d. Presence of symptomatic extranodal disease (e.g., pleural effusions, peritoneal ascites)
    e. Cytopenias due to underlying lymphoma (i.e., absolute neutrophil count < 1.0 × 10^9/L, hemoglobin < 10 g/dL, and/or platelet count < 100 × 10^9/L)
    f. Involvement of ≥ 3 nodal sites, each with a diameter of ≥ 3 cm
    g. Symptomatic splenic enlargement
6. Histologically documented CD-20-positive FL, as determined by the local laboratory
7. Eastern Cooperative Oncology Group (ECOG) performance status 0−2
8. Adequate hematologic function (unless abnormalities are related to FL), defined as follows:
    a. Hemoglobin ≥ 9.0 g/dL
    b. Absolute neutrophil count ≥ 1.5 × 10^9/L

c. Platelet count ≥ 75 × 10^9/L

9. Life expectancy of ≥ 12 months
10. For women who are not postmenopausal (≥ 12 consecutive months of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 18 months after the last dose of obinutuzumab, for at least 3 months after the last dose of bendamustine or according to institutional guidelines for CHOP or CVP chemotherapy, whichever is longer
    a. Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, established, proper use of progestogen-only hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices (IUDs), and copper IUDs
    b. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception

        Barrier methods must always be supplemented with the use of a spermicide
11. For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures and agreement to refrain from donating sperm, as defined below:
    a. With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and for at least 3 months after the last dose of study treatment. Men must refrain from donating sperm for the same period
    b. With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 3 months after the last dose of study treatment
    c. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception

<u>Exclusion Criteria</u>

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

1. Relapsed / refractory FL
2. Prior treatment for FL with chemotherapy, radiotherapy, or immunotherapy
3. Grade IIIb FL
4. Histological evidence of transformation of FL into high-grade B-cell NHL
5. Treatment with systemic immunosuppressive medications, including, but not limited to, prednisone/prednisolone/methylprednisolone (at a dose equivalent to >30 mg/day prednisone), azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor agents within 2 weeks prior to Day 1 of Cycle 1
    a. Treatment with inhaled corticosteroids and mineralocorticoids is permitted

b. Patients receiving corticosteroid treatment with ≤30 mg/day of prednisone or equivalent must be documented to be on a stable dose of at least 4 weeks' duration prior to enrolment
c. If glucocorticoid treatment is urgently required for medical reasons (e.g., complications imminent if not treated at least with glucocorticoids; strong discomfort/pain of the patient due to lymphoma), prednisone 100 mg or equivalent can be given for a maximum of 5 sequential days, but all tumor assessments must be completed prior to the start of glucocorticoid treatment. Glucocorticoid treatment must be stopped prior to enrolment
d. In cases when a glucocorticoid pre-treatment/pre-phase was done externally prior to considering the patient for study inclusion, glucocorticoids must be stopped for at least 7 days before screening assessments can begin

6. History of solid organ transplantation
7. History of anti-CD20 antibody therapy
8. History of severe allergic or anaphylactic reaction to humanized, chimeric, or murine monoclonal antibodies
9. Known sensitivity or allergy to murine products
10. Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells or any of the study drugs
11. Active bacterial, viral, fungal, or other infection or any major episode of infection requiring treatment with intravenous (IV) antibiotics within 4 weeks of Day 1 of Cycle 1
    a. Caution should be exercised when considering the use of obinutuzumab in patients with a history of recurring or chronic infections
12. Positive test results for chronic hepatitis B virus (HBV) infection (defined as positive HBsAg serology)
    a. Patients with occult or prior HBV infection (defined as negative HBsAg and positive total HBcAb) may be included if HBV DNA is undetectable, provided that they are willing to undergo DNA testing at least every 3 months (during the study and for at least 1 year after completion of lymphoma treatment). Patients who have protective titers of hepatitis B surface antibody (HBsAb) after vaccination or prior but cured hepatitis B are eligible
13. Positive test results for hepatitis C (hepatitis C virus [HCV] antibody serology testing)
    a. Patients positive for HCV antibody are eligible only if the polymerase chain reaction (PCR) is negative for HCV RNA
14. Known history of human immunodeficiency virus (HIV) positive status
    a. For patients with unknown HIV status, HIV testing will be performed at screening if required by local regulations
15. History of progressive multifocal leukoencephalopathy (PML)
16. Vaccination with a live virus vaccine within 28 days prior to Day 1 of Cycle 1 or anticipation that such a live, attenuated vaccine will be required during the study
17. History of prior other malignancy with the exception of:
    a. Curatively treated carcinoma in situ of the cervix, good-prognosis ductal carcinoma in situ of the breast, basal- or squamous-cell skin cancer, Stage I melanoma, or low-grade, early-stage localized prostate cancer

b. Any previously treated malignancy that has been in remission without treatment for ≥ 2 years prior to enrollment

18. Evidence of any significant, uncontrolled concomitant disease 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, myocardial infarction within the previous 6 months, unstable arrhythmia, or unstable angina) or significant pulmonary disease (such as obstructive pulmonary disease or history of bronchospasm)
19. Major surgical procedure other than for diagnosis within 28 days prior to Day 1 of Cycle 1, Day 1, or anticipation of a major surgical procedure during the course of the study
20. For patients who will be receiving CHOP: left ventricular ejection fraction (LVEF) < 50% by multigated acquisition (MUGA) scan or echocardiogram
21. Any of the following abnormal laboratory values:
    a. Creatinine > 1.5 × the upper limit of normal (ULN) (unless creatinine clearance normal) or creatinine clearance < 40 mL/min
    b. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 × ULN
    c. Total bilirubin ≥ 1.5 × the ULN: Patients with documented Gilbert disease may be enrolled if total bilirubin is ≤ 3.0 × the ULN.
    d. International normalized ratio (INR) > 1.5 in the absence of therapeutic anticoagulation
    e. Partial thromboplastin time or activated partial thromboplastin time > 1.5 × ULN in the absence of a lupus anticoagulant
22. Pregnant or lactating, or intending to become pregnant during the study
    a. Women who are not postmenopausal (≥ 12 months of non-therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 7 days prior to Day 1 of Cycle 1
23. Any investigational therapy within 28 days prior to the start of Cycle 1
24. Positive test results for human T-lymphotropic virus 1 (HTLV-1)
    a. HTLV testing is required in patients from endemic countries

Patients who meet the following criteria will be excluded from further study participation after Cycle 1:

- Development of a Grade 4 IRR during Cycle 1.

End of Study

The end of the study is defined as the Last Patient, Last Visit (LPLV) which will occur when the last patient to discontinue participation in the study has completed the safety follow-up visit or at the time that one of the following is documented:

- Patient has withdrawn consent

  OR
- Patient is lost to follow-up

  OR
- Patient death.

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

Length of Study

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 4 years.

Investigational Medicinal Products

Test Product (Investigational Drug)

Obinutuzumab will be administered intravenously at a flat dose of 1000 mg on Day 1, 8 and 15 during Cycle 1, and on Day 1 of subsequent cycles, according to the infusion rates shown in Table 1. Splitting of the obinutuzumab dose (i.e. 100 mg + 900 mg) will not be permitted in this study. The cycle length and number of cycles depends on the chemotherapy combination (see below).

Following induction obinutuzumab and chemotherapy, maintenance obinutuzumab monotherapy will be administered at a dose of 1000 mg once every 8 weeks (± 10 days) for 2 years or until disease progression (whichever occurs first).

Non-Investigational Medicinal Products

Combination chemotherapy

Obinutuzumab will be administered in combination with one of the following chemotherapy regimens:

- Six 28-day cycles in combination with bendamustine
- Six 21-day cycles in combination with CHOP, followed by two additional cycles of obinutuzumab alone
- Eight 21-day cycles in combination with CVP.

Chemotherapy combinations will be administered according to the standard preparation and infusion procedures of each site. Body surface area (BSA) may be capped at 2 m^2 per institutional standards.

Premedication

Premedication to reduce the risk of IRRs is mandatory for the first standard infusion of obinutuzumab (Cycle 1, Day 1) and the first infusion of obinutuzumab given as an SDI and will comprise IV corticosteroid, oral analgesic/anti-pyretic, and antihistamine (e.g. 50 mg diphenhydramine) administered according to local guidelines.

For subsequent cycles, premedication will depend on whether the patient experienced an IRR with the previous infusion.

Patients with a high tumor burden, a circulating lymphocyte count (>25 × 10^9/L), or renal impairment (CrCL <70 mL/min) will receive premedication for TLS comprising hydration and uricostatics or urate oxidase 12–24 hours before infusion of obinutuzumab according to standard practice.

Statistical Methods

The primary analysis will be analyzed and reported based on all patients' data up to the time when all patients have completed 2 cycles of obinutuzumab treatment. The End of Induction analysis will be analyzed and reported once all patients have completed the induction period. The final analysis will be performed at the end of the study and include PFS and OS rates.

The analysis populations are defined as follows:

- The SDI population includes all patients who received obinutuzumab as an SDI at cycle 2 and who did not experience a Grade 3 or 4 IRR during the infusion of obinutuzumab given at the standard rate during cycle 1. This population will be used for the analysis of the primary endpoint and one of the secondary endpoints (time to IRR during cycle 2).
- The safety population includes all patients who received at least one dose of obinutuzumab. This population will be used for all remaining analyses.

No formal statistical hypothesis tests will be performed, and all analyses are considered descriptive.

Primary Analysis

The primary objective for this study is to evaluate the safety of obinutuzumab administered as an SDI in patients with previously untreated advanced FL on the basis of the following endpoint:

- The incidence of Grade ≥3 IRRs* during cycle 2 in patients who had previously received obinutuzumab at the standard infusion rate without experiencing a Grade 3 or 4 IRR, with severity determined according to NCI CTCAE v 5.0

* *IRRs are defined as all adverse events (AEs) that occur during or within 24 hours from the end of study treatment infusion and are judged as related to infusion of study treatment components (obinutuzumab and chemotherapy during induction and obinutuzumab alone during maintenance) by the investigator.*

Determination of Sample Size

A sample size of approximately 112 patients is planned for this study.

The incidence of Grade ≥3 IRRs during cycle 2 was chosen as the safety endpoint of primary interest and used to justify the sample size. Based on experience from previous studies (BO21223/GALLIUM, GAO4915g/GATHER), it is assumed to have an incidence rate of only 1% or 2%, and hence to observe only a few events.

Observing two Grade ≥3 IRRs during cycle 2 would yield an upper bound (of the Corresponding Two-sided 95% Clopper-Pearson Confidence Interval [CI]) of 7.0% in an SDI population of 100 patients and of 7.8% in an SDI population of 90 patients. Not observing any Grade ≥3 IRRs during cycle 2 would yield upper bounds of 3.6% and 4.0%, respectively.

There will be no formal hypothesis test for the primary endpoint.

Taking into account an estimated drop-out rate of 10%, a total of approximately 112 patients will be enrolled in this study to have 100 patients in the SDI population. If the drop-out rate would be lower, accrual would be stopped after 100 patients in the SDI population. If the drop-out rate would be higher, with 112 patients enrolled into the study a drop-out rate of 19.7% would still leave 90 patients in the SDI population which would result in a reasonable precision for the CI. If there would be less than 90 patients in the SDI population at the end of the planned enrolment phase, the IMC would decide whether to continue enrolment or not.

Interim Analyses

No formal Interim analysis is planned for this study. There will be three reporting events: the primary analysis, the end of induction analysis, and the final analysis.

In addition, the data will be monitored by an Internal Monitoring Committee (IMC). The first IMC data review will take place after the first 10 patients have completed the first SDI infusion (i.e. cycle 2). The second IMC data review will happen after 50 patients have completed the first SDI infusion (i.e. cycle 2) or at 6 months after the first IMC, whichever occurs first. Furthermore, the IMC will review results obtained for the primary analysis, end of induction analysis, and final analysis. Further meetings will be scheduled as deemed necessary. See the IMC charter for details.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
(a)PTT	(activated) partial thromboplastin time
ADCC	antibody-dependent cellular cytotoxicity
AE	adverse events
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BSA	body surface area
BUN	blood urea nitrogen
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone/methylprednisolone
CI	confidence interval
CLL	chronic lymphocytic leukemia
CrCL	creatinine clearance
CR	complete response
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CVP	cyclophosphamide, vincristine, and prednisone/prednisolone/methylprednisolone
DLBCL	diffuse large B-cell lymphoma
DMC	Data Monitoring Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	electronic data capture
EOI	end of induction
FC	fludarabine plus cyclophosphamide
FDA	Food and Drug Administration
FDG-PET	fluorodeoxyglucose-positron emission tomography
FL	follicular lymphoma
G-chemo	obinutuzumab-based chemotherapy
GI	gastrointestinal
HBV/HCV	hepatitis B/C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus

HR	hazard ratio
ICH	International Council for Harmonisation
HTLV-1	human T-lymphotropic virus
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
INR	International normalized ratio
IRB	Institutional Review Board
IRC	Independent Review Committee
IRR	infusion-related reactions
IUD	intrauterine devices
IV	intravenous
IxRS	interactive voice or Web-based response system
LDH	lactate dehydrogenase
LPLV	last patient, last visit
LVEF	left ventricular ejection fraction
MDASI	MD Anderson Symptom Inventory
MUGA	multigated acquisition (scan)
MZL	marginal zone lymphoma
NCI	National Cancer Institute
NHL	non-Hodgkin lymphoma
OS	overall survival
PCR	polymerase chain reaction
PFS	progression-free survival
PML	progressive multifocal leukoencephalopathy
PR	partial response
PRO	patient-reported outcome
PT	prothrombin time
RBC	red blood cell
SD	stable disease
SDI	short duration infusion
SLL	small lymphocytic lymphoma
TLS	tumor lysis syndrome
ULN	upper limit of normal
WBC	white blood cell

1. BACKGROUND

1.1 BACKGROUND ON FOLLICULAR LYMPHOMA

1.1.1 Non-Hodgkin Lymphoma

Non-Hodgkin lymphoma (NHL) is the most common hematologic malignancy in adults. In 2018, there were estimated to be 74,680 new cases and 19,910 deaths due to the disease in the United States (Siegel et al. 2018). In Europe, there were an estimated 97,400 new cases and 39,500 deaths in 2018 (Ferlay et al. 2018).

Most NHLs (also known as malignant lymphoma) are of B-cell origin and are characterized by the expression of a membrane antigen, CD20, which is important in cell cycle initiation and differentiation (Anderson et al. 1984). NHLs encompass many different histological sub-types, including the most common subtypes, diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL), and marginal zone lymphoma (MZL). NHL can be broadly divided into indolent and aggressive lymphomas, each with unique characteristics.

1.1.1.1 Follicular Lymphoma

Indolent NHLs (iNHLs) are a heterogeneous group of malignant lymphomas and account for approximately one third of all NHLs. Follicular lymphoma is the most common subtype of iNHL, accounting for about 22% of all newly diagnosed cases of NHL (Armitage and Weisenburger 1998). Approximately 90% of the cases have a t(14;18) translocation, which juxtaposes BCL2 gene with the IgH locus and results in deregulated expression of BCL2.

Follicular lymphoma remains an incurable disease with the currently available therapies. The addition of rituximab, an anti-CD20 monoclonal antibody, to commonly used induction chemotherapy, including cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone/methylprednisolone (CHOP); cyclophosphamide, vincristine, and prednisone/prednisolone/methylprednisolone (CVP); fludarabine; or bendamustine (Marcus et al. 2005; Hiddemann et al. 2005), followed by rituximab maintenance therapy led to prolonged response and improved patient outcomes. Long-term follow-up from Study MO18264 (PRIMA trial) confirmed the benefit of 2-year rituximab maintenance in patients responding to first-line immunotherapy, with a 6-year progression-free survival (PFS) of 59.2% compared with 42.7% in the observation arm ($p<0.0001$) (Salles et al. 2013). Rituximab in combination with chemotherapy for newly diagnosed patients with advanced Stage III and IV disease requiring treatment continues to be strongly recommended by both the 2016 European Society for Medical Oncology (ESMO) Guidelines Working Group recommendations (Dreyling et al. 2016) and the 2018 National Comprehensive Cancer Network (NCCN) guidelines (NCCN 2018).

Despite significant therapeutic progress with the use of chemoimmunotherapy as first-line treatment, most patients will eventually experience disease relapse. Relapses are characterized by increasing refractoriness and decreasing duration of response to subsequent lines of therapy. Thus, new treatments are needed to improve the outcome for these patients. One such candidate is obinutuzumab (RO5072759, GA101), a novel glyco-engineered anti-CD20 monoclonal antibody that has shown efficacy with an acceptable toxicity profile in clinical trials.

1.2 BACKGROUND ON OBINUTUZUMAB

1.2.1 Obinutuzumab (RO5072759, GA101) Structure and Mechanism of Action

Obinutuzumab is a humanized and glyco-engineered monoclonal antibody, derived by humanization of the parental B-Ly1 mouse antibody and subsequent glyco-engineering leading to the following characteristics (Beers et al. 2010; Mössner et al. 2010):

- High-affinity binding to CD20
- Type II binding to the CD20 epitope, leading to low complement-dependent cytotoxicity (CDC) related to the recognition of the CD20 epitope and the lack of CD20 localization into lipid rafts after binding of the monoclonal antibody to CD20
- Compared with the chimeric Type I anti-CD20 antibody rituximab, increased antibody-dependent cellular cytotoxicity (ADCC) related to an improved binding of obinutuzumab to the different allotypes of FcγRIIIa expressed by natural killer cells and monocytes
- Compared with rituximab, increased direct cell-death induction related to an elbow hinge amino exchange of the Fab region and Type II binding of the CD20 epitope

Given the significantly greater ADCC and direct cell-death induction, it is possible that obinutuzumab may have greater efficacy than rituximab, particularly in the 80%–85% of patients who are carriers of the FcγRIIIa low-affinity receptor polymorphism (FF/FV genotype), since such patients may have decreased overall survival compared with patients with the high-affinity (V/V) polymorphism who demonstrate improved survival following therapy with chemotherapy plus either rituximab or I-131 tositumomab (Persky et al. 2009).

1.2.2 Nonclinical Efficacy with Obinutuzumab

In nonclinical studies, obinutuzumab demonstrated superior depletion of normal B cells (measured as $CD19_+$ depletion) from the blood of healthy volunteers (Mössner et al. 2010) as well as malignant B cells from the blood of patients with chronic lymphocytic leukemia (CLL; Patz et al. 2011). Nonclinical xenograft experiments performed with obinutuzumab as monotherapy and in combination with chemotherapy have consistently showed promising anti-tumor activity of obinutuzumab (Mössner et al. 2010;

2011) and superiority of obinutuzumab over rituximab (Herting et al. 2014; Herter et al. 2013).

For more detailed nonclinical information on obinutuzumab, please refer to the current version of the obinutuzumab Investigator's Brochure.

1.2.3 Clinical Experience with Obinutuzumab

As of 26 April 2018, clinical data from 18 company-sponsored clinical studies on obinutuzumab as monotherapy or combination therapy in patients with NHL or CLL are summarized in the current obinutuzumab Investigator's Brochure. These include 13 Phase I/II or Phase II studies (BO29448 [GALACTA], GAO4779g [GALTON], BO21000 [GAUDI], GAO4915g [GATHER], BO29561, BO29562, BO29563, JO29737 [GATS], GAO4768g [GAGE], BO20999 [GAUGUIN], BO21003 [GAUSS], YP25623 [GERSHWIN], JO21900) and five Phase III studies (Studies BO21004 [CLL-11], BO21223 [GALLIUM], BO21005 [GOYA], GAO4753g [GADOLIN], MO28543 [GREEN]).

As of 26th April 2018, obinutuzumab has been administered to an estimated 3745 study patients with CLL or NHL, from doses ranging from 50 mg to 2000 mg in monotherapy or in combination with CHOP, fludarabine plus cyclophosphamide (FC), bendamustine, CVP, atezolizumab or chlorambucil. An estimated 2359 patients have been observed for over 1 year, 2016 patients have been observed for ≥ 2.5 years and 1440 patients have been observed for ≥ 4 years since receiving the first administration of obinutuzumab.

Results from the Phase III trials involving patients with FL, and previous experience with obinutuzumab SDI administration in DLBCL, are described below. For details on Phase I/II studies, and clinical studies in patients with other NHL subtypes or CLL, please refer to the current version of the obinutuzumab Investigator's Brochure.

1.2.3.1 Clinical Efficacy in Previously Untreated Follicular Lymphoma (Study BO21223 [GALLIUM])

In a Phase III, open label, multicentre, randomised clinical study (BO21223/GALLIUM), 1202 patients with previously untreated Grade 1–3a advanced (stage II bulky disease, stage III/IV) FL were randomized to 1:1 to receive either obinutuzumab (n=601 patients) or rituximab (n=601 patients) combined with chemotherapy (bendamustine, CHOP or CVP), followed by obinutuzumab or rituximab maintenance in patients achieving a complete or partial response (Marcus et al. 2017). Intravenous obinutuzumab (1,000 mg) was given by regular infusion on Days 1, 8 and 15 of Cycle 1, on Day 1 of subsequent cycles for 6–8 cycles.

At a pre-planned interim analysis (20th May 2016), after a median follow-up of 34.5 months, the IDMC recommended to unblind and fully analyze the study. The results showed that obinutuzumab-based chemotherapy significantly reduced the risk of disease progression or death (PFS, as assessed by investigator) compared to rituximab-

based treatment in patients with previously untreated advanced FL (stratified hazard ratio [HR] 0.66, 95% confidence interval [CI] 0.51,0.85; log-rank p-value = 0.0012). Consistent results were observed in the analysis of PFS as assessed by the Independent Review Committee (IRC; stratified HR 0.71, 95% CI 0.54, 0.93; log-rank p-value = 0.0138). Interim overall survival (OS) data and other secondary time-to-event endpoints (including event-free survival, disease-free survival, duration of response, and time to next anti-lymphoma treatment) were consistent with the primary efficacy endpoint (HRs range from 0.65–0.81) and supportive of clinical benefit for the obinutuzumab and chemotherapy regimen in patients with FL.

An updated analysis (cut-off date 10th September 2016) reported treatment with obinutuzumab-based chemotherapy resulted in a 32% reduction in the risk of an investigator-assessed PFS compared with rituximab-based chemotherapy (stratified HR 0.68, 95% CI 0.54, 0.87; log-rank p-value = 0.0016). Results of IRC-assessed PFS were consistent with the analysis of Investigator-assessed PFS (stratified HR 0.72, 95% CI 0.56, 0.93; log-rank p-value = 0.0118).

On the basis of these results, obinutuzumab was granted approval for use in patients with previously untreated FL in the European Union, United States, and elsewhere.

1.2.3.2 Clinical Efficacy in Follicular Lymphoma Relapsed or Refractory to Rituximab (Study GAO4753g [GADOLIN])

In a Phase III, open label, multicentre, randomized clinical study (GAO4753g/GADOLIN), 396 patients with iNHL who had no response during treatment or who progressed within 6 months following the last dose of rituximab or a rituximab-containing regimen were randomized 1:1 to receive either obinutuzumab plus bendamustine (n=194) or bendamustine alone (n=202) (Sehn et al. 2016). A total of 81.1% of patients had FL. MZL was present in 11.6% of patients, and 7.1% had small lymphocytic lymphoma (SLL). Intravenous obinutuzumab (1,000 mg) was given by regular infusion on Days 1, 8 and 15 of Cycle 1, on Day 1 of subsequent cycles for 6 cycles. Patients in the obinutuzumab treatment group who had not experienced disease progression at the end of induction therapy received obinutuzumab monotherapy every 2 months for up to 2 years.

At a pre-planned interim analysis after a median follow-up of 20.3–21.9 months, the study met its primary objective of showing a difference in IRC-assessed PFS (progression or death) between treatment arms. Treatment with obinutuzumab plus bendamustine resulted in a clinically meaningful and statistically significant reduction by 45% in the risk of IRC-assessed PFS compared with bendamustine alone (stratified analysis: HR 0.55, 95% CI 0.40, 0.74; log rank p-value = 0.0001).

At the second efficacy analysis (cut-off date 1st April 2016), this improvement in PFS with obinutuzumab plus bendamustine compared with bendamustine alone was maintained

(stratified analysis: HR 0.57, 95% CI [0.44, 0.73]; log-rank p-value = 0.0001). At the cut-off date for the primary efficacy endpoint (1st May 2015), the median IRC-assessed PFS was 14.1 (95% CI: 11.7, 16.6) months in the bendamustine arm vs. 29.2 (95% CI: 20.5, NE) months in the obinutuzumab plus bendamustine arm (HR 0.53, 95% CI 0.40, 0.70; log-rank test p-value = 0.0001).

The reduction in the risk of disease progression or death seen in the iNHL population was driven by the subset of patients with FL (81.1% of patients). No conclusions could be drawn on efficacy in the MZL and SLL subgroups due to the small sample size in this sub population.

At the time of the second efficacy analysis (cut-off date 1st April 2016), 64/171 (37.4%) patients in the bendamustine arm and 39/164 (23.8%) patients in the obinutuzumab plus bendamustine arm had died. Median OS for the bendamustine arm was 53.9 months but was not yet reached for the obinutuzumab plus bendamustine arm. The stratified HR for OS in just the patients with FL was 0.58 (95% CI: 0.39, 0.86).

On the basis of these positive results obinutuzumab in combination with bendamustine was granted approval for use in patients with FL who did not respond or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen.

The data cut-off for the final analysis of the study was 30-Nov-2018, and the data are currently under assessment.

1.2.3.3 Previous obinutuzumab SDI experience (Study GAO4915g [GATHER]).

Study GAO4915g was a Phase II, open-label, multicenter study of efficacy, safety, and biomarkers in patients with previously untreated advanced DLBCL treated with obinutuzumab in combination with CHOP chemotherapy (Sharman et al. 2019). The secondary safety objective of this study was to evaluate the safety and tolerability of a shorter duration of infusion (SDI) of obinutuzumab, as measured by the incidence of Grade 3 or 4 infusion-related AEs, in patients who receive an SDI of obinutuzumab.

Once safety of obinutuzumab in combination with CHOP was established in the first 20 patients, two SDI infusion times (120 minutes and then 90 minutes) were then tested (see Table S1 for infusion rates). Patients were treated with SDI if they had received ≥3 obinutuzumab doses at the regular infusion rate without any grade ≥3 IRRs and had a lymphocyte count $<5 \times 10^9$/L. SDI safety was assessed based on the incidence of Grade 3/4 IRRs.

Obinutuzumab-related IRRs were reported in 60% of patients (60/100) administered obinutuzumab at the regular infusion rate, in 20% of patients (1/5) who received

SDI 120, and in 2.9% of patients (2/70) who received SDI 90. Three patients administered obinutuzumab at the regular infusion rate experienced Grade ≥3 AEs (of any type); none of the patients administered obinutuzumab at the SDI 120 or SDI 90 infusion rates experience Grade ≥3 AEs.

Seventy-one patients received corticosteroids for IRR prophylaxis. The safety of SDI after cycle 1 was evaluated. Twenty patients received obinutuzumab at the standard rate to establish baseline safety. Thereafter, three patients who had not experienced an IRR Grade 3 in prior infusions were treated with SDI 120 as an initial test of SDI; none experienced an IRR Grade 3 and thus SDI 90 was tested. Once declared safe, remaining patients were treated with SDI 90 after three infusions at the standard rate. Overall, 69 patients (69%) experienced 244 IRRs. The majority occurred in cycle 1 (187/244) and were predominantly Grade 2 in intensity (129/244). One Grade 4 IRR was reported (febrile neutropenia) and there were no Grade 5 IRRs. IRRs of all grades affected 60% of patients infused at the standard rate. No patients receiving SDI 90 experienced IRRs Grade 3; 3% (2/70) experienced Grade 1 to 2 IRRs. No patients withdrew from obinutuzumab treatment as a result of IRRs. Obinutuzumab concentration at the end of infusion was summarized by infusion duration and was as expected, slightly higher for SDI 90 compared with the regular rate. However, when data variability was taken into account, the difference was not marked.

1.2.4 Summary of Clinical Safety of Obinutuzumab

Overall, the safety of monotherapy obinutuzumab, or obinutuzumab combination therapy was clinically manageable. Adverse events of particular interest include infusion-related reactions (IRRs), tumor lysis syndrome (TLS), thrombocytopenia (including acute thrombocytopenia), neutropenia (including late onset and prolonged neutropenia), prolonged B-cell depletion, infections including progressive multifocal leukoencephalopathy (PML) and hepatitis B virus (HBV) reactivation, worsening of pre-existing cardiac conditions, gastrointestinal (GI) perforation, and secondary malignancies. The important identified risks associated with obinutuzumab are presented in detail in Section 5.1.1 of this protocol. Appropriate risk minimization and mitigation actions are provided in the obinutuzumab Investigator's Brochure (Section 6).

The most frequent causes of death in studies of obinutuzumab were disease progression and adverse events associated with infectious diseases. This is consistent with the study population and the disease under treatment. The incidence of fatal adverse events was similar across all completed studies. In Study GAO4768g (obinutuzumab 1000 versus 2000 mg), the incidence of deaths did not increase with increased obinutuzumab dose (7.5% and 2.6%, respectively).

A high incidence of IRRs was observed consistently in all obinutuzumab trials. IRRs appear to be linked to the release of cytokines and/or other chemical mediators from B-

cells targeted by obinutuzumab. Due to the pharmacological class of obinutuzumab, as well as the evidence from clinical trials, the Sponsor considers IRRs as related to obinutuzumab. To reduce investigator bias and to generate better comparability across trials, IRRs in studies of obinutuzumab have typically been defined as any study treatment-related AEs (as assessed by the investigator) that occur during infusion or within 24 hours of completing the infusion.

The reported incidence of IRRs varied across studies. In the pivotal studies, BO21004 (CLL-11) and BO21223 (GALLIUM), the incidence of IRRs was comparable (~71%), but Grade 3–5 IRRs were higher in CLL indication (26.8%) as compared to FL indication (12.3%). In study GAO4753g (GATHER), 66.7% of patients experienced IRRs including 11.3% with Grade 3–5 IRRs (Sharman et al. 2019). In DLBCL (aggressive NHL) in BO21005, the incidence of Grade 3–5 IRRs (9.8%) was comparable with the one observed in FL patients in BO21223 and GAO4753g.

The incidence of IRR observed with combination therapy (FC, CHOP and bendamustine) appears similar to that observed with monotherapy across indications. Furthermore, the incidence of IRRs appears to be higher in obinutuzumab compared with rituximab-exposed patients based on evidence from studies BO21003 and BO20999. There is no clear relationship between obinutuzumab dose and the incidence of IRRs based on data from Study GAO4768g. The incidence and severity of IRRs are highest with the first infusion of obinutuzumab and decrease with subsequent infusions.

In the pivotal trials, a higher incidence of IRR was observed in CLL obinutuzumab exposed patients compared to iNHL obinutuzumab exposed patients as per the summary below:

	CLL								NHL							
	CLL-11 (Stage 1a)				CLL-11 (Stage 2)				GADOLIN				GALLIUM			
	Clb (n=116)		GClb (n=241)		RClb (n=321)		GClb (n=336)		Benda (n=198)		G Benda (n=194)		R-Chemo (n=692)		G-Chemo (n=698)	
	CSR 1057363 December 2013				CSR 1056550 December 2013				CSR 1051204 CCOD 14 Sept 2014				CSR 1067980- Overall NHL population			
Infusion related reactions	0	0%	166	69%	121	38%	221	66%	125	63%	133	69%	401	58%	486	70%
Infusion related reactions (grade 3-5)	0	0%	51	21%	12	4%	67	20%	11	6%	21	11%	33	5%	48	7%

1.2.5 Pharmacokinetic and Pharmacodynamic Data for Obinutuzumab

A population PK (PopPK) model was fitted to data from Phase I/Phase II clinical studies (Studies BO20999 and BO21003) and Phase III studies (BO21004, GAO4753g, and BO21223). Obinutuzumab concentration-time course is well described by a two-compartment PK model with total clearance being the sum of time-independent and time-dependent clearance pathways. The non-linear clearance pathway (dependent on the number of CD20+ tumor cells) had a high contribution to total clearance at the start of treatment, decreased with repeated treatment, and was consistent with target-

mediated drug disposition (TMDD). The linear (time-independent) clearance of obinutuzumab is not dependent on the number of CD20+ tumor cells and remained constant during the course of treatment. For a drug exhibiting TMDD, like obinutuzumab, the PK can be used as a surrogate marker of target occupancy, i.e., the obinutuzumab PK represents the binding to CD20+ malignant cells.

Consequently, the underlying rationale in selecting an appropriate obinutuzumab dose and schedule was to saturate the target as early and quickly as possible and to maintain this saturation over the complete treatment period in all patients, while minimizing AEs. A loading dose strategy was applied in order to decrease the number of unbound CD20 malignant cells rapidly; this was achieved by administering a fixed dose of 1000 mg of obinutuzumab on Day 1, Day 8, and Day 15 during Cycle 1 and then every 21 or 28 days on Day 1 of subsequent cycles.

As is typical for monoclonal antibodies, the population PK analysis of obinutuzumab has shown that obinutuzumab time-independent clearance (linear pathway) and central volume increased with body size, thus affecting the exposure to obinutuzumab. However, the non-linear clearance was found independent of body weight as expected and the loading dose strategy used in Cycle 1 was found to maximize the target occupancy across the whole range of body weights (median [range]: 75 kg [35.3–163]) The doubling of the systemic exposure in patients weighing less than 60 kg compare with patients weighing more than 90 kg is due to the body size effect on the linear clearance of obinutuzumab, however, it does not impact the saturation of the CD20 target as the serum concentrations remain high enough across the body weight range to maintain the saturation of the CD20 target. This is consistent with the lack of exposure-efficacy (PFS) relationship determined by Cox regression analysis.

Treatment with obinutuzumab resulted in extensive B-cell depletion, with all patients showing a reduction in cell count to absolute zero at some stage of their treatment cycle. Overall, there has been no notable increase in complement levels before or after infusion, but changes have been observed in the levels of interleukin-6 and interleukin-8 before and after infusion.

1.3 STUDY RATIONALE AND BENEFIT-RISK ASSESSMENT

Despite significant therapeutic progress with the use of chemoimmunotherapy as first-line treatment, FL remains essentially an incurable disease for which more effective treatments in addition to rituximab were needed. As described in Section 1.2.3, obinutuzumab-based chemotherapy is an effective treatment for patients with untreated FL and in patients with FL who did not respond or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen. Obinutuzumab is approved for use in these populations in the European Union, United States, and elsewhere.

In addition to developing more efficacious treatments for FL, there is also a need for more convenient treatments. The administration of obinutuzumab is associated with IRRs. In the GALLIUM study (BO21223), 71.6% of patients experienced an IRR, including 12.3% who experienced a Grade 3–5 IRR. The incidence of IRRs is greatest with the first infusion and decreases significantly with subsequent infusions. To reduce the risk of IRRs, the first dose of obinutuzumab is administered at a low rate initially (50 mg/hour) and gradually increased every 30 minutes in 50 mg/hour increments to a maximum of 400 mg/hour. If no IRR occurs during the first infusion, subsequent infusions start at 100 mg/hour and gradually increase every 30 minutes in 100 mg/hour increments to a maximum of 400 mg/hour. This means that a typical infusion of obinutuzumab can take around 4 hours

Shorter infusion times would yield substantial time savings for patients and benefit outpatient infusion facilities by increasing both the number of infusion chairs available during clinic hours and nursing efficiencies.

Infusion of rituximab, another monoclonal antibody that targets the CD20 antigen, is also associated with a high incidence of IRRs (Atmar et al. 2010). Standard rituximab administration involves a similarly cautious administration schedule to obinutuzumab with a slow initial infusion rate followed by increasing the rate in 30-minute increments if tolerated (Mabthera SmPC).

To reduce the logistical challenges associated with rituximab administration, a 90-minute rapid-infusion protocol was developed (Sehn et al. 2007). This protocol administers 20% of the rituximab dose in the first 30 minutes, with the remaining 80% over the following 60 minutes. In the original study by Sehn et al, no episodes of Grade ≥3 IRRs occurred in patients who received rituximab as a rapid-infusion (Sehn et al. 2007). Two patients experienced transient grade 1 toxicity, one of whom had not received rituximab previously with induction chemotherapy. The phase IIIb MAXIMA study investigated rituximab maintenance every 2 months for 2 years in 545 patients with first-line or relapsed FL who responded to 8 cycles of rituximab-based induction (Witzens-Harig et al. 2014). 82 patients received rituximab maintenance as a rapid infusion, 370 as a standard infusion, and 82 received both. The incidence of infusion-related AEs was similar among patients receiving all standard (5.4 %) or all rapid infusions (4.9 %).

The results of other studies confirm that after the first dose of rituximab has been given in the standard manner, subsequent doses can safely be administered using a rapid infusion protocol (reviewed in Atmar et al. 2010). The RATE study (Dakhil et al. 2014) demonstrated a Safety Profile with a 90-minute infusion in cycles 2-8:

- Of the 425 patients treated with rituximab in Cycle 1, 85% (n=363) were able to receive the 90-minute infusion of rituximab in Cycle 2

- Primary endpoint of the RATE trial was the incidence of Grade 3 or 4 IRRs the day of or the day after a 90-minute infusion of rituximab in Cycle 2
- Incidence of Grade 3/4 IRRs in Days 1-2 of Cycle 2 was 1.1%
- Incidence of Grade 3/4 IRRs was 2.8% cumulatively in Cycles 2-8
- No fatal IRRs or fatal AEs on Days 1-2 of any cycle

It is now widespread practice to administer subsequent doses as a rapid 90-minute infusion, if the first dose of rituximab is well-tolerated.

In the phase 2 GAO4915g /GATHER study, in patients with previously untreated advanced DLBCL, the safety of shortening the duration of the obinutuzumab infusion to 120 minutes (24 infusions) and 90 minutes (264 infusions) was also assessed by the incidence of Grade 3/4 infusion-related AEs (Sharman et al. 2019). Fifty-three patients received at least one SDI. The SDIs were associated with three Grade 1/2 IRRs and no Grade ≥3 IRRs. In the phase 2 JO29737/GATS study evaluating obinutuzumab as a shorter duration of infusion (90 minutes) in Japanese patients with previously untreated NHL (DLBCL, FL, or MZL), there were no Grade ≥3 infusion-related reaction in 31 patients who received a shorter duration of infusion of obinutuzumab over 90 minutes in Cycle 2. Steady-state pharmacokinetics of obinutuzumab were attained in Cycle 2 despite the shorter duration of infusion (Ohmachi et al. 2018).

The aim of this study is to evaluate whether a similar short duration infusion (SDI; target 90 minute infusion) can be used for obinutuzumab induction therapy during cycle 2 and from cycle 2 onwards (including obinutuzumab maintenance therapy) in combination with chemotherapy in patients with previously untreated advanced FL. Risk mitigation measures in this study include the use of premedication to reduce the risk of IRRS as described in Section 4.3.3, safety monitoring as described in Section 5, and incorporation of a safety data review after the first patients receive the SDI, followed by periodic safety reviews.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the safety of administering obinutuzumab as a short duration infusion (SDI) during cycle 2 and from cycle 2 onwards in combination with chemotherapy in patients with previously untreated advanced FL.

Specific objectives and corresponding endpoints for the study are outlined below.

2.1 SAFETY OBJECTIVES

The primary objective of this study is to evaluate the safety of obinutuzumab administered as an SDI during cycle 2 and from cycle 2 onwards in patients with previously untreated advanced FL on the basis of the following endpoints:

Primary endpoint:

- The incidence of Grade ≥3 IRRs* during cycle 2 in patients who had previously received obinutuzumab at the standard infusion rate during cycle 1 without experiencing a Grade 3 or 4 IRR, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0.

* *IRRs are defined as all adverse events (AEs) that occur during or within 24 hours from the end of study treatment infusion and are judged as related to infusion of study treatment components (obinutuzumab and chemotherapy during induction and obinutuzumab alone during maintenance) by the investigator.*

Secondary safety endpoints:

- Incidence, nature, and severity of all AEs during cycle 1 and from cycle 1 onwards (including maintenance)
- Incidence of IRRs regardless of grade by cycle (separately)
- Time to IRR (in hours) from infusion to onset of the IRR during cycle 2
- Duration (in minutes) of obinutuzumab administration by cycle (all cycles including maintenance)
- Type and duration of Grade ≥3 IRRs, during all cycles, where obinutuzumab was administered as an SDI.

2.2 SECONDARY EFFICACY OBJECTIVE

The secondary efficacy objective for this study is to evaluate the efficacy of obinutuzumab administered as an SDI from cycle 2 in patients with previously untreated advanced FL on the basis of the following endpoints:

- Objective response rate at the end of induction therapy as determined by the investigator and according to the guidelines used at the site (Lugano [Cheson et al 2014], Cheson et al 2007, or Cheson et al 1999)
- Progression-free survival rate at the end of the study
- Overall survival at the end of the study
- Complete response (CR) rate at 30 months (CR30), as assessed by the investigator and according to the guidelines used at the site.

2.3 EXPLORATORY OBJECTIVES

The exploratory safety objectives for this study are to further evaluate the safety of obinutuzumab administered in patients with previously untreated advanced FL on the basis of the following endpoints to evaluate the impact of time to IRR:

- The incidence of Grade ≥3 IRRs* (with severity determined according to NCI CTCAE Version 5.0) during the first SDI cycle:
  - cycle 2 in patients who received obinutuzumab at the standard infusion rate without experiencing a Grade 3 IRR in cycle 1
  - cycle 3 in patients who experienced a Grade 3 IRR when administered obinutuzumab at the standard infusion rate in cycle 1 and subsequently received obinutuzumab at the standard infusion rate in cycle 2 without experiencing a Grade 3 IRR
- Time to IRR (in hours) from infusion to onset of the IRR in cycle 1 or cycle 3

* *IRRs are defined as all adverse events (AEs) that occur during or within 24 hours from the end of study treatment infusion and are judged as related to infusion of study treatment components (obinutuzumab and chemotherapy during induction and obinutuzumab alone during maintenance) by the investigator.*

The exploratory efficacy objectives for this study are to evaluate patients with a partial response (PR) at the end of induction treatment who convert to complete response (CR) during maintenance treatment and to evaluate and compare the objective response and CR rate after the end of induction treatment with and without 18F-fluorodeoxyglucose positron emission tomography (FDG-PET):

- Proportion of patients with a PR at the end of induction treatment who convert to CR during maintenance treatment, as assessed by the investigator and according to the guidelines used at the site (see above)
- Objective response rate and CR rate after the end of induction treatment, as assessed by the investigator and according to the guidelines used at the site (see above), for those with and those without 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) separately.

The exploratory patient-reported objective for this study is to evaluate the severity and interference of disease- and treatment-related symptoms in patients with previously untreated advanced FL treated with obinutuzumab administered as an SDI from cycle 2.

- Severity of disease symptoms experienced by patients and the interference with daily living caused by these symptoms, as assessed through use of the MD Anderson Symptom Inventory (MDASI; Appendix 2).

The exploratory provider-reported objective is to evaluate the site experience with the SDI, specifically:

- Physician / nurse experience on time savings with obinutuzumab SDI compared with obinutuzumab at the regular infusion rate

- Physician / nurse experience on the convenience of and preference for obinutuzumab SDI compared with obinutuzumab at the regular infusion rate.

Questionnaires for provider and patient-reported outcomes (PROs) are shown in Appendix 2.

2.4 PHARMACOKINETIC OBJECTIVE

None.

2.5 IMMUNOGENICITY OBJECTIVE

None.

2.6 BIOMARKER OBJECTIVE

None.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is an open-label, international, multicenter, single arm Phase IV study to investigate the safety and efficacy of the short duration infusion (SDI; target 90-minute infusion) obinutuzumab in patients with previously untreated advanced FL.

A total of 100 patients is needed in the SDI population (see Section 6.1). Allowing for drop-outs this means that approximately 112 patients will be enrolled in this study.

The study has two phases: in the first phase patients will receive the first cycle of obinutuzumab-based chemotherapy (G-chemo) induction therapy as usual with the first three infusions of obinutuzumab (1000 mg) administered at the regular infusion rate (Table 1) on Day 1, 8, and 15 of cycle 1. The investigator is free to choose the chemotherapy for each patient (bendamustine, CHOP [cyclophosphamide, doxorubicin, vincristine, prednisone/prednisolone/methylprednisolone], or CVP [cyclophosphamide, vincristine, and prednisone/prednisolone/methylprednisolone]). The total number of cycles of G-chemo induction therapy and the cycles length depends on the chemotherapy chosen for each patient (see Section 4.3.1).

Study treatment in this protocol refers to obinutuzumab and chemotherapy during the induction phase and obinutuzumab monotherapy during the maintenance phase.

For the purpose of this study IRRs are defined as all AEs that occur during or within 24 hours from the end of study treatment infusion and are judged as related to infusion of study treatment components (obinutuzumab and chemotherapy during induction and obinutuzumab alone during maintenance) by the investigator.

Patients who do not experience any Grade ≥3 IRRs during the first cycle will enter into the second, faster infusion, phase from Cycle 2 onwards. These patients will receive obinutuzumab at the SDI rate, starting on Cycle 2, Day 1 (Table 1).

Patients who experience a Grade 3 IRR during the first cycle will remain on the study but cycle 2 of obinutuzumab must be administered at the regular infusion rate. If these patients do not experience a Grade ≥3 IRR during cycle 2 at the regular infusion rate, then they will be eligible to receive SDI dosing from cycle 3 onwards, according to investigator judgement.

Patients who experience a first occurrence of a Grade 3 IRR during any SDI administration of obinutuzumab may continue to receive SDI dosing during the current infusion, and in the next cycle, as long as the Grade 3 IRR resolves after the infusion is interrupted and symptoms are treated, and no further IRR symptoms reoccur after restarting the SDI. Guidance on IRR management during both regular and SDI infusions is given in Appendix 6.

The obinutuzumab infusion must be stopped, and obinutuzumab must be permanently discontinued, in any patient who experiences a second occurrence of any Grade 3 IRR, regardless of the rate of infusion.

Patients who experience a Grade 4 IRR at any time during the study will permanently discontinue obinutuzumab treatment.

Table 1 Obinutuzumab Infusion Rates at Induction and Maintenance

Regular infusion rate [a]		SDI (approximately 90 minutes) [a]
First Infusion (Cycle 1, Day 1)	**Second and Third Infusions (Cycle 1, Days 8 and 15)**	**Cycle 2, Day 1 and All Other following Infusions (including maintenance) [b]**
50 mg/hr Rate increased by **50 mg/hr** every 30 min **400 mg/hr** max rate **Refer to Appendix 6a for guidance on management of IRRs during regular infusion**	If no IRR, or an IRR of Grade 1 occurred during the previous infusion and the final infusion rate was 100 mg/hr or faster: Start at a rate of **100 mg/hr** Increase rate by **100 mg/hr** every 30 min **400 mg/hr** max rate If an IRR of Grade 2–3 occurred during the previous infusion, start at **50 mg/hr**. The rate of the infusion can be escalated in increments of **50 mg/hr** every 30 min to a maximum rate of **400 mg/hr** **Refer to Appendix 6b for guidance on management of IRRs during regular infusion**	**100 mg/hr** for 30 min, then **900 mg/hr** for 60 min **Refer to Appendix 6c for guidance on management of IRRs during SDI infusion** If an IRR of Grade 1–2, or a first occurrence of Grade 3, occurred during the previous SDI infusion and the patient has **ongoing symptoms** until the time of the next cycle, then the next administration of obinutuzumab should be given at the **regular infusion rate** as per Cycle 1, Days 8 and 15. If the IRR in the previous infusion resolved, then the next cycle can be administered at the SDI rate.

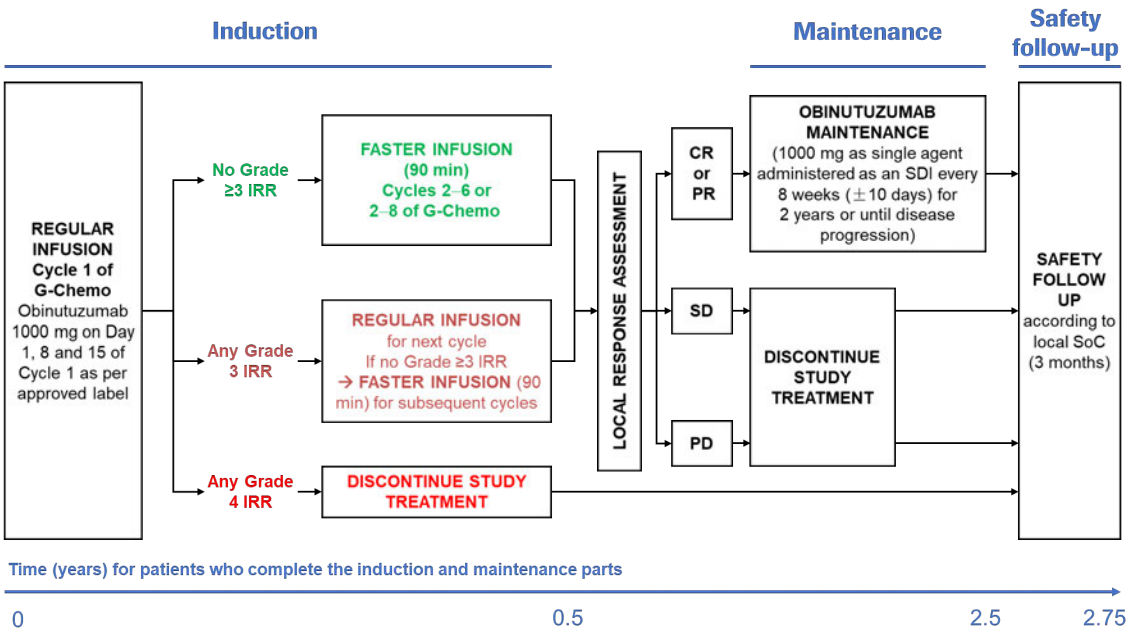
IRR=infusion-related reaction; Max=maximum; SDI=short duration infusion

a. To deliver the full dose of 1000 mg, the whole contents of the bag should be administered *in 195 (± 10) minutes for the regular infusion rate and 93 (± 5) minutes for the SDI.*

b. Patients should only start the SDI infusion in Cycle 2 if they did not experience any Grade ≥3 IRRs during Cycle 1 (on Day 1, 8, or 15). If they did experience a Grade ≥3 IRR during Cycle 1 (on Day 1, 8, or 15), then the infusion on Day 1 of Cycle 2 should be given at the regular infusion rate.

Figure 1 presents an overview of the study design. A schedule of activities is provided in Appendix 1.

Figure 1 Study Schema



CR=complete response; IRR=infusion related reaction; G-chemo=obinutuzumab (Gazyva)-containing chemotherapy PD=progressive disease; PR=partial response; SD=stable disease; SDI=short duration infusion; SoC=standard of care.

All patients will be assessed for disease response by the investigator at the end of induction therapy and end of maintenance therapy according to local practice and according to the guidelines used at the site (Lugano [Cheson et al 2014], Cheson et al 2007, or Cheson et al 1999). No central confirmation of disease response will be conducted.

Patients who achieve at least a partial response (PR) following the completion of induction therapy will receive obinutuzumab maintenance therapy (1000 mg as single agent administered as an SDI every 8 weeks (± 10 days) for 2 years or until disease progression).

The first administration of obinutuzumab maintenance therapy is expected to start 8 weeks ± 10 days from Day 1 of the last induction cycle.

Patients with stable disease or progressive disease as best response after induction therapy will discontinue study treatment and undergo a safety follow-up visit at 3 months (90 days (± 10 days)).

All patients will be followed up at 3 months (90 days (± 10 days)) from the time of the last dose of study treatment.

The first scheduled Internal Monitoring committee (IMC) data review will take place after the first 10 patients have completed the first SDI infusion (i.e. cycle 2). The second IMC data review will happen after 50 patients have completed the first SDI infusion (i.e. cycle 2) or at 6 months after the first IMC, whichever occurs first. Furthermore, the IMC will review results obtained for the primary analysis, end of induction analysis, and final analysis. Further meetings will be scheduled as deemed necessary. Further details will be specified in the IMC charter.

Safety will be evaluated by monitoring dose delays and dose intensity, adverse events, serious adverse events, and deaths. These will be graded using the NCI CTCAE, Version 5.0. Laboratory safety assessments will include regular monitoring of hematology and blood chemistry.

Provider and patient-reported measures (Appendix 2) will be assessed throughout the study as outlined in Appendix 1.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of the study is defined as the Last Patient, Last Visit (LPLV) which will occur when the last patient to discontinue participation in the study has completed the safety follow-up visit or at the time that one of the following is documented:

- Patient has withdrawn consent

  OR
- Patient is lost to follow-up

  OR
- Patient death.

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

The total length of the study, from screening of the first patient to the end of the study, is expected to be approximately 4 years.

The total length of the study for an individual patient is up to approximately 2.75 years.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Obinutuzumab Dose and Schedule

Obinutuzumab will be administered with the treatment route, dose, and dosing regimen approved for use in patients with FL, i.e. 1000 mg administered intravenously on Day 1, 8 and 15 of cycle 1 followed by 1000 mg IV on Day 1 of subsequent cycles, for 6–8 cycles depending on the chemotherapy regimen. Maintenance obinutuzumab in patients who achieve at least a partial response (PR) after induction therapy will also be administered according to the approved indication (1000 mg obinutuzumab as single-

agent therapy once every 8 weeks [± 10 days] for 2 years or until disease progression [whichever occurs first]).

3.3.2 Rationale for Patient Population

As stated in Section 3.3.1, the incidence of IRRs following obinutuzumab administration decreases substantially after the first infusion; therefore, to fully investigate the safety of obinutuzumab administered as an SDI during cycle 2 and from cycle 2 onwards in combination with chemotherapy in FL patients, the patient population should be treatment-naïve to obinutuzumab.

To assess the safety and feasibility of SDI, and to guarantee the transposition to the general patient population, this study needs to investigate a population that closely reflects clinical practice and treated according to the existing label. Patients in need of first-line treatment for FL were also selected due to the high incidence of this population.

3.3.3 Rationale for Combination Therapies

The chemotherapy combinations in this study are not limited - any approved obinutuzumab-based chemotherapy can be used at the discretion of the investigator.

The rationale for allowing any approved chemotherapy combination is to investigate the safety of administering obinutuzumab as an SDI during cycle 2 and from cycle 2 onwards in patients with previously untreated FL in chemotherapy combinations that reflect the real-world use of obinutuzumab.

3.3.4 Rationale for Provider- and Patient-Reported Outcomes

Patients with previously untreated FL may experience disease-related symptoms (e.g., B-symptoms, fatigue), treatment-related symptoms (e.g., nausea, diarrhea), and subsequently may face interference in aspects of daily functioning (e.g., physical activities, emotional functioning) (Tholstrup et al. 2011; Pettengell et al. 2008, Jerkeman et al. 2001). Assessing this directly from patients is important to help fully understand the impact and benefit-risk assessment of a treatment. The severity of symptoms experienced by patients with cancer and the interference with daily living caused by these symptoms will be assessed directly from patients using the MD Anderson Symptom Inventory (MDASI).

Given the length of time that some treatments take to administer, and the resulting impact that has on the number of patients that providers can treat, it is important to assess potential benefits that shorter duration infusions could have on providers. In this study, investigator physicians and nurses will be asked to answer questions based on their site experience with the SDI and standard infusions of obinutuzumab, across all patients enrolled in the study. The rationale for including provider-reported outcomes in this study is to see whether providers believe that adopting a 90-minute SDI at cycle 2

and beyond helps increase practice efficiency with respect to infusion chair time, waiting time, and patient scheduling.

4. MATERIALS AND METHODS

4.1 PATIENTS

Approximately 112 patients with patients with previously untreated advanced FL who meet the eligibility criteria presented below will be enrolled in this study.

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

1. Signed Informed Consent Form
2. Age ≥ 18 years at time of signing Informed Consent Form
3. Able and willing to comply with all study related procedures including completion of patient-reported outcome (PRO) endpoints
4. Ability to comply with the study protocol, in the investigator's judgment
5. Patients with previously untreated Stage III or IV FL or Stage II bulky disease scheduled to receive obinutuzumab and chemotherapy due to at least one of the following criteria:
    a. Bulky disease, defined as a nodal or extranodal (except spleen) mass ≥ 7 cm in the greatest diameter
    b. Local symptoms or compromise of normal organ function due to progressive nodal disease or extranodal tumor mass
    c. Presence of B symptoms (fever [> 38ºC], drenching night sweats, or unintentional weight loss of > 10% of normal body weight over a period of 6 months or less)
    d. Presence of symptomatic extranodal disease (e.g., pleural effusions, peritoneal ascites)
    e. Cytopenias due to underlying lymphoma (i.e., absolute neutrophil count < 1.0×10^9/L, hemoglobin < 10 g/dL, and/or platelet count < 100×10^9/L)
    f. Involvement of ≥ 3 nodal sites, each with a diameter of ≥ 3 cm
    g. Symptomatic splenic enlargement
6. Histologically documented CD-20-positive FL, as determined by the local laboratory
7. Eastern Cooperative Oncology Group (ECOG) performance status 0−2
8. Adequate hematologic function (unless abnormalities are related to FL), defined as follows:
    a. Hemoglobin ≥ 9.0 g/dL

b. Absolute neutrophil count ≥ 1.5 × 10^9/L

c. Platelet count ≥ 75 × 10^9/L

9. Life expectancy of ≥ 12 months
10. For women who are not postmenopausal (≥ 12 consecutive months of non-therapy-induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus): agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of < 1% per year during the treatment period and for at least 18 months after the last dose of obinutuzumab, for at least 3 months after the last dose of bendamustine or according to institutional guidelines for CHOP or CVP chemotherapy, whichever is longer

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

    b. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception

    Barrier methods must always be supplemented with the use of a spermicide

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

    a. With female partners of childbearing potential, men must remain abstinent or use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year during the treatment period and for at least 3 months after the last dose of study treatment. Men must refrain from donating sperm for the same period

    b. With pregnant female partners, men must remain abstinent or use a condom during the treatment period and for at least 3 months after the last dose of study treatment

    c. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception

4.1.2 Exclusion Criteria

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

1. Relapsed / refractory FL

2. Prior treatment for FL with chemotherapy, radiotherapy, or immunotherapy
3. Grade IIIb FL
4. Histological evidence of transformation of FL into high-grade B-cell NHL
5. Treatment with systemic immunosuppressive medications, including, but not limited to, prednisone/prednisolone/methylprednisolone (at a dose equivalent to >30 mg/day prednisone), azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor agents within 2 weeks prior to Day 1 of Cycle 1
    a. Treatment with inhaled corticosteroids and mineralocorticoids is permitted
    b. Patients receiving corticosteroid treatment with ≤30 mg/day of prednisone or equivalent must be documented to be on a stable dose of at least 4 weeks' duration prior to enrolment
    c. If glucocorticoid treatment is urgently required for medical reasons (e.g., complications imminent if not treated at least with glucocorticoids; strong discomfort/pain of the patient due to lymphoma), prednisone 100 mg or equivalent can be given for a maximum of 5 sequential days, but all tumor assessments must be completed prior to the start of glucocorticoid treatment. Glucocorticoid treatment must be stopped prior to enrolment
    d. In cases when a glucocorticoid pre-treatment/pre-phase was done externally prior to considering the patient for study inclusion, glucocorticoids must be stopped for at least 7 days before screening assessments can begin
6. History of solid organ transplantation
7. History of anti-CD20 antibody therapy
8. History of severe allergic or anaphylactic reaction to humanized, chimeric, or murine monoclonal antibodies
9. Known sensitivity or allergy to murine products
10. Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells or any of the study drugs
11. Active bacterial, viral, fungal, or other infection or any major episode of infection requiring treatment with IV antibiotics within 4 weeks of Day 1 of Cycle 1
    a. Caution should be exercised when considering the use of obinutuzumab in patients with a history of recurring or chronic infections
12. Positive test results for chronic HBV infection (defined as positive HBsAg serology)
    a. Patients with occult or prior HBV infection (defined as negative HBsAg and positive total HBcAb) may be included if HBV DNA is undetectable, provided that they are willing to undergo DNA testing at least every 3 months (during the study and for at least 1 year after completion of lymphoma treatment). Patients who have protective titers of hepatitis B surface antibody (HBsAb) after vaccination or prior but cured hepatitis B are eligible

13. Positive test results for hepatitis C (hepatitis C virus [HCV] antibody serology testing)
    a. Patients positive for HCV antibody are eligible only if PCR is negative for HCV RNA
14. Known history of HIV positive status
    a. For patients with unknown HIV status, HIV testing will be performed at screening if required by local regulations
15. History of progressive multifocal leukoencephalopathy (PML)
16. Vaccination with a live virus vaccine within 28 days prior to Day 1 of Cycle 1 or anticipation that such a live, attenuated vaccine will be required during the study
17. History of prior other malignancy with the exception of:
    a. Curatively treated carcinoma in situ of the cervix, good-prognosis ductal carcinoma in situ of the breast, basal- or squamous-cell skin cancer, Stage I melanoma, or low-grade, early-stage localized prostate cancer
    b. Any previously treated malignancy that has been in remission without treatment for ≥ 2 years prior to enrollment
18. Evidence of any significant, uncontrolled concomitant disease 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, myocardial infarction within the previous 6 months, unstable arrhythmia, or unstable angina) or significant pulmonary disease (such as obstructive pulmonary disease or history of bronchospasm)
19. Major surgical procedure other than for diagnosis within 28 days prior to Day 1 of Cycle 1, Day 1, or anticipation of a major surgical procedure during the course of the study
20. For patients who will be receiving CHOP: left ventricular ejection fraction (LVEF) < 50% by multigated acquisition (MUGA) scan or echocardiogram
21. Any of the following abnormal laboratory values:
    a. Creatinine > 1.5 × the upper limit of normal (ULN) (unless creatinine clearance normal) or creatinine clearance < 40 mL/min
    b. AST or ALT > 2.5 × ULN
    c. Total bilirubin ≥ 1.5 × the ULN: Patients with documented Gilbert disease may be enrolled if total bilirubin is ≤ 3.0 × the ULN.
    d. International normalized ratio (INR) > 1.5 in the absence of therapeutic anticoagulation
    e. Partial thromboplastin time or activated partial thromboplastin time > 1.5 × ULN in the absence of a lupus anticoagulant
22. Pregnant or lactating, or intending to become pregnant during the study

a. Women who are not postmenopausal (≥ 12 months of non-therapy-induced amenorrhea) or surgically sterile must have a negative serum pregnancy test result within 7 days prior to Day 1 of Cycle 1

23. Any investigational therapy within 28 days prior to the start of Cycle 1
24. Positive test results for human T-lymphotropic virus 1 (HTLV-1)
    a. HTLV testing is required in patients from endemic countries

Patients who meet the following criteria will be excluded from further study participation after Cycle 1:

- Development of a Grade 4 IRR during Cycle 1.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

Not applicable - this study is not a randomized study.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

The investigational medicinal product (IMP) for this study is obinutuzumab.

4.3.1 Study Treatment Formulation, Packaging, and Handling

4.3.1.1 Obinutuzumab

Obinutuzumab will be supplied by the Sponsor as an investigational medicinal product (IMP). Obinutuzumab will be provided as a single-dose, sterile liquid formulation in a 50-mL glass vial containing 1000 mg/40 mL of obinutuzumab. In addition to the drug substance, the liquid is also composed of histidine, trehalose, and poloxamer 188. For information on the formulation and handling of obinutuzumab, see the obinutuzumab Investigator's Brochure and the Pharmacy Manual.

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

4.3.1.2 CHOP Chemotherapy

For details on drug formulations, see the cyclophosphamide, vincristine, doxorubicin, or prednisone/prednisolone/methylprednisolone prescribing information.

4.3.1.3 CVP Chemotherapy

For details on drug formulations, see the cyclophosphamide, vincristine, or prednisone/prednisolone/methylprednisolone prescribing information.

4.3.1.4 Bendamustine

For information on the formulation, packaging, and handling of bendamustine, see the local prescribing information (for example Levact® / Treanda® / Treakisym® / Ribomustin®).

4.3.2 Study Treatment Dosage, Administration, and Compliance

The treatment regimens are summarized in Section 3.1.

Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

4.3.2.1 Obinutuzumab

Obinutuzumab should be administered as an IV infusion through a dedicated line in an environment in which full resuscitation facilities are immediately available and under the close supervision of an experienced physician.

Obinutuzumab will be administered intravenously at a flat dose of 1000 mg on Day 1, 8 and 15 during Cycle 1, and on Day 1 of subsequent cycles, according to the infusion rates shown in Table 1. The cycle length and number of cycles depends on the chemotherapy combination (see Section 4.3.2.2).

Following induction obinutuzumab and chemotherapy, maintenance obinutuzumab monotherapy will be administered at a dose of 1000 mg once every 8 weeks (± 10 days) for 2 years or until disease progression (whichever occurs first).

Splitting of the obinutuzumab dose (i.e. 100 mg + 900 mg) will not be permitted in this study. The full dose (1000 mg) should be given in one day. No dose modification for obinutuzumab is allowed. Guidelines for treatment delays or discontinuation are provided in Section 5.1.5.

Premedication to reduce the incidence and severity of IRRs and for patients at risk of TLS will be conducted according to local practice as described in Section 4.3.3.

4.3.2.2 Combination Chemotherapy

Obinutuzumab will be administered in combination with one of the following chemotherapy regimens:

- Six 28-day cycles in combination with bendamustine
- Six 21-day cycles in combination with CHOP, followed by two additional cycles of obinutuzumab alone
- Eight 21-day cycles in combination with CVP.

Chemotherapy combinations will be administered according to the standard preparation and infusion procedures of each site. Body surface area (BSA) may be capped at 2 m^2 per institutional standards.

If the duration of the obinutuzumab administration (i.e. at the regular infusion rate) does not allow time for day 1 of the chemotherapy to be administered on the same day, then

the chemotherapy can be started on the following day (i.e. Day 2). When obinutuzumab is given at the short duration infusion rate there should be sufficient time to administer both the obinutuzumab and chemotherapy on Day 1.

Bendamustine

Bendamustine will be administered on Days 1 and 2 for Cycles 1–6 at a dose of 90 mg/m^2/day. Obinutuzumab will be administered prior to bendamustine, and patients should be observed for 30 minutes prior to starting bendamustine.

CHOP

The doses and schedules of CHOP components are:

- Cyclophosphamide 750 mg/m^2 IV, Day 1
- Doxorubicin 50 mg/m^2 IV push, Day 1
- Vincristine 1.4 mg/m^2 IV push, Day 1 (dose cap at 2 mg)
- Prednisone 100 mg/day po (or prednisolone/methylprednisolone*), Days 1 through 5

* *Equivalent doses of prednisolone or methylprednisolone may be administered according to local standard practice instead of prednisone.*

When obinutuzumab and CHOP are scheduled to be administered on the same day, prednisone (100 mg; or equivalent dose of prednisolone/methylprednisolone) will be given prior to the obinutuzumab infusion. Obinutuzumab will be administered prior to CHOP, and patients should be observed for 30 minutes prior to starting CHOP.

During cycle 1, CHOP may be given on the day after obinutuzumab administration if the duration of the obinutuzumab infusion necessitates such administration.

For patients aged ≥70 years, the vincristine dose may be capped at 1.5 mg.

Primary prophylaxis with G-CSF is recommended according to American Society of Clinical Oncology, EORTC, and European Society for Medical Oncology guidelines (Smith et al 2015), or per each site's institutional standards.

CVP

The doses and schedules of CVP components are:

- Cyclophosphamide 750 mg/m^2 IV, Day 1
- Vincristine 1.4 mg/m^2 IV push, Day 1 (dose cap at 2 mg)
- Prednisone 100 mg po (or prednisolone/methylprednisolone*), Days 1 through 5

* *Equivalent doses of prednisolone or methylprednisolone may be administered according to local standard practice instead of prednisone.*

When obinutuzumab and CVP are scheduled to be administered on the same day, prednisone (100 mg; or equivalent dose of prednisolone/methylprednisolone) will be given prior to the obinutuzumab infusion. Obinutuzumab will be administered prior to CVP, and patients should be observed for 30 minutes prior to starting CVP.

For patients aged ≥70 years, the vincristine dose may be capped at 1.5 mg.

4.3.3 Premedication

4.3.3.1 Premedication for infusion-related reactions

Premedication to reduce the risk of IRRs is mandatory for the first standard infusion of obinutuzumab (Cycle 1, Day 1) and for the first infusion of obinutuzumab given as a short duration infusion (Table 2). For subsequent cycles, premedication will depend on whether the patient experienced an IRR with the previous infusion.

All premedication must be completed at least 30 minutes before the obinutuzumab infusion.

Table 2 Premedication to be Administered Before Obinutuzumab Infusion to Reduce the Risk of IRRs

Infusion	Premedication	Administration
First standard infusion (Cycle 1, Day 1) **AND** **First infusion given as an SDI**	IV corticosteroid [1,4] Oral analgesic/anti-pyretic [2] Anti-histaminic medicine [3]	• Mandatory
All subsequent infusions	IV corticosteroid [1,4]	• Mandatory if the patient had a Grade 3 IRR during the previous infusion • According to clinical judgement of the investigator for patients without a Grade 3 IRR in the previous infusion
	Oral analgesic/anti-pyretic [2]	• Mandatory
	Anti-histaminic medicine [3]	• Mandatory for patients with a Grade 1–3 IRR during the previous infusion • According to local guidelines or the clinical judgment of the investigator for patients without an IRR during the previous infusion

1. Maximum allowable dose: 100 mg prednisone/prednisolone or 20 mg dexamethasone or 80 mg methylprednisolone. Hydrocortisone should not be used as it has not been effective in reducing rates of IRR.
2. e.g. 1,000 mg acetaminophen/paracetamol.
3 e.g. 50 mg diphenhydramine.
4. For patients receiving CHOP and CVP chemotherapy, the corticosteroid can be administered as an oral medication if given at least 30 minutes prior to obinutuzumab and additional IV corticosteroid as premedication is not required.

4.3.3.2 Premedication for tumor lysis syndrome (TLS)

Patients with a high tumor burden, a circulating lymphocyte count (>25 × 10^9/L), or renal impairment (CrCL <70 mL/min) will receive premedication for TLS comprising hydration and uricostatics or urate oxidase 12–24 hours before infusion of obinutuzumab according to standard practice.

4.3.4 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (obinutuzumab) will be provided by the Sponsor. The study site will acknowledge receipt of IMPs supplied by the Sponsor using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor (if supplied by the Sponsor) with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

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

4.3.5 Continued Access to Obinutuzumab

Currently, the Sponsor does not have any plans to provide the Roche IMP (obinutuzumab) or any other study treatments to patients who have completed the study.

4.4 CONCOMITANT THERAPY AND ADDITIONAL RESTRICTIONS

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to study entry to the end of the 3-month safety follow-up visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

Patients who use oral contraceptives or hormone-replacement therapy should continue their use.

Premedication as described in Section 4.3.3 is allowed during the study, as is the use of G-CSF for the treatment of neutropenia (see Section 5.1.1.3) and transfusion of blood products for treatment of thrombocytopenia (see Section 5.1.1.4) or anemia.

The use of antibiotic, anti-viral, and/or anti-fungal prophylaxis according to institutional guidelines is also allowed.

COVID-19 vaccines that have been granted emergency use authorization or equivalent are permitted. The vaccine should be captured in the eCRF as a concomitant medication. The brand/trade name or company manufacturer should be reported if available (Examples: Pfizer COVID-19 vaccine, Moderna COVID-19 vaccine). If not available, report as "COVID-19 vaccine". Please report each dose separately. See Section 5.1.1.7 for further information concerning COVID-19 vaccines.

In general, investigators should manage a patient's care with supportive therapies as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2-receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion-associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists).

4.4.2 Prohibited Therapy

Use of the following therapies is prohibited during the study:

- Cytotoxic chemotherapy (other than bendamustine, cyclophosphamide, doxorubicin, or vincristine)

  Although MTX is a chemotherapeutic agent, due to the low doses used in treating rheumatoid arthritis (typically 7.5 to a maximum of 20 mg/week) it is not considered chemotherapy for lymphoma. Therefore, patients treated before or during study conduct with MTX for rheumatoid arthritis are still eligible to participate in the study. It is recommended to stop MTX 2-3 weeks prior to starting immunochemotherapy since the combination of MTX and immunochemotherapy increases the risk of immunosuppression and the risk of infection, but MTX may be resumed during maintenance / follow-up, if clinically indicated
- Radiotherapy
- Immunotherapy (other than obinutuzumab)

- Hormone therapy (other than contraceptives, hormone-replacement therapy, or megestrol acetate)
- Hormonal therapy (e.g., GnRH-agonists) for egg cell harvest/fertility preservation prior to enrolment is allowed in women of childbearing age
- Any therapies intended for the treatment of NHL, whether FDA approved or experimental (outside of this study)
- The safety of immunization with live virus vaccines following obinutuzumab therapy has not been studied. Vaccination with live virus vaccines is not recommended during treatment and until B-cell recovery

Patients who require the use of any of these prohibited therapies will be discontinued from study treatment. The end of induction or end of maintenance response assessment should be performed before the therapy is started, unless a recent response assessment is already available. For the timing of the safety follow-up assessment please see Appendix 1.

4.5 STUDY ASSESSMENTS

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

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

Results from local laboratory assessments (hematology and biochemistry) must be reviewed, and the review documented, prior to study drug administration.

4.5.1 Informed Consent Forms and Screening Log

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

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before enrollment. Re-screening is possible at any time. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history, including clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history,

will be recorded at baseline. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by the patient within 7 days prior to study entry will be recorded. At the time of each follow-up physical examination, an interval medical history should be obtained and any changes in medications and allergies should be recorded.

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

The following clinical parameters relative to disease history, diagnosis, and prognostic indices will be recorded at screening:

- Date of initial diagnosis
- ECOG performance status (see Appendix 3)
- B symptoms (unexplained fever >38ºC, night sweats, unexplained weight loss >10% of body weight over 6 months)
- Ann Arbor staging (see Appendix 4)
- Follicular Lymphoma International Prognostic Index (FLIPI) and FLIPI2 (see Appendix 5)

4.5.3 Physical Examinations

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

As part of tumor assessment, the physical examination should include evaluation for the presence of enlarged nodes, palpable hepatomegaly, and splenomegaly. This information will be recorded on the appropriate tumor assessment eCRF.

At the end of induction and end of maintenance visits, targeted (limited, symptom-directed) physical examinations should be performed. Targeted physical examinations should be limited to systems of primary relevance (e.g., cardiovascular and respiratory systems), systems associated with symptoms (newly emergent or monitored from baseline), and areas associated with tumor assessment (lymph nodes, liver, spleen, and any other areas identified at baseline). Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

Changes from baseline abnormalities should be recorded in patient notes.

4.5.4 Vital Signs

Vital signs will include measurements of blood pressure, pulse rate and temperature as outlined in the schedule of assessment (Appendix 1), but the associated data do not need to be recorded on the eCRF (except in the case of an adverse event as described in Section 5.3.5.6).

For the first cycle (i.e., includes Day 1, Day 8, and Day 15), vital signs will be measured prior to the infusion, every 15 minutes for the first 90 minutes of the infusion, then every 30 minutes until end of the infusion and approximately every 60 minutes until the infusion line is removed.

In subsequent cycles, for patients who experienced a Grade 3 IRR in the previous cycle vital signs will be measured at the same frequency as for the first cycle. For patients without a Grade 3 IRR in the previous cycle (i.e., those with no IRR or Grade ≤2 IRR), vital signs will be measured prior to the infusion and every 30 minutes during the infusion. If any abnormal values are observed during any infusion, the site should continue to monitor vital signs until stabilization of the abnormal values.

4.5.5 Tumor and Response Evaluations

All known sites of disease must be documented at screening within 28 days of Cycle 1, Day 1 (e.g. CT with or without FDG-PET) and re assessed at the end of induction therapy and end of maintenance therapy for disease response by the investigator according to local practice and the guidelines used at the site (including Lugano [Cheson et al 2014], Cheson et al 2007, or Cheson et al 1999).

No central confirmation of disease response will be conducted.

A bone marrow biopsy (trephine) with or without aspirate must be obtained at screening according to local practice and guidelines used at the site. If bone marrow data are available in the patient's medical record that were obtained within 3 months prior to Cycle 1, Day 1, these data can be used instead, and the patient does not need to undergo a new bone marrow biopsy with or without aspirate.

If there was bone marrow infiltration at screening, then a subsequent bone marrow biopsy with or without aspirate may be needed at the end of induction and/or end of maintenance visits to confirm response according to local practice.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent to the study site's local laboratory for analysis:

- Hematology: WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Serum or plasma chemistry: bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, blood urea nitrogen (BUN) or urea, creatinine, total protein, albumin, phosphorus, calcium, total and direct bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), uric acid, beta-2 microglobulin, and lactate dehydrogenase (LDH)
- Coagulation: International normalized ratio (INR), activated partial thromboplastin time (aPTT) (or PTT), prothrombin time (PT)
- Pregnancy test
  - All women who are not postmenopausal (≥12 months of non-therapy-induced amenorrhea) or surgically sterile will have a serum pregnancy test at screening (within 7 days of Day 1 of Cycle 1)
- Urinalysis, including dipstick (pH, specific gravity, glucose, protein, ketones, blood) and, if routinely performed, microscopic examination (sediment, RBCs, WBCs, casts, crystals, epithelial cells, bacteria)
- HBV/HCV DNA PCR in patients with resolved HBV/HCV infection.
- HTLV-1 serology (for patients from endemic countries only)

No samples in this study will be sent to a central laboratory for analysis.

4.5.7 Electrocardiograms

Single, resting, 12-lead ECG recordings will be obtained at screening (see Appendix 1), and may be obtained at unscheduled timepoints as clinically indicated. ECGs for each patient should be obtained using the same machine wherever possible. Interpretation of the ECG should be performed by the investigator.

4.5.8 Echocardiogram or MUGA

For patients receiving CHOP, LVEF will be assessed by echocardiography or MUGA scan at screening (see Appendix 1).

4.5.9 Clinical Outcome Assessments

A patient-reported outcome (PRO) instrument will be completed to assess the severity of disease, treatment-related symptoms, and how symptoms interfere with aspects of the patient's life. PRO data will be collected using the MD Anderson Symptom Inventory (MDASI) instrument (Appendix 2).

Provider-reported outcome instruments will be completed to evaluate the site experience with the SDI and standard infusions of obinutuzumab. Provider-reported data will be collected using a questionnaire (Appendix 2).

The MDASI and provider-reported questionnaires, translated into the local language as appropriate, will be provided by the sponsor. The sheets will be labeled with the timepoint of administration.

4.5.9.1 Data Collection Methods for Clinical Outcome Assessments

Patient-Reported Outcomes

To ensure instrument validity and that data standards meet health authority requirements, the MDASI will be self-administered at the clinic at specified timepoints during the study (see schedule of activities in Appendix 1). At the clinic, the instrument will be administered before the patient receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment, unless otherwise specified.

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

- Patients' health status should not be discussed prior to administration of the instruments.
- Sites must administer the official version of each instrument, as provided by the Sponsor. Instruments must not be copied from the protocol.
- Sites should allow sufficient time for patients to complete the instruments, estimated to be 5 minutes at each specified visit.
- Sites should administer the instruments in a quiet area with minimal distractions and disruptions.
- Patients should be instructed to answer questions to the best of their ability; there are no right or wrong answers.
- Site staff should not interpret or explain questions, but may read questions verbatim upon request.
- Patients should not obtain advice or help from others (e.g., family members or friends) when completing the instruments.
- Site staff should review all completed instruments and should ask the patient to rectify any response that is not clearly marked in the appropriate location. If a response is missing, site staff should ask the patient to complete the item or confirm that the item was intentionally left blank.

Provider-reported outcomes

Provider-reported outcome instruments will be completed at the clinic at specified timepoints during the study (see schedule of activities in Appendix 1). Provider-reported

outcome instruments will be self-administered at the timepoints specified in Appendix 1. The instruments will be provided by the Sponsor. Physicians/nurses must complete the official version of each provider-reported outcome instrument, as provided by the Sponsor. Instruments must not be copied from the protocol.

4.5.9.2 Description of Clinical Outcome Assessment Instruments

MD Anderson Symptom Inventory (MDASI)

The MD Anderson Symptom Inventory (MDASI; Appendix 2) is a validated and reliable self-report measure (Cleeland et al., 2000) that was developed to assess symptom severity and interference. Thirteen items (i.e., pain, fatigue, nausea, disturbed sleep, distressed, shortness of breath, remembering things, lack of appetite, drowsy, dry mouth, sad, vomiting, and numbness or tingling) ask patients to rate how severe the symptoms were when "at their worst" in the last 24 hours. An additional 6 items ask patients to rate how much the symptoms have interfered with 6 areas of function (i.e., general activity, walking, work, mood, relations with other people, and enjoyment of life) in the last 24 hours. It takes approximately 5 minutes to complete.

Provider-Reported Outcomes Instrument

Investigator physicians and nurses involved in this study will be asked to answer four questions (Appendix 2) based on their experience with administering both the SDI and standard infusions of obinutuzumab, to patients enrolled in the study. It should take approximately 5 minutes to complete.

4.6 TREATMENT, PATIENT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

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

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment
- Investigator or Sponsor determination that treatment discontinuation is in the best interest of the patient
- Pregnancy
- Symptomatic deterioration attributed to disease progression
- Confirmed disease progression per investigator assessment

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF.

Patients will return to the clinic for a safety follow-up visit at 3 months (90 days (±10 days)) after the final dose of study drug (see Appendix 1 for additional details).

4.6.2 Patient Discontinuation from the Study

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for patient discontinuation from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Completed the safety follow-up after discontinuing obinutuzumab for patients in the maintenance or induction phase
- Adverse event
- Loss to follow-up
- Patient non-compliance, defined as failure to comply with protocol requirements as determined by the investigator or Sponsor

Every effort should be made to obtain a reason for patient discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn.

If a patient withdraws consent, this request must be documented in the source documents and signed by the investigator.

4.6.3 Study Discontinuation

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

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

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

4.6.4 Site Discontinuation

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

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Council for Harmonisation (ICH) guidelines for Good Clinical Practice

- No study activity (i.e., all patients have completed the study and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

The safety plan for patients in this study is based on clinical experience with obinutuzumab in completed and ongoing studies. The anticipated important safety risks for obinutuzumab are outlined below. Please refer to the obinutuzumab Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of patients participating in this study. Eligibility criteria have been designed to exclude patients at higher risk for toxicities. Patients will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for treatment interruption or discontinuation, are provided below.

5.1.1 Risks Associated With Obinutuzumab

The following adverse events are considered to be important risks associated or potentially associated with obinutuzumab: IRRs, TLS, thrombocytopenia (including acute thrombocytopenia), neutropenia (including late onset and prolonged neutropenia), prolonged B-cell depletion, infections (including PML and HBV reactivation), worsening of pre-existing cardiac conditions, GI perforation, and secondary malignancies. These events are described below.

5.1.1.1 Infusion-Related Reactions and Hypersensitivity Reactions

IRRs have been reported predominantly during the first infusion of obinutuzumab. The incidence and severity of IRRs decreased substantially with the second and subsequent infusions. In the majority of patients, irrespective of indication, IRRs were mild to moderate and could be managed by the slowing or temporary halting of the first infusion, but severe and life-threatening IRRs requiring symptomatic treatment have also been reported. The commonly experienced IRRs have been characterized by hypotension, fever, chills, dyspnea, flushing, nausea, vomiting, hypertension, fatigue, headache, tachycardia, dizziness, diarrhea, and other symptoms.

IRRs may be clinically indistinguishable from IgE-mediated allergic reactions (e.g. anaphylaxis).

Patients who have pre-existing cardiac or pulmonary conditions should be monitored carefully throughout the infusion and the post-infusion period. Hypotension may occur during obinutuzumab intravenous infusions. Therefore, withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each

obinutuzumab infusion and for the first hour after administration. Patients at acute risk of hypertensive crisis should be evaluated for the benefits and risks of withholding their anti-hypertensive medication.

Premedication to reduce the risk of IRRs is described in Section 4.3.3.1. Guidelines for medical management of IRRs and anaphylaxis are provided in Section 5.1.5 and Appendix 6 and Appendix 7.

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

5.1.1.2 Tumor Lysis Syndrome

TLS, including fatal events, has been reported with obinutuzumab administration. TLS is a potentially serious condition that can lead to acute electrolyte imbalance (e.g., hyperkalemia and hypocalcemia), arrhythmia, acute renal failure, and sudden death.

Patients at risk for TLS (e.g. patients with a high tumor burden or a high circulating lymphocyte count [>25 x 10^9/L] and/or renal impairment [CrCl <70 mL/min]) should receive prophylaxis as indicated in Section 4.3.3.2. Guidelines for the management of patients who experience TLS in this study are provided in Section 5.1.5.

For reporting purposes, TLS can be classified as laboratory or clinical. Laboratory TLS requires that two or more of the following metabolic abnormalities occur within 3 days before or up to 7 days after the initiation of therapy: hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. Clinical TLS is present when laboratory TLS is accompanied by an increased creatinine level, seizures, cardiac dysrhythmia, or death (Howard et al. 2011). TLS of any grade, irrespective of causality, are considered an Adverse Event of Special Interest and must be reported to the Sponsor immediately (see Section 5.2.3). Whilst reporting the event, if diagnosis is available, diagnosis should be reported as an event rather than individual signs and symptoms i.e. in this case, TLS should be reported. Further guidance is provided in Section 5.3.5.2.

5.1.1.3 Neutropenia

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

been reported. The use of G-CSF is allowed for treatment of neutropenia in this study. Prophylactic treatment with antibiotics should be administered as per standard practice.

5.1.1.4 Prolonged B-cell depletion

Prolonged B-cell depletion is defined as the absence of B-cell recovery 12 months after the end of treatment. Prolonged B-cell depletion is considered an important identified risk, due to the potential of severe infections. Prolonged B-cell depletion may be related to the risks of PML and HBV, which are described separately. No severity scale has been established for this condition. No preventative action is envisaged. Patients with prolonged B-cell depletion should be closely monitored for infections.

5.1.1.5 Thrombocytopenia

Severe and life-threatening thrombocytopenia, including acute thrombocytopenia (occurring within 24 hours after the infusion), has been observed during treatment with obinutuzumab. In CLL patients exposed to obinutuzumab, fatal hemorrhagic events have also been reported in Cycle 1. A clear relationship between thrombocytopenia and hemorrhagic events has not been established. Patients receiving concomitant medication that could possibly worsen thrombocytopenia related events (e.g., platelet inhibitors and anticoagulants) may be at greater risk of bleeding. When possible, replace prior vitamin K antagonist therapy with LMWH prior to Day 1 of Cycle 1. Patients should be closely monitored for thrombocytopenia, especially during the first cycle. For patients who experience thrombocytopenia, regular laboratory tests should be performed until the event resolves, and dose delays should be considered in case of severe or life-threatening thrombocytopenia. Transfusion of blood products (i.e., platelet transfusion) may be performed at the discretion of the treating physician, according to institutional practice.

5.1.1.6 Infections

On the basis of its mechanism of action, resulting in profound B-cell depletion, obinutuzumab may be associated with an increased risk of infections. Obinutuzumab should not be administered to patients with active infection, and caution should be exercised when including patients with a history of recurrent or chronic infections. Serious bacterial, fungal, and new or reactivated viral infections can occur during and following the completion of obinutuzumab therapy. Fatal infections have been reported.

In the FL studies, a high incidence of infections was observed in all phases of the studies, including follow-up, with the highest incidence seen during maintenance. Details are provided in the Obinutuzumab Investigator’s Brochure.

Reactivation of hepatitis B in patients with chronic hepatitis (HBsAg positive) with evidence of prior hepatitis B exposure, or in patients who are carriers (HBsAg negative and HBcAb positive) has been reported with other anti-CD20 antibodies. The risk is

increased particularly when anti-CD20 antibodies are administered with immunosuppressive therapies, such as steroids or chemotherapy. In obinutuzumab studies, patients with active HBV infection are excluded. However, patients with prior HBV infection or carriers are eligible to participate if HBV DNA is undetectable at screening and provided they agree to DNA testing at least every 3 months (during the study and for at least 1 year after completion of lymphoma treatment). These patients with positive HBcAb should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis reactivation. HBV reactivation in these patients with positive HBcAb at screening is defined as confirmed presence of HBV DNA >100 IU/mL in the serum or positive after baseline.

John Cunningham (JC) viral infection resulting in PML has been reported in patients treated with obinutuzumab. The diagnosis of PML should be considered in any patient presenting with new-onset neurologic manifestations. The symptoms of PML are unspecific and can vary depending on the affected region of the brain. Motor symptoms with corticospinal tract findings (e.g., muscular weakness, paralysis, and sensory disturbances), sensory abnormalities, cerebellar symptoms, and visual field defects are common. Some signs or symptoms regarded as “cortical” (e.g., aphasia or visual-spatial disorientation) may occur. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture (cerebrospinal fluid testing for JC viral DNA). Therapy with obinutuzumab should be withheld during the investigation of potential PML and permanently discontinued in case of confirmed PML. Discontinuation or reduction of any concomitant chemotherapy should also be considered.

5.1.1.7 Immunizations

The safety of immunization with live virus vaccines following obinutuzumab therapy has not been studied. Vaccination with live virus vaccines is not recommended during treatment and until B-cell recovery.

Given the mechanism of action of obinutuzumab, it is expected that the efficacy of COVID-19 vaccines may be diminished in patients receiving obinutuzumab. Patients should be informed that vaccine efficacy may be diminished. The discussion should be documented in the patient records.

Patients who are vaccinated should be instructed to continue to adhere to personal hygiene measures, social distancing and other measures to prevent infection.

Currently there are no data that support precise recommendations for the timing of COVID-19 vaccine administration in patients receiving obinutuzumab. The investigator should use clinical judgement to decide on the most suitable timing of vaccination.

Suppression of response to vaccination may persist for more than 12–18 months after treatment with obinutuzumab. Hence, there is no strong rationale for withholding or delaying therapy to allow immune recovery prior to vaccination.

COVID-19 vaccines must be given in accordance with the approved vaccine label.

5.1.1.8 Worsening of Preexisting Cardiac Condition

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

5.1.1.9 Gastrointestinal Perforation

GI perforation has been reported in patients treated with obinutuzumab, mainly in NHL, including fatal events. Patients with GI involvement should be monitored for signs of GI perforation.

5.1.1.10 Secondary Malignancies

Epidemiology data suggest that patients with CLL and NHL are at a higher risk of experiencing a secondary malignancy compared with the general population and this appears to be independent of exposure to treatment. The increased incidence of secondary malignancies in patients with CLL and NHL may be attributable to multiple factors, including immune dysfunction associated with the underlying disease (especially in patients with CLL,) carcinogenic and immunosuppressive effects of the various chemotherapeutic agents and radiotherapy, and the increased and close medical surveillance that patients with CLL and NHL receive from trained oncologists leading to earlier diagnosis of malignancies (Faguet 1979, Hisada et al. 2001). To date, in patients treated with obinutuzumab, the risk is considered an important potential risk.

5.1.2 Risks Associated With Bendamustine

Refer to prescribing information for bendamustine for risks related to bendamustine.

5.1.3 Risks Associated With CHOP

Refer to prescribing information for doxorubicin, cyclophosphamide, vincristine, and prednisone/prednisolone/methylprednisolone for risks related to CHOP chemotherapy.

5.1.4 Risks Associated With CVP

Refer to prescribing information for cyclophosphamide, vincristine, and prednisone/prednisolone/methylprednisolone for risks related to CVP chemotherapy.

5.1.5 Management of Patients Who Experience Adverse Events

5.1.5.1 Management Guidelines

There will be no dose reductions of obinutuzumab. Study treatments may be delayed for toxicity for a maximum amount of time, as specified in the table below. Treatment delays apply to all toxicities described below; dose modifications apply only to toxicities that are considered to be related to any of the study treatment components. Toxicities that occur during the cycle and subside prior to the next cycle should not trigger the suggested dose modifications. Guidelines for management of specific adverse events are outlined in Table 3 and Table 4. Additional guidelines are provided in the subsections below.

The guidelines for management of patients who experience adverse events for "Other non-hematologic toxicities" during induction treatment (Table 3) do not apply to toxicity related to vincristine in patients receiving CHOP/CVP. Such toxicity can be managed according to the clinical judgement of the investigator. A decrease in vincristine dose is permitted and study treatment may be withheld for up to a maximum of 21 days, however obinutuzumab dose must resume at full dose (no dose reductions are permitted).

Table 3 Guidelines for Management of Patients who Experience Adverse Events During Induction Treatment

Event	Action to Be Taken
General guidance for treatment delays and discontinuation	• If toxicity occurs before Cycle 1 Day 8 or Cycle 1 Day 15, requiring delay of obinutuzumab treatment, these doses should be given after resolution of toxicity. In such instances, all subsequent visits and the start of Cycle 2 will be shifted to accommodate for the delay in Cycle 1. • If study treatment is withheld for > 21 days permanently discontinue study treatment • When a treatment cycle is delayed because of toxicity resulting from any component of the regimen, all study treatment should generally be held and resumed together to remain synchronized.
Hematologic toxicity: Grade 1 or 2	• No action required.

Event	Action to Be Taken
Hematologic toxicity: Grade 3 & 4	• Withhold all study treatment for a maximum of 21 days.[a] • If improvement to Grade ≤2 or baseline does not occur within 21 days discontinue all study treatment. • Give supportive treatment. • Administer RBCs or platelets as required. • If patient has not already initiated G-CSF, initiate prophylactic G-CSF for current and subsequent cycles. • For patients who develop platelet count[c] of <20,000/μL while receiving LMWH, reduce the dose of LMWH. For patients who develop platelet count of <20,000/μL while receiving platelet inhibitors, consider temporarily withholding platelet inhibitors. • If improvement to Grade ≤2 or baseline within 13 days after the scheduled date for the next cycle, resume obinutuzumab at full dose and resume chemotherapy components at current dose. • If improvement to Grade ≤2 or baseline 14–21 days after the scheduled date for the next cycle, resume obinutuzumab at full dose and resume chemotherapy components at a reduced dose[a,b] for current and subsequent cycles as outlined below: • First episode: If improvement to Grade ≤2 or baseline, decrease cyclophosphamide dose to 500 mg/m^2, doxorubicin dose to 35 mg/m^2 and bendamustine dose to 70 mg/m^2 for subsequent cycles. • Second episode: If improvement to Grade ≤2 or baseline, decrease cyclophosphamide dose to 375 mg/m^2, doxorubicin dose to 25 mg/m^2 and bendamustine dose to 50 mg/m^2 for subsequent cycles. • No more than two dose reductions of chemotherapy are allowed. For patients who have had two prior chemotherapy dose reductions: • Permanently discontinue study treatment.
IRRs and anaphylaxis	• See Appendix 6 for guidance on managing IRRs. • In case of anaphylaxis, study treatment should be permanently discontinued. Anaphylaxis precautions are provided in Appendix 7.
TLS	• Withhold study treatment. • Perform chemistry panel on a regular basis during the first week • Correct electrolyte abnormalities, monitor renal function, cardiac function and fluid balance, and administer supportive care, including dialysis as indicated. • If symptoms have resolved completely, resume obinutuzumab at full dose and resume chemotherapy components at current dose.

Event	Action to Be Taken
New-onset neurologic manifestations suggestive of PML	• Withhold study treatment. • Consult with a neurologist if PML is suspected (refer to Section 5.1.1.6 for guidance on investigations). • If PML is ruled out, resume obinutuzumab at full dose and resume chemotherapy components at current dose. • If PML is confirmed, permanently discontinue study treatment.
Other non-hematologic toxicities: Grade 1	• No action required.
Other non-hematologic toxicities (excluding alopecia): Grade 2	• Withhold all study treatment for a maximum of 21 days. • If improvement to baseline or Grade 1 or better does not occur within 21 days, discontinue all study treatment. • If improvement to baseline or Grade 1 or better, resume chemotherapy components at current dose and resume obinutuzumab at full dose.
Other non-hematologic toxicities: Grade 3 or 4	• Withhold all study treatment for a maximum of 21 days.[a] • If improvement to baseline or Grade 1 or better does not occur within 21 days, discontinue all study treatment. • First episode: If improvement to baseline or Grade 1 or better, decrease cyclophosphamide dose to 500 mg/m^2, doxorubicin dose to 35 mg/m^2 and bendamustine dose to 70 mg/m^2 for subsequent cycles. • Second episode: If improvement to baseline or Grade 1 or better, decrease cyclophosphamide dose to 375 mg/m^2, doxorubicin dose to 25 mg/m^2 and bendamustine dose to 50 mg/m^2 for subsequent cycles. • No more than two dose reductions of chemotherapy are allowed. For patients who have had two prior chemotherapy dose reductions: • Permanently discontinue study treatment.

Event	Action to Be Taken
Infections	• Advice should be given to patients to minimize the risks of acquiring infections from endogenous sources e.g., oral hygiene, avoidance of constipation etc. Dental assessment may be warranted prior to starting treatment in some cases. • Signs or symptoms of infection should result in prompt evaluation and collection of appropriate samples for bacteriological investigation prior to starting antibiotic or other treatment by the treating physician. • Empiric therapy with broad-spectrum antibiotics should be initiated promptly in all patients with suspected infections (including those receiving antimicrobial prophylaxis) to reduce the risk of serious morbidity and mortality. • Antibiotic prophylaxis may be considered in high risk patients as it is associated with significantly reduced occurrence of fever, fewer clinically documented and microbiologically documented infections, fewer infections due to both gram-positive and gram-negative bacteria, fewer cases of bacteremia, and a lower risk of infection related death.
Hepatitis B reactivation	1. Patients with positive hepatitis B serology should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis reactivation. 2. HBV DNA level of > 100 IU/mL: • Hold study treatment. • Begin anti-viral medication immediately as per local medical standards and immediately refer the patient to a gastroenterologist or hepatologist for additional management. • Patients may resume study treatment once HBV DNA levels decrease to undetectable levels. • If the HBV DNA level exceeds 100 IU/mL while a patient is receiving anti-viral medication, permanently discontinue study treatment.

CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisone/prednisolone/ methylprednisolone; G-CSF = granulocyte colony-stimulating factor; LMWH = low-molecular-weight heparin.

Note: A hematologic toxicity is defined as neutropenia, anemia, or thrombocytopenia.

[a] Treatment delays apply to all toxicities; dose modifications apply only to toxicities that are considered to be related to any of the study treatment components. Toxicities that occur during the cycle and subside prior to the next cycle should not trigger the suggested dose modifications.

[b] If cytopenia is thought to be caused mainly by iNHL infiltration of the bone marrow, the investigator may decide not to reduce the chemotherapy doses.

[c] Severe thrombocytopenia is defined as a platelet count $<10{,}000/\mu L$ for patients who are not receiving concomitant anticoagulants or platelet inhibitors and $<20{,}000/\mu L$ for patients who are receiving concomitant anticoagulants or platelet inhibitors.

Table 4 Guidelines for Management of Patients Who Experience Adverse Events during Maintenance Treatment

Event	Action to Be Taken
Hematologic toxicity: Grade 3 or 4 [b]	• Withhold obinutuzumab[a] • Administer G-CSF for neutropenia per institutional guidelines. • Administer RBCs or platelets as required. • If improvement to Grade ≤2, resume obinutuzumab at full dose. • If obinutuzumab is withheld for > 42 days, permanently discontinue study treatment.
Non-hematologic toxicity: Grade ≥2 [b]	• Withhold obinutuzumab[a] • If improvement to Grade ≤1 or baseline, resume obinutuzumab at full dose. • If obinutuzumab is withheld for > 42 days, permanently discontinue study treatment.

[a] Treatment delays apply to all events; dose modifications apply only to events that are considered to be related to obinutuzumab. Dose reduction for obinutuzumab is not allowed during the study. Toxicities that occur during the cycle and subside prior to the next cycle should not trigger the suggested dose modifications.

[b] For additional guidance on AE management refer to Table 3.

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

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

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.9 and 5.3.5.10 for more information)

- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

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

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

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

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

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

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

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

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

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

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

5.2.4 Selected Adverse Events

Adverse events of special interest are listed in Section 5.2.3. Selected adverse events in this study are defined as adverse events for which additional data collection or analyses will be performed. Selected adverse events do not require immediate reporting if they are not serious.

The following adverse events are considered selected adverse events:

- Thrombocytopenia, including acute thrombocytopenia (events occurring during and within 24 hours following obinutuzumab infusion)
- Hepatitis B reactivation
- Cardiac events
- IRRs
- All infections, including PML
- Neutropenia, including prolonged neutropenia (neutropenia <1000 cells/µL that does not resolve after 28 days without obinutuzumab treatment) and late-onset neutropenia (neutropenia <1000 cells/µL occurring ≥28 days after obinutuzumab treatment has been completed or stopped)
- GI perforation

Events for which additional data collection will be required are PML, and hepatitis B reactivation.

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

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

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

5.3.1 Adverse Event Reporting Period

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

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

After initiation of study drug, all adverse events will be reported until 3 months (90 days (± 10 days)) after the last dose of study treatment. After this period, the investigator should report any serious adverse events that are believed to be related to prior study treatment (see Section 5.6).

An exception is made for Grade 3–4 infections (related and unrelated to study treatment), which should be reported until resolution or until up to 2 years after the last dose of obinutuzumab.

All study drug–related SAEs and secondary malignancies are to be reported and data collected indefinitely from the last study drug administration (even if the study has been closed) (see Section 5.6). Secondary malignancies are an AESI and must therefore be reported within 24 hours to the sponsor regardless of the seriousness.

5.3.2 Eliciting Adverse Event Information

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

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

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

Physicians should elicit AE information at every patient study visit.

5.3.3 Assessment of Severity of Adverse Events

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. Table 5 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 5 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

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

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

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

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

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

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

5.3.4 Assessment of Causality of Adverse Events

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

- Temporal relationship of event onset to the initiation of study drug

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

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

5.3.5 Procedures for Recording Adverse Events

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

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

5.3.5.1 Infusion-Related Reactions

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

5.3.5.2 Diagnosis versus Signs and Symptoms

A diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. If a diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

5.3.5.3 Adverse Events That Are Secondary to Other Events

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

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

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

5.3.5.4 Persistent or Recurrent Adverse Events

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

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

5.3.5.5 Abnormal Laboratory Values

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

- Is accompanied by clinical symptoms

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

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

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

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

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

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

5.3.5.6 Abnormal Vital Sign Values

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

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

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

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

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

5.3.5.7 Abnormal Liver Function Tests

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

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

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

Deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1) that are attributed by the investigator solely to progression of FL should be recorded on the Study Completion/Early Discontinuation and Death Attributed to Progressive Disease eCRF. All other deaths that occur during the adverse event reporting period, regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). The IMC will monitor the frequency of deaths from all causes.

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

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

5.3.5.9 Preexisting Medical Conditions

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

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

5.3.5.10 Lack of Efficacy or Worsening of Follicular Lymphoma

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. The determination of clinical progression will be based on the investigator assessment in routine clinical practice. In most cases, the expected pattern of progression will be based on the Lugano 2014 criteria (Cheson et al 2014) and the Cheson et al 2007 criteria. In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event. The disease progression will be captured on the early discontinuation CRF.

5.3.5.11 Hospitalization or Prolonged Hospitalization

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

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

- Hospitalization for respite care
- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration)

- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

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

  The patient has not experienced an adverse event

- Hospitalization due solely to progression of the underlying cancer

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

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

5.3.5.12 Cases of Accidental Overdose and Medication Error

Accidental overdose and medication error (hereafter collectively referred to as "special situations"), are defined as follows:

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

  In some cases, a medication error may be intercepted prior to administration of the drug.

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

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.

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

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.
- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.

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

5.3.5.13 Patient-Reported Outcome Data

Adverse event reports will not be derived from PRO data by the Sponsor, and safety analyses will not be performed using PRO data. Sites are not expected to review the PRO data for adverse events.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

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

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

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

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

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

5.4.1 Emergency Medical Contacts

To ensure the safety of study patients, an Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the investigator with a Roche Medical Responsible (listed above and/or on the Roche Medical Emergency List), and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

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

5.4.2.1 Events That Occur prior to Study Drug Initiation

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

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until 3 months (90 days (± 10 days)) after the final dose of study drug. After this period, the investigator should report any serious adverse events that are believed to be related to prior study treatment (see Section 5.6).

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

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

Instructions for reporting post-study adverse events are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 18 months after the last dose of study treatment.

A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study treatment immediately counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus.

Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF. In addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Pregnancies in Female Partners of Male Patients

Male patients will be instructed through the Informed Consent Form to immediately inform the investigator if their partner becomes pregnant during the study or within 3 months after the last dose of study treatment.

A paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the

pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. When permitted by the site, the pregnant partner would need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. If the authorization has been signed, the investigator should submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

5.4.3.3 Abortions

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

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

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

5.4.3.4 Congenital Anomalies/Birth Defects

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

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all

serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

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

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

5.5.2 Sponsor Follow-Up

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

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

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 as 3 months (90 days (± 10 days)) after the last dose of study treatment), 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.

An exception is made for Grade 3–4 infections (related and unrelated), which should be reported until up to 2 years after the last dose of study treatment.

The Sponsor should also be notified of events of secondary malignancies indefinitely (related and unrelated) for patients who received obinutuzumab.

If the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial 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 HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

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

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of these events using the following reference document:

- Obinutuzumab Investigator's Brochure

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

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

The purpose of this study is to evaluate the safety of administering obinutuzumab as a short duration infusion (SDI; target 90-minute infusion) during cycle 2 and from cycle 2 onwards in combination with chemotherapy in patients with previously untreated advanced FL.

The primary analysis will be analyzed and reported based on all patients' data up to the time when all patients have completed 2 cycles of obinutuzumab treatment. The End of Induction (EOI) analysis will be analyzed and reported once all patients have completed the induction period. The final analysis will be performed at the end of the study and include PFS and OS rates.

The analysis populations are defined as follows:

- The SDI population includes all patients who received obinutuzumab as an SDI at cycle 2 and who did not experience a Grade 3 or 4 IRR during the infusion of obinutuzumab given at the standard rate during cycle 1. This population will be used for the analysis of the primary endpoint and one of the secondary endpoints (time to IRR during cycle 2).
- The safety population includes all patients who received at least one dose of obinutuzumab. This population will be used for all remaining analyses.

No formal statistical hypothesis tests will be performed, and all analyses are considered descriptive.

6.1 DETERMINATION OF SAMPLE SIZE

A sample size of approximately 112 patients is planned for this study.

The incidence of Grade ≥3 IRRs during cycle 2 was chosen as the safety endpoint of primary interest and used to justify the sample size. Based on experience from previous studies (BO21223/GALLIUM, GAO4915g/GATHER), it is assumed to have an incidence rate of only 1% or 2%, and hence to observe only few events.

The upper bounds of two-sided 95% Clopper-Pearson confidence intervals (CIs) according to the sample size and the number of observed Grade ≥3 IRRs during cycle 2 are shown in Table 6.

Table 6 Relationship Between the Sample Size, the Number of Observed ≥G3 IRRs and the Upper Bound of the Corresponding Two-sided 95% Clopper-Pearson Confidence Interval

	Number of observed ≥G3 IRRs				
Sample size	0	1	2	3	4
90	4.0%	6.0%	7.8%	9.4%	11.0%
100	3.6%	5.4%	7.0%	8.5%	9.9%

For instance, observing two Grade ≥3 IRRs during cycle 2 would yield an upper bound of 7.0% in an SDI population of 100 patients and of 7.8% in an SDI population of 90 patients. Not observing any Grade ≥3 IRRs during cycle 2 would yield upper bounds of 3.6% and 4.0%, respectively.

There will be no formal hypothesis test for the primary endpoint.

Taking into account an estimated drop-out rate of 10%, a total of approximately 112 patients will be enrolled in this study to have 100 patients in the SDI population. If the drop-out rate would be lower, accrual would be stopped after 100 patients in the SDI population. If the drop-out rate would be higher, with 112 patients enrolled into the study a drop-out rate of 19.7% would still leave 90 patients in the SDI population which would result in a reasonable precision for the CI. If there would be less than 90 patients in the SDI population at the end of the planned enrolment phase, the IMC would decide whether to continue enrolment or not.

6.2 SUMMARIES OF CONDUCT OF STUDY

The number of patients who enroll, discontinue, or complete the study will be summarized. Reasons for premature study discontinuation will be listed and summarized. Major protocol deviations will be listed and evaluated for their potential effects on the interpretation of study results.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (including age, sex, etc.) will be summarized using means, standard deviations, medians, and ranges for continuous variables and frequencies and percentages for categorical variables, as appropriate.

6.4 SAFETY ANALYSES

The primary objective of this study is to evaluate the safety of obinutuzumab administered as an SDI from cycle 2 in patients with previously untreated advanced FL on the basis of the following endpoints:

Primary endpoint:

- The incidence of Grade ≥3 IRRs* during cycle 2 in patients who had previously received obinutuzumab at the standard infusion rate during cycle 1 without experiencing a Grade 3 or 4 IRR, with severity determined according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5.0.

* *IRRs are defined as all adverse events (AEs) that occur during or within 24 hours from the end of study treatment infusion and are judged as related to infusion of study treatment components (obinutuzumab and chemotherapy during induction and obinutuzumab alone during maintenance) by the investigator.*

Secondary safety endpoints:

- Incidence, nature, and severity of all AEs from during cycle 1 and from cycle 1 onwards (including maintenance)
- Incidence of IRRs regardless of grade by cycle (separately)
- Time to IRR (in hours) from infusion to onset of the IRR during cycle 2
- Duration (in minutes) of obinutuzumab administration by cycle (all cycles including maintenance)
- Type and duration of Grade ≥3 IRRs, during all cycles, where obinutuzumab was administered as an SDI.

The SDI population will be used for the analysis of the primary endpoint and of the time to IRR during cycle 2. The analysis of the primary endpoint will occur once all patients have completed cycle 2.

The safety population which includes all patients who received at least one dose of obinutuzumab will be the analysis set used for all remaining analyses.

All verbatim adverse event terms will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus terms, and adverse event severity will be graded according to NCI CTCAE v5.0.

Descriptive summaries of discrete data will present the number of patients and incidence as a frequency and as a percentage. For the primary endpoint a two-sided 95% Clopper-Pearson confidence interval will be presented. Moreover, the incidence of IRRs for cycle 1 will be described by day of the cycle (day 1, day 8, or day 15).

The duration of obinutuzumab administration and infusion-related AEs will be summarized descriptively (mean, median, standard deviation, minimum, and maximum duration) by cycle.

6.5 SECONDARY EFFICACY ANALYSES

The secondary efficacy objective for this study is to evaluate the efficacy of obinutuzumab administered as an SDI from cycle 2 in patients with previously untreated advanced FL on the basis of the following endpoints:

- Objective response rate at the end of induction therapy as determined by the investigator and according to the guidelines used at the site (Lugano [Cheson et al 2014], Cheson et al 2007, or Cheson et al 1999).
- Progression-free survival rate at the end of the study
- Overall survival at the end of the study
- Complete response (CR) rate at 30 months (CR30), as assessed by the investigator and according to the guidelines used at the site.

There were no power calculations for the efficacy endpoints. No formal statistical hypothesis tests will be performed, and all analyses are considered descriptive.

The ORR will be presented along with a 95% Clopper-Pearson confidence interval; overall and by type of response assessment. ORR will be reported at the primary analysis, for patients that have already reached end of induction. In addition, ORR will be reported at the EOI analysis and at the final analysis for all patients.

PFS in patients with follicular lymphoma is defined as the time from start of treatment to the first occurrence of progression or relapse as assessed by the investigator according to the used at the site (Lugano [Cheson et al 2014], Cheson et al 2007, or Cheson et al 1999), or death from any cause. It will be presented as the Kaplan-Meier estimate at the end of the study along with its 95% confidence interval. Note that with different criteria and tumour assessment schedules between sites the value of these data will be limited.

OS is defined as the time from start of treatment to death from any cause. It will be presented as the Kaplan-Meier estimate at the end of the study along with its 95% confidence interval.

PFS and OS will be analysed only once, as part of the final analysis at the end of the study.

Note that the follow-up time is not driven by PFS and OS. With a study duration of only approximately 4 years very few events are expected to have occurred in this patient population. This study will not make a substantial contribution to the data on these

endpoints. But, as the progression dates are used for treatment management and OS data are easy to obtain these data will be collected and reported.

6.6 EXPLORATORY ANALYSES

6.6.1 Exploratory Safety Analyses

The exploratory safety objectives for this study are to further evaluate the safety of obinutuzumab administered in patients with previously untreated advanced FL on the basis of the following endpoints to evaluate the impact of time to IRR:

- The incidence of Grade ≥3 IRRs* (with severity determined according to NCI CTCAE Version 5.0) during the first SDI cycle:
  - cycle 2 in patients who received obinutuzumab at the standard infusion rate without experiencing a Grade 3 IRR in cycle 1
  - cycle 3 in patients who experienced a Grade 3 IRR when administered obinutuzumab at the standard infusion rate in cycle 1 and subsequently received obinutuzumab at the standard infusion rate in cycle 2 without experiencing a Grade 3 IRR
- Time to IRR (in hours) from infusion to onset of the IRR in cycle 1 or cycle 3

* *IRRs are defined as all adverse events (AEs) that occur during or within 24 hours from the end of study treatment infusion and are judged as related to infusion of study treatment components* (obinutuzumab and chemotherapy during induction and obinutuzumab alone during maintenance) *by the investigator.*

Descriptive summaries of discrete data will present the number of patients and incidence as a frequency and as a percentage. The time from obinutuzumab administration to AEs will be summarized descriptively (mean, median, standard deviation, minimum, and maximum duration) over all and by cycle.

6.6.2 Exploratory Efficacy Analyses

The exploratory efficacy objectives for this study are to evaluate patients with a partial response (PR) at the end of induction treatment who convert to complete response (CR) during maintenance treatment and to evaluate and compare the objective response and CR rate after the end of induction treatment with and without 18F-fluorodeoxyglucose positron emission tomography (FDG-PET):

- Proportion of patients with a PR at the end of induction treatment who convert to CR during maintenance treatment, as assessed by the investigator and according to the guidelines used at the site (see above)
- Objective response rate and CR rate after the end of induction treatment, as assessed by the investigator and according to the guidelines used at the site (see

above), with and without 18F-fluorodeoxyglucose positron emission tomography (FDG-PET).

Again, descriptive summaries of these discrete data will present the number of patients and incidence as a frequency and as a percentage.

6.6.3 Exploratory Provider and Patient-reported Analyses

The exploratory patient-reported objective for this study is to evaluate the severity and interference of disease- and treatment-related symptoms in patients with previously untreated advanced FL treated with obinutuzumab administered as an SDI during cycle 2 and from cycle 2 onwards, on the basis of the following endpoint:

- Severity of disease symptoms experienced by patients and the interference with daily living caused by these symptoms, as assessed through use of the MD Anderson Symptom Inventory (MDASI; Appendix 2).

The exploratory provider-reported objective is to evaluate the site experience with the SDI, specifically:

- Physician / nurse experience on time savings with obinutuzumab SDI compared with obinutuzumab at the regular infusion rate
- Physician / nurse experience on the convenience of and preference for obinutuzumab SDI compared with obinutuzumab at the regular infusion rate.

For all patients that completed the questionnaire, the MDASI items and subscales will be summarized by the mean and median change from baseline. The MDASI subscales will be plotted over time.

For the provider-reported questions, the frequency of individuals reporting the responses to each question will be obtained and reported.

6.7 INTERIM ANALYSIS

No formal Interim analysis is planned for this study. There will be three reporting events: the primary analysis, the end of induction analysis, and the final analysis.

In addition, the data will be monitored by an Internal Monitoring Committee (IMC). The first IMC data review will take place after the first 10 patients have completed the first SDI infusion (i.e. cycle 2). The second IMC data review will happen after 50 patients have completed the first SDI infusion (i.e. cycle 2) or at 6 months after the first IMC, whichever occurs first. Furthermore, the IMC will review results obtained for the primary analysis, end of induction analysis, and final analysis. Further meetings will be scheduled as deemed necessary. See the IMC charter for details.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

A contract research organization (CRO) will be responsible for the data management of this study, including quality checking of the data. Data entered manually will be collected via EDC through use of eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the CRO will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will perform oversight of the data management of this study. The CRO will produce eCRF Specifications for the study based on Sponsor's templates including quality checking to be performed on the data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

Patient- and provider-reported data will be collected on paper questionnaires. The data from the questionnaires will be entered into the EDC system by site staff.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the CRO.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review to confirm that critical protocol data (i.e., source data) entered into the eCRFs by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, patient-reported outcomes, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate

and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly into the eCRFs (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered into the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.5.

To facilitate source data verification and review, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and IRB/EC review. The study site must also allow inspection by applicable health authorities.

7.4 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

7.5 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, paper PRO data, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 15 years after completion or discontinuation of the study or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

Roche will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the applicable laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union or European Economic Area will comply with the E.U. Clinical Trial Directive (2001/20/EC) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as an Assent Form or Mobile Nursing Informed Consent Form, if applicable) will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC–approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each patient the objectives, methods, and potential risks associated with each optional procedure. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a patient's agreement to participate in optional procedures. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient or the patient's legally authorized representative before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient

to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Patients must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in data sets that are transmitted to any Sponsor location.

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

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication (see Section 9.5).

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.5).

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (see definition of end of study in Section 3.2).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and

governmental approval. In addition, at the end of the study, the investigator will receive the patient data, including an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of ICH Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patients' medical records, and eCRFs. The investigator will permit national and local health authorities; Sponsor monitors, representatives, and collaborators; and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

This trial will be sponsored and managed by F. Hoffmann-La Roche Ltd. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 40 sites globally will participate to enroll approximately 112 patients. Enrollment will occur through an IxRS.

Accredited local laboratories will be used for routine monitoring; local laboratory ranges will be collected.

An IMC will be employed to monitor and evaluate patient safety throughout the study. Tumor response and progression will be evaluated locally.

9.5 DISSEMINATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for more details), and redacted Clinical Study Reports and other summary reports will be made available upon request, provided the requirements of Roche's global policy on data sharing have been

met. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following website:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective Clinical Study Report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel.

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

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

10. REFERENCES

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Appendix 1
Schedule of Activities

Day	Screening [a]		Treatment								Follow-up (3 months)[aa]
			Induction (6–8 cycles) [b]					EOI	Maintenance [e] (every 8 weeks ± 10 days)	EOM	
			Cycle 1			Cycle 2	Cycles 3–6/8				
	D–28 to D–1	D–7 to D–1	D1	D8	D15	D1	D1				
Informed consent	x [f]										
Demographic data	x										
Medical history and baseline conditions	x										
Ann Arbor, FLIPI, and FLIPI2	x										
ECOG performance status	x										
Vital signs [g]	x		x	x	x	x	x	x	x	x	x
Weight	x										
Height	x										
ECG	x										
LVEF (echocardiography or MUGA scan) [z]	x										
Complete physical examination [h,i]	x										x
Targeted physical examination [j,k]								x		x	
B symptoms [l]	x										
Hematology [m]		x	x	x	x	x	x	x	x	x	
Chemistry [n]		x		x	x	x	x	x	x	x	
Pregnancy test [o]		x									
Coagulation INR, aPTT or PTT and PT		x									
Urinalysis [p]		x						x		x	
HIV, HTLV-1, Hep B / C testing [q]	x										
Study drug administration: obinutuzumab [r]			x [c]	x [c]	x [c]	x [d]	x [d]		x [d]		
Study drug administration: chemotherapy [s]			x			x	x				
Tumor assessment [t]	x							x		x	
Concomitant medications [u,v]	x [u]	x [u]	x [u]	x	x	x	x	x	x	x	x
Adverse events [w]	x [w]	x [w]	x [w]	x	x	x	x	x	x	x	x
Provider-reported measures							x [x]				
Patient-reported measures [y]			x			x	x	x	x	x	x

(a)PTT=(activated) partial thromboplastin time; D=day; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOI=end of induction; EOM=end of maintenance; FLIPI=Follicular Lymphoma International Prognostic Index; HIV, human immunodeficiency virus; HTLV-1, human T-lymphotropic virus 1; INR=International Normalized Ratio; LVEF=left ventricular ejection fraction; MUGA= multigated acquisition (scan); PT=prothrombin time.

Appendix 1: Schedule of Activities

Notes: Dosing (i.e., Day 1 of each cycle), in induction phase should be done within ± 2 days of the scheduled visit date, with the exception of C1D1 which should take place within 28 days of the patient entering screening. All assessments should be performed within 2 days of the scheduled visit, unless otherwise specified. On treatment days, all assessments should be performed prior to dosing, unless otherwise specified. Results from hematology and biochemistry must be reviewed, and the review documented, prior to study drug administration.

[a] Results of standard-of-care tests or examinations performed prior to obtaining informed consent and within the defined window may be used; such tests do not need to be repeated for screening.

[b] The total number of cycles of G-chemo indication therapy and the cycles length depends on the chemotherapy chosen for each patient (see Section 4.3.2.2 Combination chemotherapy).

[c] Obinutuzumab administered according to the regular infusion rate (see Table 1, Section 3.1).

[d] Obinutuzumab administered according a 90-minute short duration infusion (see Table 1, Section 3.1) for patients who do not experience any Grade ≥3 IRRs during the first or previous cycle. If a patient experiences any Grade 3 IRRs during any SDI administrations of obinutuzumab (i.e. after Cycle 1, Day 1), the next dose of obinutuzumab will be administered at the regular infusion rate. If the patient experiences a second occurrence of a Grade 3 IRR, the obinutuzumab infusion must be stopped and the therapy must be permanently discontinued.

[e] Patients who achieve at least a partial response (PR) following the completion of induction therapy will receive obinutuzumab maintenance therapy (1000 mg as single agent every 8 weeks (± 10 days) for 2 years or until disease progression). The first administration of obinutuzumab maintenance therapy is expected to start 8 weeks ± 10 days from Day 1 of the last induction cycle. Patients with stable disease or progressive disease will go to safety follow-up. For the timing of the safety follow-up assessment, please see footnote aa.

[f] Informed consent must be documented before any study-specific screening procedure is performed, and may be obtained more than 28 days before initiation of study treatment.

[g] Includes blood pressure, pulse rate and temperature. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[h] Includes evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems. Record abnormalities observed at baseline on the General Medical History and Baseline Conditions eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[i] As part of tumor assessment, the physical examination should include evaluation for the presence of enlarged nodes, palpable hepatomegaly, and splenomegaly. This information will be recorded on the appropriate tumor assessment eCRF.

[j] Includes systems of primary relevance (e.g., cardiovascular and respiratory systems), systems associated with symptoms (newly emergent or monitored from baseline), and areas associated with tumor assessment (lymph nodes, liver, spleen, and any other areas identified at baseline). Record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

[k] Perform at the same time as tumor assessments after the end of induction treatment.

[l] Unexplained fever >38ºC, night sweats, unexplained weight loss >10% of body weight over 6 months.

[m] Hematology includes WBC count, RBC count, hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[n] Chemistry panel (serum or plasma) includes bicarbonate or total carbon dioxide (if considered standard of care for the region), sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, phosphate, calcium, total and direct bilirubin, ALP, ALT, AST, urate, beta-2 microglobulin (at screening and EOI only) and LDH.

[o] All women of childbearing potential will have a serum pregnancy test at screening.

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

[q] To include assessment of HBV/HCV DNA PCR in patients with resolved HBV/HCV infection at baseline. HBV DNA PCR testing at least every 3 months should also be conducted (during the study and for at least 1 year after completion of lymphoma treatment) for patients with prior HBV infection or who are carriers of HBV. HTLV-1 testing will be performed at baseline in patients from endemic countries only. HIV testing will be performed at baseline if required by local regulations.

[r] Obinutuzumab administered on Days, 1, 8 and 15 of cycle 1 and Day 1 of subsequent cycles.

[s] Chemotherapy comprises either bendamustine (Days 1 and 2, Cycles 1–6; 28-day cycles), CHOP (Days 1–5, Cycles 1–6; 21-day cycles; followed by 2 cycles of obinutuzumab alone), or CVP (Days 1–5, Cycles 1–8; 21-day cycles). See Section 4.3.2.2 Combination chemotherapy.

[t] By the investigator according to local practice and according to the guidelines used at the site (Lugano [Cheson et al 2014], Cheson et al 2007, or Cheson et al 1999). Including bone marrow where applicable. If bone marrow data are available in the patient's medical record that were obtained within 3 months prior to study inclusion, these data can be used instead, and the patient does not need to undergo a new bone marrow biopsy with or without aspirate at screening.

[u] Medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment from 7 days prior to study entry until 3 months after the final dose of study drug.

[v] Concomitant medications and adverse events will be collected throughout the study.

[w] After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported. After initiation of study drug, all adverse events will be reported until 3 months (90 days (± 10 days)) after the final dose of study drug. After this period, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that is believed to be related to prior study treatment (see Section 5.6). An exception is made for Grade 3–4 infections (related and unrelated), which should be reported until resolution or until up to 2 years after the last dose of obinutuzumab and secondary malignancies should be reported indefinitely. The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent.

[x] After administration of SDI at Cycle 4 Day 1, providers will complete the evaluation of site experience questionnaire.

[y] Before administration of treatment at Day 1 of Cycles 1–6, at the end of induction, during maintenance, at end of maintenance, and at end of study, patients will complete the MDASI. The MDASI will be self-administered before the patient receives any information on disease status, prior to the performance of non-PRO assessments, and prior to the administration of study treatment.

[z] LVEF required for patients who receive CHOP only.

[aa] Safety follow-up assessment at 3 months (90 days (+/- 10 days)) after the final dose of obinutuzumab. If a patient discontinues obinutuzumab early and requires another anticancer therapy, then a safety follow up visit must be performed prior to the initiation of the new anticancer therapy.

Appendix 2
Provider and Patient-reported Measures

M.D. Anderson Symptom Inventory (MDASI) Core Items

*Part I. How **severe** are your symptoms?*

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been ***in the last 24 hours***. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	Not Present										**As Bad As You Can Imagine**
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
1. Your **pain** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
2. Your **fatigue (tiredness)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
3. Your **nausea** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
4. Your **disturbed sleep** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
5. Your feelings of being **distressed (upset)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
6. Your **shortness of breath** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
7. Your problem with **remembering things** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
8. Your problem with **lack of appetite** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
9. Your feeling **drowsy (sleepy)** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
10. Your having a **dry mouth** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

	Not Present										As Bad As You Can Imagine
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
11. Your feeling **sad** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
12. Your **vomiting** at its WORST?	○	○	○	○	○	○	○	○	○	○	○
13. Your **numbness or tingling** at its WORST?	○	○	○	○	○	○	○	○	○	○	○

*Part II: How have your symptoms **interfered** with your life?*

Symptoms frequently interfere with how we feel and function. How much have your **symptoms interfered** with the following items in the last 24 hours:

	Did Not Interfere										Interfered Completely
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
14. **General activity?**	○	○	○	○	○	○	○	○	○	○	○
15. **Mood?**	○	○	○	○	○	○	○	○	○	○	○
16. **Work (including work around the house)?**	○	○	○	○	○	○	○	○	○	○	○
17. **Relations with other people?**	○	○	○	○	○	○	○	○	○	○	○
18. **Walking?**	○	○	○	○	○	○	○	○	○	○	○
19. **Enjoyment of life?**	○	○	○	○	○	○	○	○	○	○	○

Provider-Reported Outcomes: Evaluation of Site Experience

Investigator physicians and nurses involved in this study will be asked to answer questions based on their site experience with the SDI and standard infusions of obinutuzumab, across all patients enrolled in the study. After each patient enrolled, physicians and nurses will be asked to complete the four questions below at one time points after Cycle 4 SDI administration or after the last cycle of SDI treatment if treatment is discontinued earlier.

Physician / Nurse Experience on Time Savings

If used in routine practice, on average, how much staff time could be saved with each administration of obinutuzumab SDI as compared to obinutuzumab at the standard infusion rate?

□ Less than 1 hour

□ At least 1 hour but less than 2 hours

□ At least 2 hours but less than 3 hours

□ At least 3 hours but less than 4 hours

□ 4 or more hours

□ No time savings

□ Not applicable

Physician / Nurse Experience on Convenience

Which administration of obinutuzumab (SDI or standard) do you think is more convenient?

□ Obinutuzumab SDI is much more convenient

□ Obinutuzumab SDI is a little more convenient

□ Both administrations are equally convenient

□ Obinutuzumab at the standard infusion rate is a little more convenient

□ Obinutuzumab at the standard infusion rate is much more convenient

Physician / Nurse Experience on Preference

Which formulation of obinutuzumab (SDI or standard) do you prefer?

□ Obinutuzumab SDI

□ Obinutuzumab at the standard infusion rate

□ Have no preference

If you have a preference for one of the formulations, what are the main reasons for your preference?

□ Clinic/staff time savings

□ Patient time savings

□ Patient comfort

□ Other

If 'other' please specify:

……..……...……

……..……..……

..……..……..…….

……..……..……

Appendix 3
Eastern Cooperative Oncology Group Performance Status Scale

Grade	Description
0	Fully active; able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework or office work).
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about >50% of waking hours.
3	Capable of only limited self-care; confined to a bed or chair >50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

Appendix 4
Ann Arbor Staging

Grade	Description
Stage I	Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (IE) [a]
Stage II	Involvement of two or more lymph node regions or lymphatic structures on the same side of the diaphragm alone (II) or with involvement of limited, contiguous extralymphatic organ or tissue (IIE)
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III), which may include the spleen (IIIS) or limited, contiguous extralymphatic organ or site (IIIE), or both (IIIES)
Stage IV [b]	Diffuse or disseminated foci of involvement of one or more extralymphatic organs or tissues, with or without associated lymphatic involvement

Note: All cases are subclassified to indicate the absence (A) or presence (B) of the systemic B symptoms of significant unexplained fever (>38ºC), night sweats, or unexplained weight loss exceeding 10% of body weight during the 6 months prior to diagnosis.

[a] The designation “E” generally refers to extranodal contiguous extension (i.e., proximal or contiguous extranodal disease) that can be encompassed within an irradiation field appropriate for nodal disease of the same anatomic extent. A single extralymphatic site as the only site of disease should be classified as IE, rather than Stage IV.

[b] Involvement of bone marrow at screening will always qualify for Ann Arbor Stage IV and should be recorded as extranodal involvement.

Adapted from:

Carbone PP, Kaplan HS, Musshoff K, et al. Report of the committee on Hodgkin’s disease staging classification. Cancer Res 1971;31:1860–1.

Lister TA, Crowther D, Sutcliffe SB, et al. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin’s disease: Cotswolds Meeting. J Clin Oncol 1989;7:1630–6.

Appendix 5
Follicular Lymphoma International Prognostic Index

Table 1 Follicular Lymphoma International Prognostic Index

FLIPI risk factors

- Ann Arbor Stage III or IV
- Age > 60 years
- Serum LDH > 1 x ULN
- Anemia (hemoglobin < 120 g/L)
- Involved nodal areas > 4

FLIPI risk group	Number of FLIPI risk factors
Low	0 or 1
Intermediate	2
High	3 to 5

FDG=fluorodeoxyglucose; FLIPI=Follicular Lymphoma International Prognostic Index; PET=positron emission tomography; ULN=upper limit of normal.

Note: The results of FDG-PET should not be taken into account for calculation of FLIPI since this prognostic score was established without FDG-PET.

Adapted from: Solal-Celigny P, Roy P, Colombat P, et al. Follicular lymphoma international prognostic index. Blood 2004;104:1258–64.

Appendix 5
Follicular Lymphoma International Prognostic Index (cont)

Table 1 Follicular Lymphoma International Prognostic Index 2

FLIPI2 risk factors

- Bone marrow involvement
- Age > 60 years
- β2 microglobulin > 1 x ULN
- Anemia (hemoglobin < 120 g/L)
- Longest diameter of largest involved node > 6 cm

FLIPI2 risk group	Number of FLIPI2 risk factors
Low	0
Intermediate	1 or 2
High	3 to 5

FDG=fluorodeoxyglucose; FLIPI=Follicular Lymphoma International Prognostic Index; PET=positron emission tomography; ULN=upper limit of normal.

Note: The results of FDG-PET should not be taken into account for calculation of FLIPI2 since this prognostic score was established without FDG-PET.

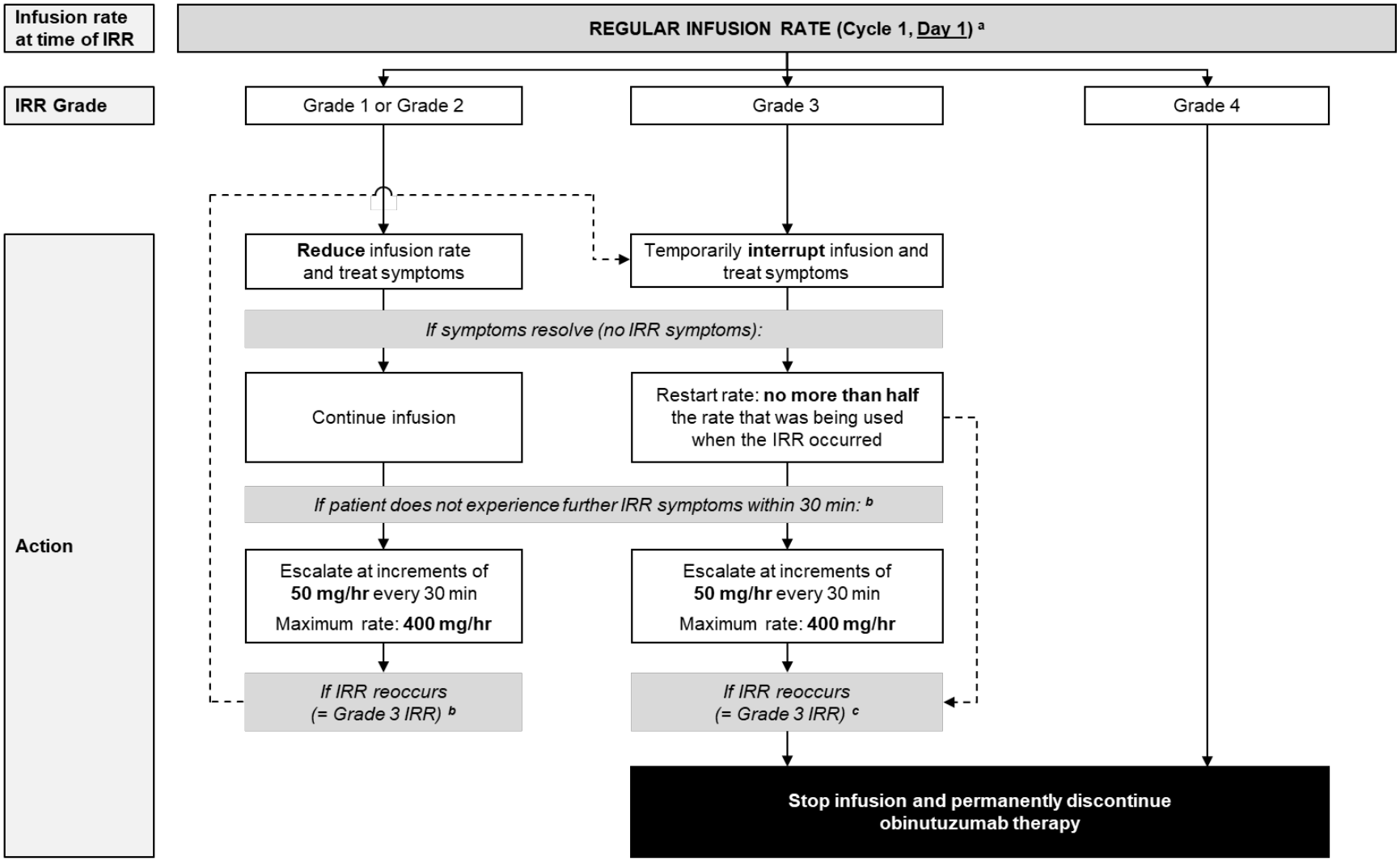
Adapted from: Federico M, Bellei M, Marcheselli L, et al. Follicular Lymphoma International Prognostic Index 2: a new prognostic index for follicular lymphoma developed by the International Follicular Lymphoma Prognostic Factor Project. J Clin Oncol 2009;27:4555–62.

Appendix 6
Management of Infusion-Related Reactions

Management of IRRs may require temporary interruption and/or reduction in the rate of infusion, or treatment discontinuations of obinutuzumab, and is dependent on the infusion rate being used at the time the IRR occurred. Please refer to the flow charts on the following pages.

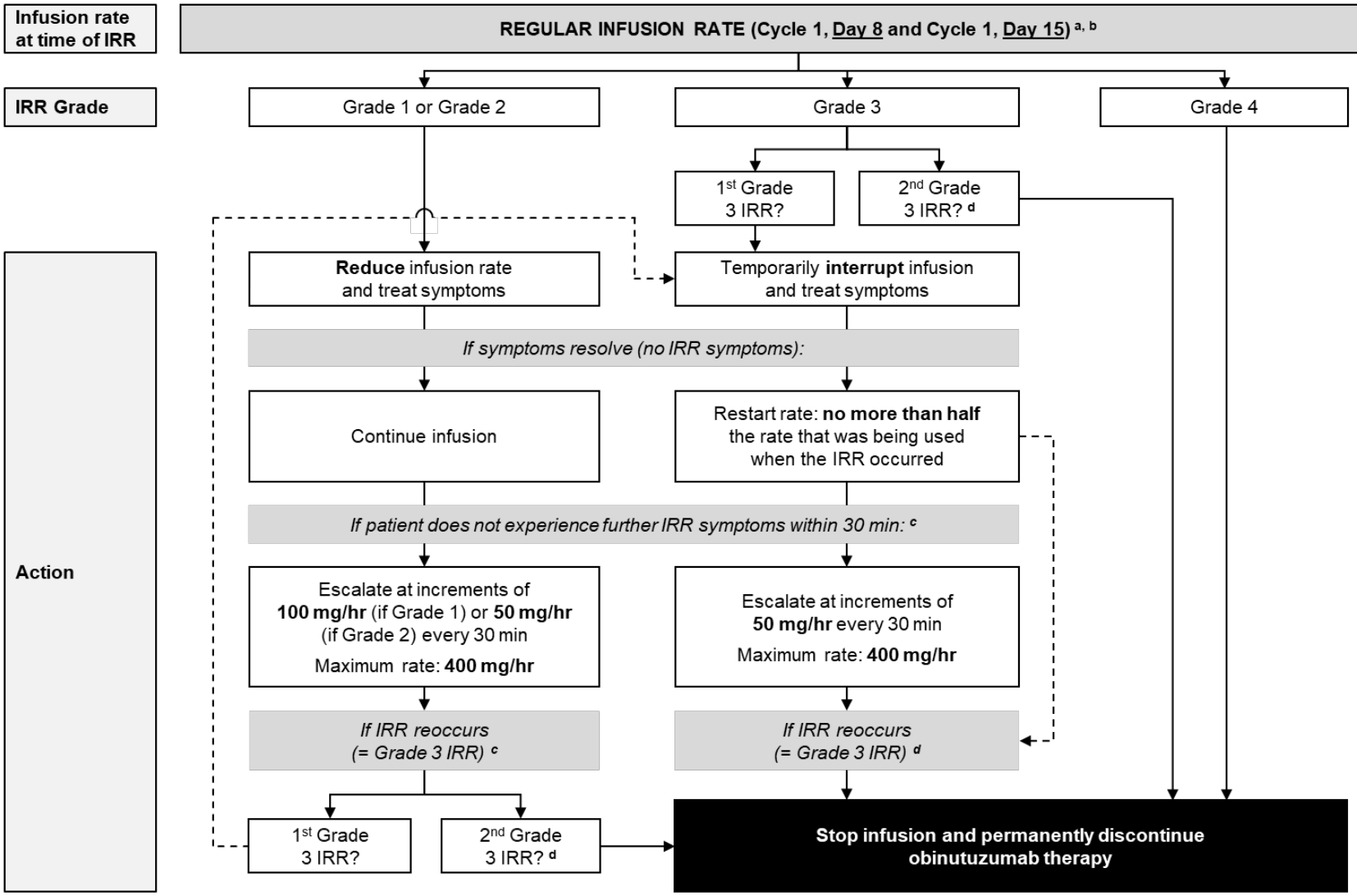
In case of anaphylaxis, study treatment should be permanently discontinued. Anaphylaxis precautions are provided in Appendix 7.

Appendix 6 (a)
Management of Infusion-Related Reactions During Cycle 1, Day 1



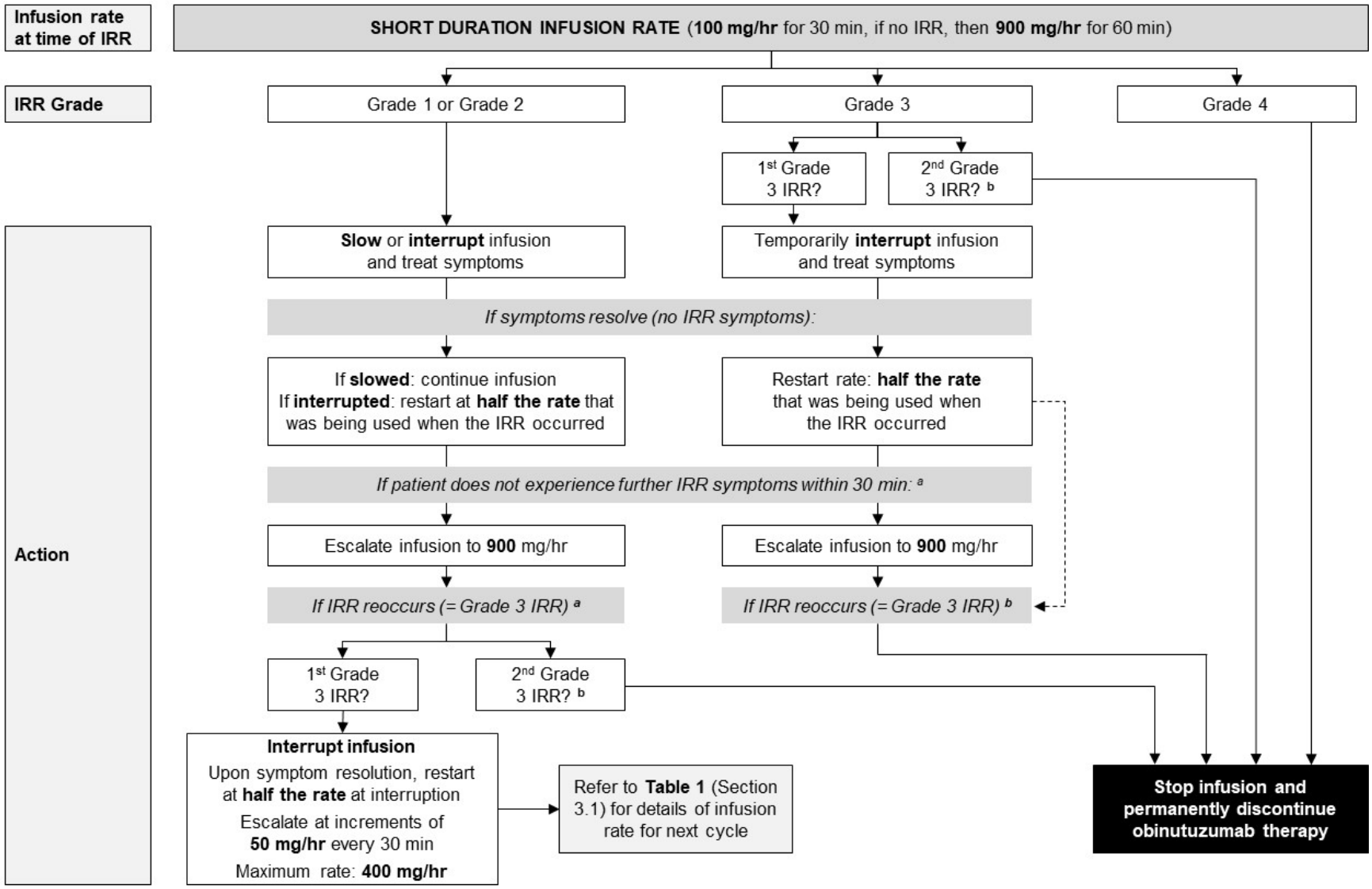
[a] Refer to Table 1 (Section 3.1) for details of regular infusion rates.
[b] An initial IRR of Grade 1 or Grade 2 becomes a Grade 3 IRR if the IRR is prolonged, if symptoms reoccur following initial improvement, or if hospitalization is indicated for clinical sequelae.
[c] This would be the second occurrence of a Grade 3 IRR; therefore, the infusion should be stopped and obinutuzumab permanently discontinued.

Appendix 6 (b)
Management of Infusion-Related Reactions During Cycle 1, Day 8 and Day 15



[a] Refer to Table 1 (Section 3.1) for details of regular infusion rates.
[b] This flowchart also applies to patients who receive obinutuzumab at the regular infusion rate in any other cycle
[c] An initial IRR of Grade 1 or Grade 2 becomes a Grade 3 IRR if the IRR is prolonged, if symptoms reoccur following initial improvement, or if hospitalization is indicated for clinical sequelae.
[d] This would be the second occurrence of a Grade 3 IRR; therefore, the infusion should be stopped and obinutuzumab permanently discontinued.

Appendix 6 (c)
Management of Infusion-Related Reactions During Short Duration Infusions



[a] An initial IRR of Grade 1 or Grade 2 becomes a Grade 3 IRR if the IRR is prolonged, if symptoms reoccur following initial improvement, or if hospitalization is indicated for clinical sequelae.
[b] This would be the second occurrence of a Grade 3 IRR; therefore, the infusion should be stopped and obinutuzumab permanently discontinued.

Appendix 7
Anaphylaxis Precautions

These guidelines are intended as a reference and should not supersede pertinent local or institutional standard operating procedures.

REQUIRED EQUIPMENT AND MEDICATION

The following equipment and medication are needed in the event of a suspected anaphylactic reaction during study treatment infusion:

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for subcutaneous, intramuscular, intravenous, and/or endotracheal administration in accordance with institutional guidelines
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment infusion, the following procedures should be performed:

1. Stop the study treatment infusion.
2. Call for additional medical assistance.
3. Maintain an adequate airway.
4. Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring if possible.
5. Administer antihistamines, epinephrine, or other medications and IV fluids as required by patient status and as directed by the physician in charge.
6. Continue to observe the patient and document observations.