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

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STATISTICAL ANALYSIS PLAN

TITLE:	**A MULTICENTER, OPEN-LABEL, SINGLE ARM STUDY OF GAZYVA SHORT DURATION INFUSION (SDI) IN PATIENTS WITH PREVIOUSLY UNTREATED ADVANCED FOLLICULAR LYMPHOMA**
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STATISTICAL ANALYSIS PLAN APPROVAL

Date and Time(UTC)	Reason for Signing	Name
28-Jul-2020 07:32:56	Company Signatory	[redacted]

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List of abbreviations

Abbreviation	Definition
AE	adverse event
AESI	adverse event of special interest
CHOP	cyclophosphamide, doxorubicin, vincristine, prednisone/prednisolone/methylprednisolone
CI	confidence interval
CR	complete response
CR30	complete response rate at 30 months
CSR	clinical study report
CVP	cyclophosphamide, vincristine, and prednisone/prednisolone/methylprednisolone
EOI	end of induction
EOS	end of study
FDG-PET	18F-fluorodeoxyglucose positron emission tomography
FL	follicular lymphoma
G-chemo	obinutuzumab-based chemotherapy
GI	gastrointestinal
IMC	internal monitoring committee
IRR	infusion-related reaction
MDASI	MD Anderson Symptom Inventory
MedDRA	Medical Dictionary for Regulatory Activities
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	objective response rate
OS	overall survival
PFS	progression-free survival
PR	partial response
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SDI	short duration infusion
SOC	system organ class
TEAE	treatment-emergent adverse event

1. BACKGROUND

This Statistical Analysis Plan (SAP) describes the analyses that are planned to be performed for the Internal Monitoring committee (IMC) and the Clinical Study Reports (CSRs) of Study MO40597.

2. STUDY DESIGN

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 follicular lymphoma (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 cycle's length depends on the chemotherapy chosen for each patient.

Study treatment refers to obinutuzumab plus chemotherapy during the induction phase and obinutuzumab monotherapy during the maintenance phase.

For the purpose of this study infusion-related reactions (IRRs) are defined as all AEs that occur during or within 24 hours from the end of study treatment infusion and are judged by the investigator as related to infusion of study treatment components (obinutuzumab or chemotherapy during induction and obinutuzumab alone during maintenance). In addition, IRRs are also defined as AEs within a pre-defined list of terms that occur during or within 24 hours from the end of study treatment infusion. Refer to Section 4.6.2 for a detailed definition of IRRs.

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.

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 IRRs during cycle 2 at the regular infusion rate, then they will be eligible to receive SDI dosing from cycle 3 onwards, according to investigator's 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 re-occur after restarting the SDI. 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 in the study will permanently discontinue obinutuzumab treatment.

Table 1 Obinutuzumab infusion rates at induction and maintenance

Regular infusion rate		**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	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**	[redacted] 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.

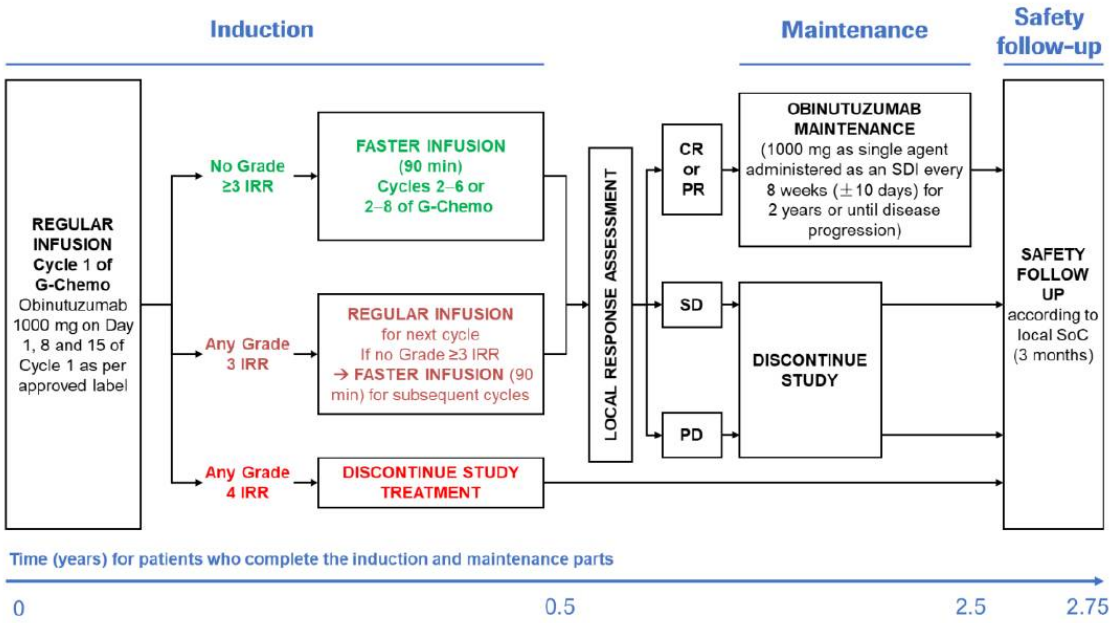
IRR=infusion-related reaction; Max=maximum; SDI=short duration infusion

[a] To deliver the full dose of 1000 mg, the whole contents of the bag should be administered, in approximately 93 minutes.

[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.

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 a maximum of 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.

2.1 PROTOCOL SYNOPSIS

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

2.2 OUTCOME MEASURES

See the Protocol Synopsis in Appendix 1 for a description of the outcome measures.

2.2.1 Primary Safety Endpoint

- The incidence of Grade ≥3 IRRs* during cycle 2, in patients who had previously received obinutuzumab at the standard infusion rate only during cycle 1 without experiencing any Grade 3 or 4 IRR during Cycle 1, 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 or chemotherapy during induction and obinutuzumab alone during maintenance) by the investigator.*

2.2.2 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 start of 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

2.2.3 Secondary Efficacy Endpoints

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

2.2.4 Exploratory Safety Endpoints

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

2.2.5 Exploratory Efficacy Endpoints

The exploratory efficacy objectives for this study are to evaluate patients with a 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
- 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, for those with and those without 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).

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

- 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.

2.3 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 2.

Table 2 Relationship Between the Sample Size, the Number of Observed ≥Grade 3 IRRs and the Upper Bound of the Corresponding Two-sided 95% Clopper-Pearson Confidence Interval

Sample size	Number of observed Grade ≥3 IRRs				
	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%

Observing two Grade ≥3 IRRs during cycle 2 would yield an upper bound (of the Corresponding Two-sided 95% Clopper-Pearson 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 after enrolment, the IMC would decide whether to continue enrolment or not.

2.4 ANALYSIS TIMING

The primary study data will be analyzed and reported based on all patients' data up to the clinical cut-off date, corresponding to the time when all patients have completed 2 cycles of obinutuzumab treatment. The EOI analysis will be performed and reported

based on all patients' data up to the clinical cut-off date, corresponding to the time when all patients have completed the induction treatment period. The final analysis will be performed at the end of the study and include PFS, OS and CR30 rates (Table 3). PFS, OS and CR30 will be analyzed only once, as part of the final analysis at the end of the study (except for the Japanese subgroup on which PFS and OS will be analyzed in the EOI analysis). The exploratory patient-reported endpoint and provider-reported endpoints, as well as the ORR at EOI, will not be part of the primary analysis, and will be included in the EOI and final analyses only. 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.

No formal Interim analysis is planned for this study. An IMC will conduct full formal interim reviews (see Section 3.3).

Table 3 Analysis Timings

Analysis	Timing of Analysis
Primary	all patients have completed 2 cycles of obinutuzumab treatment
EOI	end of induction treatment period (i.e. all patients have completed the induction treatment period)
Final	end of the study

EOI=end of induction

3. STUDY CONDUCT

3.1 RANDOMIZATION

Not applicable

3.2 INDEPENDENT REVIEW FACILITY

Not applicable

3.3 DATA MONITORING

The first scheduled 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, EOI analysis and final analysis. Further meetings will be scheduled as deemed necessary. Further details will be specified in the IMC charter.

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.

4. STATISTICAL METHODS

The analysis specifications described in this SAP supersede the specifications available in the protocol.

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

Categorical data will be summarized using frequencies and percentages. Continuous data will be summarized using descriptive statistics (N, mean, standard deviation, median, minimum and maximum). Other analysis methods will be specified (below) where applicable.

4.1 ANALYSIS POPULATIONS

4.1.1 All Patients Population

The all patients population includes all enrolled patients.

4.1.2 Short Duration Infusion Population

The SDI population includes all enrolled patients who did not experience a Grade 3 or 4 IRR during cycle 1 (i.e. at any of the three Cycle 1 infusions), received obinutuzumab given at the standard rate only during Cycle 1, and received obinutuzumab as an SDI at cycle 2 (refer to Section 4.6.1 for definition of SDI infusion). The SDI population will be used for the analysis of the primary endpoint and the secondary safety endpoint 'Time to IRR (in hours) from infusion to onset of the IRR during cycle 2'.

4.1.3 Safety Population

The safety population includes all patients who received at least one dose of obinutuzumab.

4.2 ANALYSIS OF STUDY CONDUCT

Patient disposition and reason for study termination will be presented on All patients population, as well as on the SDI population and Safety population. Chemotherapy assignment and reasons for discontinuation from the study treatment will also be summarized, for the Safety population.

Major protocol deviations, including violations of inclusion/exclusion criteria and deviations during study conduct will be summarized for All patients population.

Major protocol deviations related to COVID-19 will be summarized and listed on the Safety population.

4.3 ANALYSIS OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic characteristics, such as age, sex, race/ethnicity, and other relevant baseline characteristics will be presented for the SDI population and for the Safety population, using appropriate descriptive statistics.

The other analyses described here below will be based on the safety population only.

The relevant advanced FL characteristics will be presented using appropriate descriptive statistics.

The summaries of baseline and demographic characteristics and of FL characteristics will be repeated on the subset of patients with at least one Grade ≥3 IRR at any cycle.

The baseline value will be defined as the last available value recorded on or prior to the first administration of any study medication.

Prior cancer therapy, radiotherapy and surgery, for any cancer other than FL, as well as follow-up anti-lymphoma therapy, will be summarized.

Previous and concurrent medical history, as well as medications, will also be summarized. Medications will be mapped to the WHODrug Global B3 Format dictionary.

4.4 EFFICACY ANALYSIS

Unless otherwise stated, all efficacy analyses are based on the safety population.

4.4.1 Secondary Efficacy Endpoints

4.4.1.1 Objective Response Rate at the EOI

ORR at the end of induction therapy is defined as the proportion of patients with either a CR, CR unconfirmed or PR at the EOI visit, 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).

Patients without response assessment at the EOI visit will be considered as non-responders.

The ORR will be presented along with a 95% Clopper-Pearson CI; overall and by type of response assessment (i.e. guidelines used). In addition, the ORR will also be presented separately for patients with FDG-PET used for the response assessment and for patient without FDG-PET.

At each planned visit, the results of the response assessment will be summarized descriptively.

4.4.1.2 Progression-Free Survival

PFS is defined as the time from start of treatment (date of first intake of any study treatment component) to the first occurrence of disease progression as assessed by the investigator according to the guidelines used at the site (Lugano [Cheson et al. 2014], Cheson et al. 2007, or Cheson et al. 1999), or death from any cause.

Data for patients who have not experienced disease progression or death at the time of analysis data cut-off will be censored at the last tumor assessment date.

The PFS rate at 12, 24 and 30 months will be presented as the Kaplan-Meier estimate along with its 95% CI, overall and by type of response assessment (i.e. guidelines used). In addition, the Kaplan-Meier curve will be provided for the PFS overall.

4.4.1.3 Overall Survival

OS is defined as the time from start of treatment (date of first intake of any study treatment component) to death from any cause. For patients who are alive at the time of analysis data cut-off, OS time will be censored at the date the patient was last known to be alive.

The OS rate at 12, 24 and 30 months will be presented as the Kaplan-Meier estimate along with its 95% CI and the Kaplan-Meier curve will be provided.

4.4.1.4 Complete Response (CR) Rate at 30 months (CR30)

The CR30 rate is defined as the proportion of patients with a CR at 30 months from study treatment initiation (date of first intake of any study treatment component), as determined by the investigator according to the guidelines used at the site (Lugano [Cheson et al. 2014], Cheson et al. 2007, or Cheson et al. 1999).

Month 30 occurs at Study Day 913. Allowing 3 months either side of the exact Month 30 study day, assessments that occur between Month 27 (Study Day 811) and Month 33 (Study Day 991) inclusive will be considered as a Month 30 assessment.

Patients with a CR at 30 months from study treatment initiation are patients:

- With a CR assessed within the window of Month 27 (Study Day 811) – Month 33 (Study Day 991) inclusive.
- Or With two consecutive assessments of CR, before and after the 30-month timepoint (Study Day 913)

CR30 rate will be presented together with a 95% Clopper-Pearson CI, overall and by type of response assessment (i.e. guidelines used).

4.4.2 Exploratory Efficacy Endpoints

4.4.2.1 Proportion of Patients with a PR at EOI Who Convert to CR During Maintenance

The proportion of patients with a PR at the EOI visit and with a CR during the maintenance period, as assessed by the investigator according to the guidelines used at the site (Lugano [Cheson et al. 2014], Cheson et al. 2007, or Cheson et al. 1999) will be provided, overall and by type of response assessment (i.e. guidelines used). The number of patients with a PR at the EOI visit will be used for the denominator.

4.4.2.2 ORR and CR Rate After the EOI by FDG-PET Status

The ORR and the CR rates are defined as the proportion of patients with best response either a CR or PR and with a CR, respectively, as determined by the investigator according to the guidelines used at the site (Lugano [Cheson et al. 2014], Cheson et al. 2007, or Cheson et al. 1999), at any time after the EOI visit.

The ORR and the CR rate will be summarized separately for patients with FDG-PET used for the response assessment and for patient without FDG-PET. This summary will be provided overall and type of response assessment (i.e. guidelines used).

4.4.2.3 MD Anderson Symptom Inventory (MDASI)

Patient-reported data on the severity of disease and treatment-related symptoms, and the interference from those symptoms, is assessed by MDASI. The MDASI includes 13 items for the severity of symptoms (pain, fatigue, nausea, disturbed sleep, distressed, shortness of breath, remembering things, lack of appetite, drowsy, dry mouth, sad, vomiting, and numbness or tingling) and an additional 6 items for the interference of the symptoms with 6 areas of function (general activity, walking, work, mood, relations with other people, and enjoyment of life).

The MDASI severity and interference subscales (see Appendix 3 [Cleeland 2009]), as well as each of the 19 items, will be summarized at each visit, together with the change from baseline at each visit. The severity and interference subscales will also be plotted over time.

The number and percentage of patients who complete the MDASI will be summarized at each scheduled time point. The compliance rate will be provided. The compliance rate is based on the total number of patients expected to complete the questionnaire at a particular time point – i.e., those patients who had the opportunity to complete the scale.

4.4.2.4 Site Experience

Provider-reported data will be summarized in a frequency table:

- Time Savings
- Convenience
- Preference

- Main reason for preference.

4.4.3 Subgroup Analysis

A subgroup analysis will be performed and the subgroups to be considered include (but may not be limited to):

- sex (female, male)

The analyses of the following endpoints will be repeated by subgroup:

- Secondary efficacy endpoints
  - ORR at EOI (see Section 4.4.1.1)
  - PFS (see Section 4.4.1.2)
  - OS (see Section 4.4.1.3)
  - CR30 (see Section 4.4.1.4)
- Safety endpoints
  - 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 (see Section 4.6.2.1)
  - All IRRs of any grade (see Section 4.6.2.2)
  - All AEs (see Section 4.6.3)
  - All SAEs (see Section 4.6.3)

In addition, some of the safety and efficacy analyses will be repeated on the subgroup of Japanese patients (EOI analysis only).

4.5 PHARMACOKINETIC AND PHARMACODYNAMIC ANALYSES

Not applicable.

4.6 SAFETY ANALYSES

Unless otherwise stated, safety analyses are based on the safety population.

4.6.1 Exposure of Study Medication

Secondary Safety Endpoint:

The duration of obinutuzumab administration (in minutes) by cycle (all cycles including maintenance) is defined as the difference between the end time and the start time of obinutuzumab administration and will be summarized descriptively.

The following summaries on obinutuzumab exposure will also be provided:

- Proportion of patients with SDI infusion, defined as an infusion with a duration ≤110 minutes (i.e. target of 90 minutes with a tolerance of plus 20 minutes), by cycle

- Overall duration of obinutuzumab treatment (in weeks)
- Number of initiated cycles of obinutuzumab
- Dose of obinutuzumab (in mg) administered, by cycle
- Cumulative dose of obinutuzumab (in mg) overall, during induction period and during maintenance period
- Proportion of patients with low dose intensity of obinutuzumab, by cycle up to Cycle 2, in the rest of induction period and in the maintenance period

For summaries by cycle, the cycle 1 will be described by day of the cycle (day 1, day 8, or day 15).

The infusion modifications and infusions delayed will also be summarized for obinituzumab.

For chemotherapy exposure, the number of initiated cycles of bendamustine, CHOP, and CVP will be provided.

The number of patients receiving premedication and the type of premedication will be summarized by visit.

4.6.2 Infusion Related Reactions

IRRs are defined as:

Definition A: IRRs

IRRs are defined as all AEs that:

- occur during or within 24 hours from the end of infusion of any study treatment component,
- are judged as related to any study treatment component (i.e. the corresponding AE) by the investigator.

Definition B: IRRs related to Obinutuzumab

Some of the analyses will be restricted to IRRs related to obinituzumab only, defined as all AE's that:

- occur during or within 24 hours from the end of infusion of obinutuzumab,
- are judged as related to obinutuzumab by the investigator.

Definition C: IRRs based on pre-defined list of terms related to Obinutuzumab

IRRs are defined as all AEs with PT within a pre-defined list of terms (see Appendix 4) that:

- occur during or within 24 hours from the end of infusion of obinutuzumab,
- are judged as related to obinutuzumab by the investigator.

"Any study component" refers to obinutuzumab and chemotherapy during induction period and obinutuzumab alone during maintenance period.

By default, analysis of IRRs will be based on Definition A of IRRs.

IRRs will be linked to the cycle corresponding to the last infusion received on or prior to the onset of the IRR.

In a general manner, in analyses performed by cycle, the cycle 1 will be summarized by day of the cycle: day 1, day 2 (if applicable), day 8 or day 15. Day 2 is applicable only to analyses of all IRRs and not to analyses of IRRs related to obinutuzumab.

4.6.2.1 Primary Safety Endpoint

The proportion and number of patients with Grade ≥3 IRRs during cycle 2, in patients who had previously received obinutuzumab at the standard infusion rate during cycle 1 without experiencing any Grade 3 or 4 IRR during cycle 1, with severity determined according to NCI CTCAE Version 5.0 will be displayed. The proportion will be presented along with a 95% Clopper-Pearson CI. The analysis of the primary safety endpoint is based on the SDI population.

All IRRs during cycle 2 will also be summarized on the SDI population at the EOI analysis.

4.6.2.2 Secondary Safety Endpoints

The proportion and number of patients with IRRs of any grade will be provided by cycle and by highest NCI CTCAE grade. This analysis will be repeated on the subset of patients who received obinutuzumab as SDI in the given cycle.

Time to IRR (in hours) during cycle 2 is defined as the time from the start of infusion (i.e. start date/ time of infusion of the first component of study treatment) in Cycle 2 to the onset of the IRR during cycle 2 and will be summarized descriptively. The analysis of time to IRR during cycle 2 will be based on the SDI population.

For each cycle from the cycle 2, the type and duration (in minutes) of symptoms of Grade ≥3 IRRs, in patients who received obinutuzumab as SDI in the given cycle, will be summarized overall and by cycle. This summary will be repeated for all symptoms of IRRs of any grade from the cycle 2, as well as for all symptoms of IRRs of any grade in

cycle 1. In addition, the symptoms of Grade ≥3 IRRs will be listed together with the details on the planned and actual infusion rate of obinutuzumab at the corresponding cycle.

4.6.2.3 Exploratory Safety Endpoints

The proportion and number of patients with Grade ≥3 IRRs during:

- Cycle 2, in patients who had received obinutuzumab at the standard infusion rate without experiencing a Grade 3 or 4 IRR in cycle 1,

  Or

- Cycle 3, in patients who had received obinutuzumab at the standard infusion rate and experienced a Grade 3 or 4 IRR in cycle 1 and subsequently had received obinutuzumab at the standard infusion rate without experiencing a Grade 3 or 4 IRR in cycle 2, with severity determined according to NCI CTCAE Version 5.0, will be provided.

Time to IRR (in hours) from start of infusion (i.e. start date/time of infusion of the first component of study treatment) to onset of the IRR in cycle 1 or cycle 3 will be summarized descriptively overall and by cycle. The time to IRR will be summarized separately for patients with SDI and with regular infusion.

The proportion and number of patients with IRRs of any grade and by highest NCI CTCAE grade will be provided for the first cycle received as SDI, by the highest NCI CTCAE grade of IRR in any previous cycle.

4.6.2.4 Sensitivity Analysis

The analysis of 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, as described in Section 4.6.2.1, will be repeated based on IRRs related to obinutuzumab only (Definition B) for the SDI population.

The summary with the proportion and number of patients with IRRs of any grade by cycle and by highest NCI CTCAE grade will be repeated based on:

- IRRs related to obinutuzumab only (Definition B);
- IRRs based on pre-defined list of terms related to Obinutuzumab (Definition C).

4.6.3 Adverse Events

Verbatim description of AEs will be mapped to Medical Dictionary for Regulatory Activities (MedDRA) thesaurus levels and graded according to the NCI CTCAE Version 5.0.

AEs will be summarized by MedDRA term, appropriate MedDRA levels (system organ class [SOC] and PT), and when specified by NCI CTCAE grade. For each patient, multiple occurrences of the same event will be counted once at the maximum severity.

AEs will be reported by study period (induction, maintenance, follow-up) as well as overall. The summary of all AEs by highest NCI CTCAE grade will display AEs during cycle 1 and from cycle 2 onwards separately.

Treatment-emergent AEs (TEAEs) are AEs that occur during or after the first dose of study treatment and on or before the last dose of study treatment +90 days. TEAEs will be included in the summary tables. All AEs will be listed.

The following AEs will be summarized:

- All AEs
- All AEs by highest NCI CTCAE grade
- SAEs
- SAEs by highest NCI CTCAE grade
- NCI CTCAE Grade ≥3 AEs
- NCI CTCAE Grade ≥3 AEs by highest NCI CTCAE grade
- Adverse events of special interest (AESIs)
- Selected AEs:
- AEs related to i) obinutuzumab, ii) any study treatment
- NCI CTCAE Grade ≥3 AEs related to any study treatment (EOI analysis only)
- AEs leading to interruption of i) obinutuzimab, ii) any study treatment
- AEs leading to infusion rate reduction of obinutuzimab
- AEs leading to dose modification of chemotherapy
- AEs leading to discontinuation of i) obinutuzumab, ii) any study treatment, iii) each chemotherapy component separately
- AEs leading to discontinuation from the study
- Fatal AEs
- AEs occurring during infusion or within 24 hours from end of infusion of any study treatment, during the induction period (EOI analysis only)
- NCI CTCAE Grade ≥3 AEs occurring during infusion or within 24 hours from end of infusion of any study treatment, during the induction period (EOI analysis only)
- AEs reported in ≥5% of patients by highest NCI CTCAE grade

All deaths and causes of death will be summarized.

AEs associated with COVID-19 and AEs associated with COVID-19 leading to discontinuation from the study will be listed.

4.6.4 Laboratory Data

Laboratory data will be summarized over time including change from baseline. Values outside the normal ranges will be summarized.

Additionally, laboratory data will be classified in accordance with NCI CTCAE v5.0. Highest NCI CTCAE grade post-baseline will be reported, and shift tables from baseline to worst value during the study post-baseline will be presented.

4.6.5 Vital Signs

Changes in selected vital signs will be summarized by cohort and by change over time including change from baseline.

4.7 MISSING DATA

Please refer to Section 4.4 for methods of handling missing data for the efficacy endpoints.

Any incomplete or missing death date will be handled separately for safety and efficacy analyses. In safety analyses, all deaths will be included, regardless of completeness of death date; patients who died with a partial or missing death date will be included as an event. In efficacy analyses, a death is considered an event only if a complete death date is available; patients who died with only a partial or missing death date will be censored.

4.8 INTERIM ANALYSES

No formal Interim analysis is planned for this study.

The IMC will review safety data as described in the IMC charter. The IMC reviews will be performed after the first 10 patients had their second cycle (first SDI infusion), after 50 patients had their second cycle or at 6 months from first patient enrolled, whichever occurs first. Furthermore, the IMC will review results obtained for the primary analysis and end of induction analysis. Further meetings will be scheduled as deemed necessary. IMC analyses will be based on all enrolled patients' data up to fixed clinical cut-off defined based on each IMC milestone.

The outputs provided for IMC review will be a subset of the outputs planned for the CSR.

5. REFERENCES

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Appendix 1
Protocol Synopsis

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:	4
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		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***	[redacted] ***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 approximately 93 minutes.

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:
   - Bulky disease, defined as a nodal or extranodal (except spleen) mass ≥ 7 cm in the greatest diameter
   - Local symptoms or compromise of normal organ function due to progressive nodal disease or extranodal tumor mass
   - 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)
   - Presence of symptomatic extranodal disease (e.g., pleural effusions, peritoneal ascites)
   - 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)
   - Involvement of ≥ 3 nodal sites, each with a diameter of ≥ 3 cm
   - 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
   - Absolute neutrophil count ≥ 1.5×10^9/L
   - 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

    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

    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

    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

    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

    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

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

    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

    Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 × ULN

    Total bilirubin ≥ 1.5 × the ULN: Patients with documented Gilbert disease may be enrolled if total bilirubin is ≤ 3.0 × the ULN.

    International normalized ratio (INR) > 1.5 in the absence of therapeutic anticoagulation

    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 l*ost to follow-up

  OR
- *Patient d*eath.

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.

Appendix 2
Schedule of Assessments

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.

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

[c] Obinutuzumab administered according to the regular infusion rate.

[d] Obinutuzumab administered according a 90-minute short duration infusion 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).

[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. 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 3
MDASI: Details on Scoring

Scoring the MDASI as an Outcome Measure (Cleeland 2009):

The MDASI assesses the severity of symptoms at their worst in the last 24 hours on a 0–10 numerical rating scale, with 0 being “not present” and 10 being “as bad as you can imagine.”

In addition, the MDASI measures how much the symptoms have interfered with six daily activities: general activity, mood, work, relations with others, walking, and enjoyment of life. Interference is rated on a 0–10 numerical rating scale, 0 being “did not interfere” and 10 being “interfered completely.”

The ratings in the MDASI can be averaged into several subscale scores, including mean core symptom severity (13 core symptom items) and mean interference (6 interference items only). Symptom items and interference items may be presented individually.

For each subscale, the score is defined as the arithmetic mean of items in the subscale.

When calculating any subscale score, more than 50% of the subscale’s items must have been responded to (i.e., 7 of the 13 core symptom severity items or 4 of the 6 interference items), on a given administration. If the patient responded to fewer than half of the subscale’s items, consider the subscale “missing”.

Appendix 4
Infusion Related Reactions: List of Predefined Preferred Terms

- Infusion related reaction
- All PTs containing “anaphylactoid,” “anaphylactic” or “anaphylaxis” (e.g., anaphylactic shock, anaphylactic reaction, anaphylactoid reaction)
- All PTs containing “hypersensitivity”
- All PTs containing “tachycardia”, “arrhythmia”, or “ventricular”, alone or in part (e.g., tachyarrhythmia) Gleich’s syndrome
- All PTs containing the term “allergic,” or “urticaria”
- All PTs containing “angioedema,” “edema,” or “dyspnea,”
- All PTs containing “pruritus” or “pruritic”
- Cytokine release syndrome
- Circulatory collapse
- Peripheral circulatory failure
- Swelling face
- Eye swelling
- Circumoral swelling
- Mouth swelling
- Palatal swelling
- Swollen tongue
- Lip swelling
- Oropharyngeal swelling
- Pharyngeal swelling
- Gingival swelling
- Limbal swelling
- Oculorespiratory syndrome
- Oxygen saturation decreased
- Hypoxia
- Conjunctival hyperemia
- Hypotension
- Wheezing
- Flushing
- Throat tightness
- Chest discomfort, chest pain, chest crushing, noncardiac chest pain, palpitations
- All PTs containing “shock”, with the exception of septic shock
- Pyrexia
- Pulmonary congestion
- Respiratory distress
- Stridor
- Reversible airways obstruction
- Upper airway obstruction
- Obstructive airway disorder
- Upper airway cough syndrome

- Chills
- Kounis syndrome
- Bronchospasm
- Laryngospasm
- Rhonchi
- Back pain