NOVARTIS

Division: Oncology Global Development
Information Type: Statistical Analysis Plan

Title:	A Randomized, Open Label Study of Ofatumumab and Bendamustine Combination Therapy Compared with Bendamustine Monotherapy in Indolent B-cell Non-Hodgkin's Lymphoma Unresponsive to Rituximab or a Rituximab-Containing Regimen During or Within Six Months of Treatment
Compound Number:	OMB157/GSK1841157
Version	Amendment 1.0
Effective Date:	23-Apr-2018

Description: This document provides a detailed statistical analysis plan for study OMB157E2301, a randomized, open label study of Ofatumumab and Bendamustine Combination Therapy compared with Bendamustine Monotherapy in Indolent B-cell Non-Hodgkin's Lymphoma unresponsive to Rituximab or a Rituximab-Containing regimen during or within six months of treatment.

Subject: Statistical Analysis Plan for Indolent Non-Hodgkin's Lymphoma study OMB157E2301

Author's Name, Title and Functional Area:

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Date	Version number	Summary of changes
5-Jul-2017	1.0	First final version
23-Apr-2018	Amendment 1.0	Section 2.3: Derivation rule details are added for FLIPI-1 and FLIPI-2 scores
		Section 8.3: Text for subgroup analysis is updated to be more consistent with data collection
		Section 9.2.7: Text is added to clarify the definition of baseline for the optional ofatumumab period for subjects taking optional ofatumumab in Arm B.
		Section 11.1: Text is modified to make the Cox model for sensitivity analysis more consistent with the Cox model in the primary analysis. Text for subgroup analysis is updated to be more consistent with data collection
		Section 11.2.11: Text for B-cell monitoring was updated to be more consistent with data collection
		Section 11.2.12: Text for subgroup analysis is updated to be more consistent with data collection
		Section 13.1: Text is added to clarify what scores will be analyzed for PRO

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ABBREVIATIONS

ADaM	Analysis Data Model
AE	Adverse Event
ALC	Absolute Lymphocyte Count
ALT	alanine transaminase
ALP	alkaline phosphatase
AST	aspartate transaminase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
BUN	blood urea nitrogen
CBC	Complete Blood Count
CDISC	Clinical Data Interchange Standards Consortium
Cmax	Maximum observed plasma concentration
CR	Complete Remission
DNA	Deoxyribonucleic Acid
eCRF	Electronic Case Report Form
ECOG	Eastern Cooperative Oncology Group
EOI	End of Infusion
EQ-5D	EuroQoL Five Dimension
FACT-Lym	Functional Assessment of Cancer Therapy – Lymphoma
FA	Futility Analysis
FISH	Fluorescent in-situ Hybridization
FL	Follicular Lymphoma
GSK	GlaxoSmithKline
HACA	Human Anti-chimeric Antibodies
HAHA	Human Anti-Human Antibodies
HARP	Harmonization (Analysis and Reporting) Programmed
HCQ	Health Change Questionnaire
HRQL	Health Related Quality of Life
IA	Interim Analysis
IDMC	Independent Data Monitoring Committee
IDSL	Independent Data Standards Library
INHL	Indolent Non-Hodgkin's Lymphoma
IRC	Independent Review Committee
IR	Independent Review(er)
IRR	Independent Radiological Review
LLN	Lower Level of Normal
NHL	Non-Hodgkin's Lymphoma
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
[redacted]	[redacted]
PFS	Progression-Free Survival

PK	Pharmacokinetic(s)
PML	Progressive multifocal leukoencephalopathy
POP	Data set with indicators for different study populations
PR	Partial Remission
PRO	Patient Reported Outcome
RAMOS	Registration and Medication Ordering System
RAP	Report and Analysis Plan
RRCML	Revised Response Criteria for Malignant Lymophoma
SAE	Serious Adverse Event
SD	Stable Disease; Standard Deviation
SDTM	Study Data Tabulation Model
SMT	Safety Monitoring Team
SPM	Study Procedures Manual
SRT	Safety Review Team
t½	Terminal phase half-life
tmax	Time of maximum observed plasma concentration
TLS	Tumor Lysis Syndrome
TTP	Time To Progression
ULN	Upper Level of Normal
Vss	Volume of distribution at steady state

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1. INTRODUCTION

This statistical analysis plan (SAP) details planned analyses for a Clinical Study Report (primary analysis) to support a possible regulatory submission of study OMB157E2301. This is a phase III, randomized, open label, multi-center trial to evaluate the efficacy and safety of ofatumumab in combination with bendamustine versus bendamustine monotherapy in subjects with indolent Non-Hodgkin's Lymphoma (iNHL) that is unresponsive to rituximab or a rituximab-containing regimen during or within six months of treatment.

Initially, this study was planned with an adaptive-like design - to allow a potential change to the dosing regimen of Bendamustine in combination with Ofatumumab based on tolerability of the combination. Upon the first planned review of the data, the IDMC recommended no change was required to the dosing of Bendamustine. Therefore, the study continued with the original dosing regimen and an adaptive approach was no longer necessary for this study.

The IDMC review of an Interim Analysis for efficacy and futility occurred (22Feb2016) after 180 PFS events by IRC were reached (31Oct2015). The IDMC recommended to continue the study without any changes. The interim analysis of PFS was performed by an independent Statistical Data Analysis Centre. As per the IDMC charter, unblinded results were not communicated to the sponsor in order to maintain the integrity of the trial. The protocol defined randomization of 346 patients was achieved as of 16May2016. For further information on the study design, see Protocol Amendment 09, dated 13-Apr-2017.

The content of this SAP is based on protocol OMB157E2301 Amendment 09. All decisions regarding final primary endpoint analysis, as defined in this SAP document, have been made prior to SDTM Database Freeze of the study data. The planned analyses are specified in Section 4.

Analyses of the [redacted] biomarker components of the study will be provided in separate documents as appropriate.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Statistical Hypotheses

The primary endpoint is progression-free survival (PFS) as assessed by the IRC. The primary efficacy analysis will be the comparison of the distribution of PFS between the two treatment groups. Assuming proportional hazards for PFS, the following statistical hypothesis will be tested to address the primary efficacy objective:

$$H_{01}: \theta_1 = 1 \quad \text{vs.} \quad H_{A1}: \theta_1 \neq 1$$

where θ_1 is the PFS hazard ratio (ofatumumab + bendamustine arm vs bendamustine arm).

2.2. Study Objectives

Primary Objective:

- To establish effectiveness of ofatumumab in combination with bendamustine in subjects with indolent B-cell NHL disease refractory to rituximab-containing therapy

Secondary Objectives:

- To establish effectiveness of ofatumumab in combination with bendamustine in subjects with follicular lymphoma (FL) refractory to rituximab-containing therapy
- To evaluate and compare ORR, OS, time to and duration of response, and time to progression (TTP) in subjects treated with ofatumumab and bendamustine combination therapy to those treated with bendamustine alone
- To evaluate and compare ORR, OS, time to and duration of response, and time to progression (TTP) in subjects with follicular lymphoma treated with ofatumumab and bendamustine combination therapy to those treated with bendamustine alone
- To evaluate and compare the safety and tolerability in subjects treated with ofatumumab and bendamustine combination therapy to those treated with bendamustine alone
- To evaluate and compare the two treatment arms with respect to changes in subjects' health-related quality of life
- To evaluate and compare the two treatment arms with respect to changes in subjects' health-related quality of life in patients with follicular lymphoma
- To evaluate and compare known and exploratory prognostic markers and their correlation with clinical responses in subjects treated with ofatumumab and bendamustine compared to those treated with bendamustine monotherapy (i.e. absolute lymphocyte count (ALC), FcR gamma 3A genetic variants, human anti-chimeric antibody [HACA])
- To evaluate the ORR to ofatumumab monotherapy in subjects who progress during or following single-agent bendamustine
- To evaluate ofatumumab pharmacokinetics (PK) when given as monotherapy to subjects who progress during or following single-agent bendamustine

[redacted]

[redacted]

2.3. Study Endpoints

Primary Endpoint:

- Progression-free survival (PFS) as assessed by the IRC, defined as the time interval between randomization until disease progression or death (due to any cause). Investigator-assessed PFS will be supportive.

Secondary Endpoints:

Clinical

- Overall response rate (ORR) in all patients and patients with follicular lymphoma - for both IRC and Investigator assessments
- Overall survival (OS) in all patients and patients with follicular lymphoma
- Time to response and duration of response – for both IRC and Investigator assessments in all patients and patients with follicular lymphoma
- Time to progression in all patients and patients with follicular lymphoma - for both IRC and Investigator assessments
- Time to next therapy (defined as time to next therapy or death) in all patients and patients with follicular lymphoma
- Changes in health-related quality of life (HRQL) measures in all patients and patients with follicular lymphoma
- Reduction in tumor size
- Improvement in Eastern Cooperative Oncology Group (ECOG) Performance status
- Incidence and severity of AEs, serious adverse events (SAEs) and other safety parameters including frequency of transfusions, development of Human Anti-Human Antibodies (HAHA), incidence of grade ≥3 infections, and myelosuppression (anemia, neutropenia, and thrombocytopenia)
- Overall response rate (ORR) to optional ofatumumab monotherapy in subjects who progress during or following single-agent bendamustine
- Changes in clinical laboratory values
- Quantitative assessments of immunoglobulins G, A and M (IgG, IgA, IgM)
- Plasma ofatumumab concentrations
- B-cell monitoring ($CD19^+$, $CD20^+$)

Known and Exploratory Prognostic Markers Correlating with Response to ofatumumab:

- Baseline Follicular Lymphoma International Prognostic Index (FLIPI score)
- Baseline Absolute Lymphocyte Count (ALC)
- Genetic variation in FcR gamma 3A

  Human Anti-Chimeric Antibodies (HACA)

Table for the Five Parameters Retained for Building the FLIPI-1

Parameter	Adverse Factor	Source
Age	≥60 years	Screening value
Ann Arbor Stage	III-IV	Screening value
Hemoglobin Level	< 120 g/L	Baseline value (likely to be from Cycle 1 Day 1)
Serum LDH Level	> ULN	Baseline value (likely to be from Cycle 1 Day 1)
Number of Nodal Sites	> 4	From screening assessment by investigator

Abbreviations: LDH: lactate dehydrogenase;
ULN: upper limit of normal

Table for the Five Parameters Retained for Building the FLIPI-2

Parameter	Adverse Factor	Source
Beta-2-microglobulin	> ULN	Baseline value (likely to be from Cycle 1 Day 1)
LoDLIN	>6cm	From screening assessment by investigator
Bone marrow involvement presence	yes	From screening assessment from central lab
Hemoglobin	<120 g/L	Baseline value (likely to be from Cycle 1 Day 1)
Age	>60	Screening value

	years	

Abbreviations: LLoDLIN= longest diameter of the largest involved node; ULN: upper limit of normal

[redacted]

3. STUDY DESIGN

This randomized, open label, two-arm, Phase III study consists of two treatment groups: ofatumumab and bendamustine combination therapy (Arm A) or bendamustine monotherapy (Arm B). Subjects in Arm B may be offered optional Ofatumumab monotherapy after progressive disease (PD) has been reported.

Randomization and Stratification

Subjects were randomized to receive treatment arm A or B in a 1:1 ratio for the duration of treatment period.

Assignment of study drug was stratified according to two stratification factors (i) type of last prior rituximab therapy: rituximab plus chemotherapy or rituximab alone (either in maintenance or monotherapy) and (ii) prior exposure to bendamustine: exposed or not exposed.

Centralized randomization numbers within each stratum were created for treatment assignment to ensure balance, with respect to the number of subjects assigned to each treatment group within each stratum, using the GSK RandALL randomization system. The investigator accessed the GSK Randomization and Medication Ordering System (RAMOS) (or the Clinphone system after study transfer to Novartis) by telephone to receive the subject's randomization number and initial study medication container number. (The transfer to the ClinPhone system occurred on 13May16. Previously, 245 of the 246 patients were randomized with the RAMOS system. Only one subject was randomized after transfer to the ClinPhone system.)

3.1. Treatment Phase

Subjects randomized to treatment arm A received ofatumumab in combination with bendamustine and subjects randomized to arm B received bendamustine.

Treatment Arm A:

Up to 8 cycles of bendamustine (90 mg/m^2 Days 1 and 2, every 21 days) given in combination with 12 doses of ofatumumab (1000 mg). Ofatumumab will be given on Day 1 of each cycle of bendamustine as long as subjects in Arm A receive bendamustine. Once subjects in Arm A complete bendamustine therapy, the remaining doses of ofatumumab will be given monthly (q28 days) until all 12 doses are completed.

OR

Treatment Arm B:

Bendamustine (120 mg/m^2 Days 1 and 2, every 21 days, up to 8 cycles).

Subjects in Arm A and Arm B who cannot complete 8 cycles of therapy with bendamustine must still have all planned Day 1 assessments (Visits 1-20) done including scheduled CT scans and assessments that occur on Days 84, 168, and 252.

At the discretion of the investigator, ofatumumab will be offered to those with progressive disease (PD) in Arm B. If these subjects select ofatumumab, therapy must begin ≤120 days following PD. PD must be verified by CT scan. This CT scan must be confirmed by an independent radiologist before ofatumumab therapy begins. Subjects will receive ofatumumab (1000 mg for the first infusion on Week 1 followed by 2000 mg, one infusion every week for a total of 3 infusions (Weeks 2-4) followed by 2000 mg, one infusion every month for 8 infusions, total: 12 doses).

3.2. Follow-up Phase

Following study treatment, subjects who have CR, PR or SD will receive regular follow-up for 5 years – every 3 months to 18 months then every 12 months.

Subjects demonstrating disease progression will be followed for survival status until study completion.

PRO measures (FACT-Lym, EQ-5D, HCQ) will be administered for completion by the subjects at all follow-up visits.

3.3. Post PD follow-up

Follow-up assessment for subjects experiencing disease progression during the treatment phase will include a 1 month post-treatment safety assessment and subsequent follow up visits to assess survival status and date of next iNHL therapy.

Subjects demonstrating disease progression during the follow up phase require a complete follow-up visit. In subsequent visits the subject will continue to be followed as per the post PD follow up schedule, for survival status, until the end of the 5 years.

Patient Reported Outcomes (PRO) measures (FACT-Lym, EQ-5D, HCQ) will be administered for completion by the subjects Post PD follow-up. If a subject demonstrates

disease progression, all the measures will be completed at the progression visit and again one time after determination of PD. If a subject withdraws from the study then all the PRO questionnaires will be administered at the point of withdrawal.

3.4. Ofatumumab Salvage Following Progressive Disease for Arm B

At the discretion of the physician in consultation with the study subject, ofatumumab may be administered to subjects within 120 days who develop PD during or following treatment with bendamustine monotherapy in Arm B. Subjects with PD in Arm B must have a CT scan done with Independent Reviewer confirmation of PD.

Subjects in Arm B who choose to receive optional ofatumumab monotherapy will receive ofatumumab, 1000 mg for the first infusion (Week 1) followed by 2000 mg weekly (+1 day) for 3 doses (Weeks 2-4), followed by 2000 mg every month (±3 days; q28 days) for 8 additional doses (total: 12 doses).

The first follow-up visit will occur one month following the last infusion of ofatumumab monotherapy and continue every 3 months to month 18, then every 12 months to Month 54. The 1 month follow-up visit will include CT-scan and response evaluation. All follow-up visits will include survival follow-up and safety assessments.

4. PLANNED ANALYSES

4.1. Interim Analyses

An Interim Analysis (IA) for efficacy of the primary endpoint, progression free survival, was planned when approximately two thirds (or approximately 172) of the initial total 259 PFS events by IRC is achieved. The interim analysis was planned to be conducted at a significance level of 0.012. At the same time as the IA for efficacy, a Futility Analysis (FA) was planned. The Independent Data Monitoring Committee (IDMC) was expected to review the efficacy and futility data at this timepoint. Further details are specified in the IDMC charter.

The actual significance level at the interim and the primary analysis was planned to be updated according to the actual number of events at the time of analysis - utilizing the O'Brien-Fleming boundary.

The IA occurred with 180 PFS events by IRC and the actual alpha spent at IA was calculated to be 0.0144. The IDMC recommended that the study continue without changes.

4.2. Primary Analysis

As described in **Protocol Amendment 9**, the primary analysis will be performed after approximately 215 PFS events confirmed by IRC have been observed. This will correspond to a power of approximately 84% to detect a 50% improvement in PFS between study arms. The critical boundary to be used at primary analysis was recalculated

using EAST v6.0 software and was derived from the pre-specified error spending functions using the actual number of events observed at interim analysis (180) and assuming the primary event number is 215 in order to maintain a cumulative type I error smaller than two-sided 5%. Using the interim monitoring function in EAST v6.0, the boundary for IA was 0.0144 alpha spent, and the final boundary should be 0.0483.

If the actual PFS event counts differ for the primary analysis, the significance level (0.0483 for the primary analysis) would be adjusted as appropriate according to the Lan and DeMets spending function for the O'Brien-Fleming boundary. At the time of primary analysis, the primary clinical study report will be produced. Following the primary analysis time point, the study will remain open. Patients still being followed on the study will continue as per the schedule of assessments described in the protocol.

4.3. Final Analyses

The study will end once all patients have completed 5 years of follow-up or discontinued earlier, and the final analysis of study data will be conducted at that time. All available data from all patients up to this cutoff date will be analyzed, and the final clinical study report will be produced.

5. SAMPLE SIZE CONSIDERATIONS

5.1. Sample Size Assumptions

The primary endpoint is PFS (as assessed by the IRC) and the analysis will be conducted using stratified log-rank test. The following assumptions are made in the estimation of the required sample size:

- Event times are exponentially distributed
- Median PFS for bendamustine is 9 months
- Median PFS for ofatumumab + bendamustine is 13.5 months
- A 1:1 stratified randomization scheme
- A 90% chance of successfully declaring a difference in the presence of a true underlying difference (power)
- A 5% two-sided risk of erroneously claiming a difference in the presence of no true underlying difference
- Accrual rate is 5.1 subjects per month

Under the above assumptions, approximately 259 total events from both treatment arms combined were needed for the study to have 90% power. With a sample size of 304 subjects, the duration of the study was expected to be about 70 months (under H_1) to obtain the 259 total events. Assuming a dropout rate of 12%, the total sample size randomized for both arms combined was expected to be 346 subjects, with approximate study duration of 77 months.

Assuming a screening failure rate of 15%, the total number of subjects screened was planned to be approximately 408.

Per **Protocol Amendment 9**, the primary analysis will take place after approximately 215 PFS events confirmed by IRC have been reported which will correspond to approximately 84% power. The other assumptions are not modified. See Section 4.2 - Primary Analysis for details.

As stated, this trial uses an event-driven study design. A cut-off date will be established after the targeted number of events (approximately 215 PFS events confirmed by IRC) for the planned primary analysis has been documented. All statistical analyses will be performed using all data collected in the database up to the data cut-off date.

5.2. Sample Size Sensitivity

The robustness and sensitivity of the above sample size calculation is considered in order to assess the impact on power if the assumed median PFS varies. The following table shows the estimated power for different median values of PFS for ofatumumab + bendamustine. The total number of events is 215.

Primary Endpoint power calculation

Median PFS for Ofatumumab + Bendamustine	Median PFS for Bendamustine	Estimated Power
12	9	0.553
13	9	0.763
13.5	9	0.840
14	9	0.895
15	9	0.961

5.3. Sample Size Re-estimation

Sample size re-estimation will not be performed for this study.

6. ANALYSIS POPULATIONS

Analysis populations in the protocol made reference to analysis ‘stage’, assuming an adaptive-like design would be implemented. Since multiple stages were not required, this text has been removed from the population definitions.

The protocol also makes reference to a Safety Population (Dose Confirmation Cohort). This population was utilized for the IDMC tolerability analyses and is not planned for any further presentation.

6.1. Intent-to-Treat Population

The Intent-to-Treat (ITT) population will include subjects who are randomized in the study. This will be the primary population used for evaluation of the efficacy data for all efficacy assessments. In the analyses, subjects will be grouped according to the treatment and strata to which they were randomized. The ITT population will also be used for all PRO analyses.

6.2. Safety Population

The Safety population will include all subjects who receive at least one dose of a study drug. This population will be used for evaluation of all safety measurements. In the analyses, subjects will be grouped based on the treatment they received regardless of how they are randomized.

The subjects' actual treatment will be derived from exposure data. If a subject's actual treatment is the same as the assigned treatment at least once, then actual treatment is the assigned treatment. If a subject receives a study treatment that is different from the assigned treatment for the entire time of treatment, then actual treatment is the different treatment (the treatment actually received).

Patients receiving Bendamustine and any Ofatumumab (not Optional Ofatumumab) will be included in the Ofatumumab + Bendamustine group. Patients receiving only Bendamustine will be included in the Bendamustine group. Patients receiving Bendamustine and Optional Ofatumab salvage therapy will be summarized with the Bendamustine group up to the time of administration of Optional Ofatumumab. Data collected after the administration of Optional Ofatumumab will be reported separately.

6.3. Per Protocol Population

The Per-Protocol (PP) population will comprise all randomized subjects and will exclude subjects with important protocol deviations that will impact the efficacy outcome. The Per Protocol Population will be used in the primary endpoint analysis to check the robustness of the results when using the ITT population. However, if the difference between the ITT and the Per-Protocol population is 10% or less, then the Per-Protocol analysis will not be performed.

Subjects who meet the following conditions will be excluded from the Per Protocol Population:

- Subject did not meet definition of Indolent B-cell Non-Hodgkin's Lymphoma (Inclusion Criteria 1 violation)
- Subject did not meet response criteria to previous therapy (Inclusion Criteria 2 violation)
- Subject has transformed aggressive Lymphoma (Exclusion Criteria 1 violation)
- Subject is taking high dose steroids (Exclusion Criteria 3 violation)
- Prohibited therapy or procedure

- Subjects who are exposed to less than <80 % or >120% of planned total dose (during the whole treatment phase) for both of the study drugs, unless due to adverse events and/or protocol defined dose reductions criteria for each planned cycle.

6.4. Optional Ofatumumab Population

The Optional Ofatumumab Population will consist of all subjects in the ITT population for whom at least one dose of optional ofatumumab salvage therapy (for patients in Arm B) was administered.

6.5. Pharmacokinetic Population

The Pharmacokinetic Population includes all subjects who provide at least one evaluable PK concentration. For a concentration to be evaluable, subjects are required to:

- take a dose of Ofatumumab within -1 to +2 weeks of the planned 28 day cycle during which the PK was collected
- *(for pre-dose samples):* have the sample collected before the start of the next infusion
- *(for EOI samples):* have the sample collected after the end of infusion

6.6. Analysis Datasets

The primary data set for efficacy will be based on the response assessments. The primary data set for safety will be the adverse events and the laboratory data sets.

The response will be assessed by the investigators and by the Independent Review Committee (IRC). Data will be summarized for investigator assessed response as well as for IRC assessed response, unless specified otherwise. Statistical inference for efficacy claim(s) will be based on the data assessed by the IRC.

7. TREATMENT COMPARISONS

7.1. Primary Comparisons of Interest

The primary efficacy analysis will be the comparison of the distribution of PFS between the two treatment groups performed at the time of primary analysis using the ITT population. . Refer to Section 4.2 - Primary Analysis for the timing of the IA and primary analysis.

The primary efficacy endpoint will serve as a gatekeeper for the interpretation of treatment comparisons for the 'inferential' secondary endpoints. If H_0 is rejected, the conclusion will be that there is a treatment difference between ofatumumab in combination with bendamustine and bendamustine monotherapy, and the p-value for the 'inferential' secondary endpoints may be interpreted.

As described in section 4.1, the significance levels for the primary analysis will be adjusted as appropriate using the O'Brien-Fleming spending function.

7.2. Secondary and other Comparisons of Interest

The secondary comparisons of interest will include ofatumumab + bendamustine vs. bendamustine, based on the PFS in patients with follicular lymphoma, ORR in all patients and patients with follicular lymphoma, and OS in all patients and patients with follicular lymphoma. These will be considered as "inferential secondary endpoints" and will be tested hierarchically only if the primary endpoint, PFS, is significant in all patients. One spending function will be used for each of these hypotheses. Each hypothesis will be tested at the remaining alpha level for primary analysis determined based on actual information fraction at IA for that hypothesis (assuming that the same alpha level for each hypothesis [i.e. 0.0144] was spent). This conservative approach ensures strong control of the type I error for the entire study, including IA and primary analysis for all comparisons of interest. The following sequence of secondary endpoints will be tested, and the subsequent one will be tested only if all the previous endpoints are tested and deemed statistically significant:

1. PFS in patients with follicular lymphoma
2. ORR in all patients
3. ORR in patients with follicular lymphoma
4. OS in all patients
5. OS in patients with follicular lymphoma

(e.g. only if the PFS in all patients and PFS in patients with follicular lymphoma are significant then the ORR in all patients will be tested. This hierarchical testing procedure ensures a strong type I error control at a two sided 0.05 level).

The other comparisons of interest will be ofatumumab + bendamustine vs. bendamustine, based on PRO assessments.

Per **Protocol Amendment 9**, the primary analysis will be performed after approximately 215 PFS events confirmed by IRC have been reported. See Section 4.2 - Primary Analysis for details.

7.3. Data Display Treatment and Other Subgroup Descriptors

For tabulations comparing treatment groups "ofatumumab + bendamustine" and "bendamustine" will be presented.

For patients taking "optional ofatumumab" following progression after bendamustine monotherapy - separate efficacy tables for response after optional ofatumumab will be presented to display data for this single treatment group. The safety data collected after administration of optional ofatumumab will be displayed as a separate treatment column on the safety displays.

All listings will be presented by individual treatment arm.

Efficacy Data:

The following treatment descriptors will be used on all applicable efficacy displays except displays summarizing response after administration of optional ofatumumab:

Treatment Group		**Data Display**	**Order of Treatment Groups**
Code	**Description**		
A	Ofatumumab + Bendamustine combination followed by Ofatumumab monotherapy	Ofatumumab+ Bendamustine	1st treatment column
B	Bendamustine monotherapy	Bendamustine	2nd treatment column

For efficacy tables assessing 'Optional Ofatumumab Salvage' after progression on Treatment Arm B (Bendamustine monotherapy), a single treatment column displaying 'Optional Ofatumumab' will be presented.

The following treatment descriptors will be used on displays summarizing response after administration of optional ofatumumab:

Treatment Group		**Data Display**	**Order of Treatment Groups**
Code	**Description**		
B	Optional Ofatumumab (administered after progression on Bendamustine monotherapy)	Optional Ofatumumab	1st treatment column

Safety Data:

The following treatment descriptors will be used on all applicable safety displays:

Treatment Group		**Data Display**	**Order of Treatment Groups**
Code	**Description**		
A	Ofatumumab + Bendamustine combination followed by Ofatumumab monotherapy	Ofatumumab+ Bendamustine	1st treatment column
B	Bendamustine monotherapy	Bendamustine	2nd treatment column
B*	Optional Ofatumumab (administered after progression on Bendamustine monotherapy)	Optional Ofatumumab	3rd treatment column

B/B* = Patients receiving Bendamustine and Optional Ofatumab will be summarized with the Bendamustine group up to the time of administration of Optional Ofatumumab.

Data collected after the administration of Optional Ofatumumab will be reported separately in the Optional Ofatumumab group.

It is anticipated that only a small number of subjects, approximately 25, will receive optional ofatumumab during the study.

If there appears to be an imbalance in the follow-up periods for adverse events, due to differing follow-up after treatment, exploratory analyses may be conducted to further investigate this, such as a supplementary analysis using 'patient years' as the denominator.

Stratification factors and other subgroups are specified in Section 8.3 and will be used for subgroup analyses if sample size permits.

Pharmacokinetic Data:

For pharmacokinetic analyses, only data from the Ofatumumab+Bendamustine arm (Arm A) will be displayed as only results corresponding to Ofatumumab dosing will be collected. Patients in Arm B taking Bendamustine will not be assessed, unless the patient receives Optional Ofatumumab. Data after receiving Optional Ofatumumab will not be summarized, but will be included in the data listings.

The following treatment descriptors will be used on all applicable pharmacokinetic displays:

Treatment Group		**Data Display**	**Order of Treatment Groups**
Code	**Description**		
A	Ofatumumab + Bendamustine combination followed by Ofatumumab monotherapy	Ofatumumab+ Bendamustine	1st treatment column

Data listings will display all pharmacokinetic data available including data that may be collected from patients taking optional ofatumumab.

8. GENERAL CONSIDERATIONS FOR DATA ANALYSES

Analysis datasets will be created according to CDISC/ADaM standards, and data will be listed and summarized according to GSK Integrated Data Standards Library (IDSL) reporting standards. Formatting for dates, times, and decimal places will follow GSK standards except where specified.

The currently supported version of SAS (Version 9.3) will be used to perform all data analyses and to generate tables, listings, and figures. All data in the database will be presented in subject data listings. Data displays will follow the agreements proposed by the IDSL where possible.

Unless otherwise stated, continuous variables will be summarized with the following statistics: mean, median, standard deviation, minimum, and maximum. Categorical variables will be summarized with frequency counts and percentages.

All data up to the time of study completion/withdrawal from study will be included in the analysis, regardless of duration of treatment.

All confidence intervals will be two-sided and will use a 95% confidence level.

In the protocol and other study-related documents the terms Independent Review Committee (IRC), Independent Radiological Review (IRR) and Independent Reviewer (IR) have been used to represent the blinded indpendent assessment of the efficacy response data. For this document and the supporting displays, the terminology IRC will be used throughout.

Deviations from the analyses in the SAP will be identified in the CSR.

8.1. Multicenter Studies

Data from all participating centers will be pooled prior to analysis. It is anticipated that subject accrual will be spread thinly across centers and summaries of data by center would not be informative and will not be provided. However, a summary of enrollment by center will be provided.

8.2. Other Strata and Covariates

Prior to randomization, eligible subjects were stratified according to the following stratification factors:

- Last prior rituximab therapy (rituximab plus chemotherapy vs. rituximab alone)
- Prior exposure to bendamustine (exposed vs. not exposed)

For analysis purposes, subjects will be analyzed based on the stratification details entered at randomization, e.g. the data as recorded in RAMOS (Registration and Medication Ordering System).

A sensitivity analysis of the primary endpoint (PFS based on IRC assessment) using stratification according to the actual data recorded in the eCRF will also be provided. Hence, if any misallocations took place in the stratification, the actual data will be used to determine the stratification of the subject rather than the data as recorded at randomization in RAMOS. If the eCRF data is missing or incomplete, the stratification item(s) will be populated with the randomization details recorded in RAMOS.

8.3. Examination of Subgroups

Summary tables for PFS as assessed by the IRC will be provided by stratification factors as noted in section 8.2.

Other subgroups of interest may include age (<65 vs ≥65), gender (male vs female), race (white vs non-white), geographic distribution (North America, European Union, Asia-Pacific, and Emerging Markets), Ann Arbor Stage (I-II vs III-IV), FLIPI Score (0-2 vs 3-5), ECOG (0-1 vs 2), baseline absolute lymphocyte count/ALC (<LLN vs ≥LLN), FcR gamma 3A variation (G/G, G/T and T/T), FcR gamma 2A variation (T/T, T/C and C/C) and Human Anti-Chimeric Antibodies/HACA status (positive vs negative).

For geographic region, countries will be assigned as follows:

- North America: Canada, United States
- European Union & Neighbors: Austria, Belgium, France, Germany, Greece, Italy, Poland, Slovakia, United Kingdom, Russia, Ukraine
- Emerging Markets & Asia-Pacific (EMAP): Argentina, Hong Kong, Japan

For the regulatory requirements in Japan, efficacy, safety and pharmacokinetic analysis for Japanese and non-Japanese subgroups will be performed. TFLs necessary for the Japanese subgroup are described in the TFL TOC.

8.4. Multiple Comparisons and Multiplicity

To control the overall type I error rate, a hierarchical testing procedure will be applied to the primary endpoint (PFS assessed by the IRC) and inferential secondary endpoints (PFS in patients with follicular lymphoma, ORR in all patients, ORR in patients with follicular lymphoma, OS in all patients, OS in patients with follicular lymphoma) analyses.

The detailed procedure is specified in Section 7.2.

As described in Section 4.1 and 4.2, the significance levels for the interim and primary analysis will be adjusted as appropriate using the O'Brien-Fleming spending function and the actual number of events for the analysis.

Assuming ~70% of the patients enrolled in the study had FL, the boundaries used in the primary analysis for each endpoint are shown in the table below.

	Sample size (# of events for PFS/OS and # of patients randomized for ORR)		Boundary for primary analysis
	IA	Final	Final
PFS	180	215	0.0483
PFS in FL	126	151	0.0483
ORR	331	346	0.0500
ORR in FL	235	239	0.0500

OS	115	145	0.0474
OS in FL	81	102	0.0475

The actual boundaries to be used for primary analysis will be updated according to the actual number of events observed in subgroups of interest.

9. DATA HANDLING CONVENTIONS

9.1. Premature Withdrawal and Missing Data

Because study treatment is dependent on the study endpoints (e.g., progression, rather than a fixed treatment duration), the length of treatment for each subject will depend on the efficacy and toxicity of the treatment, so the duration of treatment will vary across subjects. Similarly, the duration of follow up will also vary. All available data will be analyzed using suitable statistical methods; subjects with shorter treatment and follow-up due to the natural history of their disease or medical necessities of the treatment of their disease will not be considered to have missing data. For endpoints which determine the percentage of responders, subjects with not evaluable or missing best overall response will be assumed to be non-responders, and will be included in the denominator when calculating the percentages.

Missing data occurs when any requested data are not provided, leading to blank fields on the collection instrument. These data will be indicated by the use of a “blank” in subject listing displays. Answers such as “Not applicable” and “Not evaluable” are not considered to be missing data and should be displayed as such.

Subjects with the designation of treatment relationship for adverse events (AEs) and serious adverse events (SAEs) missing will have the worst case assumed to impute the relationship: if relationship to study treatment is missing it will be assumed to be “Yes”. There will be no other imputation for missing data other than what is described in Section 9.2 for partial dates and for missing exposure end dates.

9.2. Derived and Transformed Data

The following sections provide a general description of the derived and transformed variables used to describe and analyze the data. Separate analysis dataset specifications provide full details on all data derivations and transformations including descriptions of core standard algorithms and standard Oncology algorithms. The analysis dataset specifications will clearly communicate the content and source of the datasets supporting the statistical analyses.

9.2.1. Reference Dates

There are four reference dates:

- The **reference date for age** is the date of screening.

- The **safety reference date** is the treatment start date, and will be used to calculate study day for safety measures.
- The **efficacy reference date** is the date of randomization and will be used to calculate study day for efficacy measures and baseline characteristics (such as time since initial diagnosis), as well as efficacy durations.

- The **last contact reference date** is derived for patients not known to have died at the analysis cut-off using the latest complete date on the database.
    - The following dates will be considered for the latest complete date: date of treatment assignment; start/last date of study treatment; all assessment dates (e.g. assessment date of vital signs or performance status, and assessment date in third-party data such as tumor imaging, central laboratory, ECG, etc.); adverse event dates including start and stop date of AEs; medication dates including study medication, concomitant medications, blood products, next anti-cancer therapy, etc.; last known date patient was alive from survival or end of study eCRF page; date of discontinuation from treatment or study.
    - Only dates associated with patient visits or actual examinations of the patient will be used in the derivation. Dates associated with a technical operation unrelated to patient status such as the date a blood sample was processed, will not be used.
    - An imputed partial date will not be used to derive the last contact date.
    - The assessment dates after the cutoff date will not be applied to derive the last contact date.
    - The last contact date will be used for censoring of patients in the analysis of overall survival and time to next therapy.

9.2.2. Study Day for Safety Measures

If the date of interest occurs on or after the safety reference date, then the safety study day will be calculated as (date of interest - safety reference date) + 1. If the date of interest occurs before the safety reference date, then the safety study day will be calculated as (date of interest – safety reference date). There is no safety study day 0.

9.2.3. Study Day for Efficacy

If the date of interest occurs on or after the efficacy reference date, then efficacy study day will be calculated as (date of interest - efficacy reference date) + 1. If the date of interest occurs prior to the efficacy reference date, then efficacy study day will be calculated as (date of interest – efficacy reference date). There is no efficacy study day 0.

9.2.4. Duration and Elapsed Time

Durations (e.g., the duration of an adverse event, duration of exposure, etc.) are calculated as the stop date minus the start date plus one.

For elapsed time (e.g., the time since initial diagnosis):

- If the reference date is on or after the event date, then the elapsed time is the reference date minus the event date + 1.
- If the reference date is before the event date, then the elapsed time is the reference date minus the event date.

When reporting time to event (TTE) durations [e.g. PFS, time to next treatment, overall survival] in months, divide the number of days by 30.4375; to report in weeks divide the number of days by 7; to report in years divide the number of days by 365.25. These algorithms for time to event return decimal numbers, and ignore the actual numbers of days in the months or years between start date and stop date. The "year" used in these algorithms is 365.25 days long, and the "month" is one twelfth of that year.

The algorithms above for age and duration return whole numbers for months and years, accurately accounting for the actual numbers of days in the months or years between the start date and the stop date.

9.2.5. Imputation of Partial Dates

Imputed partial dates will not be used to derive study day, duration (e.g., duration of adverse events), or elapsed time variables. In addition, imputed dates are not used for deriving the last contact date (as noted in Section 9.2.1) in overall survival analysis dataset.

With the exception of new anti-cancer start date on the time to event analysis dataset and exposure end date in the Exposure analysis dataset, imputed dates will also not be stored in datasets.

Imputed dates will not be displayed in listings. However, where necessary, display macros may impute dates as temporary variables for the purpose of sorting data in listings only. In addition partial dates may be imputed for ‘slotting’ data to study time periods (see Section 9.3) or for specific analysis purposes as outlined below.

The partial date imputation will follow ADaM conventions. The ADaM approach is to populate the numeric date variables with the imputed date and add a flag variable to the dataset that indicates the level of imputation.

The flag variable can contain the values: blank, 'D', 'M', 'Y'.

blank: indicates that no imputation was done

D='Day': indicates that the day portion of the date is imputed

M='Month': indicates that the month and day portions of the date are imputed

Y='Year': indicates that the entire date (year, month, and day) is imputed

Example of Date Variables:

XYZD_ - character date variable

XYZDT - numeric date variable

XYZDTFL - flag variable

Details on imputing partial dates for specific datasets are outlined below.

Adverse Events (AE):

Imputations in the adverse events dataset are used for slotting events to the appropriate study time periods and for sorting in data listings.

Dataset	Date	Missing Element	Rule
Adverse Events (AE)	Start Date	day, month, and year	• No Imputation for completely missing dates
		day, month	• If study treatment start date is missing (i.e. subject did not start study treatment), then set start date = January 1. • Else if study treatment start date is not missing: o If year of start date = year of study treatment start date then • If stop date contains a full date and stop date is earlier than study treatment start date then set start date = January 1. • Else set start date = study treatment start date. o Else set start date = January 1.

Dataset	Date	Missing Element	Rule
		day	• If study treatment start date is missing (i.e. subject did not start study treatment), then set start date = 1st of month. • Else if study treatment start date is not missing: o If month and year of start date = month and year of study treatment start date then • If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 1st of month. • Else set start date = study treatment start date. o Else set start date = 1st of month.
	End Date		• No imputation for partial end dates will be performed

Anti-Cancer Therapy and Radiotherapy:

Start and end dates are generally not imputed. If start or end dates need to be imputed for an analysis (e.g., to calculate duration or elapsed time as covariates for efficacy analyses), the rules for imputation will be defined within the algorithm of the derived covariate. Additionally, post treatment anti-cancer therapy and radiotherapy start dates may be imputed to determine date of new anti-cancer therapy. In this case only, the date of new anti-cancer therapy (not all anti-cancer therapy and radiotherapy start dates) will be stored on appropriate efficacy datasets. Imputed partial dates will not be used to derive time since most recent prior therapy. In addition, the cancer therapy treatment status variable, and not any variables that use imputed partial dates, will be used to differentiate prior and follow-up anti-cancer therapy and radiotherapy.

Dataset	Date	Missing Element	Rule
Anti-Cancer Therapy Radiotherapy	Start Date	day, month, and year	• No Imputation for completely missing dates
		day, month	• If partial date contains a year only set to January 1st.
		day	• If partial date contains a month and year set to the 1st of the month.
	End Date		• No imputation for partial end dates will be performed

Surgery:

The date of surgery or procedure is generally not imputed. If the date of surgery or procedure needs to be imputed for an analysis (e.g., to calculate duration or elapsed time as covariates for efficacy analyses), the rules for imputation will be defined within the algorithm of the derived covariate. Additionally, post treatment surgery or procedure dates maybe imputed (where applicable) to determine date of new anti-cancer therapy. In this case only, the date of new anti-cancer therapy (not specific surgery or procedure date) will be stored on appropriate efficacy datasets. The category for surgical procedure variable, and not any variables that use imputed partial dates, will be used to differentiate prior, on, and follow-up surgical procedure data. The derived time in relation to treatment variables are not needed for reporting of data because the category for surgical procedure variable can be used. Therefore, imputed dates are not needed for derivation of time in relation to treatment.

Dataset	Missing Element	Rule
Surgical Procedures	day, month, and year	• No Imputation for completely missing dates
	day, month	• If partial date contains a year only set to January 1st.
	day	• If partial date contains a month and year set to the 1st of the month

Concomitant Medication and Blood and Blood Supportive Care Products:

Impute start and end dates for use in derivation of the reference variables concomitant medication start and end relative to treatment and blood and blood supportive care start and end relative to treatment, but do not permanently store the imputed start and end dates in the analysis datasets. The reference variables will be used to differentiate before, during and after for the concomitant medication or blood or blood supportive care start and end dates. The derived time in relation to treatment variables are not needed for reporting of these data.

Dataset	**Date**	**Missing Element**	**Rule**
Concomitant Medication Blood and Blood Supportive Care Products	Start Date	day, month, and year	• No Imputation for completely missing dates
		day, month	• If study treatment start date is missing (i.e. subject did not start study treatment), then set start date = January 1. • Else if study treatment start date is not missing: o If year of start date = year of study treatment start date then ▪ If stop date contains a full date and stop date is earlier than study treatment start date then set start date = January 1. ▪ Else set start date = study treatment start date. o Else set start date = January 1.
		day	• If study treatment start date is missing (i.e. subject did not start study treatment), then set start date = 1st of month. • Else if study treatment start date is not missing: o If month and year of start date = month and year of study treatment start date then ▪ If stop date contains a full date and stop date is earlier than study treatment start date then set start date= 1st of month. ▪ Else set start date = study treatment start date.

Dataset	Date	Missing Element	Rule
			○ Else set start date = 1st of month.
	End Date	day, month, and year	• No Imputation for completely missing dates
		day, month	• If partial end date contains year only, set end date = earliest of December 31 or date of last contact.
		day	• If partial end date contains month and year, set end date = earliest of last day of the month or date of last contact.

Time to Event, Overall Response, and Overall Response for Independent Review:

Start dates for follow-up anti-cancer therapy, radiotherapy (where applicable), and surgical procedures (where applicable) will be temporarily imputed in order to define event and censoring rules for progression-free survival, response rate, or duration of response (i.e., start date for new anti-cancer therapy). Dates will only be imputed when a month and year are available but the day is missing. The imputed date(s) will not be stored on the anti-cancer therapy, or radiotherapy, datasets. The following rules will be used to impute the date when partial start dates are present on anti-cancer therapy radiotherapy, and/or surgical procedures dataset[s]:

Dataset	Date	Missing Element	Rule
Anti-Cancer Therapy Where applicable: Radiotherapy Surgical Procedures	Start Date	day, month, and year	• No Imputation for completely missing dates
		day, month	• No imputation for missing day and month (note the eCRF should only allow for missing day)
		day	• If partial date falls in the same month as the last dose of study treatment, then assign to earlier of (date of last dose of study

Dataset	Date	Missing Element	Rule
			treatment+1, last day of month). • If partial date falls in the same month as the subject's last assessment and the subject's last assessment is PD, then assign to earlier of (date of PD+1, last day of month). • If both rules above apply, then assign to latest of the 2 dates • Otherwise, impute missing day to the first of the month.
	End Date		• No imputation for partial end dates will be performed

The date of new anti-cancer therapy is derived as the earliest date of new anti-cancer therapy (e.g., chemotherapy), radiotherapy (where applicable), or cancer related surgical procedure (where applicable) and will include imputed dates. If the date of new anti-cancer therapy is an imputed date, then the date of new anti-cancer therapy flag variable is assigned the value of 'D' to indicate that the day portion of the date is imputed (following ADaM convention).

As multiple dates are used to derive the date of new anti-cancer therapy ensure that the date of new anti-cancer therapy flag is only set to 'D' if the derived date is imputed. For example if the date of new radiotherapy is imputed but the date of new anti-cancer therapy is prior to date of new radiotherapy and the new anti-cancer therapy date is not a partial date then the flag should be set to missing as the date used for the new anti-cancer therapy is not an imputed date.

Covariates:

The following imputation rules are the standard rules to be used when algorithms for covariates require date imputations.

Variable	Example of when to impute	Rule
Prior anti-cancer therapy start date Prior radiotherapy start date	• Impute to derive duration o Duration of prior Therapy	• Only impute when a month and year are available but the day is missing. • Impute to first day of the month. • Do not store imputed date

Variable	Example of when to impute	Rule
		• Use only for relevant efficacy analyses (i.e. not to be used for general radiotherapy or anti-cancer therapy summaries)
Prior anti-cancer therapy end date Prior radiotherapy end date	• Impute to derive elapsed time and duration o Duration of prior Therapy o Time from Last dose of prior therapy to Randomization	• Only impute when a month and year are available but the day is missing. • Impute to last day of the month, also must be prior to 'start' o if 'start' is the first of the month assign to 'start', else assign to 'start'-1), where 'start' is either the date of randomization or the start of study treatment. • Do not store imputed date • Use only for relevant efficacy analyses (i.e. not to be used for general radiotherapy or anti-cancer therapy summaries)
Any disease characteristic dates. For example: • Date of initial diagnosis • Date of last recurrence • Date of last progression	• Impute to derive elapsed time o Time from initial diagnosis to randomization for use as a covariate o Time from progression on last therapy until randomization for use as a covariate	• If both month and day are missing, impute to January 1st • else if day is missing, impute to first day of the month. • Do not store imputed date • Use only for relevant efficacy analyses (i.e. not to be used for general disease characteristic summaries)

9.2.6. Imputation of Missing Exposure End Dates

In general, completely missing dates are not imputed. However, subjects in oncology trials may still be on study treatment when analyses are performed and so may have missing exposure end dates. For subjects with missing exposure end dates at the time of data cutoff, the exposure end date will be imputed to the earliest of: the date of the

clinical cutoff, the date of withdrawal from the study, or the death date. The imputed exposure end date will be used to calculate cumulative dose and exposure duration. The imputed exposure end date will be stored in the exposure analysis dataset and an exposure end date imputation flag variable will be derived indicating which exposure end date records are imputed. Imputed exposure end dates will also be stored on the study treatment end date variable.

For subjects who have missing end dates in their last exposure record because they are still on study treatment, the on-therapy indicator variables (time in relation to study treatment) are assigned to on-therapy for all records where the 'dataset'.'date' is after or on the study treatment start date.

9.2.7. Baseline Definition

Baseline will be defined as the most recent, non-missing value prior to or on the first study treatment dose date. For laboratory data, baseline will be defined as the most recent, non-missing value from a central laboratory prior to or on the first study treatment dose date.

For subjects taking optional ofatumumab in Arm B, another baseline is defined for the optional ofatumumab period as the the most recent, non-missing value prior to or on the first optional ofatumumab dose date.

For subjects who did not receive study treatment during the study, baseline will be defined as the latest, non-missing collected value.

9.2.8. Change from baseline

Change from baseline will be presented for safety data.

Change from baseline is calculated as:

- For records occurring after baseline: (visit value) – baseline value.

Percent change from baseline is calculated as:

- For records occurring after baseline: ((change from baseline) / baseline value) * 100

If either the baseline or visit value is missing, the change from baseline and/or percent change from baseline is set to missing as well.

9.2.9. Multiple Assessments

Summaries of by visit safety data include data from scheduled assessments only. Unscheduled data are included only in summary sections labeled “worst case”. Data from all assessments (scheduled and unscheduled), including multiple assessments, will be included in listings

9.2.10. Actual Treatment

The subjects' actual treatment will be derived from exposure data. If a subject's actual treatment is the same as the assigned treatment at least once, then actual treatment is the assigned treatment. If a subject receives a study treatment that is different from the assigned treatment for the entire time of treatment, then actual treatment is the different treatment (the treatment actually received).

9.2.11. Treatment Cycle

In order to differentiate cycle variables based on the "assessment" cycle (timeslicing/eCRF collected) versus actual treatment cycle variables based on exposure cycle start dates, treatment cycle, treatment cycle description, day with treatment cycle, day of start within treatment cycle, and day of end within treatment cycle, as appropriate, will be added to adverse events, blood and blood supportive care products, ECG, laboratory, and vital sign analysis datasets.

Treatment cycle:

- For non-planned visits/assessments select the cycle record for each subject where the dataset date variable is greater than or equal to cycle start date and less than or equal to cycle end date.
- For planned visits/assessments where Day 1 assessments are assumed to be done prior to dosing, add 1 to the cycle start date and cycle end date from the cycle dataset. For each subject, select the cycle record where the dataset date variable is greater than or equal to the cycle start date and less than or equal to the cycle end date.

Treatment cycle description:

- Set treatment cycle description to the cycle dataset cycle description where the cycle dataset cycle is equal to the dataset treatment cycle.

Day within treatment cycle:

- For each subject, dataset date variable minus the cycle start date from the cycle dataset + 1 where the dataset date variable is greater than or equal to the cycle dataset start date and less than or equal to the cycle end date and the cycle dataset cycle is equal to the dataset treatment cycle.

Day of start within treatment cycle:

- For each subject, dataset start date variable minus the cycle start date from the cycle dataset + 1 where the dataset start date variable is greater than or equal to the cycle dataset start date and less than or equal to the cycle end date and the cycle dataset cycle is equal to the dataset treatment cycle.

Day of end within treatment cycle:

- For each subject, dataset end date variable minus the cycle start date from the cycle dataset + 1 where the dataset end date variable is greater than or equal to the cycle dataset start date and less than or equal to the cycle end date and the cycle dataset cycle is equal to the dataset treatment cycle.

9.2.12. Extended Loss to Follow-up or Extended Time without an Adequate Assessment

If two or more scheduled disease assessments are missed and are then followed by an assessment of PD or death, PFS will be censored at the last adequate assessment prior to PD or death. For example, when the scheduled disease assessment is every 4 weeks, a window of 70 days (8 weeks + 14 day window) will be used to determine whether there was an extended time without adequate assessment. That is, if the time difference between PD/death and last adequate assessment is more than 70 days, then PFS will be censored at the last adequate assessment prior to PD/death.

9.3. Study Time Periods

9.3.1. Time in Relation to Treatment

Adverse events, concomitant medications, blood product, death, subject disposition, ECOG, laboratory, image data, vital signs, constitutional symptoms, lymph node examination, organ examination, biomarker, and questionnaire data (FACT-Lym and EQ-5D) will be assigned to the treatment periods defined below. Flag variables indicating the treatment period will be added to these datasets.

Pre-therapy is defined as the time prior to the subject's first dose of study treatment.

On-treatment is defined as the time from start date/time of study treatment until the earlier of the end date/time of the study treatment + 60 days and the date prior to start date/time of the optional ofatumumab for subjects in Arm B (if applicable). The start date of the on-treatment phase is the earlier date of the first dose for each study drug. The end of study treatment is defined as the *last dose of planned treatment* which includes the latter date of the last dose for each study drug in the regimen for combination trials.

There are specific rules to handle the cases where start date/time is equal to start date/time of study treatment or the start date/time is missing for different classes of data sets:

- For interventions and events, including adverse event, concomitant medications, blood product, death, and disposition, i.e., if the date/time is equal to start date/time of study treatment or time is not available and the date is equal to start date of study treatment, the flag will be set to on-treatment. If the start date is missing, and the end date/time is before start date/time of study treatment, the flag will be set to pre-treatment. If start date is missing and end date/time is not before the start date/time of study treatment, or both start date and end date are missing, the flag will be set to on-treatment.

- For findings including ECOG status, laboratory data, imaging data , vital signs, constitutional symptoms, lymph node examination, organ examination, and biomarker if the date/time is equal to start date/time of study treatment, the flag will be set to pre-treatment. If time is not available and the date is equal to start date of study treatment, the flag will be set to pre-treatment. If the date is missing, the flag will be set to on-treatment.

Post-treatment is defined as any time beyond the on-treatment period.

9.3.2. Study Time Periods for Concomitant Medications and Blood and Blood Supportive Care Products

Concomitant Medication and Blood and Blood Supportive Care Product start and end dates will be assigned to study time periods in relation to first dose of study treatment as defined below. The start date references time flag variables and end date reference time flag variables will be added to the concomitant medications and blood and blood supportive products datasets, respectively.

- Start relative to treatment**:** Assign to 'BEFORE' if start date is prior to study treatment start date or if subject has not taken any study treatment or (start date is missing and end date is before study treatment start date). Else assign to 'DURING' if the start date falls into the on-therapy period as defined above or if subject is ongoing (not all study treatment discontinuation records completed) or start date is missing. Else assign to 'AFTER' if start date is after the on-therapy period.
- End relative to treatment: Assign to 'BEFORE' if end date is prior to study treatment start date or if subject has not taken any study treatment. Else assign to 'DURING' if start date falls into the on-therapy period or if subject is ongoing (not all study treatment discontinuation records completed) or (end date is missing and start relative to treatment not 'AFTER'). Else assign to 'AFTER' if start date is after the on-therapy period or (end date is missing and start relative to treatment='AFTER').

Only on-therapy blood and blood supportive care products that start after the start of study treatment are included in the Blood Products and Blood Supportive Care Product summaries. Therefore, for summary tables, include blood and blood supportive care product records where start relative to treatment in ('DURING') and end relative to treatment in ('DURING','AFTER'). All data will be reported in listings.

Concomitant medication start relative to treatment and end relative to treatment flags are used to select data to include in the Concomitant Medication summaries as follows:

- Summary of Concomitant Medications: This summary will contain medications including those with start date prior to study treatment start date and continue (missing end date or end date after study treatment start date) on therapy. Note that any medications with start date and end date prior to study treatment start date will be excluded. In addition, any medication that was started during post-therapy will be excluded.

9.4. Values of Potential Clinical Importance

9.4.1. Laboratory Parameters

Reference ranges for all laboratory parameters collected throughout the study are provided by the laboratory. A laboratory value that is outside the reference range is considered either high abnormal (value above the upper limit of the reference range) or low abnormal (value below the lower limit of the reference range). Note: a high abnormal or low abnormal laboratory value is not necessarily of clinical concern. The laboratory reference ranges will be provided on the listings of laboratory data. Clinical laboratory test results outside of the reference range will be flagged in the listings.

A summary of values outside the normal range will be provided.

9.4.2. Vital Signs

To identify heart rate values of potential clinical importance, NCI-CTCAE v4.0 will be used to assign categories that align with the grades for 'Sinus bradycardia', 'Sinus tachycardia', 'Supraventricular tachycardia', and 'Ventricular tachycardia'.

The following criteria will be used to flag vital sign values that are values of potential clinical importance:

Vital Sign Parameter	Potential Clinical Importance (PCI) Range	Unit
Decrease from baseline Heart Rate	Decrease to <60	bpm
Increase from baseline Heart Rate	Increase to >100	bpm

To identify blood pressure values of potential clinical importance, NCI-CTCAE v4.0 will be used to assign categories that align with the grades for 'Hypertension'.

Vital Sign Parameter	Potential Clinical Importance (PCI) Range	Unit
Increase from baseline Systolic Blood Pressure	≥120 to <140 (Grade 1) ≥140 to <160 (Grade 2) ≥160 (Grade 3)	mmHg
Increase from baseline Diastolic Blood Pressure	≥80 to <90 (Grade 1) ≥90 to <100 (Grade 2) ≥100 (Grade 3)	mmHg

To identify temperature values of potential clinical importance, NCI-CTCAE v4.0 will be used to assign categories that align with the grades for 'Hypothermia' and 'Fever'.

Vital Sign Parameter	Potential Clinical Importance (PCI) Range	Unit
Increase from baseline Temperature	Increase to ≥38	Degrees C
Decrease from baseline Temperature	Decrease to ≤35	Degrees C

10. STUDY POPULATION

Unless otherwise stated, all tables and listings in this section will be based on the ITT population and all summaries and data listings will use treatment labels specified in Section 7.

10.1. Disposition of Subjects

A summary of the number of subjects in each of the analysis populations described in Section 6. will be provided. In addition, the number of subjects enrolled by investigator will be summarized by treatment group using the ITT population. A listing of subjects excluded from analysis populations will also be provided.

A summary of subject status and reason for study withdrawal will be provided. This display will show the number and percentage of subjects who withdrew from the study, including primary reasons for study withdrawal. Reasons for study withdrawal will be presented in the order they are displayed in the eCRF.

A summary of study treatment status will be provided. This display will show the number and percentage of subjects who have completed the study treatment, are ongoing, or have discontinued study treatment and a summary of the primary reasons for discontinuation of study treatment. Reasons for study treatment discontinuation will be presented in the order they are displayed in the eCRF. A listing of study treatment discontinuation will be generated. The listing will include last dose date, and reasons for study treatment discontinuation.

10.2. Protocol Deviations

All important protocol deviations as collected per the Protocol Deviation Management Plan (PDMP) will be summarized and listed and will include inclusion/exclusion criteria deviations as well as other deviations. Protocol deviations will be classified as 'Deviations that require exclusion from per-protocol population' (as described in section 6.3) and 'Deviations that do not require exclusion from per-protocol population'.

A separate summary and listing of inclusion/exclusion deviations will also be provided.

10.3. Demographic and Baseline Characteristics

The demographic characteristics (e.g., age, race, ethnicity, sex, baseline height, and baseline weight) will be summarized and listed. Age, height and weight will be

summarized using the mean, standard deviation, minimum, median, and maximum. In addition, age will also be categorized and summarized for the following categories:

- <18, 18-64, 65-74, and ≥75
- <65 and ≥65 years.

The count and percentage will be presented for sex and ethnicity.

Race and racial combinations will be summarized and listed.

The number of subjects enrolled by country and by site will be summarized.

The disease history and characteristics at screening will be summarized. The summaries of disease characteristics at initial diagnosis will also be provided. Medical conditions present at screening will be listed and will be summarized, along with liver and spleen organ examination, physical lymph node examination, anti-cancer therapies, and concomitant medications.

Prior anti-cancer therapy will be coded using the WHODrug coding dictionary, then summarized by type of therapy and listed. A listing of prior anti-cancer therapy will show the relationship between ATC Class (e.g. ATC Level 1), Preferred Term (e.g. Ingredient), and verbatim text. A summary of the best response to the most recent prior anti-cancer therapy will be provided. A summary of the number of prior anti-cancer therapy regimens will also be produced.

A summary of pre-medications required prior to infusion will also be provided. Prior anti-cancer radiotherapy will be summarized and listed. Prior cancer and non-cancer related surgeries will be summarized.

The baseline stratification factors, will be summarized. A cross-tabulation showing the differences between stratification based on the randomization (RAMOS/RANDALL) and stratification based on the eCRF data will be provided.

Summaries of baseline covariates included in Cox proportional hazards model regression analyses (see Section 11.1.) will be provided.

The summaries will be produced in all patients using ITT population as well as in patients with and without FL.

10.4. Treatment Compliance

A listing of planned and actual treatments will be produced.

A listing of drug accountability data (date, actual dose, total volume infused) will be produced.

A summary and listing of overall study medication compliance will be produced for ofatumumab. Compliance will be based on the total dose of ofatumumab received (mg) divided by the total dose (mg) expected taking into account withdrawal from treatment. Therefore, the denominator is based on the total dose received during the time that a subject is actually eligible to receive drug.

For example, if the dosing period for a study is 6 cycles and during that 6 cycles, a subject received 100 mg of drug each cycle, then the denominator (total dose expected) would be 600 mg as a total dose, if the subject was actually in the study for the 6 cycles. However, if the subject discontinued treatment at the end of the 3 cycles, then total dose in mg expected for this case would be 300 mg.

Overall Compliance = (total dose in mg received / total dose in mg expected) * 100

Overall compliance will be categorized into the following intervals: <80%, 80% - <100%, 100%, >100% - < 120%, and ≥120%.

Overall compliance will also be provided for bendamustine, using the same formula as ofatumumab.

In addition, summaries of study treatment exposure and dose modifications (e.g., number of dose reductions, number of dose interruptions) will further characterize compliance. These analyses are described in Section 12.1, 'Extent of Exposure'.

10.5. Concomitant Medications

Concomitant medications will be coded using WHODrug coding dictionary, summarized, and listed. The summary of concomitant medications will show the number and percentage of subjects taking concomitant medications by Ingredient. Multi-ingredient products will be summarized by their separate ingredients rather than as a combination of ingredients.

In the summary of concomitant medications, each subject is counted once within each unique ingredient. For example, if a subject takes Amoxycillin on two separate occasions, the subject is counted only once under the ingredient "Amoxycillin".

In the summary of concomitant medications, the ingredients will be summarized by the base only (and will not be shown separately for different base + salt combinations).

Blood products or blood supportive care products with onset date within the on-therapy window will be included in the summary tables. The frequency and percentage of subjects using blood products and blood supportive care products after the start of study medication will be provided. Supporting listings will also be provided

10.6. Subsequent Anti-Cancer Therapies

The number and percentage of subjects that received chemotherapy, immunotherapy, hormonal therapy, biologic therapy, radioactive therapy, and small molecule targeted therapy as post study treatment anti-cancer therapy, including the optional ofatumumab for subjects in Arm B, will be summarized. Time from study treatment discontinuation to the first post study treatment anti-cancer therapy will also be included in this summary table.

Follow-up anti-cancer therapy will be coded using the WHODrug coding dictionary, then summarized by ingredient. A listing of the type of follow-up anti-cancer therapy received (chemotherapy, immunotherapy, hormonal therapy, biologic therapy, radioactive therapy, small molecule targeted therapy) for each subject will be provided.

11. EFFICACY

All efficacy analyses, with the exception of analyses of response after optional ofatumumab, will be based on the ITT population as defined in Section 6, unless otherwise specified. Analyses will be presented by treatment arm: ofatumumab+bendamustine vs. bendamustine.

Analyses of response after optional ofatumumab salvage therapy will be based on the Optional Ofatumumab Population as defined in Section 6. Analyses will be presented by a single treatment arm: optional ofatumumab.

The Revised Response Criteria for Malignant Lymphoma [RRCML] guidelines (Cheson, 2007) will be used to assess clinical activity and disease status. IRC assessments will be considered as primary assessments. Investigator assessments will be considered as supplementary.

11.1. Primary Efficacy Analysis

Progression-free survival (PFS)

The primary endpoint, progression-free survival (PFS), is defined as the interval of time (in months) between the date of randomization and the earlier of the date of disease progression or death due to any cause. The IRC assessment of response will be used for the primary analysis.

The date of documented disease progression will be defined as the date of disease progression based on imaging data. The date of death should be taken from the Record of Death page. Death on study due to any cause will be included as an event for calculation of PFS.

If there is no adequate baseline assessment, the subjects will be censored at their date of randomization. Subjects without any adequate post-baseline assessments will be censored at the date of randomization.

Subjects who progressed or died after an extended period without an adequate assessment will be censored at their date of last adequate assessment prior to progression or death even if subsequent information is available regarding progression or death. An adequate assessment is defined as an assessment where the IRC determined response is CR, PR, or SD. The date of response at that assessment will be used for censoring. As the assessment schedule may change through the course of the protocol, specific rules for identifying extended loss to follow-up or extended time without an adequate assessment are provided in Section 9.

For subjects who receive subsequent anti-cancer therapy, the following rules will apply:

- If the start date of the anti-cancer therapy is partial (i.e. either missing the day but has the month and year available or missing both day and month) the imputation rules described in Section 9 will be applied. No imputation will be made for completely missing dates.

- If anti-cancer therapy is started without documented disease progression or is started prior to documented disease progression, then PFS will be censored at the date of the last adequate assessment that is no later than the date of initiation of anti-cancer therapy (i.e. if an assessment occurs on the same day as the start of new anti-cancer therapy the assessment will be used as it will be assumed the assessment occurred prior to the administration of new anti-cancer therapy). The date of response at the last adequate assessment will be used as the censoring value.

- If a subject has only a baseline visit or does not have an adequate assessment that is not later than the date of initiation of anti-cancer therapy, PFS will be censored at the date of randomization.

If a subject has not progressed, has not died and has not started new-anti-cancer therapy, then PFS will be censored at the date of the last adequate assessment defined as an assessment where the IRC determined response is CR, PR, SD. The date of response will be used as the censoring date.

A summary of the assignments for progression and censoring dates for PFS are specified in the following table.

Table 1 Assignments for Progression and Censoring Dates for PFS Analysis

Situation	**Date of Event (Progression/Death) or Censoring**	**Outcome** **Event (Progression/Death) or Censored**
No (or inadequate) baseline assessment and the subject has not died	Randomization	Censored
No post-baseline response	Randomization	Censored

assessments and the subject has not died		
Progression documented between scheduled visits	Date of assessment of progression	Event
No progression (or death)	Date of last adequate assessment of response[1]	Censored
New anticancer treatment started (prior to documented disease progression)[2]	Date of last adequate assessment of response[1] (on or prior to starting anti-cancer therapy)	Censored
Death before first PD assessment (or Death at baseline or prior to any adequate assessments)	Date of death	Event
Death between adequate assessment visits with no PD	Date of death	Event
Death or progression after more than one missed visit	Date of last adequate assessment of response (prior to missed assessments)[3]	Censored

[1]An adequate assessment is defined as an assessment where the Independent Reveiwerer determined response is CR, PR, or SD.

[2]If PD and new anti-cancer therapy occur on the same day, assume that progression was documented first (i.e. outcome is progression and the date is the date of the assessment of progression). If anti-cancer therapy is started prior to any adequate assessments, censoring date should be the date of randomization.

[3]For the rare case where a subject dies after more than 1 missed visit, and there are no post-baseline response assessments, the date of censoring will be defined as the randomization date.

An interim analysis of the primary endpoint, PFS confirmed by IRC, was planned to be performed when approximately 2/3 of the initial number of PFS events confirmed by IRC occurred (172 PFS events by IRC). The interim analysis for PFS was planned to be reviewed by an IDMC utilizing a significance level of 0.012 (for 172 events or adjusted as appropriate using an O'Brien-Fleming spending function). The interim analysis of PFS was conducted in the same manner as described for the primary analysis. Details of the interim analysis are also provided in the IDMC Charter. The IA occurred with 180 PFS events by IRC and the actual alpha spent at IA was calculated to be 0.0144.

The primary analysis of PFS was planned to be based on a two-sided test with a significance level of 0.046. The primary analysis will be conducted at a significance level of 0.0483 (with 215 events) to maintain an overall study significance level of 0.05 (See Section 4.2 - Primary Analysis for details). The survival distributions will be estimated using Kaplan-Meier survival curves and will be compared using a log-rank test stratified

by randomization stratification factors. A Cox regression model stratified by randomization stratification factors will be used to estimate the hazard ratio (HR) of PFS, along with 95% CI based on the Wald test.

If there are a sufficient number of progressions or deaths, median PFS, first and third quartiles and 95% CI, will be estimated using the Brookmeyer-Crowley method [Brookmeyer, 1982]. A figure and listing of progression-free survival time will also be provided.

A supplementary table showing the details of the number at risk, number of events, and number censored with the event time will also be produced.

A Cox regression model stratified by randomization stratification factors will be used as supportive analysis and will include covariates for treatment and other baseline data deemed appropriate including age, gender, race, Ann Arbor stage at screening, histology at screening, FLIPI score, and ECOG. The hazard ratio for treatment will represent the risk of experiencing disease progression or death for 'ofatumumab+bendamustine' vs 'bendamustine'.

PFS will be evaluated for the ITT population. If the ITT population and Per Protocol population differ by more than 10%, then PFS will also be evaluated for the Per-Protocol population to check the robustness of the result.

Sensitivity Analyses for PFS

Five sensitivity analyses of PFS will be performed. All sensitivity analyses will be performed as described for the primary analysis of PFS. If the primary efficacy analysis is not significant, the supportive and sensitivity analyses will be considered exploratory in nature. The sensitivity analyses are specified as follows:

- The first sensitivity analysis will be conducted using the Investigator assessed response data.

- The second sensitivity analysis will be conducted using stratification based on the eCRF data rather than stratification based on randomization details (see Section 8.2).

- The third sensitivitity will treat all progressions and deaths as events, regardless of whether they occurred after starting new anti-cancer therapy, including the optional ofatumumab for subjects in Arm B.

- The fourth sensitivitity will treat all progressions and deaths as events, regardless of whether they occurred after starting new anti-cancer therapy or after 2 or more missed scheduled assessments.

- The fifth sensitivity analysis will treat progression, death and new anti-cancer therapy, whichever occurs earlier, as events.

Subgroup Analyses for PFS

If the primary efficacy analysis is statistically significant, the primary endpoint of PFS will be summarized for the subgroups specified in Section 8.3 (FL subgroup, gender, age group, race, geographic region, Ann Arbor Stage, FLIPI Score, ECOG, ALC, FcR gamma 3A, FcR gamma 2A and HACA status) and using the same conventions as for the primary analysis, provided subgroups are large enough to result in meaningful analyses. Figures displaying the survival curves will also be provided by treatment arms as well as for each of the stratification factors. PFS will also be summarized by stratification factors provided the subgroups are large enough to result in a meaningful analysis. Efficacy analyses in subgroups are intended to explore the consistency (homogeneity) of treatment effect. Forest plot (including sample size/number of events and HR with 95% CI) will be produced to graphically depict the treatment effect estimates in different subgroups. No inferential statistics (p-values) will be produced for the subgroups

11.2. Secondary Efficacy Analyses

A hierarchical testing procedure will be applied to inferential secondary endpoints (PFS in patients with follicular lymphoma, ORR in all patients, ORR in patients with follicular lymphoma, OS in all patients, OS in patients with follicular lymphoma) analyses should the analysis of primary endpoint show significant results (see section 8.3 for further details).

11.2.1. Overall Response Rate (ORR)

Overall Response Rate (ORR) is defined as the percentage of subjects achieving a CR or PR from the start of randomization until disease progression or the start of new anti-cancer therapy, including the optional ofatumumab for subjects in Arm B. This will be based on responses from the IRC assessment of best overall response using the Revised Response Criteria for Malignant Lymophoma (RRCML) with response criteria defined as CR, PR, SD, PD or NE. The best response data will be summarized by treatment arm in all patients using ITT population as well as in patients with and without FL.

Subjects with Not Evaluable (NE) or missing response will be treated as non-responders; i.e., they will be included in the denominator when calculating the percentage.

The 95% CI for response rates in each arm will be calculated and responses rates will be compared between treatment arms using a chi-square test adjusting for stratification factors (last prior rituximab therapy and prior exposure to bendamustine). 95% CI for the difference in response rates will be calculated.

All data relating to response from the IRC will be listed (including individual response assessments and best response).

The Investigator determined best response data will also be summarized by treatment arm.

11.2.2. Overall Survival (OS)

Overall Survival (OS) is defined as the interval of time (in months) between the date of randomization and the date of death due to any cause. For subjects who are alive, time of death will be censored at the date of last contact (as defined in Section 9.2.1). The date of death should be taken from that recorded on the Record of Death page.

Survival will be summarized using the Kaplan-Meier method, and survival curves will be compared using a stratified log-rank test by randomization stratification factors along with 95% Confidence Intervals (CI). In addition, for each treatment group, the Kaplan-Meier estimates for the median overall survival time, the first and third quartiles will be presented, along with approximate 95% CIs if there are a sufficient number of deaths. The analysis will be performed based on all patients using ITT population as well as for patients with and without FL.

A graph of survival curves and a listing of survival times will also be provided.

Analyses will be conducted at the time of the primary endpoint PFS analysis as well as at the end of the study.

11.2.3. Time to response

Time to response is defined as time from randomization to the first response (CR/ PR). If no CR/PR value is present data will be censored at last adequate assessment. Kaplan-Meier estimates will be provided for the treatment arms over time. The median time to response along with the associated 95% confidence will be provided by treatment group. The analysis will be performed in all patients using ITT population as well as in patients with and without FL.

Both IRC assessed and Investigator assessed time to response will be provided.

11.2.4. Duration of response

The duration of response is defined as the time (in months) from the initial response (CR/PR) to first documented sign of disease progression or death due to any cause. If sample size permits, the median duration of response will be calculated from the Kaplan-Meier estimates. First and third quartiles will also be calculated along with associated 95% confidence intervals if there are a sufficient number of responders who subsequently progress or die due to any cause. Censoring rules will follow those of the primary PFS analysis defined in Section 11.1. No treatment comparison will be provided for duration of response. The subset of ITT (subjects who are responders) will be used for this analysis. The analysis will be performed in all patients as well as in patients with and without FL.

Both IRC assessed and Investigator assessed duration of response will be provided.

A listing of duration of response will be provided.

11.2.5. Time to progression

Time to progression is defined as the time from randomization until disease progression. The same analysis will be performed as described for time to response analysis. The analysis will be performed in all patients using ITT population as well as in patients with and without FL.

Both IRC assessed and Investigator assessed time to progression will be provided.

11.2.6. Time to next therapy

Type and time to next therapy will be provided. Time to next therapy is defined as the time (in months) from randomization date to the date of receiving the next line treatment as collected on the "Follow up anti-cancer therapy" CRF page (including all therapy types) or death (due to any cause). Next line treatments given after a PD or those given without a PD are both considered. For subjects who do not receive another next line therapy or die, time of next therapy will be censored at the date of last contact. The same analysis will be conducted as described for the primary endpoint, PFS.

Patients taking optional Ofatumumab will be considered to have received next therapy.

Both the ITT population and a subset of the ITT (subjects who take next therapy) will be used for this analysis. The data structure for treatment comparisons used in PFS will also be applied. The analysis will be performed in all patients as well as in patients with and without FL.

11.2.7. Reduction in tumor size

Tumor sizes and reduction in tumor size will be measured by the absolute value of, and percentage change in the sum of products of the diameters of the largest abnormal nodes from baseline to post-baseline.

11.2.8. Improvement in ECOG performance status

Improvement is defined as a decrease from baseline by at least one step on the ECOG performance status scale (improvement categorized as yes or no). The proportion of subjects with improvement will be compared between treatment groups with the Cochran-Mantel-Haenszel test adjusting for stratification factors.

ECOG performance status will also be summarized at baseline and the worst-case post-baseline. Summaries will present the frequency and percentage of subjects with worst-case changes during the study (improved, no change, deteriorated).

A supporting listing will also be provided.

11.2.9. Constitutional Symptoms (or B-Symptoms)

A summary of the number and percentage of subjects with any constitutional symptom/B-symptom will be displayed at each assessment time during the study. A summary of improvement at each post-baseline assessment will also be provided.

A plot of proportion of subject with B-symptoms by visit will also be provided.

11.2.10. Organ Examination

The number and percentage of subjects with normal or enlarged organs based on liver and spleen examination by palpation/CT scan will be summarized by scheduled visits.

A supporting listing will also be provided.

11.2.11. Disease Markers

B-cell Monitoring

The change and percent change of $CD45^+CD19^+$ and $CD45^+CD20^+$ from baseline will be summarized to assess the treatment effect, to monitor the normal B-cell population, and to follow their recovery. In addition, frequency and percentage of subjects with complete B-cell depletion and near-complete B-cell depletion will be summarized. Complete B-cell depletion is defined as the absolute value of $CD45^+CD19^+$ and $CD45^+CD20^+$ both equal to zero cells/uL. Near complete B-cell depletion is defined as the sum of the absolute value of $CD45^+CD19^+$ and $CD45^+CD20^+$ <5 cells/uL.

Tables that will be provided are:

- Summary of $CD45^+CD19^+$ counts over time
- Summary of $CD45^+CD20^+$ counts over time
- Summary of $CD45^+CD19^+$ change from baseline (counts and percentage)
- Summary of $CD45^+CD20^+$ percent change from baseline (counts and percentage)
- Summary of $CD45^+CD19^+$ change from baseline (counts and percentage)
- Summary of $CD45^+CD20^+$ percent change from baseline (counts and percentage)
- Summary of subjects with near-complete B-cell depletion
- Summary of subjects with complete B-cell depletion
- Summary of subjects with complete B-cell depletion by IRC assessed responder (CR or PR)

Summaries for $CD45^+CD19^+$ will use ITT population while $CD45^+CD20^+$ will use safety population (since this requires subjects to be on treatment to have an effect).

11.2.12. Prognostic and biological markers correlating with clinical response

Univariate regression analyses will be used to assess the relationship between PFS as assessed by the IRC and the following prognostic factors: Stratfication Factors (previous rituximab and prior bendamustine exposure), age, gender, race, Ann Arbor stage, FLIPI score, ECOG, Baseline Absolute Lymphocyte count (ALC), , FcR gamma 3A, and Human Anti-chimeric Antibodies (HACA) at baseline including the factor and treatment in the model.

Logistic regression will be conducted to explore the relationship between IRC assessed overall response and the same set of variables specified above.

[redacted]

11.2.14. Optional Ofatumumab – Investigator-Assessed Response Rate

Investigator-Assessed Response Rate is defined as the percentage of subjects achieving a CR or PR one month after last dose of optional ofatumumab. The best response data will also be summarized.

Subjects with Not Evaluable (NE) or missing response will be treated as non-responders; i.e., they will be included in the denominator when calculating the percentage.

Only subjects receiving optional ofatumumab will be included in the analysis.

A data listing of the individual response data will also be provided.

11.3. Other Efficacy Analyses

11.3.1. Concordance Analysis of Overall Response Rate

An assessment of the concordance between IRC assessment and Investigator Assessment of the Best Overall Response for each subject will be provided, overall and by treatment group. A summary by responder (CR or PR) and non-responder status and a separate

summary showing agreement of each individual response category (CR, PR, SD, PD, NE, missing) will be provided.

The calculation will be based on the percent agreement (the proportion of response outcomes that agree or match across both IRC and Investigator Assessments):

Percent Agreement = (Number of matched responders + Number of matched non-responders) /Total number of subjects assessed.

11.3.2. Concordance Analysis of PFS

A cross-tabulation will be produced displaying the Progression-free survival timings for the Investigator data compared to the IRC data. For progression assessments, the frequency and percent of subjects with complete agreement, progression later, progression earlier, and cases where progression was called by one method and censored by the other will be displayed. Similarly, if censoring was recorded, the frequency and percent of subjects with complete agreement, censoring called later, censoring called earlier, and cases where censoring was called by one method and progression was called by the other method will be displayed.

This summary will be displayed overall and by treatment group.

A figure may also be produced displaying the PFS assessment for Investigator data overlaid with the PFS assessment from the IRC to provide a visual display to assess discordance.

12. SAFETY ANALYSES

Unless otherwise specified, all the safety analyses will be based on the Safety population as defined in Section 6 and summaries will include all events or assessments collected during the study. All the analyses will be performed by treatment arm.

12.1. Extent of Exposure

Extent of exposure to study drugs will be summarized separately.

The Ofatumumab exposure (mg) and Bendamustine exposure (mg) by cycle will be provided.

The dose (mg) and duration of exposure to treatment will be summarized by each infusion using summary statistics mean, standard deviation, median, minimum value, and

maximum. The total number of infusions administered will also be summarised with mean, median, standard deviation, minimum, and maximum. The number and percentage of subjects who received infusions will be reported.

The frequency of infusion interruptions and incomplete infusions will also be provided.

Listings will also be provided for all exposure data.

The number of subjects discontinuing study treatment will also be summarized and listed along with the reasons for discontinuation.

12.2. Adverse Events

An overview summary of AEs, including counts and percentages of subjects with any AE, AEs related to study treatment, AEs leading to permanent discontinuation of study treatment, AEs leading to dose reductions, delays or interruptions, SAEs, SAEs related to study treatment, fatal SAEs, and fatal SAEs related to study treatment will be produced.

A summary of all non-serious AEs will be provided. The summary will be displayed by SOC and PT.

The relationship between MedDRA SOC, PT, and Verbatim Text will be displayed.

Adverse events (AEs) will be graded according to the CTCAE (Version 4.0). Adverse events will be coded to the preferred term (PT) level using the Medical Dictionary for Regulatory Affairs (MedDRA dictionary, using the latest version available at the time of database release).

A summary of number and percentage of subjects with any adverse events by maximum grade will be produced. AEs will be sorted by Preferred term (PT) in descending order of the 'Ofatumumab + Bendamustine' arm. The summary will use the following algorithms for counting the subject:

- **Preferred term row**: Subjects experiencing the same AE preferred term several times with different grades will only be counted once with the maximum grade.
- **Any event row**: Each subject with at least one adverse event will be counted only once at the maximum grade no matter how many events they have.

In addition, the frequency and percentage of AEs (all grades) will be summarized and displayed in two ways: 1) in descending order of incidence in 'Ofatumumab + Bendamustine' arm by PT only and 2) in descending order of incidence in 'Ofatumumab + Bendamustine' arm by System Organ Classes (SOC) and PT. In the SOC row, the number of subjects with multiple events under the same system organ class will be counted once.

A separate summary will be provided for study treatment-related AEs. A study treatment-related AE is defined as an AE for which the investigator classifies the relationship to

study treatment as "Yes". A worst case scenario approach will be taken to handle missing relatedness data, i.e. the summary table will include events with the relationship to study treatment as 'Yes' or missing. The summary table will be displayed in descending order of incidence in 'Ofatumumab + Bendamustine' arm by PT only.

For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables adverse events which are not serious adverse events with an incidence and serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

If for a same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

All AEs will be listed. Additionally, a listing of subject IDs for each individual AE will be produced.

Summaries based on the following subgroups: FL subgroup, gender, age, race, and geographic region (as defined in Section 8.3) will be provided for all AEs.

12.3. AEs of Special Interest

A comprehensive list of MedDRA terms based on clinical review will be used to identify each type of event. Changes to the MedDRA dictionary may occur between the start of the study and the time of reporting and/or emerging data from on-going studies may highlight additional adverse events of special interest, therefore the list of terms to be used for each event of interest and the specific events of interest will be based on the safety monitoring team (SMT) agreements in place at the time of reporting.

The events of special interest include:

- Infusion related AEs
- Infections
- Myelosuppression Events (anemia, neutropenia, thrombocytopenia)
- Progressive multifocal leukoencephalopathy (PML)

- Tumor Lysis Syndrome (TLS)
- Mucotaneous Reactions
- Reactivation of Hepatitis B
- Cardiac events
- Bowel Obstruction
- Neoplasms

Summaries of the number and percentage of subjects with these events will be provided for each type of event separately.

Infusion related AEs

Infusion reactions will be summarized using the preferred terms from the AE dataset.

The process for defining and reporting the infusion reactions is the following:

1) Select the candidate AEs

For each infusion, only AEs occur during and within 24 hours following the end of infusion will be included as candidate AEs.

If the AE onset date is available but the onset time is missing, then the AE will be included if it occurs on the same day as the infusion and the day following the infusion.

2) The list of candidate events based on the above criteria will be reviewed by the clinical and safety review team to select the final set of terms for inclusion in the analysis tables. This will be conducted at the Preferred Term (PT) level.

Infections

Summaries of infections will be based on treatment period and follow-up period pooled together by each grade and will be provided for grade 3, 4 and 5, respectively, as well as all infections regardless of grades.

In addition, the following summaries will be presented:

1) Summary of worst-grade infections

2) Summary of type of infections by all infections, all respiratory tract infections, lower respiratory tract infections, upper respiratory tract infections, sepsis and other infections.

3) Summary for drug-related infections

4) Summary of infections for subjects with baseline neutropenia.

The number and percentage of subjects with grade 3,4, and 5 infections will also be provided by responders and non-responders.

Myelosuppression events

A summary of AEs associated with anemia, neutropenia, and thrombocytopenia will be provided combined and separately. The frequency and percent of subjects with myelosuppression will also be provided by responders and non-responders.

A subject listing of all events will be provided.

Progressive multifocal leukoencephalopathy (PML)

A summary of AEs associated with progressive multifocal leukoencephalopathy (PML) will be provided.

A subject listing of all events will be provided.

Tumor Lysis Syndrome (TLS)

A summary of AEs associated with progressive multifocal leukoencephalopathy (PML) will be provided. Candidate events include: hyperuricemia, hyperphosphatemia, hyperkalemia, hypocalemia, and acute kidney injury.

A subject listing of all events will be provided.

Mucotaneous Reactions

A summary of AEs associated with mucotaneous reactions will be provided.

A subject listing of all events will be provided.

Reactivation of Hepatitis B

A summary of AEs associated with reactiviation of Hepatitis B will be provided.

A subject listing of all events will be provided.

Cardiac Events

A summary of AEs associated with cardiac events will be provided.

A subject listing of all events will be provided.

Bowel Obstruction

A summary of AEs associated with Bowel obstruction will be provided.

A subject listing of all events will be provided.

Neoplasms

A summary of AEs associated with Neoplasms will be provided.

A subject listing of all events will be provided

12.4. Deaths and Serious Adverse Events

No programming will be done to validate or remove death data from the dataset. All deaths will be summarised based on the number and percentage of subjects. This summary will classify subjects by time of death (on treatment, "<= 60 days after last dose", "> 60 days after last dose") and primary cause of death. A supportive listing will be generated to provide subject-specific details on subjects who died.

All SAEs will be tabulated based on the number and percentage of subjects who experienced the event. Separate summaries will also be provided for study treatment-related SAEs, fatal SAEs and study treatment related fatal SAEs. The summary tables will be displayed in descending order of incidence in 'ofatumumab + bendamustine' arm by PT only.

A study treatment-related SAE is defined as an SAE for which the investigator classifies the relationship to study treatment as "Yes". A worst case scenario approach will be taken to handle missing data, i.e. the summary table will include events with the relationship to study treatment as 'Yes' or missing.

SAEs are included in the listing of all adverse events. Separate supportive listings with subject-level details will be generated for

- Fatal SAEs
- Non-Fatal SAEs.

A summary of all serious adverse events and deaths will also be provided.

12.5. Adverse Events Leading to Discontinuation of Investigational Product and/or Withdrawal from the Study and Other Significant Adverse Events

The following categories of AEs will be summarized separately in descending order of 'ofatumumab + bendamustine' arm by PT only and separate supportive listings will be generated with subject level details for those subjects:

- AEs Leading to Discontinuation of Study Treatment
- AEs Leading to Dose Interruptions/Delay
- AEs Leadings to Dose Reductions

12.6. Pregnancies

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE as described in the protocol. If subjects become pregnant while on the study, the information will be included in the narratives and no separate table or listing will be produced.

12.7. Clinical Laboratory Evaluations

Summaries of worst case grade increase (shift) from baseline grade will be provided for all the lab tests that are gradable by CTCAE v4.0. The summary will include the baseline grade vs. worst-case post-baseline grade. Categories will be displayed as Grade 0, 1, 2, 3, 4, or missing. For laboratory tests that are graded for both low and high values, summaries will be done separately and labeled by direction, e.g., sodium will be summarized as hyponatremia and hypernatremia.

For lab tests that are not gradable by CTCAE v4.0, summaries of worst case changes (shifts) from baseline with respect to normal range will be generated. The summary will include the baseline grade vs. worst-case post-baseline grade. Worst-case (Extreme) Categories will be displayed as Low, Normal, High, High & Low, or missing..

Separate summary tables for hematology and chemistry laboratory tests will be produced.

A supporting listing of laboratory data for subjects with abnormalities of potential clinical concern (grade 3 or 4 toxicities) will be provided. A separate listing of laboratory data with character values will also be provided.

Detailed derivation of baseline assessment is specified in Section 9.2.7.

Unless otherwise specified, the denominator in percentage calculation at each scheduled visit will be based on the number of subjects with non-missing value at each particular visit.

Figures for median hemoglobin/neutrophil count/platelet count for all subjects, and for all subjects excluding those who received blood supportive care products over time will also be generated.

12.7.1. Analyses of Liver Function Tests

Summaries of hepatobiliary laboratory events including possible Hy's law cases will be provided.

Possible Hy's law cases are defined as (ALT>3×ULN or AST>3xULN) and Total Bilirubin>2×ULN and Alkaline Phosphatase <2xULN.

12.8. Other Safety Measures

Unless otherwise specified, the denominator in percentage calculation at each scheduled visit will be based on the number of subjects with non-missing value at each particular visit.

12.8.1. Vital Signs

Summary statistics of values and changes from baseline at worst value for the study will include count, mean, median, standard deviation, minimum, and maximum. Baseline is defined as the assessment closest to but prior to first dose without time (e.g., Day 1 if available otherwise screening).

Summaries of the number and percentage of subjects with increases in each vital sign for the worst-case post baseline value will be produced. Increases will be categorized as follows:

- Systolic Blood Pressure: 'Any Grade Increase', 'Increase to Grade 2 (140-159)' and 'Increase to Grade 3 (≥160)'
- Diastolic Blood Pressure: 'Any Grade Increase', , 'Increase to Grade 2 (90-99)', 'Increase to Grade 3 (≥100)'
- Heart Rate: 'Decrease to <60', 'Increase to > 100'
- Temperature: 'Decrease to ≤35', 'Increase to ≥38'

Summaries of shift from baseline values for the worst-case post baseline will be provided for all vital signs. Shifts will be categorized at baseline and worst-case assessment times as follows:

- Systolic Blood Pressure: '<120', '120-139', '140-159', '≥160'
- Diastolic Blood Pressure: '<80', '80-89', '90-99', '≥100'
- Heart Rate: '<60', '60-100', '>100'
- Temperature: '≤35', '36-37', ≥38'

Vital signs (blood pressure, heart rate, temperature, respiration rate, and weight) will be listed for each subject.

12.8.2. ECG

A summary of the number and percentage of subjects who had normal and abnormal (clinically significant and not clinically significant) ECG findings at screening/baseline will be provided.

A supporting listing will also be provided.

12.8.3. Liver Events

Any liver events occurring during the study will be summarized based on data recorded on the Liver Events eCRF pages. Timing of the event will be summarized (while on treatment, after stopping treatment) and summary statistics for time from first dose to start of liver event and time from last dose to start of liver event will be provided. A summary table for subjects who meet the liver event stopping criteria will also be provided.

The following listings will be provided:

- Listing of liver event results and time of event relative to treatment.
- Listing of liver chemistry laboratory for subjects with at least one liver event
- Listing of ofatumumab concentration and time relative to liver event for subjects with at least one liver event.

12.8.4. Frequency of transfusions

The number and percentage of subjects who receive blood transfusions during the study will be provided by treatment group.

12.8.5. Human Anti-Human Antibodies (HAHA)

Human Anti-Human Antibodies (HAHA) sample analysis will be conducted by a contract research organization using a validated assay. The number and percentage of subjects with positive and negative HAHA results will be provided for each HAHA timepoint. A summary table with the overall HAHA assessment for each subject, considering ofatumumab concentration at the time of each HAHA sample collection, will be provided. A listing of HAHA results with the ofatumumab concentration at that time will be provided.

12.8.6. Human Anti-Chimeric Antibodies (HACA)

Human Anti-Chimeric Antibodies (HACA) sample analysis will be conducted by a contract research organization using a validated assay. The number and percentage of subjects with positive and negative HACA results will be provided for each HACA timepoint.

A summary table with the number of subjects with positive HACA in the pre-dose samples will be reported.

HACA results prior to ofatumumab administration will be listed.

12.8.7. Quantitative IgG, IgA, IgM

Summaries of IgG, IgA, and IgM will be provided at scheduled visits for actual values as well as for change from baseline.

Plots of this data over time will also be provided as appropriate.

13. HEALTH OUTCOMES ANALYSES

All analyses described in this section will be performed using the ITT population, and the same analysis will be repeated in patients with FL. Summaries will be presented by treatment group. A data listing with individual subject data for each questionnaire will also be provided.

The FACT-Lym and EQ-5D should be administered at the screening visit and at all post-baseline visits per protocol. The Health Change Questionnaire (HCQ) should be administered at all post-screening visits. If a subject demonstrates disease progression, the measures should be completed at the progression visit and again one time after the determination of the progression. If a subject withdraws from the study then the questionnaires should be administered at the point of withdrawal.

PRO analysis will be performed in all patients and patients with follicular lymphoma based on ITT population. No formal statistical test will be performed and hence no multiplicity adjustment will be applied.

All PRO measures will be scored as per the developers instructions, with scores created for each pre-specified domain. Each PRO domain will be summarized by treatment group and time point, which will be presented in tabular format as mean, standard deviation, median, minimum and maximum.

A mixed-model repeated measurement (MMRM) for longitudinal data will be used to compare the two treatment arms in terms of the domain scores over time. This longitudinal model will include terms for treatment, the randomization stratification factors, time of visit, baseline value and an interaction term for treatment by time as fixed effects, and time will be treated as the repeated variable within subject. This analysis will be restricted to patients with an evaluable baseline score and at least one evaluable post-baseline score. Time will be considered as a continuous variable in this analysis. As a first approach, an unstructured correlation matrix will be used to model the correlation within patients, if the model fitting is inadequate, AR(1) structure will be experimented. Nominal p-values will be presented without any statistical inference since there is no adjustment for multiplicity.

For the model considered, the SAS code will therefore be:

```
PROC MIXED data=dataset method=reml;

     CLASS subject trt timeC strat_factors;
```

```
      MODEL score = trt strat_factors time score_B
      trt*time / noint s ddfm=kr;

      REPEATED timeC / subject=subject type=AR(1);

RUN;

/* score refers to the observed scores after Baseline

score_B refers to the baseline score

trt is the treatment variable

timeC refers to the time window as class variable

time refers to the time window

method=reml specifies that the restricted Maximum Likelihood
Estimation method used

type= AR(1) specifies that the first order autoregressive
covariance matrix is used */
```

Handling of missing data

Missing items data in a scale will be handled based on each instrument manual. No imputation will be applied if the total or subscale scores are missing at a visit, since all available data during the study will be used in the repeated measures model analyses which assume that the missing scores at any time point are missing-at-random.

Time Windows for PRO analyses

If more than one assessment is available in the same time window, the assessment closest to the planned date will be considered. If two assessments are obtained with the same time difference compared to the scheduled visit day, the assessment obtained prior to visit will be considered. The assessment at end of treatment visit will be considered as a scheduled time-point and in the time window definition if collected within 28 days of the last date of study treatment in the treatment phase, before crossover and before the start of any further anti-neoplastic therapies based on the definitions in table below.

The same time window definitions will be used for assessing the compliance rates over time-points for the PRO scores. A patient will be considered as eligible for a time-point assessment if the lower bound of the time window for that scheduled time point is within 28 days of the last date of study treatment in the treatment phase, before crossover and start date of new antineoplastic therapy.

Table Time Windows for PRO

Scheduled Time point	Planned Visit Timing	Time Window Definition
On treatment – includes assessment visits when treatment is ongoing and within 28 days of last dose		
Screening (Baseline, except for HCQ)	On or before Day 1*	≤ Study Day 1

Cycle 1 Day 1	Day 1	Day 1 - 22
Cycle x Day 1 (starting from Cycle 3 Day 1, every 2 cycles, till Cycle 7 Day 1)	Day (x-1)*21+1	Day (x-1)*21+1-20 to (x-1)*21+1+21
Cycle 9 Day 1	Day 169	Day 149 to 197
Cycle 11 Day 1	Day 225	Day 198 to 253
Follow-up Cycle 1 Day 1	Day (8*21)+(4*28)+28*2+1=337	Day 254 to 379
Follow-up Cycle x Day 1 (starting from Follow-up Cycle 4 Day 1, every 3 cycles, till Follow-up Cycle 16 Day 1)	Day 337+(x-1)*28	Day 337+(x-1)*28-28*1.5+1 to 337+(x-1)*28+28*1.5
Follow-up Cycle 30 Day 1	Day 337+30*28 = 1177	Day 800 to 1345
Follow-up Cycle 42 Day 1	Day 337+42*28 = 1513	Day 1346 to 1681
Follow-up Cycle 54 Day 1	Day 337+54*28 = 1849	Day 1682 to 2017

* Day 1 = date of randomization

13.1. Functional Assessment of Cancer Therapy - Lymphoma (FACT-Lym)

Background:

The FACT-Lym is comprised of a 5 dimension health status measure: physical well-being (7 items); social/family well-being (7 items); emotional well-being (6 items); functional well-being (7 items); and additional concerns (15 items). Subjects respond to the individual questions within a dimension on a five point Likert scale ranging from 0 *'Not at all'* to 4 *'Very much'* and are asked to think back over the past 7 days when responding to each of the items.

Summaries and Analyses:

Instructions for FACT-Lymphoma Scoring Guidelines:

1. Record answers in "item response" column. If missing, mark with an X
2. Perform reversals as indicated, and sum individual items to obtain a score.
3. Multiply the sum of the item scores by the number of items in the subscale, then divide by the number of items answered. This produces the subscale score.
4. Add subscale scores to derive total scores
5. The higher the score, the better the QOL.

Subscale	Item Code	Reverse item?		Item response	Item Score
PHYSICAL	GP1	4	-	_____	=_____
WELL-BEING	GP2	4	-	_____	=_____

(PWB)	GP3	4	-	_____	=_____
	GP4	4	-	_____	=_____
Score range: 0-28	GP5	4	-	_____	=_____
	GP6	4	-	_____	=_____
	GP7	4	-	_____	=_____

Sum individual item scores: _____

Multiply by 7: _____

Divide by number of items answered: _____=**PWB subscale score**

SOCIAL/FAMILY	GS1	0	+	_____	=_____
WELL-BEING	GS2	0	+	_____	=_____
(SWB)	GS3	0	+	_____	=_____
	GS4	0	+	_____	=_____
Score range: 0-28	GS5	0	+	_____	=_____
	GS6	0	+	_____	=_____
	GS7	0	+	_____	=_____

Sum individual item scores: _____

Multiply by 7: _____

Divide by number of items answered: _____=**SWB subscale score**

EMOTIONAL	GE1	4	-	_____	=_____
WELL-BEING	GE2	0	+	_____	=_____
(EWB)	GE3	4	-	_____	=_____
	GE4	4	-	_____	=_____
Score range: 0-24	GE5	4	-	_____	=_____
	GE6	4	-	_____	=_____

Sum individual item scores: _____

Multiply by 6: _____

Divide by number of items answered: _____=**EWB subscale score**

FUNCTIONAL	GF1	0	+	_____	=_____
WELL-BEING	GF2	0	+	_____	=_____
(FWB)	GF3	0	+	_____	=_____
	GF4	0	+	_____	=_____
Score range: 0-28	GF5	0	+	_____	=_____
	GF6	0	+	_____	=_____
	GF7	0	+	_____	=_____

Sum individual item scores: _____

Multiply by 7: _____

Divide by number of items answered: _____=**FWB subscale score**

Subscale	**Item Code**	**Reverse item?**		**Item response**	**Item Score**
LYMPHOMA	P2	4	-	_____	=_____
SUBSCALE	LEU1	4	-	_____	=_____
(LYMS)	BRM3	4	-	_____	=_____
	ES3	4	-	_____	=_____
Score range: 0-60	LYM1	4	-	_____	=_____
	LYM2	4	-	_____	=_____
	BMT6	4	-	_____	=_____
	C2	4	-	_____	=_____
	GA1	4	-	_____	=_____
	HI8	4	-	_____	=_____
	N3	4	-	_____	=_____
	LEU6	4	-	_____	=_____
	LEU7	4	-	_____	=_____
	BRM9	4	-	_____	=_____

LEU4 4 - _____ =_____

Sum individual item scores: _____

Multiply by 15: _____

Divide by number of items answered: _____**=LYM Subscale score**

To derive a FACT-Lymphoma Trial Outcome Index (TOI):
Score range: 0-116
_____ + _____ + _____ =_____**=FACT-Lymphoma TOI**

(**PWB** score) (**FWB** score) (**LymS** score)

To Derive a FACT-G total score:
Score range: 0-108
_____ + _____ + _____ + _____=_____**=FACT-G Total score**

(**PWB** score) (**SWB** score) (**EWB** score) (**FWB** score)

To Derive a FACT-Lymphoma total score:
Score range: 0-168
_____ + _____ + _____ + _____ + _____ =_____**=FACT-Lymphoma Total**

(**PWB** score) (**SWB** score) (**EWB** score) (**FWB** score) (**LymS** score) **score**

Handling missing items for FACT-Lym

If there are missing items, subscale scores can be prorated. This is done by multiplying the sum of the subscale by the number of items in the subscale, then dividing by the number of items actually answered. This can be done on the scoring guide or by using the formula below:

Prorated subscale score = [Sum of item scores] x [N of items in subscale] ÷ [N of items answered]

When there are missing data, prorating by subscale in this way is acceptable as long as more than 50% of the items were answered (e.g., a minimum of 4 of 7 items, 4 of 6 items, etc). The total score is then calculated as the sum of the un-weighted subscale scores. The FACT scale is considered to be an acceptable indicator of patient quality of life as long as overall item response rate is greater than 80% (e.g., at least 22 of 27 FACT-G items completed). This is not to be confused with individual subscale item response rate, which allows a subscale score to be prorated for missing items if greater than 50% of items are answered. In addition, a total score should only be calculated if ALL of the component subscales have valid scores.

The analyses will be prepared by domain and will be summarized as follows:

- Summary of raw score and change from baseline by domain (PWB score, SWB score, EWB score, FWB score, LymS score, as well as FACT-Lymphoma TOI, FACT-G Total score FACT-Lymphoma Total), by time point and treatment group
- Summary of MMRM (PWB score, SWB score, EWB score, FWB score, LymS score, as well as FACT-Lymphoma TOI, FACT-G Total score FACT-Lymphoma Total)

13.2. EuroQoL Five-Dimension (EQ-5D)

Background:

The EQ-5D is comprised of a 5-item health status measure and a visual analogue rating scale/feeling thermometer. These components are administered independently which results in the derivation of two utility measures. It is a simple, effective, validated and globally accepted generic instrument which is being used in this study as a two part measure (part one is the five dimensional Health State Classification and part two is the visual analogue scale 'Thermometer') [EuroQol, 1990] .

The first utility value will be derived from the five domains of the EQ-5D and the second utility value will be derived from the feeling thermometer.

Summaries and Analyses:

Using the five dimensional Health State Classification [EQ-5D User Guide,1992], subjects are asked to respond to five questions on different aspects of their health status that assess mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each question is responded to on a three-point scale which indicates the level of impairment (level 1 = no problem; level 2 = some or moderate problem(s) and level 3 = unable, or extreme problems). This generates a unique description of the subjects' health status, which is valued between zero (representing death) and one (representing perfect health). Negative health status describes health state worse than death. Details of the method for calculating this score are provided below.

In addition to completing the five dimensional Health State Classification to generate a single health status index and a health profile, subjects are asked to rate their current health status using the visual analogue scale 'Thermometer'. The 'Thermometer' has endpoints of 100 (best imaginable health state) and 0 (worse imaginable health state). The subject rates their current health state by drawing a line from the box marked 'Your health state today' to the appropriate point on the 'Thermometer' scale.

Tariff for the 243 health states defined by the EuroQoL classification are calculated from regression coefficients which have been used to derive the decrements shown in the following table.

Table for EuroQoL Health State Decrements

EuroQoL Health State	Level 2	Level 3
Mobility (A)	0.069	0.314
Self-care (B)	0.104	0.214
Usual activity (C)	0.036	0.094
Pain/discomfort (D)	0.123	0.386
Anxiety/depression (E)	0.071	0.236
	Constant=0.081	N3=0.269

The arithmetic needed to recover the estimated value for any health state from this table of decrements is shown in the following equation:

Tariff (utility score) = Full health tariff – constant – A level – B level – C level – D level – E level – N3

where:

- full health has a state of 1 1 1 1 1 and a tariff of 1.0,
- a level of 1 for any question has a decrement of 0,
- the constant is only subtracted if at least one state has level 2 or level 3 and
- N3 is only subtracted if at least one state has level 3

For example:

Overall Health state 1 1 2 2 3		
where:	Level	Subtract
Mobility	1	0
Self-care	1	0
Usual activity	2	0.036
Pain/discomfort	2	0.123
Anxiety/depression	3	0.236

The estimated tariff (utility score) is therefore: 1.0 – 0.081 – 0.036 – 0.123 - 0.236 – 0.269 = 0.255

The following summary tables will be provided:

- Summary of utility score and change from baseline score in EQ-5D by time point and treatment group
- Summary of Visual Analog Scale (VAS) and change from baseline score in EQ-5D by time point and treatment group
- Summary of MMRM on utility score and VAS

13.3. Health Change Questionnaire

The Health Change Questionnaire (HCQ) used is a nine item scale that asks the patient to rate change in status since beginning treatment on this study. Scale choices are :

- A great deal better
- Moderately better
- A little better
- Almost the same, hardly any better
- Unchanged
- Almost the same, hardly any worse
- A little worse
- Moderately worse
- A great deal worse

A summary of the percentage of subjects in each category will be provided by time point and treatment group.

14. PHARMACOKINETIC ANALYSES

The reconciliation of the pharmacokinetic Case Report Form (CRF) and Pharmacokinetic (PK) data will be performed by, or under the direct auspices of, Data Sciences - Oncology, Novartis.

The merge of pharmacokinetic concentration data and CRF data to generate a dataset with actual blood sampling times, actual time relative to dosing, and concentrations will be performed after DBF by, or under the direct auspices of, Novartis Oncology Clinical Data Review and Reporting. Analysis datasets will be created according to CDISC/ADaM standards.

Derivation of pharmacokinetic parameters will be performed by Novartis Oncology Clinical Pharmacology. A population pharmacokinetic approach will be used to estimate ofatumumab pharmacokinetic parameters. The details of the analysis will be included in a separate analysis plan, and the results will be reported in a separate Population Pharmacokinetic report.

Unless otherwise stated, all tables, figures and listings in this section will be based on the Pharmacokinetic population, and all summaries, figures and data listings will use treatment labels as specified in Section 7.

14.1. Drug Concentration Measures

Concentrations of ofatumumab in plasma will be listed by actual relative time and summarized by nominal time. Standard summary statistics will be calculated (i.e., mean, standard deviation, median, minimum and maximum). Refer to the PK Guidance "Pharmacokinetic / Pharmadynamic Analysis Manual" document for more information regarding the handling of ofatumumab plasma concentration data.

Below the limit of quantitation (BLQ) values will be set to zero by the Bioanalyst, and will be displayed in the listings as zero and flagged. BLQ values will be treated as missing for the calculation of the geometric means and geometric CV%.

Individual plasma concentration-time profiles and median/mean profiles by treatment group will be plotted using actual elapsed time for individual plots and nominal time for median/mean profiles. Each of the figures will contain one plot on the untransformed scale (i.e., a linear plot) and one plot on the log-transformed scale (i.e., log-linear plot).

Any concentration falling outside of pharmacokinetic sample collection windows will be excluded from summary tables and figures.

14.2. Statistical Analyses

Only data for patients taking Ofatumumab will be analyzed. Summary data will only be reported for patients on Arm A (Ofatumumab + Bendamustine). Data Listings will include all data, including data for patients taking Optional Ofatumumab.

The following tables and listings will be created:

- Summary of Plasma Ofatumumab Concentration -Time Data
- Listing of Plasma Ofatumumab Concentration -Time Data

Additionally, the figures listed below will also be provided:

- Mean Plasma Ofatumumab Concentration –Time Plot
- Median Plasma Ofatumumab Concentration –Time Plot
- Individual Plasma Ofatumumab Concentration –Time Plots

15. PHARMACOKINETIC/PHARMACODYNAMIC ANALYSES

If data permit, [redacted] analyses may be performed by Novartis Oncology Clinical Pharmacology as part of the Population Pharmacokinetic analyisis. Any Pharmacokinetic/Pharmacodynamic (PK/PD) analyses will be described in the Population Pharmacokinetic Analysis Plan, and will be reported as part of the Population Pharmacokinetic Report, which will be issued separately.

16. REFERENCES

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17. ATTACHMENTS

17.1. Table of Contents for Data Display Specifications

The table of contents for the data displays as well as the data display specifications will be available as a separate document from the SAP.