NOVARTIS

Clinical Development

GSK1841157

Protocol OMB110918 / NCT01077518

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

Authors	[redacted]
Document type	Amended Protocol Version
EUDRACT number	2008-004177-17
Version number	11
Development phase	III
Document status	Final
Release date	13-Apr-2017
Novartis internal reference number	COMB157E2301

Amendment 9 (13-Apr-2017)

Amendment rationale

The purpose of amendment 9 is to revise the total number of events required for the primary analysis of the primary end point PFS.

The primary analysis was planned after reaching 259 PFS events as determined by an Independent Review Committee (IRC). Based on the current status of the study and PFS event count by IRC, it is highly unlikely that the 259 PFS events will be achieved.

The study has been ongoing since September 2010 when the first patient was enrolled and the study sponsorship changed in February 2016 from GSK to Novartis (Amendment 8, dated 18Mar2016). Per protocol, Interim Analysis for efficacy and futility and IDMC review occurred (22Feb2016) after 180 PFS events by IRC were reached (31Oct2015). IDMC recommended to continue the study without changes. The interim analysis of PFS was performed by an independent Statistical Data Analysis Centre. As per IDMC charter, unblinded results were not communicated to the sponsor in order to maintain the integrity of the trial. The protocol defined full recruitment of 346 patients was achieved as of 16May2016.

As of 31Jan2017, 203 PFS events by IRC were reported with 56 events remaining to achieve the planned 259 events. Furthermore, there were approximately 58 patients at risk of having a future event at that time, so it was highly unlikely that 259 PFS events would ever be reached. The overall rate of discontinuation before PFS event was 21% (n=71 out of 346), due to reasons such as withdrawal from study, start of new anti-cancer therapy and lost to follow-up. This was higher than the protocol assumed discontinuation rate of 12%.

This amendment defines an updated targeted number of PFS events by IRC of approximately 215 for the primary analysis. This number of events was selected as it is achievable in a timely manner (considering the current rate of PFS events), and it allows to keep an appropriate level of power (84%) to demonstrate the targeted treatment effect. The critical value for the primary analysis has been updated using the targeted number of events at the cut-off date, and considering the α-level spent at interim analysis, in order to achieve a cumulative type I error smaller than 5%.

Sixty nine percent of enrolled patients in this study have the diagnosis of follicular lymphoma (FL) and 31% have other histological subtypes of indolent non-Hodgkin lymphoma (iNHL). Prior experience with the anti-CD20 monoclonal antibody obinutuzumab in the GADOLIN trial with very similar trial design showed that the efficacy of this drug was demonstrated in the FL sub-type only (80% of the trial population), which led to the approval of obinutuzumab in combination with bendamustine in that particular subset of iNHL patients only. Since the current protocol does not include an analysis of efficacy per histological subtypes (i.e. in FL and non-FL patients) and based on the above considerations, secondary objectives are added in order to formally compare efficacy in the FL patients between treatment arms (i.e. “inferential secondary endpoints”). Efficacy analyses will also be performed in the non-FL patients to allow accurate interpretation of the results. Consequently, the hierarchical testing procedure is updated to include PFS, ORR and OS in the FL patients, in addition to PFS, ORR and OS in all patients.

The initial testing plan for inferential secondary endpoints (i.e. PFS according to IRC assessment in FL patients, overall survival and ORR in overall patients and in FL patients) has been updated to incorporate the additional objectives [redacted]. The updated approach allows to control the type I error probability by using a separate alpha spending function for each inferential secondary endpoint, independent of the one used for the primary efficacy analysis of PFS.

A total of 173 patients were randomized to Arm B (Bendamustine monotherapy). Over time, there were inconsistencies in the protocol amendments regarding the need for collection of HACA samples for Arm B patients at Cycle 1 Day 1 (C1D1). Despite these inconsistencies, the general interpretation was that samples should be collected at C1D1, which resulted in collection of approximately 83% of Arm B (n=143 of total 173) HACA samples at that time point. This amendment clarifies HACA sample collection for Arm B patients stating that HACA samples should be collected at C1D1 for all patients in the trial.

The amendment also clarifies timing of primary and final analysis. Primary analysis will take place after approximately 215 PFS events by IRC are achieved and final analysis will take place after all patients have completed 5 year follow up or discontinued earlier.

This amendment replaces IRR (Independent Radiology Review) with IRC (Independent Review Committee which includes radiology and Oncology review) to correctly reflect the review of PFS events being done.

Changes to the protocol

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underline for insertions.

Sponsor Information Page: Medical lead contact information changed to reflect current medical lead information

Protocol Summary: updated to add the Amendment 9 changes related to the revised number of events needed for the primary PFS analysis. Objective section modified to add new secondary objectives. Study end points updated to add new secondary end points. In the study design section, added primary analysis information. Interim analysis section updated to clearly define IRC.

Independent Radiology (IRR) changed to Independent Review Committee (IRC) throughout the document where applicable.

Summary of previous amendments was added.

Updated the list of abbreviations to add IRC.

For clarity, the term “primary analysis” is used throughout the document, to replace the previous term of “final analysis”, for the analysis which is planned when approximately 215 PFS events by IRC occurs. Additionally, in Section 8.2, the definition of “final analysis” has been added for the analysis to be conducted at the end of study.

Section 2: Secondary objectives are added for patients with follicular lymphoma.

Section 3.1: Added the revised number of PFS events needed for the primary analysis.

Section 6.3.3: Updated to clarify collection of HACA samples.

Section 8.2: Primary analysis and final analysis are clearly described. Final was changed to primary wherever applicable throughout the document. Added the number of revised events required for primary analysis, including statistical justification.

Sections 8.2.1, 8.3.3.1, 8.3.3.2, 8.3.5, 8.3.6.1: Added when the primary analysis will take place.

Section 8.3.3.2: Hierarchical testing scheme is modified to accommodate additional secondary endpoints in patients with follicular lymphoma.

Section 8.3.3 and 8.3.6.1: Analyses related to patients with follicular lymphoma are added.

Section 8.3.6.3 Language regarding PRO analyses is updated

Appendix 3 is updated to reflect change of IRR to IRC

Information for IRB

A copy of this amended protocol will be sent to all applicable Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

Amendment 8 (18-Mar-2016)

Amendment rationale

Subsequent to the acquisition of GlaxoSmithKline (GSK) compound ***GSK1841157***, the purpose of this protocol Amendment **8** is to:

- Delete or replace references to GSK or its staff with that of Novartis and its authorized agents to align with the change of sponsorship;
- Make administrative changes to align with Novartis processes and procedures;

As of ***11-JAN-16***:

336 patients have received study treatment in ***16*** countries;

The changes described in this amended protocol require Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) approval prior to implementation.

A copy of this amended protocol will be sent to the IRBs/IECs and Health Authorities (HAs).

The changes herein affect the Informed Consent and all sites are required to update and submit for approval, a revised Informed Consent that takes into account the change of study sponsorship described in the protocol amendment.

Upon approval of this amendment, patients who have already been enrolled in the study will sign a new informed consent form indicating Novartis is the new study sponsor and continue the appropriate visit schedule.

Revision Chronology

GlaxoSmithKline Document Number	Date	Version
UM2008/00047/00	**2009-AUG-07**	**Original**
UM2008/00047/01	**2009-NOV-16**	**Amendment No. 1**
Logo updated to describe meaning of COMPLEMENT. Sponsor information page: Medical Monitor contact information updated. Addition of secondary endpoint: Overall response rate to optional ofatumumab monotherapy in subjects in Arm B who progress during or following single-agent bendamustine. Spelling correction in the Exclusion Criteria: fludaranine replaced by fludarabine and addition of criteria excluding prior treatment with anti-CD20 mAb within 3 months of randomization. Administer bendamustine therapy as monotherapy or in combination with ofatumumab for up to 8 cycles. There will be a total of 12 ofatumumab infusions in Arm A. 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 until all 12 doses are completed		
UM2008/00047/02	**2010-MAY-12**	**Amendment No. 2**
Sponsor information page: Medical Monitor phone number corrected. Introduction includes additional rationale for infusion of 1000 mg dose upon first infusion in and 2000 mg dose upon 2nd infusion (for those who receive ofatumumab following PD in Arm B) at protocol defined rate. Inclusion criterion #1 updated: Removed reference to bulky stage. Clarified screening procedures. Inclusion criterion #2 updated: to allow CT imaging performed at least 60 days after the last dose of rituximab-based therapy. Modified text for prior rituximab infusions. Exclusion criterion #3 updated timeframe from previous autologous stem cell transplant, or fludarabine therapy, or radioimmunotherapy from past 12 months to last 6 months. Exclusion criterion #5 updated timeframe for high dose steroids (7 consecutive days) and dose of prednisone before randomization (≥100 mg). Exclusion criterion #7 update to exclude prior use of any monoclonal antibody (other than anti-CD20) within 3 months of randomization and anti-CD20 therapy first dose was administered 60 days prior to randomization. Exclusion criteria #15 updated: specifies liver metastases related to indolent NHL. Exclusion criterion #18 updated to include hypersensitivity to bendamustine and mannitol. Removed exclusion criterion #20 since it duplicated criterion #7. Subjects in Arm B who choose to receive optional ofatumumab monotherapy will receive ofatumumab 1000 mg for the first dose. CT scans, lymphoma symptoms, and response assessments will be done Days 84, 168, and 252 (±7 days). Whole body CT scan (contrast imaging of neck when lesion is palpable, thorax, abdomen, pelvis). Section 6.2.4.2: removed mention of physical examination as part of CR assessment. Updated FACT-Lym Version 4, removed FACT-G Patient Reported Outcomes (PRO) questionnaire. HACA test done before first dose of ofatumumab.		

Additional PK sampling in Appendix 3 (if ofatumumab selected following PD in Arm B).

A pharmacokinetic sample (and a HAHA sample) will be collected with other withdrawal assessments for subjects who withdraw from treatment when receiving ofatumumab. For subjects who experience progressive disease, a PK sample (and a HAHA sample) will be collected on one occasion after disease progression.

Investigator Brochure updated now dated 28 April 2010.

In the event the 1st infusion of bendamustine is administered on Day 2 of a cycle (in Arm A only), then some assessments done on Day 1 will need to be done on Day 2 and assessments done on Day 2 will need to be completed on Day 3.

Visit window between cycles specified: ofatumumab and bendamustine must be given consecutively. An "on within 3 days after" visit window will be allowed between cycles.

Visit window for each week of optional ofatumumab updated to ±1 day with a minimum 7 day interval between weekly infusions.

[redacted]

The time to infuse for 1000 mg and 2000 mg is the same (4.5 hours first infusion and 4.0 hours subsequent infusions).

Appendix 6: Update FLIP-1 and FLIPI-2 tables.

[redacted]

UM2008/00047/04	**2012-JAN-19**	**Amendment 3**

CT scans may be whole body or done according to local practice

No required bone marrow aspirate

Known and exploratory prognostic markers [redacted] objectives clarified.

Inclusion Criterion #1: Type of previous biopsy changed from "lymph node" to "tissue" biopsy.

Inclusion Criterion #1 clarified. Tumor verified to be CD20+ positive from a previous or current tissue biopsy.

No longer excludes fludarabine and radioimmunotherapy.

No longer excludes external beam radiation therapy to pelvis and to bony disease to the cranium, mediastinum, and axilla, or > 3 vertebral bodies.

Removed Exclusion criterion restricting anti-CD20 antibody within the last 60 days

Section 3.1.1.1: Copy of documentation confirming PD (for example, an imaging report, clinical documentation) after subject deemed unresponsive or relapsed to rituximab-based regimen is required.

Follow-up visits begin 2 months after PD is confirmed by CT scan. For all other responses, follow-up visits begin on Day 336 (this is 3 months after Day 252) for both arms.

Section 4.4 clarifications: Withdrawal Criteria: If a subject withdraws from study drug but does not withdraw from the study, the subject is expected to complete all scheduled visits without study drug. The subject may then enter follow-up.

Section 5.1.3, Bendamustine: Added guidance for instances when bendamustine may be given <8 cycles.

Section 6.2.5: Removed requirement to exclude target and non-target lesions not previously-irradiated.

Bendamustine dosage must be delayed in subjects with a serum creatinine > 1.5 ULN if the calculated creatinine clearance or creatinine clearance from a 24-hour urine collection is ≤40 mL/min.

Section 6.4.1: Update to liver stopping criteria.

Clarification on timing of vital signs during and after ofatumumab infusion.

Section 6.7 updated to reflect changes in ofatumumab pharmacokinetic sample collection. Section 8 updated to reflect changes in data analysis. Time and events tables updated to reflect changes in ofatumumab pharmacokinetic sample collection (Appendix 2, Appendix 3). Change to frequency of HAHA sampling in Time and Events tables (Appendix 2, Appendix 3). [redacted]. Clarification: Monthly ofatumumab dosing in Arm A begins 28 days after Day 1 of the previous cycle. Acceptable but not encouraged for blood draw to be taken no more than 3 days ahead of the visit date, however, absolute neutrophil count, platelet count, peripheral blood lymphocytes, and hemoglobin local results must also be entered into the eCRF if it is used for a treatment decision. Follow-up #1 schedule, in both arms, begins on Day 336 and continues every 3 months until Month 18 of the F/U phase. The frequency of Follow-up #2 schedule comes after the end of follow-up schedule #1 and continues until Month 60. The last required CT scan is done on month 54. The frequency of follow-up 2 will be every 12 months until Month 54. Clarification: The one month follow-up in Arm A will occur regardless of response. Time and Events tables updated to reflect changes throughout protocol. Screen failure rate changed from 10% to 15% and dropout rate changed from 10% to 12%; impacts estimated subject numbers. Screening period is 21 days. IDMC section updated to reflect their decision to not alter the dose of bendamustine in Arm A. Section 6.5.7: All SAEs and AEs will be collected from the first dose of investigational product to 60 days after the last dose of investigational product and will be documented on the eCRF. Only SAEs, regardless of causality, will be reported from 61 Days after the last dose of treatment to the end of the follow-up period.		
UM2008/00047/05	**2013-FEB-07**	**Amendment 4**
Minor changes for spelling, grammar, consistency throughout document. Administrative changes. Edited text due to updates found in Investigator Brochure update. Correction in footnotes to Time and Events Table (Appendix 1): baseline CT scans required ≤1 month of randomization. Section 6.5.7: Correct reference for Table updated. High dose steroids ≥ 25 mg prednisolone/day (or equivalent) for 7 consecutive days are excluded. Updated from excluding ≥ 100 mg prednisolone/day (or equivalent). Section 6.5.7: All SAEs regardless of causality will be reported from 61 days after the last dose of investigational product to the end of the follow-up period or until initiation of subsequent anti-lymphoma therapy is initiated. Any SAE brought to the investigator's attention after the start of subsequent anti-lymphoma therapy and considered by the investigator as possibly related to either ofatumumab or bendamustine must be reported to GSK. Additional biochemistry testing added to time and events table for ofatumumab monotherapy following progression in Arm B. For Japan only: additional directions for Hepatitis monitoring added to an Appendix. Minor updates for consistency throughout protocol and in time and events tables. Investigator Brochure reference updated.		
UM2008/00047/06	**2013-FEB-07**	**Amendment 5**
[redacted] safety related information from the Study Procedures Manual (SPM) was added into Section 6.5.4.		
UM2008/00047/07	**2013-DEC-02**	**Amendment 6**
Added additional instructions for monitoring subjects who are HBsAg negative, anti-HBc positive		

and HBV DNA negative. This instruction was added to the relevant Time and Events tables. Exclusion criteria now specifies that physician experienced in care and management of subjects with Hepatitis B to manage/treat subjects who are anti-HBc positive must be consulted Changes for countries currently using Amendment 4 include specific details on how to manage AEs and SAEs such as infusion reactions, tumor lysis syndrome, progressive multifocal leukoencephalopathyand hepatitis are described. Minor clarifications throughout document Universal Trial Number added Administrative changes		
UM2008/00047/08	**2015-JUN-30**	**Amendment 7**
Authors and Sponsor Contact Information Updated Table of Contents updated to include Appendix 15: Protocol Changes for Amendment #7 from Amendment #6 Total number of events increased to 259 events Total study duration increased to 77 months Total accrual rate decreased to 5.1pt/month Clarification of randomization strategy An Interim Analysis added for efficacy when two thirds of IRR events occur. Details of a further Independent Data Monitoring Committee (IDMC) added to review the safety, efficacy, and futility data and recommend whether the study should continue without any changes, be stopped to further enrollment, or be terminated. Liver stopping criteria updated to reflect stopping criteria applies to all patients on study, regardless of Arm assignment. Clarification of instructions regarding how patients move into Survival Follow-Up Administrative changes		
UM2008/00047/09	**2015-JUL-07**	**Amendment 7**
Republished due to typographical error		
UM2008/00047/10	**2016-MAR-18**	**Amendment 8**
The purpose of this protocol amendment is to: • Delete or replace references to GSK or its staff with that of Novartis and its authorized agents to align with the change of sponsorship • Make administrative changes to align with Novartis processes and procedures		

Sponsor Signatory:

[redacted]

Date

Novartis Pharmaceuticals Corporation

SPONSOR INFORMATION PAGE

Clinical Study Identifier: OMB110918

Sponsor Contact Information:

Novartis Pharmaceuticals Corporation

In some countries, the clinical trial sponsor may be the local Novartis and its authorized agents. Where applicable, the details of the Sponsor and contact person will be provided to the relevant regulatory authority as part of the clinical trial submission. Please refer to Study Procedures Manual for further details on contact information.

Sponsor Serious Adverse Events (SAE) Contact Information: For study conduct questions not related to patient safety, the first line of contact will be with the designated local country company contact. In the event that the designated company contact is not available please contact the Medical Lead.

[redacted] **Contact Information:**

[redacted], MD

Telephone: [redacted]

Email: [redacted]

[redacted] **Contact Information:**

[redacted]

Telephone: [redacted]

Email: [redacted]

If you have any questions regarding the protocol, please contact your local Novartis office.

Agency Identifying Numbers: IND Numbers: 11,465; EudraCT Number 2008-004177-17

Universal Trial Number (UTN): U1111-1145-5175

Investigator PROTOCOL Agreement Page

For protocol number: OMB110918 (COMPLEMENT A+B):

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name: _____

Investigator Signature Date

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LIST OF ABBREVIATIONS

[redacted]	[redacted]
AE	Adverse Event
ALC	Absolute Lymphocyte Count
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
AUC	Area under the concentration-time curve
B	Bendamustine
BP	Blood Pressure
CBC	Complete Blood Count
CD	Cluster of differentiation
[redacted]	[redacted]
CHOP	Cyclophosphamide, doxorubicin, vincristine, prednisone
CLL	Chronic Lymphocytic Leukemia
CR	Complete Remission
eCRF	Electronic Case Report Form
CT	Computed Tomography
D, d	Day(s)
DILI	Drug Induced Liver Injury
DLBCL	Diffuse Large B Cell Lymphoma
DNA	Deoxyribonucleic Acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EOI	End of Infusion
EORTC-QLQ-C30	European Organization for Research and Treatment of Cancer
EQ-5D	EuroQoL Five Dimension
EU	European Union
FA	Futility Analysis
FcR	Fc Gamma Receptor
FL	Follicular Lymphoma
FACT-Lym	Functional Assessment of Cancer Therapy-Lymphoma
FACT-Lym TOI	Functional Assessment of Cancer Therapy-Lymphoma- Trial Outcome Index
FDA	Food and Drug Administration (US)
FLIPI	Follicular Lymphoma International Prognostic Index
GCSP	Global Clinical Safety and Pharmacovigilance

GSK	GlaxoSmithKline
HACA	Human Anti-Chimeric Antibody
HAHA	Human Anti-Human Antibody
HBcAb	Hepatitis B Core Antibody
HBsAg	Hepatitis B Surface Antigen
HCG	Human Chorionic Gonadotrophin(s)
HCQ	Health Change Questionnaire
HRQL	Health Related Quality of Life
HIV	Human Immunodeficiency Virus
h, hr	Hour(s)
IA	Interim Analysis
IB	Investigator Brochure
IDMC	Independent Data Monitoring Committee
IND	Investigational New Drug
INR	International normalized Ratio
IEC	Independent Ethics Committee
IgA, IgG, IgM	Immunoglobulin A, G, M
IRB	Internal Review Board
IRR	Independent Radiology Review
ITT	Intent to Treat
IRC	Independent Review Committee
IV/i.v.	Intravenous
LDH	Lactate Dehydrogenase
M	Month(s)
m^2	Meter squared
mAb	Monoclonal Antibody
MeDRA	Medical Dictionary for Regulatoy Activities
mg	Milligram(s)
MSDS	Material Safety Data Sheet
MTD	Maximum Tolerated Dose
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NHL	Non-Hodgkin's Lymphoma
O	Ofatumumab
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
[redacted]	[redacted]
(m)PFS	(median) Progression-Free Survival
PI	Prescribing Information
PP	Patient Population

PPD	Product of perpendicular diameters
po	Orally (Per Os, Latin: by mouth)
PR	Partial Remission / Response
PRO	Patient reported outcome
q	Every (quaque, Latin)
R	Rituximab
RAP	Reporting and Analysis Plan
RR	Response Rate
RRCML	Revised Response Criteria for Malignant Lymphoma
SAE	Serious Adverse Event
SD	Stable Disease
SPC	Summary of Product Characteristics
SPD	Sum of the products of the greatest diameter
SPM	Study Procedures Manual
t½	Half-life
TTP	Time to progression
t_{max}	Time at which maximum concentration is observed
ULN	Upper Limit Normal
US	United States
VAS	Visual Analogue Scale
Vss	Volume of distribution at steady state
yr, YR	Year(s)

PROTOCOL SUMMARY

Rationale

Patients with indolent lymphomas have a variable course. Most present with stage III or IV disease and eventually require treatment. Indolent lymphomas are sensitive to alkylating agents and to combinations with biologics, but subsequently follow a pattern of multiple relapses and progressively shorter periods of remission between relapses. Options are limited for those who no longer respond to rituximab-containing regimens.

Bendamustine is a synthetic nitrogen mustard compound that has been approved by Food and Drug Administration (FDA) for the treatment of chronic lymphocytic leukemia, and has activity in the treatment of indolent non-Hodgkin's lymphoma (NHL) that has progressed during or within 6 months of treatment with rituximab or a rituximab–containing regimen [Treanda Prescribing Information , 2010; Kahl, 2010; Friedberg, 2008]. Biologics have demonstrated enhanced efficacy when added to chemotherapeutic combinations in the frontline treatment for indolent NHL. Ofatumumab is an anti-CD20 mAb shown to have monotherapy activity in a Phase I/II study in relapsed follicular lymphoma following rituximab-containing therapy. The combination of ofatumumab and bendamustine may provide additional clinical benefit to those who no longer respond to rituximab or rituximab-containing regimens.

Objectives

The primary objective of the study is to test whether the ofatumumab and bendamustine combination therapy will improve disease progression-free survival (PFS) in subjects with indolent B-cell NHL who had stable disease to, or progressed during or within 6 months of the end of a rituximab or a rituximab-containing regimen.

Secondary objectives evaluate clinical benefit, changes in health-related quality of life (HRQL) measures, safety, tolerability, exploratory prognostic markers in subjects treated with ofatumumab and bendamustine, and ofatumumab pharmacokinetics in subjects receiving ofatumumab alone after disease progression. In addition, secondary objectives are added in order to formally compare efficacy in the FL patients between treatment arms (i.e. "inferential secondary endpoints").

[redacted]

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 will be randomized to receive:

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

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).

Eligible subjects will be stratified by type of last prior rituximab therapy: rituximab plus chemotherapy or rituximab alone (either in maintenance or monotherapy) and by prior exposure to bendamustine: exposed or not exposed.

Screening assessments include physical exam, vital signs, biochemistry, and blood tests. Blood samples (hematology and biochemistry including human anti-human antibodies, human anti-chimeric antibodies), flow cytometry and immunoglobulin assessments, vital signs are taken throughout the treatment phase. Follow-up assessments begin on Day 336 post randomization (3 months after Day 252), then according to Appendix 1 and Appendix 2 time and events tables. In the event of PD, Survival Follow-Up visits begin 2 months after PD is confirmed by CT scan. A bone marrow examination is required to confirm Complete Remission (CR) when a subject fulfills the complete response criteria, based on the Revised Response Criteria for Malignant Lymphoma definition of a CR if the subject had bone marrow involvement at baseline. CT imaging is required for confirmation of all responses (CR, PR, SD, PD). During this study, CT imaging of the neck (when lesion is palpable), thorax, abdomen, and pelvis will be performed at baseline, and on Days 84, 168, and 252 (+7 days), regardless of the number of completed cycles of therapy in Arm A and Arm B.

A total of 259 events in a sample size of 304 evaluable subjects (152 subjects per arm) are needed for the study to have a 90% power to detect a 50% improvement in PFS (PFS) between study arms. Assuming a dropout rate of 12%, the total sample size randomized for both arms combined will be 346 subjects, with approximate study duration of 77 months. Assuming a screening failure rate of 15%, the total number of subjects screened will be approximately 408.

Per **Amendment 9**, the primary analysis will be performed after approximately 215 PFS events by IRC have been observed. This targeted number of 215 PFS events by IRC for the primary analysis was calculated in order to achieve a cumulative power of 84% to detect a 50% improvement in PFS between study arms. See Section 8.2 - Primary Analysis for details.

Dose Confirmation Cohort

Subjects will be randomized (1:1) into 2 arms: Arm A (OB) vs. Arm B (B) from the start of study.

The Independent Data Monitoring Committee (IDMC) reviewed safety and tolerability data for Arm A at specific points throughout the study. The IDMC initially reviewed the data to determine whether the bendamustine cycle length (q21 days) should be lengthened to 28 days in Arm A or if the cycle length should remain unchanged.

The IDMC met after the first 20 subjects in Arm A received at least 3 cycles of OB. Based on the review of the data available as well as the IDMC charter-defined criteria to alter the dose in Arm A, the IDMC recommended that the study continue without any changes to the dosage of Arm A [IDMC Communication, 2011]. Consequently, there will be no further IDMC meetings to assess dose safety and no further dose modifications other than the protocol-directed dose reductions and delays already described. The safety of subjects enrolled into the study will continue to be monitored by Novartis.

Interim Analysis

An Interim Analysis (IA) for efficacy of the primary endpoint, progression free survival, occured when approximately two thirds of the total Independent Review Committee (IRC, including radiology and oncology review) initial number of events was achieved. At the same time as the IA, a Futility Analysis (FA) was performed and an Independent Data Monitoring Committee (IDMC) reviewed the data. Based on the IDMC review of the data available the IDMC recommended that the study continue without any changes.

Study Endpoints and Assessments

Primary Endpoint:

- Progression-free survival, defined as the time interval between randomization and disease progression or death

Secondary Endpoints

Clinical

- Progression-free survival in patients with follicular lymphoma
- Overall response rate in all patients and patients with follicular lymphoma
- Overall survival in all patients and patients with follicular lymphoma
- Changes in HRQL measures in all patients and patients with follicular lymphoma

- Time to response and duration of response in all patients and patients with follicular lymphoma
- Time to progression and time to next therapy 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 adverse events (AEs), serious adverse events (SAEs), and other safety parameters including frequency of transfusions, development of Human Anti-Human Antibodies (HAHA), incidence of Grade 3 and 4 infections and myelosuppression (anemia, neutropenia, and thrombocytopenia)
- Overall response rate to ofatumumab monotherapy in subjects in Arm B who progress during or following single-agent bendamustine
- Quantitative assessments of immunoglobulins (IgG, IgA, IgM)
- Changes in clinical laboratory values
- 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-1 and FLIPI-2) scores Appendix 6 and Appendix 7
- Baseline Absolute Lymphocyte Count (ALC)
- Genetic variation in FcR gamma 3A
- Human Anti-Chimeric Antibodies (HACA)

[redacted]

1 Introduction

1.1 Indolent Non-Hodgkin's Lymphoma

The projected worldwide incidence in 2009 for Non-Hodgkin's Lymphoma (NHL) is 335,500 persons (195,042 men; 140,458 women) with 193,671 deaths (111,452 men; 82,219 women) [IARC, 2002; Ferlay, 2004]. Follicular lymphoma (FL) accounts for 11% to 35% of all NHL [WHO, 2008], and is the most common lymphoma in the United States (US) and Europe. Between 10–15% of patients with FL are diagnosed with Stage I or II disease. Patients with Stage III or IV disease make up the majority and are generally not cured by conventional therapeutic approaches [Ardeshna, 2003; Apostolidis, 2000]. Other indolent NHL histologies include small lymphocytic, marginal zone, and lymphoplasmacytic lymphomas.

Indolent lymphomas have a variable course. Some patients have waxing and waning disease for years before they become symptomatic. Other patients present with disseminated disease, symptoms and lymphoma progression, which require treatment. Indolent lymphomas are sensitive to chemotherapy combined with biologics, but subsequently follow a pattern of multiple relapses and progressively shorter periods of remission between relapses. At presentation of disease, median survival is 9.2 years. [Johnson, 1995; Fisher, 2005; Swenson, 2005].

1.2 Current Treatment for Indolent Non-Hodgkin's Lymphoma

1.2.1 Frontline Treatment

Early-stage, indolent NHL is managed with primary radiation therapy. However, patients with newly diagnosed, disseminated disease have multiple treatment options. Current treatment strategies focus on establishing maximal disease control and prolonged survival. Asymptomatic, non-bulky disease may be observed, but single-agent rituximab has activity in this population. Patients with symptomatic or bulky disease are managed with combination chemotherapy, which includes alkylating agents or purine analogs and rituximab. While indolent lymphoma is responsive to single-agent and combination chemotherapy, thirty years of clinical research has not produced a chemotherapy regimen that provides superior definitive progression-free survival (PFS) or overall survival (OS) [Marcus, 2005; Hiddemann, 2005; Herold, 2007].

Bendamustine hydrochloride (Ribomustin) is currently approved in Germany (i.e., 60 mg/m² IV on days 1-5, vincristine 2 mg IV on day 1, prednisone 100 mg/m² IV on days 1-5; cycle repeated after 3 weeks) for the primary treatment of advanced, indolent NHL in combination regimens and as a single agent or combination therapy for multiple myeloma and chronic lymphocytic leukemia (CLL) [Ribomustin Prescribing Information, 2009; Levact SPC, 2010]. Bendamustine is approved for indolent NHL that relapsed during or within 6 months of receiving a rituximab-containing regimen. In the US, bendamustine hydrochloride (Treanda) as a single agent is also approved for the treatment of CLL and rituximab-refractory indolent NHL [Treanda Prescribing Information, 2010].

Rituximab (R), a chimeric, anti-CD20$^+$ monoclonal antibody (mAb), as a single agent or in combination with chemotherapy, is part of standard, primary treatment for newly-diagnosed, CD20 positive, indolent NHL. Prolonged treatment with rituximab enhances response rates and PFS [Hoechster, 2009; Collins-Burow, 2007; Wenger, 2008]. Studies of R-CHOP (rituximab added to cyclophosphamide, doxorubicin, vincristine, prednisone) have demonstrated 96% overall response rate (ORR), with 20% complete remission (CR); while patients treated with R-CVP (rituximab added to cyclophosphamide, vincristine, prednisone) have shown 81% ORR, with 41% CR [Marcus, 2005; Ghielmini, 2004; Hainsworth, 2005; Hiddemann, 2005; Van Oers, 2006].

1.2.2 Treatment for Relapsed and Refractory Diseases

Despite complete remission with biologic therapy in combination with chemotherapy, most patients develop progressive disease (PD) and require salvage therapy. Radioimmunoconjugates directed against CD20-expressing B cells have high response rates in patients that require salvage treatment for relapsed or refractory indolent NHL. Yttrium-90 ibritumomab tiuxetan (Zevalin) received Food and Drug Administration (FDA) approval in 2002 for the treatment of relapsed, refractory, or transformed indolent NHL. Compared to the 56% ORR achieved with rituximab in this population, yttrium-90 ibritumomab tiuxetan achieved an 80% ORR (30%CR, 50% partial response [PR]), and 11 months PFS [Witzig, 2002a; Witzig, 2002b]. I-131-tositumomab (BEXXAR™; 33% CR, 35% PR, >11 month PFS) achieved similar results. Nevertheless, these modalities remain underutilized in the clinical setting [Vose, 2004; Witzig, 2003].

Autologous and allogeneic hematopoietic stem cell transplants are also performed for patients with relapsed FL [Apostolidis, 2000; Van Besien, 1998]. An International Bone Marrow Transplantation Registry study evaluated 904 patients undergoing transplantation for FL. In multivariate analyses, allotransplantation had higher transplant-related mortality and lower disease recurrence [Van Besien, 2003]. Purged autotransplantation had a 26% lower recurrence risk than unpurged autotransplantation. Five-year survivals were 51%, 62% and 55% after allogeneic, purged and unpurged autotransplantation, respectively. More research is needed; however, there is a subset of recurrent autologous transplant patients who could benefit from salvage therapy.

1.2.2.1 Bendamustine in the Relapsed and Refractory Settings

Bendamustine (Treanda, Ribomustin, Levact, bendamustine hydrochloride) is a cytostatic drug which structurally combines a purine-like benzamidazol nucleus and a bifunctional alkylating nitrogen mustard group. It has shown monotherapy activity in the treatment of rituximab-relapsed and refractory-indolent NHL [Treanda Prescribing Information ,2010; Kahl, 2010; Friedberg, 2008; Rummel, 2005; Weide, 2007] and is indicated in the for the treatment of indolent NHL that has progressed during or within 6 months of treatment with rituximab or a rituximab-containing regimen (120 mg/m^2 Days 1,2 q21 days, up to 8 cycles).

Bendamustine has a unique mechanism of action that is not yet fully understood [Leoni, 2003]. Several studies show that it has a substantial effect against lymphomas resistant to alkylators or purine analogues [Schöffski, 2000; Heider, 2001; Friedberg, 2008].

Bendamustine approval for the treatment of indolent B-cell NHL was based on its high ORR in a single arm, Phase II study (4% ORR, 25% CR, 49% PR) and its prolonged PFS in a single arm, pivotal study (84% ORR, 29% CR, 53% PR, 9.3 m median PFS (mPFS) [Kahl, 2010; Friedberg, 2008]. The primary grade 3, 4 toxicities were hematologic (leukopenia 60%, neutropenia 60%, thrombocytopenia 24%, lymphocytopenia 95%, and anemia 5%).

Two single-arm studies of bendamustine and rituximab were done for the treatment of relapsed mantle cell and relapsed low grade indolent B-cell NHL [Rummel, 2005; Robinson, 2008]. In both studies, bendamustine was dosed at 90 mg/m^2 on Days 1, 2 of each cycle, every 28 days. Activity increased when bendamustine was combined with rituximab. Median PFS reached approximately 24 months with less toxicity than with bendamustine 120 mg/m^2 monotherapy dose on Days 1, 2, every 21 days [Rummel, 2005; Robinson, 2008]. Patients with FL (96% ORR; 1% CR; 25% PR) experienced higher response rates than mantle cell lymphoma (5% ORR; 50% CR; 25% PR) [Rummel, 2005].

1.3 Ofatumumab

Ofatumumab is an immunoglobulin G1κ (IgG1κ) human monoclonal antibody that specifically recognizes a distinct epitope encompassing both large and small extracellular loops on the human CD20 molecule expressed on B cells [Teeling, 2006] and binds to this site with high affinity with a dissociation half-life of 3 hours [Teeling, 2004]. Ofatumumab induces more efficient complement-dependent cytotoxicity (CDC) mediated cell lysis in-vitro, compared to rituximab, especially in low CD20 density cells [Teeling, 2004]. The FDA recently approved ofatumumab (ARZERRA™) for chronic lymphocytic leukemia (CLL) refractory to fludarabine and alemtuzumab.

In a Phase I dose-ranging trial of ofatumumab for the treatment of relapsed or refractory CLL [Study Hx-CD20-402], subjects were given ofatumumab weekly for 4 weeks [100 mg + 3 x 500 mg (n=3), 300 mg + 3 x 1000 mg (n=3), and 500 mg + 3 x 2000 mg (n=27)]. Among relapsed CLL subjects, a 48% partial remission was observed in the highest dose group [Coiffier, 2008]. The MTD (maximum tolerated dose) was not reached.

The pivotal trial Study OMB111773 (Hx-CD20-406) in subjects with fludarabine-refractory CLL [refractory to both fludarabine and alemtuzumab (DR, n=95) or refractory to fludarabine and with bulky lymphadenopathy for whom alemtuzumab is not suitable (BFR, n=112)] evaluated 300 mg + 7 x 2000 mg for eight weekly doses, followed by four monthly 2000 mg doses. The investigator-determined overall objective response rate of patient refractory to fludarabine and alemtuzumab was 49% with a median duration of response of 5.5 months. The best response was CR in two subjects in the BFR group. In this study, ofatumumab was generally well tolerated. Specifically, in the DR group, the most frequently reported adverse events (AEs) (>15% frequency) were pyrexia, diarrhea, dyspnea, cough, neutropenia, anemia and pneumonia. There were no unexpected safety findings [OFATUMUMAB, 2012]. The interim results of this pivotal study served as the basis for the grant of accelerated approval by

the FDA for ofatumumab (ARZERRA) for the treatment of patients with CLL refractory to fludarabine and alemtuzumab (DR population) in October 2009.

A Phase I/II dose escalation study of ofatumumab in subjects with relapsed or refractory FL tested four weekly doses of ofatumumab at 300, 500, 700, or 1000 mg [Study Hx-CD20-001; Hagenbeek, 2008]. Results demonstrated clinical activity with reversible Grade 3, 4 AEs occurring on the day of initial infusion. Those AEs included chills, rash, fatigue, pruritus, pyrexia, and uricaria. The ORR in 37 evaluable subjects was 41%. Median duration of response was 29.9 months. Response did not correlate with ofatumumab dose.

A Phase II study in patients with previously untreated FL (Study Hx-CD20-409, Study OMB111775) compared ofatumumab at two dose levels in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) [OFATUMUMAB, 2012]. Patients were randomized into two dose groups (N= 29 per group): 300 mg of ofatumumab at the first infusion, followed by 5 infusions of either 500 or 1000 mg of ofatumumab every 3 weeks in combination with 6 cycles of CHOP. Results demonstrated an ORR of 90% and CR of 21% for the 500 mg group, N=29. In patients treated with 1000 mg of ofatumumab (n=29), the ORR was 100% including 31% CR. There were no unexpected safety findings reported during treatment and within 30 days after last infusion. The most common AEs of grade 3 or 4 (>10%) were leukopenia and neutropenia.

In a single-arm, double-blind study of single-agent ofatumumab (Study Hx-CD20-405, Study OMB111772), a total of 116 rituximab-refractory FL patientsubjects were treated with two dose levels of ofatumumab [OFATUMUMAB, 2012]. This group of patients was highly refractory with 65% refractory to their last chemotherapy. Patients in the study had previously received a median of 4 prior treatment regimens. The 1000 mg dose group (N=86) demonstrated an ORR of 10% (included 1 CR, 8 PR). In addition, 50% (43) of patients in the 1000 mg treatment arm had stable disease (SD). The ORR among patients who were refractory to prior rituximab monotherapy (N=27) was 22%. For patients considered refractory to rituximab in combination with chemotherapy the RR was 7% and among patients considered refractory to rituximab maintenance the RR was 9%. The PFS was 6 months. There were no unexpected safety findings reported during treatment and within 30 days after last infusion. The most common AEs (>10%) were rash, urticaria, pruritus, fatigue, nausea, pyrexia, asthenia, peripheral edema, and cough.

1.4 Rationale

Treatment options are limited for patients who become refractory to rituximab or rituximab-containing therapy. Testing new treatments for this population may advance clinical care for this population.

Ofatumumab is an anti-CD20 mAb shown to have monotherapy activity in a Phase I/II study in patients with FL that has relapsed following rituximab-containing therapy. Bendamustine is a synthetic nitrogen mustard compound that has shown activity in the treatment of indolent NHL that has progressed during or within 6 months of treatment with rituximab or a rituximab–containing regimen [Treanda Prescribing Information, 2010; Ribomustin Prescribing Information, 2009; Levact SPC, 2010]. Bendamustine has been shown to have activity in lymphoma that is refractory to other alkylators. Furthermore, biologics have

enhanced the efficacy of primary chemotherapy for indolent NHL and may also enhance the efficacy of an active agent in the refractory settings. The addition of ofatumumab to bendamustine may provide additional clinical benefit for subjects who no longer respond to rituximab or rituximab-containing regimens.

2 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 refractory to rituximab-containing therapy
- To evaluate and compare ORR, OS, time toand 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]

3 investigational plan

3.1 Study Design

This randomized, open label, two-arm Phase III study consists of two treatment groups: Arm A which is ofatumumab and bendamustine (OB), or Arm B, which is bendamustine monotherapy (B). Subjects will be stratified by type of last prior rituximab: R-chemotherapy or rituximab alone, and by prior exposure to bendamustine: exposed or not exposed.

An independent data monitoring committee (IDMC) reviewed safety and tolerability data for Arm A at a specific time point in the study, as specified in the IDMC charter and summarized in Section 9.7. Briefly, the IDMC initially reviewed data from the first 20 subjects to complete 3 cycles (or complete bendamustine therapy with fewer than 3 cycles) in Arm A to determine whether the bendamustine cycle length should be lengthened to q28 days or if the cycle length should remain unchanged. If cycle length of bendamustine was lengthened in Arm A, the IDMC would review the data to determine whether the dose of bendamustine in Arm A should be reduced to 70 mg/m^2 or if it is appropriate for the dose to remain as it is. If the dose of bendamustine in Arm A was reduced, the IDMC will once more review the data to determine if it is appropriate for the study to continue. For each decision the IDMC would follow a decision rule that will be defined in the IDMC charter. Arm B data will be made available to the IDMC each time they assess Arm A.

Update: Decision from IDMC Meeting (Stage 1):

The IDMC met after the first 20 subjects in Arm A received at least 3 cycles of OB. Based on the review of the data available as well as the IDMC charter-defined criteria to alter the dose in Arm A, the IDMC recommended that the study continue without any changes to the dosage of Arm A in the study [IDMC communication, 2011]. Consequently, there will be no further IDMC meetings to assess dose safety and no further dose modifications other than the protocol-directed dose reductions and delays already described. The safety of subjects enrolled into the study will continue to be monitored by Novartis.

Primary Analysis

The primary analysis of PFS was planned to use 90% power to detect a 50% treatment effect; a 13.5 vs. 9 month improvement in Arm A (ofatumumab and bendamustine combination therapy) vs. Arm B (bendamustine monotherapy). This trial is an event-driven study design with an event-driven sample size. The final primary analysis was planned to take place at the time of occurrence of the 259th event. The guideline for the study reaching 259 total events with respect to previously stated assumptions was planned to require the screening of 408 subjects to ensure 346 subjects are randomized and to have a study duration of approximately 77 months from the first day of first subject until the time of the 259th event.

Per **Amendment 9**, the primary analysis will be performed after approximately 215 PFS events by IRC have been observed. This targeted number of 215 PFS events by IRC for the primary analysis was calculated in order to achieve a cumulative power of 84% to detect a 50% improvement in PFS between study arms. See Section 8.2 - Primary Analysis for details.

Interim Analysis

An Interim Analysis (IA) for efficacy of the primary endpoint, progression free survival, was planned when approximately two thirds (or approximately 172) of the total 259 PFS events by IRC is achieved. The IA was planned to be conducted at a significance level of 0.012.

At the time of amendment 9, the IA occurred when 180 PFS events by IRC were recorded. At the same time as the IA, a Futility analysis (FA) occured. The IDMC reviewed the efficacy and futility data at this timepoint.

Figure 1 Study Schema

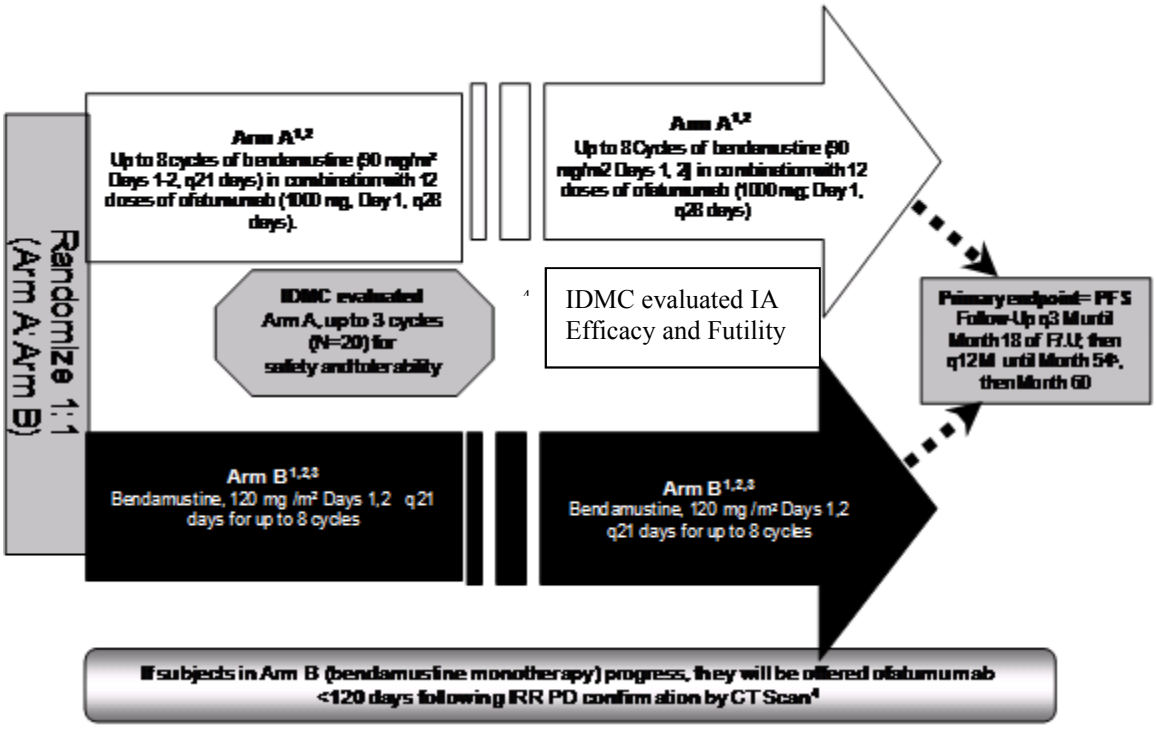

Figure 1 abbreviations: CT= computed tomography; F/U= Follow-Up; IDMC=independent data monitoring committee; IRC= independent review committee; M= month; N= number of subjects; PD= progressive disease; PFS= progression-free survival; q= every.

1. A total of 12 ofatumumab infusions will be administered in Arm A regardless of the number of completed ofatumumab + bendamustine cycles (q 21 days). Once subjects in Arm A complete bendamustine therapy, the remaining doses of ofatumumab will be given monthly (q28 days) until 12 doses are completed.
2. Refer to Section 5.1.3.1 for any changes in bendamustine dose.
3. Subjects who cannot complete 8 cycles of therapy with bendamustine in Arm A and Arm B must come to the clinic for all planned Day 1 assessments (Visits 1-20) and all planned CT scans.
4. The IDMC met and confirmed the safety and tolerability of the Arm A combination therapy. A further IDMC meeting will review the IA and FA data.
5. PD must be confirmed by an IRC prior to receiving ofatumumab monotherapy. See Figure 2.
6. The last required CT scan will be done on Month 54 of the F/U phase. Following Month 54, there will be a Month 60 F/U visit without a required CT scan. In addition to the required CT scans within the F/U period, unscheduled CT scans will be done to confirm clinical signs or suspicion of progression.

Figure 2 Study Schema for those who progress on Arm B

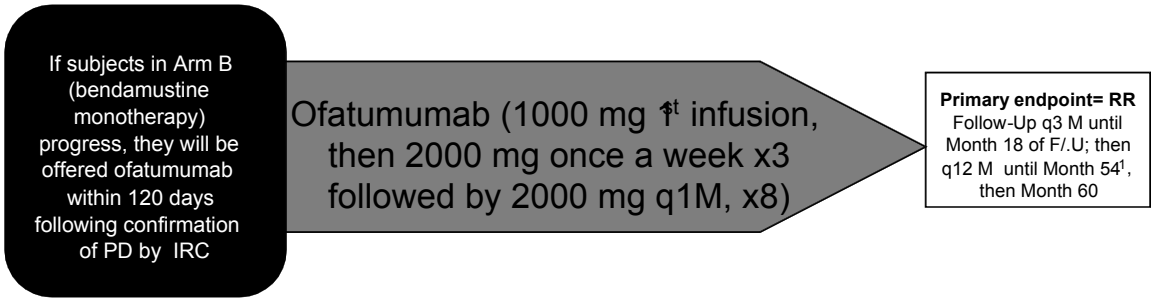

Figure 2 abbreviations: F/U= Follow-Up; IRC = Independent Review Committee;; M= month; PD= progressive disease, q= every; RR= response rate.

1. The last required CT scan will be done on Month 54 as part of the F/U phase (Table 1). Following Month 54, there will be a Month 60 F/U visit without a required CT scan. Outside the F/U schedule, unscheduled CT scans will be done to confirm clinical signs or suspicion of progression.

3.1.1 Screening Phase

Please refer to Appendix 1 and Appendix 2 for a complete list of screening timing and procedures.

Subjects will provide informed consent before protocol-specific screening assessments.

Baseline Bone Marrow Sample:

Two types of bone marrow samples will be accepted:

1. An historical bone marrow biopsy sample (obtained at any time prior to study entry) may be used to fulfill the study's needs if:
   - The bone marrow biopsy showed involvement by lymphoma **and**
   - The subject has received no lymphoma therapy in the intervening time period.
2. A study specific (screening) sample will be required if **any** of the following points are met:
   - The subject has no previous bone marrow biopsy, or
   - The bone marrow biopsy was taken >1 month prior to randomization and showed no involvement by lymphoma, or
   - The subject has received lymphoma therapy in the intervening time period since the prior bone marrow biopsy.

Biopsy if Transformation to Diffuse Large B-cell Lymphom is Suspected:

If the investigator has clinical suspicion that the protocol candidate has transformed to Diffuse Large B-cell Lymphoma (DLBCL), the investigator must not consider that subject for the trial unless a biopsy or fine needle aspiration is performed prior to enrolment. To confirm that disease has not transformed to a DLBCL, an incisional or excisional lymph node biopsy of accessible adenopathy is highly recommended. In less accessible lymph nodes, 4 to 8 core biopsies are recommended, but not required.

Review of Materials:

Bone marrow biopsy slides will be sent for central review. It is recommended that both the core and aspirate be sent for review, but a core alone or aspirate alone may be sent if an adequate aspirate or core sample is not available. If bone marrow biopsy slides are not available, a tissue pathology report including details confirming CD20+ tumor status will be sent for central review. Please see SPM for more details. Blood samples, physical examination, and computed tomography (CT) imaging (with contrast imaging of the neck when lesion is palpable, thorax, abdomen, and pelvis; may be whole body CT scan or according to standard of care) will be provided to determine baseline disease and study eligibility (See Imaging Acquisition Guidelines). All examinations must be performed ≤ 21 days prior to randomization with the exception of the CT imaging and bone marrow biopsy and aspirate as mentioned above. CT imaging done ≤1 month (+7 days) prior to randomization may be used as the baseline CT scan. If the investigator wants to use a CT scan done >1 month (+7 days) prior to randomization, the Medical Lead must be contacted to determine if CT scan can be accepted.

3.1.1.1 Documentation of indolent B-cell NHL that is stable or has progressed during or within six months of the end of treatment with rituximab or a rituximab–containing regimen

A documentation worksheet verifying the investigator's diagnosis of SD following, or progression during or within 6 months of treatment with rituximab or a rituximab-containing regimen will be required at screening. This documentation worksheet must be sent to Novartis prior to randomization and will ask for:

Information about last qualifying rituximab therapy:

- Dates before and dates after last qualifying rituximab-containing regimen
- Type of rituximab therapy and regimen (examples: weekly, monthly):
    - Rituximab (includes monotherapy and maintenance), or
    - Rituximab added to chemotherapy
- Date and type of response associated with last qualifying rituximab-containing regimen

Information regarding imaging:

- Copy of documentation (for example, an imaging report, clinical documentation) prior to last qualifying rituximab-containing regimen is required (if available)
- Copy of documentation confirming PD (for example, an imaging report, clinical documentation) after subject deemed unresponsive or relapsed to rituximab-based regimen is required

- Assurance of an ability to submit, for each subject
  - imaging or other documentation showing disease status before the start of the last qualifying rituximab-containing regimen is requested
  - imaging or other documentation confirming unresponsive or relapse following the last qualifying rituximab regimen is required
  - CT imaging is performed at screening

Subjects will not be enrolled in the study unless the investigator or designate verifies SD following, or progression during or within six months of treatment with rituximab or a rituximab–containing regimen. Submission of the subject's imaging is expected be sent to Novartis within one month following randomization.

Further details will be provided in the SPM.

3.1.2 Randomization and Stratification

Subjects will be randomized 1:1 to Arm A (OB combination therapy) or to Arm B (B monotherapy) for the duration of the treatment period.

Subjects will be stratified according to the type of last prior rituximab therapy: rituximab-chemotherapy or rituximab alone (administered as monotherapy or maintenance therapy) and by prior exposure to bendamustine: exposed or not exposed.

Centralized randomization numbers within each stratum will be created for treatment assignment to ensure balance, with respect to the number of subjects assigned to each treatment group within each stratum, using a randomization system (with randomly permuted blocks within strata). The investigator will access the Interactive Voice Response System by telephone to receive the subject's randomization number and initial study medication container number.

3.1.3 Dose Confirmation for Safety and Tolerability

The first 20 subjects who entered and completed 3 cycles (or upon complete bendamustine therapy if less than 3 cycles) in Arm A of this study were part of a dose confirmation cohort for evaluation of safety and tolerability of ofatumumab and bendamustine combination therapy. Data from Arm B were made available during each of the IDMC reviews.

The IDMC involved in this study followed a decision rule, described in the IDMC charter and summarized in Section 9.7, to decide whether the cycle length of OB in Arm A should be changed to q28 days for improved safety and tolerability. The IDMC decision rule accounted for dose delays, the nature and severity of serious adverse events, and dose-limiting toxicities in Arm A. If the cycle length was changed, the IDMC would compare the nature and severity of serious adverse events and dose-limiting toxicities of another 10 subjects who would enroll in Arm A. Data from Arm B was to be made available at this time. The IDMC would have had the option to make a second treatment regimen change and reduce the bendamustine dose from 90 mg/m^2, Days 1, 2; every 28 days to 70 mg/m^2, Days 1, 2; every 28 days.

If the IDMC decided to change the cycle length or reduce the dose of bendamustine if the nature and severity of serious adverse events or dose-limiting toxicities in Arm A are

considered excessive even though they do not exceed the toxicities observed in Arm B, then the dose and dose reduction schedule found in the IDMC charter will be followed for the remainder of the study. Also see Section 9.7 for further details.

Update: Decision from IDMC Meeting (Stage 1):

The IDMC met after the first 20 subjects in Arm A received at least 3 cycles of OB. Based on the review of the data available as well as the IDMC charter-defined criteria to alter the dose in Arm A, the IDMC recommended that the study can continue without any changes to the dosage of Arm A in the study [IDMC communication, 2011]. Consequently, there will be no further IDMC meetings to assess dose safety and no further dose modifications other than the protocol-directed dose reductions and delays already described. The safety of subjects enrolled into the study will continue to be monitored by Novartis.

3.1.4 Treatment Phase

Subjects will be followed as described in Appendix 1 and Appendix 2 with specified visit windows. Subjects will be randomized 1:1 to receive either:

- Arm A: Up to 8 cycles of bendamustine (90 mg/m^2, Days 1, 2; q21 days) in combination with 12 doses of ofatumumab (1000 mg). Beginning in Cycle 2, ofatumumab may be given on Day 1 (or within 3 days after 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 (on or within 3 days after Day 1 of each month) until all 12 doses are completed. Administer the first dose of ofatumumab monotherapy 28 days after Day 1 of the last cycle where combination (ofatumumab+bendamustine) was scheduled to be given.
- Arm B: Up to 8 cycles of bendamustine (120 mg/m^2, on or within 3 days after Days 1, 2; q21 days.).

Subjects who cannot complete the planned therapy with bendamustine (in Arm A and Arm B) must still come in for all planned Day 1 visits and assessments (Visits 1-20) according to the schedule presented in Appendix 1 and Appendix 2. Also see SPM for more details. Subjects in Arm A and Arm B are required to come for all planned CT scans with corresponding assessments for these days (Days 84, 168, 252; +7 days).

Subjects with PD in Arm B may receive ofatumumab after PD is confirmed by an IRC (See Section 3.1.6).

Blood samples are required at the start of each cycle and throughout the treatment phase.

Assessments to determine subject response or progression will be performed for both arms including:

- Peripheral blood sample evaluation for complete blood count (CBC) and differential with both percent and absolute number of lymphocytes
- CT scans, assessment of lymphoma disease symptoms, and response assessments will be done on Days 84, 168, and 252 (+7 days) to assess clinical response based on the Revised Response Criteria for Malignant Lymphoma (RRCML; Section 6.2). Subjects who are unable to complete 8 cycles of therapy with bendamustine must still have CT scans, assessment of lymphoma disease symptoms, and response assessments done on Days 84, 168, and 252 (+7 days).
- In subjects whose bone marrow biopsy was positive at the start of the study, a confirmatory bone marrow examination is required ≤ 8 weeks after a subject fulfils requirements based on the RRCML for CR (Section 6.2.5.2).
- In addition, subjects will be monitored for safety and efficacy (Appendix 1 and Appendix 2 for a complete list of treatment phase procedures.

Patient reported outcome (PRO) questionnaires (FACT-Lym and EQ-5D) are described in Appendix 1. The Health Change Questionnaire (HCQ) questionnaire is not administered at the baseline (screening visit), but administered on all other visits, as per Section 6.6 and Appendix 1.

3.1.5 Follow-up Phase

Following study treatment, subjects who have CR, PR or SD will receive regular follow-up for 5 years in Arm A. The last required CT scan will be done on Month 54 (Table 1). Unscheduled CT scans will be required in addition to the scheduled CT scans if there are clinical signs or suspicion of progression throughout the study. Arm B will also follow this schedule if Arm B subjects do not select ofatumumab monotherapy.

Table 1 Follow-up visit schedule and CT scan requirements for Arm A and Arm B

F/U phase	CT scan
3 M F/U 1	Required
6 M F/U 1	Required
9 M F/U 1	Required
12 M F/U 1	Required
15 M F/U 1	Required
18 M F/U 1	Required
30 M F/U 2	Required
42 M F/U 2	Required
54 M F/U 2	Required
60 M F/U 2	Not required[1]

Abbreviations: Follow-Up 1= F/U 1; Follow-Up 2= F/U 2; Month= M

1. CT scans are required during scheduled F/U 1 and F/U 2 visits in Arm A and Arm B (Appendix 1) with the last required CT scan on Month 54. CT scans for ofatumumab monotherapy following PD in Arm B will be done according to the schedule presented in Appendix 1. CT scans will be required to confirm clinical signs or suspicion of progression if observed outside all scheduled F/U 1 and F/U 2 visits. CT scans are not required for Survival F/U.

For patients with SD, PR, or CR, follow-up assessments begin on Day 336 (3 months after Day 252), then continue according to Appendix 1, Appendix 2 and Table 1 (also see SPM).

For patients with PD during the treatment period, Survival Follow-Up visits begin 2 months after PD is confirmed by CT scan and will follow the time intervals described in Appendix 1, Appendix 2 and Table 1, beginning with the 3M F/U visit one month after the 2 M F/U visit. .

For patients with PD during the follow up period, Survival Follow-Up visits begin 2 months after PD is confirmed by CT scan. After the 2M F/U visit they will continue on their current follow up schedule according to Appendix 1, Appendix 2 and Table 1.

Each follow-up visit and assessment will have a time window of ±7 days for Follow-Up Visit #1 and a time window of ±14 days for Follow-Up Visit #2. Follow-up visits will include collection of survival status, concomitant medications, and response assessments, based on RRCML. Survival follow-up visits may be phone calls instead of physician office visits. In addition, subjects will be monitored for safety and efficacy as described. See Appendix 1 and Appendix 2 for a complete list of follow-up procedures.

Subjects without PD who stop protocol treatment and begin non-protocol treatment must enter Survival Follow-Up.

Bone marrow biopsy results will confirm complete remission and is required ≤ 8 weeks after the subject achieves CR (as decided by investigator) if positive for lymphoma at baseline. CT imaging is required for confirmation of response.

PRO measures (FACT-Lym, EQ-5D, HCQ) will be administered for completion by the subjects at all follow-up visits as per Section 6.6 and Appendix 1.

Subjects who withdraw from treatment will follow the withdrawal schedule in Section 4.4.

Please also refer to Section 6, Study Assessments and Procedures, for detailed instructions.

If a subject in Arm B decides to receive ofatumumab monotherapy following PD, they will not follow the schedule described in Section 3.1.5, Appendix 1 and Appendix 2, but will be monitored according to the follow-up schedule described in Section 3.1.6, Appendix 3, and Table 1 (where 3 month F/U begins 3 months after last dose of ofatumumab).

FOLLOW-UP FOR PROGRESSIVE DISEASE

Subjects receiving ofatumumab and bendamustine combination therapy (Arm A) or bendamustine monotherapy (Arm B) who experience disease progression, as defined in Section 6.2.5.5, will be assessed for safety and followed as described in Appendix 1 and Appendix 2 (Survival/PD). Progressive disease must be confirmed by a CT scan. A PD Worksheet will be completed following the CT scan. Instructions for this worksheet are found in the SPM.

Survival Follow-up visits will begin 2 months after PD is confirmed by CT scan as described in Appendix 1 and Appendix 2 and Table 1. Each follow-up visit will have a time window of ±7 days for Follow-Up Visit #1 and a time window of ±14 days for Follow-Up Visit #2. Survival follow-up visits may be a phone call instead of physician office visit.

If an Arm B subject selects ofatumumab monotherapy following PD, the subject will not follow the schedule described in Section 3.1.5, Appendix 1 and Appendix 2, but follow the treatment and follow-up schedules described in Section 3.1.6 and Appendix 3.

Subjects who withdraw from treatment will follow the withdrawal schedule in Section 4.4.

Supplementary study conduct information is provided in the accompanying Study Procedures Manual (SPM). The SPM will provide the site personnel with additional administrative and detailed technical information.

3.1.6 Ofatumumab 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, as defined in Section 6.2.5.5 (See Appendix 3 for follow-up procedures). Subjects with PD in Arm B must have a CT scan done with IRC confirmation of PD. This CT scan (or a CT scan done after IRC confirmation) will determine baseline measurements of pre-ofatumumab disease before exercising the option to receive ofatumumab. A PD Worksheet must be completed upon diagnosis of PD (See SPM for details).

Subjects who receive ofatumumab following diagnosis of PD must fulfill the inclusion criteria found in Section 4.2 and the exclusion criteria found in Section 4.3 (except for exclusion criteria #4). 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 as described in Appendix 3 and Table 1.

3.1.7 Study Endpoints

PRIMARY ENDPOINT:

- Progression-free survival (PFS), defined as the time interval between randomization until disease progression or death

SECONDARY ENDPOINTS

Clinical

- Overall response rate (ORR) in all patients and patients with follicular lymphoma
- Overall survival (OS) in all patients and patients with follicular lymphoma
- Time to response and duration of response in all patients and patients with follicular lymphoma
- Time to progression and time to next therapy 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 3 and 4 infections, and myelosuppression (anemia, neutropenia, and thrombocytopenia)
- Overall response rate (ORR) to ofatumumab monotherapy in subjects in Arm B 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) (FLIPI-1 and FLIPI-2) (and)
- Baseline Absolute Lymphocyte Count (ALC)
- Genetic variation in FcR gamma 3A
- Human Anti-Chimeric Antibodies (HACA)

[redacted]

The Study Procedures Manual (SPM) provides supplementary study conduct information. The SPM will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

3.2 Discussion of Design and Dose Rationale

3.2.1 Bendamustine Dosing

We acknowledge the existence of different bendamustine regimens based on clinical practice and prescribing information. Bendamustine is approved in Germany for the primary treatment of advanced indolent NHL in a combination regimen (i.e., 60 mg/m² IV on days 1-5, vincristine 2 mg IV on day 1, prednisone 100 mg/m² I.V. on days 1-5; cycle repeated after 3 weeks) Ribomustin Prescribing Information, 2009]. Bendamustine, as monotherapy, was approved by the FDA and European Medicines Agency (EMA) for the treatment of indolent NHL that has progressed during or within 6 months of treatment with rituximab or a rituximab-containing regimen (120 mg/m^2 Days 1, 2 q21 days, up to 8 cycles) [Treanda Prescribing Information, 2010; Levact SPC, 2010].

In a multi-center, single-arm, Phase II study, bendamustine monotherapy (120 mg/m^2, Days 1, 2 q21 days) resulted in a median 9.3 month duration of response and mPFS of 9.3 months [Treanda Prescribing Information, 2010]. These results corroborate data from a multi-center, Phase II study using bendamustine monotherapy (120 mg/m^2 Days 1, 2 q21days, up to 8 cycles) in rituximab-refractory FL subjects (for FL: 3% CR/CRu; 44% PR; 9 months duration of response) [Friedberg, 2008; Treanda Prescribing Information, 2010].

In subjects who relapsed after prior therapy, the combination of rituximab with bendamustine (90 mg/m^2 Days 1, 2 q28 days) produced a high objective response rate. The subject population included subjects with indolent B-cell NHL who may have been refractory to prior chemotherapy but who had never received rituximab. Data from these trials suggest that the bendamustine at a 90 mg/m^2 dose could provide clinical benefit when added to an anti-CD20 mAb (1% CR; 25% PR; 24 months mPFS) [Rummel, 2005; Ribomustin, 2009; Kahl, 2010; Friedberg, 2008].

In a Phase II study by the German Low Grade Lymphoma Study Group, the combination of a CD20 mAb with bendamustine and mitoxantrone allowed for a lower bendamustine dose, 90 mg/m^2 Days 1, 2, q28D in a relapsed and refractory FL subject population who had received

between 1-2 prior regimens without compromising overall responses (55% CR; 41% PR; 19m mPFS) [Weide, 2007]. The ability to lower the bendamustine dose in combination with an anti CD20 mAb and mitoxantrone allowed AEs to be less frequent than at the higher, monotherapy dose.

The FDA has approved a bendamustine monotherapy regimen [Treanda Prescribing Information, 2010]. As such, the FDA-approved bendamustine monotherapy regimen (120 mg/m^2 Days 1, 2; q21 day) will serve as the control for this study, OMB110918. Although the FDA has not defined a bendamustine regimen to be used in combination therapy, the precedence of different dosing regimens for bendamustine in combination with rituximab justifies the evaluation of the 90 mg/m^2 q21 day regimen of bendamustine in Arm A of this trial and the use of a dose confirmation cohort of 20 subjects in Arm A.

3.2.2 Ofatumumab dosing when administered with bendamustine

The ofatumumab dose in this study, 1000 mg, was selected based on several considerations: preclinical data with ofatumumab and clinical population PK modeling and simulation; prior clinical experience with ofatumumab (Study Hx-CD20-001, [Hagenbeek, 2008]); ongoing clinical experience with ofatumumab (Studies Hx-CD20-405 and Hx-CD20-409); and prior clinical experience with rituximab.

A total of 12 doses of ofatumumab will be given in Arm A. Ofatumumab will be given on Day 1 of each cycle of bendamustine as long as subjects in Arm A receive bendamustine (up to 8 cycles). Once subjects in Arm A complete bendamustine therapy, additional doses of ofatumumab will be given monthly (q28 days) for a total of 12 ofatumumab doses.

Preclinical data suggest that ofatumumab plasma concentrations >10 μg/mL are sufficient to suppress peripheral B-cell recovery in cynomolgus monkeys as well as to suppress tumor cell growth in Daudi tumor-bearing SCID mice [Bleeker, 2008]. Severe combined immunodeficiency (SCID) mice previously inoculated with Daudi B-cells received ofatumumab at 0.5 and 50 mg/kg and were observed for tumor growth. Tumor growth was delayed 3-4 weeks after ofatumumab administration, with a greater duration of tumor growth inhibition at the higher dose level. Acceleration of tumor growth was observed at the time point at which ofatumumab concentrations had dropped below 0.4 μg/mL.

In the Bleeker study, cynomolgus monkeys received ofatumumab at three dose levels: 1.25, 6.25, or 12.5 mg daily for four consecutive days (cumulative doses 5, 25, or 50 mg/kg). A profound B-cell depletion was induced both peripherally and in the lymph nodes, with a longer time to recovery at higher dose levels. Ofatumumab concentrations above 50 μg/mL were sufficient for complete B-cell depletion. Recovery of CD20$^+$ cells in peripheral blood and lymph nodes was detected when plasma ofatumumab concentrations had dropped below 5-10 μg/mL. Thus, a potential target in developing ofatumumab dosing regimens is prolonged maintenance of plasma concentrations >10 μg/mL.

Pharmacokinetic data from the Phase I study in subjects with relapsed or refractory FL (Study Hx-CD20-001) were analyzed using a two-compartment model with a decrease in clearance after the first dose and assuming a stepped-rate infusion using a nonlinear mixed-effects modeling approach (NONMEM). The resulting model was used to simulate concentration-time data for 500 subjects receiving ofatumumab infusions at 1000 mg on the first day of each

21-day or 28-day cycle for a total of six cycles. Based on the simulations, the probability of maintaining plasma ofatumumab concentrations >10 µg/mL was high with both dosing schedules. With a 21-day cycle length, the probability of maintaining Cp >10 µg/mL was >90% after the first cycle and >95% throughout the remainder of the six-cycle dosing period and for four weeks after the last dose; the probability of Cp >10 µg/mL was approximately 89% at eight weeks after the last dose. With a 28-day cycle length, the probability of maintaining Cp >10 µg/mL was 84% after the first cycle and >95% throughout the remainder of the six-cycle dosing period and for four weeks after the last dose; the probability of Cp >10 µg/mL was approximately 85% at eight weeks after the last dose. Thus, a dosing schedule of 1000 mg infusions on Day 1 of each 21-day or 28-day cycle for 12 doses is expected to achieve prolonged maintenance of plasma concentrations >10 µg/mL in a high proportion of subjects with FL.

Prior clinical experience in a Phase I/II trial of ofatumumab in subjects with relapsed or refractory FL suggests that four weekly infusions of 300 mg to 1000 mg are effective [Study Hx-CD20-001; Hagenbeek, 2008]. Responses were observed in all four dose groups [300 mg: 5 of 8 subjects (63%); 500 mg: 3 of 9 subjects (33%); 700 mg: 2 of 10 subjects (20%); and 1000 mg: 5 of 10 subjects (50%)]. Thus, a regimen using twelve 1000 mg doses of ofatumumab at 21-day or 28-day intervals is expected to be effective.

In ongoing studies in subjects with FL, repeated doses of 500 mg or 1000 mg of ofatumumab have been administered. In Study Hx-CD20-405, ofatumumab was administered at 500 mg or 1000 mg weekly for seven weeks after an initial infusion of 300 mg in subjects with FL refractory to rituximab in combination with chemotherapy; in Study Hx-CD20-409, ofatumumab doses of 500 mg or 1000 mg were administered every three weeks after an initial infusion of 300 mg in combination with CHOP for a total of six cycles in subjects with previously untreated FL. In these two studies, there were no unexpected safety findings reported during treatment and within 30 days of last infusion. The results from these studies suggest that administration of 1000 mg at 21- or 28-day intervals is expected to be well tolerated.

An important safety factor of any antibody therapy concerns infusion reaction, particularly following the first intravenous administration. Both the proportion of patients experiencing infusion reactions to rituximab and the severity of the reactions are higher for the first infusion than for subsequent infusions [Chung, 2007]. Early experience with ofatumumab showed a similar pattern of infusion reactions [Coiffier, 2008; Hagenbeek, 2008], and a first infusion dose of 300 mg was therefore adopted in all studies in the ofatumumab development program to minimize first dose infusion reaction. However, upon further review of the data collected in the phase I/II study of ofatumumab in subjects with relapsed or refractory FL grade I-II (Study Hx-CD20-001), no clinically significant differences in the severity or frequency of AEs were observed with increasing dose. As a result, the median duration of the first infusion and the number of infusion reactions between subjects with FL receiving ofatumumab at doses of 300 mg, 500 mg, 700 mg, or 1000 mg did not differ significantly [OFATUMUMAB, 2012; Hagenbeek, 2008]. Thus, the use of 1000 mg at first infusion is proposed in study OMB110918.

Prior clinical experience with rituximab suggests that prolonged administration schedules enhance response duration in subjects with NHL [reviewed in Collins-Burow, 2007;

Ghielmini, 2004; Cersosimo, 2003]. Prior clinical experience with ofatumumab demonstrated longer median duration of response with the addition of four infusions at four-week intervals after the end of weekly ofatumumab treatment in subjects with fludarabine-refractory CLL (Study Hx-CD20-406). The proposed regimen is twelve infusions of ofatumumab to be administered with up to 8 cycles of bendamustine. The proposed ofatumumab regimen of 12 doses increases the duration of ofatumumab exposure, which should maintain chemo-sensitization of FL to concomitant chemotherapy while enhancing response duration.

3.2.2.1 Ofatumumab monotherapy for subjects who progress in Arm B

Subjects who progress during or after therapy in Arm B (bendamustine alone) will be offered ofatumumab monotherapy. Data regarding ofatumumab monotherapy in this population were obtained in Study Hx-CD20-405, in which subjects with rituximab-refractory FL were randomized to single agent ofatumumab at 500 mg or 1000 mg weekly for 7 doses after a 300 mg initial dose (total of 8 doses). The response rate was 11%, and mPFS was 6 months, with no difference between the dose groups. Experience in CLL indicates that increasing the dose intensity of rituximab was able to improve the ORR significantly from 10-15% to 45% [Byrd, 2001]. In addition, ofatumumab at a dose of 2000 mg showed significant clinical activity with an acceptable safety profile in subjects with fludarabine-refractory CLL in Study Hx-CD20-406. Therefore, it is reasonable to examine the 2000 mg dose in patients with refractory indolent NHL.

The optimal duration of therapy in this setting is unclear. Study Hx-CD20-406 administered eight weekly doses of ofatumumab 2000 mg (first dose 300 mg) followed by four monthly doses of 2000 mg; however, the standard length of weekly rituximab therapy in FL is four weeks, and there are no convincing data that increasing the number of weekly rituximab infusions from 4 to 8 is of benefit.

The rituximab-refractory FL population in this study may have more disease (and thus, faster clearance) and shorter PFS following four weeks of ofatumumab monotherapy than subjects with rituximab-sensitive FL. Thus, more frequent administration may be necessary for extended dosing in this refractory population, similar to the subjects with fludarabine-refractory CLL in Study Hx-CD20-406, who received monthly extended doses.

Infusion reactions occur more frequently at the initial infusion. Patients with indolent NHL are less likely to have severe infusion toxicity than CLL patients because they do not have circulating peripheral blood tumor cells which react with antibody.

To date, no subjects have received 2000 mg as the initial dose, while subjects with FL received an initial infusion of 1000 mg in Study Hx-CD20-001. Thus, a first dose of 1000 mg will be used in Arm A (Appendix 1 , Section 3.1.4) and for subjects that progress on Arm B and select optional ofatumumab (Appendix 3, Section 3.1.6). Study Hx-CD20-001 infused a 2 mg/mL concentration of ofatumumab at an initial rate of 25 mL/hr. Due to the observed tolerability associated with this concentration and rate, Study OMB110918 will infuse ofatumumab (2 mg/mL) at a starting rate of 25 mL/hr for infusions that follow the initial infusion for subjects that select ofatumumab following PD in Arm B (Appendix 3, Section 3.1.6).

Thus, a regimen of 1000 mg at the first week, followed by 2000 mg ofatumumab for three doses at weekly intervals, then 2000 mg ofatumumab every month for eight additional doses (for a total of 12 doses) will be offered to the subjects in Arm B who have PD during or after bendamustine monotherapy.

4 subject selection and withdrawal criteria

4.1 Number of Subjects

Subjects who meet all the following inclusion and exclusion criteria will be eligible for enrollment into the study. Approximately 408 subjects will be screened to randomize 346 subjects. See Section 8.2 for further details on assumptions for subject numbers.

4.2 Inclusion Criteria

The current investigator brochure provides specific information regarding warnings, precautions, contraindications, AEs and other pertinent information about ofatumumab that may affect subject eligibility.

Subjects eligible for enrollment in the study must meet all of the following criteria:

1. Small lymphocytic lymphoma (SLL), lymphoplasmacytic lymphoma, marginal zone lymphoma, and follicular lymphoma; grades 1, 2 and 3A, defined according to World Health Organization guidelines. Subjects with a diagnosis of SLL who have a peripheral blood monoclonal B lymphocyte count of ≥5,000/μL are considered to have CLL and are not eligible for this study.
   - Tumor verified to be CD20+ positive from a previous or current tissue biopsy.
   - CT imaging in screening phase (based on local evaluation) showing 2 or more clearly demarcated lesions/nodes with a long axis >1.5 cm and short axis ≥ 1.0 cm or 1 clearly demarcated lesion/node with a long axis >2.0 cm and short axis ≥1.0 cm (Section 6.2.5). CT imaging performed at screening as baseline image.
2. Indolent B-cell NHL with failure to achieve at least a partial response lasting 6 months beyond the end of treatment with rituximab or a rituximab-containing regimen (See Section 6.2.5.4– Section 6.2.5.5 for details on response criteria), i.e.:
   - Stable disease (SD) after rituximab or a rituximab-containing regimen (imaging will support this finding. NOTE: in cases of SD after rituximab monotherapy as induction treatment, the minimum time to confirm SD by imaging is 60 days from start of first rituximab infusion)

     or,
   - Disease progression during or within 6 months of treatment with rituximab or a rituximab-containing regimen. Imaging must support this finding and will be done ≤ 6 months after the last infusion of rituximab.

Note: Subjects must have received a minimum of 4 rituximab infusions as monotherapy or 3 infusions as part of rituximab-containing combination regimens

3. ECOG Performance Status of 0, 1, or 2
4. Age ≥ 18 years
5. Life expectancy of at least 6 months
6. Signed written informed consent prior to performing any study-specific procedures

French subjects: In France, a subject will be eligible for inclusion in this study only if either affiliated to or a beneficiary of a social security category.

4.3 Exclusion Criteria

Subjects meeting any of the following criteria will not be enrolled in the study:

1. Grade 3b FL or evidence that the indolent lymphoma has transformed to aggressive lymphoma as verified by biopsy confirmation [e.g., constitutional symptoms, poor performance status, fast growing tumor or increasing lactate dehydrogenase (LDH) level]
2. Previous autologous stem cell transplant in the last 6 months or previous allogeneic stem cell transplant at any time.
3. High dose steroids ≥ 25 mg prednisolone/day (or equivalent) for 7 consecutive days, given as concomitant medication, within 3 months prior to randomization. No more than 10 mg prednisone daily at the time of randomization
4. Prior bendamustine treatment within 1 year of randomization not resulting in a CR or PR for at least 6 months
5. Prior use of any monoclonal antibody (other than anti-CD20) within 3 months prior to randomization
6. Known central nervous system (CNS) involvement by indolent lymphoma
7. Other past or current malignancy. Subjects who have been free of malignancy for at least 5 years, or have a history of definitively treated non-melanoma skin cancer, or successfully treated in situ carcinoma, are eligible*
8. Chronic or current active infectious disease requiring systemic antibiotics, antifungal, or antiviral treatment such as, but not limited to, chronic renal infection, chronic chest infection with bronchiectasis, tuberculosis, and active Hepatitis C
9. Clinically significant cardiac disease as judged by the investigator including unstable angina, acute myocardial infarction within 6 months of randomization, congestive heart failure, and arrhythmia requiring therapy
10. History of significant cerebrovascular disease or event with significant symptoms or sequelae
11. Significant concurrent, uncontrolled medical condition that in the opinion of the investigator or Novartis Medical Lead contraindicates participation this study

12. Positive serology for Hepatitis B (HB) defined as a positive test for Hepatitis B surface antigen (HbsAg). In addition, if negative for HBsAg but Hepatits B core antibody (HBcAb) positive (regardless of HBsAb status), a HBV DNA test will be performed and if positive the subject will be excluded
    - Consult with a physician experienced in care and management of subjects with Hepatitis B to manage/treat subjects who are anti-HBc positive
    - If HBV DNA is negative, subject may be included but must undergo HBV DNA monitoring (see Section 6.5.7.1). Prophylactic antiviral therapy may be initiated at the discretion of the investigator
13. Current active liver or biliary disease (subjects with Gilbert's syndrome or asymptomatic gallstones, liver metastases related to indolent NHL or otherwise stable chronic liver disease per investigator assessment, are eligible)
14. Known human immunodeficiency virus (HIV) positive
15. Screening laboratory values:
    - platelets < 100 x 10^9/L (unless due to indolent lymphoma involvement of the bone marrow)
    - neutrophils < 1.5 x 10^9/L (unless due to indolent lymphoma involvement of the bone marrow)
    - Serum creatinine > 1.5 times the institution's upper limit of normal (ULN); subjects with a serum creatinine > 1.5 ULN will be eligible if the calculated creatinine clearance [Cockcroft, 1976] or creatinine clearance from a 24-hour urine collection is ≥ 40 mL/min
    - Total bilirubin > 1.5 times ULN (unless due to liver involvement by FL or Gilbert's disease)
    - Transaminases > 3 times ULN
16. Known or suspected hypersensitivity to ofatumumab, bendamustine, or mannitol
17. Treatment with any known non-marketed drug substance or experimental therapy within 5 terminal half-lives or 4 weeks prior to Visit 1, whichever is longer or currently participating in any other interventional clinical study
18. Known or suspected inability to comply with study protocol
19. Lactating women, women with a positive pregnancy test at Visit 1 or women (of childbearing potential) as well as men with partners of childbearing potential, who are not willing to use adequate contraception from study start through one year following last treatment dose. Adequate contraception is defined as abstinence, oral hormonal birth control, hormonal birth control injections, implants of levonorgestrel, estrogenic vaginal ring, percutaneous contraceptive patches, intrauterine device, and male partner sterilization if male partner is sole partner for that subject. The double barrier method can be used in regions where considered acceptable and adequate

(condom and/or occlusive cap plus spermicidal agent, as per local acceptable standards)

**Subjects can participate in the study if in the opinion of the investigator and Medical Lead it is thought not to affect the subject's safety, the conduct of the study or the interpretation of the data*

4.4 Withdrawal Criteria

Two types of withdrawal exist in this study:

1. Withdrawal from investigational product:

Subjects may withdraw early from investigational product for any reason at any time if it is their wish, or if the investigator judges it necessary for medical reasons. Following withdrawal, the subject will be asked to complete all regularly scheduled visit assessments (per time and events tables in Appendix 1 and Appendix 2 or Appendix 3).

2. Withdrawal from study:

Subjects may withdraw from study participation (i.e. withdraw consent) at any time for any reason, or if the investigator judges it necessary for medical reasons. The reason for withdrawal from study participation must be documented in the electronic Case Report Form (eCRF). The investigator must make every effort to perform and document the following assessments in the eCRF as per the WD visit in the Time and Events tables in Appendix 1 and Appendix 2 or Appendix 3, when applicable:

- Disease assessment
- Response Assessment
- Survival Assessment
- ECOG
- CT scans
- Constitutional symptoms
- Subject completion of PRO measures (FACT-Lym, EQ-5D, HCQ) (Appendix 1). PRO not required for subjects in Arm B who receive optional ofatumumab following PD (Appendix 3)
- Concomitant medication assessment
- Physical examination, vital signs and body weight assessment
- Hematology and Chemistry
- AE/SAE Assessment
- HAHA and ofatumumab PK concentration (as indicated in Appendix 2 and Appendix 3)

For data collection purposes, subjects are considered to have completed the study if they completed all scheduled visits, died during the treatment or follow-up phases, are lost to follow-up, or withdraw consent.

5 Study treatments

5.1 Investigational Product and Reference Therapy

The contents of the label will be in accordance with all applicable regulatory requirements.

Under normal conditions of handling and administration, the investigational product is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. Notify the monitor of any unintentional occupational exposure. A Material Safety Data Sheet (MSDS) describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from Novartis upon request.

Adequate precautions must be taken to avoid direct contact with the investigational product. The occupational hazards and recommended handling procedures are provided in the MSDS.

Investigational product must be stored in a secure area under the appropriate physical conditions for the product. Access to and administration of the investigational product will be limited to the investigator and authorized site staff. Investigational product must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

The investigational medical product, ofatumumab, is a liquid concentrate for solution for infusion.

Please refer to the SPM for instructions related to:

- infusion preparation
- pre-medication
- dosing schedule
- active comparator dose reduction/modifications
- handling of infusion reactions
- observations required during infusions

5.1.1 Pre-Medication

Pre-medication before each infusion is given within 30 minutes to 2 hours prior to the treatment. Pre-medication will be **required for the first infusion of ofatumumab**. If there are no severe infusion reactions, investigators will be allowed to choose whether pre-medication is required for further infusions (See Table 2). Pre-medication for ofatumumab infusion is as follows:

- Acetaminophen (PO) approximately 1000 mg or equivalent
- Antihistamine (IV or PO) equivalent to approximately 50 mg diphenhydramine
- Glucocorticoid (IV) equivalent to approximately 50 mg prednisolone

Please refer to the SPM for glucocorticoid equivalent doses and further details.

Table 2 Pre-Medication Schedule

Infusion Number	30 minutes to 2 hours prior to treatment		
	Acetaminophen (PO) ~1000 mg or equivalent	Antihistamine (IV or PO) equivalent to ~50 mg diphenhydramine	Glucocorticoid (IV) equivalent to ~50 mg prednisolone
1st	X	X	X
>1[1]	X[1]	X[1]	X[1]

1. Administration of premedication in Arm A (and in Arm B, as applicable) will be at investigator discretion if severe infusion reactions did not occur during first infusion.

5.1.2 Ofatumumab

The contents of the ofatumumab label will be in accordance with all applicable regulatory requirements. See Section 5.1 for more details on the MSDS. Ofatumumab must be stored in a secure area under the appropriate physical conditions for the product. Access to and administration of ofatumumab will be limited to the investigator and authorized site staff. Ofatumumab must be dispensed or administered only to subjects enrolled in the study and in accordance with the protocol.

Refer to the SPM for details on the ofatumumab supply, preparation of infusions, observations required during infusions and management of supplies.

In Arm A, ofatumumab 1000 mg 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 until all 12 doses have been administered. A total of 12 ofatumumab infusions will be administered in Arm A regardless of the number of bendamustine cycles completed.

Subjects developing PD in the bendamustine monotherapy arm (Arm B) will have the option to receive ofatumumab. Subjects who select this option will receive ofatumumab, 1000 mg for the first infusion (Week 1) followed by 2000 mg once a week for 3 infusions (Weeks 2-4) followed by additional ofatumumab (2000 mg) infusions, once every month for 8 doses (total:

12 doses). Subjects in Arm B who select this option must begin ofatumumab therapy within 120 days following diagnosis of PD, which can occur at any time during treatment or follow-up. Progressive disease must be confirmed by an IRC.

When ofatumumab and bendamustine are given on the same day, ofatumumab will be administered first. Response assessments will be done according to the schedule presented in Appendix 1 and Appendix 2. If a subject from Arm A (OB) develops PD, treatment with both bendamustine and ofatumumab will be terminated. The subject will remain in the study for follow-up.

5.1.2.1 Ofatumumab Treatment Schedule

Infusion rate escalation schedules in this section are recommendations. The investigator may use clinical judgment to optimize subject safety by escalating the infusion more slowly.

Please refer to the SPM for the preparation of the ofatumumab infusion.

Initial Infusion of ofatumumab

The starting rate of the initial infusion of 1000 mg (Section 3.1.4, Appendix 1, Section 3.1.6 and Appendix 3) ofatumumab (1.0 mg/mL) will be 12 mL/hour (hr). If no infusion reactions occur, we recommend that the infusion rate be increased every 30 minutes, to a maximum of 400 mL/hr, according to Table 3. If this schedule is followed, the 1000 mg infusion duration will be approximately 4.5 hours.

Table 3 Infusion rate at Initial ofatumumab infusion

Time	mL/hour
0 – 30 minutes	12
31 – 60 minutes	25
61 – 90 minutes	50
91 – 120 minutes	100
121 - 150 minutes	200
151 - 180 minutes	300
181+ minutes	400

If an infusion reaction develops, the infusion must be temporarily slowed or interrupted, as described in the SPM. We recommend that the infusion rate restart at half the infusion rate at the time the infusion was interrupted. If, however, the infusion rate was 12 mL/hr before the pause, the recommendation is for the infusion to be restarted at 12 mL/hr. Thereafter, the infusion rate may be increased according to the judgment of the investigator, in the manner described in this Section.

Subsequent infusions of ofatumumab

If the previous infusion has been completed without grade ≥ 3 infusion-associated AEs, we recommend that the subsequent infusion of 1000 mg (Section 3.1.4, Appendix 1) or 2000 mg (Section 3.1.6 and Appendix 3) ofatumumab (1.0 mg/mL or 2.0 mg/mL) start at a rate of 25 mL/hr. We recommend that the rate be doubled every 30 minutes up to a maximum of 400 mL/hr, according to Table 4. Duration of the infusion will be approximately 4 hours if this schedule is followed. If the previous infusion has been completed with grade ≥ 3 infusion associated AEs, we recommend that the subsequent infusion start at a rate of 12 mL/hr according to Table 3.

Table 4 Infusion rate at subsequent ofatumumab infusion

Time	mL/hour
0 – 30 minutes	25
31 – 60 minutes	50
61 – 90 minutes	100
91 – 120 minutes	200
121+ minutes	400

During infusion, the subject must be monitored closely and appropriate measurements must be performed whenever judged necessary. For details, please refer to the study procedures manual.

5.1.3 Bendamustine

Bendamustine (IV) is available as a single-use vial of bendamustine HCl as lyophilized powder. In the combination arm (Arm A), the bendamustine dose is 90 mg/m^2, given on days 1 and 2, every 21 days for up to 8 cycles. In the monotherapy arm (Arm B), the bendamustine dose is 120 mg/m^2, given on Days 1 and 2, every 21 days for up to 8 cycles. Investigators will follow the label dose reduction schedule if subjects require lower doses as they advance through treatment.

Bendamustine will be given for up to 8 cycles in both Arm A and Arm B. However, in the following instances, bendamustine may be given for fewer than 8 cycles:

1. If a subject cannot tolerate bendamustine and is unable to receive further treatment with bendamustine, the subject may stop bendamustine treatment.
    - If this occurs in Arm A: the subject will continue to receive all 12 doses of ofatumumab and continue to attend all scheduled visits on Day 1. Day 2 visits are not required unless the investigator requires additional tests.
    - If this occurs in Arm B: the subject will continue to attend all scheduled visits. Note: Subjects will only be required to attend the equivalent of the Day 1 visit. The Day 2 visit is not required unless assessed as necessary by the investigator.

2. The number of cycles will be contingent upon the response to the first 4 cycles. Subjects achieving CR after 4 cycles in either Arm will be treated with a total of 6 cycles only, whereas all other subjects will receive 8 courses of bendamustine as monotherapy (Arm B) or in combination with ofatumumab (Arm A).
    - If this occurs in Arm A: the subject will continue to receive all 12 doses of ofatumumab and continue to attend all scheduled visits
    - If this occurs in Arm B: the subject will continue to attend all scheduled visits on Day 1 of each cycle
3. Subjects with PD at any time during bendamustine monotherapy (Arm B) or OB combination therapy (Arm A) will be taken off treatment and will continue with survival follow-up (Section 3.1.6 describes subjects with PD in Arm B that continue on to ofatumumab monotherapy).

For subjects randomized to Arm A, bendamustine may be initiated within 1 day of scheduled start for logistical reasons (example: first cycle dose of bendamustine can be administered on Day 1 or Day 2 of the cycle). Once the first infusion occurs, the second infusion must occur the following day. The start of Cycles 2-8 may be delayed due to toxicity by up to 2 weeks for medical reasons at the investigator's discretion.

If the subject is medically unable to receive a subsequent cycle of treatment after 2 weeks' delay, a decision will be made about whether the subject will withdraw from treatment. Please see Section 5.1.3.1.

Please refer to the SPM for bendamustine preparation instructions and infusion times [as described in Treanda Prescribing Information, 2010].

5.1.3.1 Bendamustine Dose Reduction

The dose of bendamustine will be reduced if, with any cycle, a subject develops grade 4 hematologic or grade 3/4 non-hematologic toxicities, according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version 4.0 [NCI-CTCAE, 2009]. Arm B will follow the bendamustine dose reduction specified by the FDA label, Table 6 [Treanda Prescribing Information, 2010]. Arm A will follow the bendamustine dose reduction described in Table 5.

Non-hematological toxicities must be resolved to grade 1 or baseline before beginning the next cycle. Absolute neutrophil count (ANC) must have recovered to at least 1,000 cells/mm^3 (1.0 x 10^9 cells/L) and platelets to at least 75,000 cells/mm^3 (75 x 10^9 cells/L) by the start of the next cycle. Subjects who fail to meet these requirements will have therapy held until counts recover to these levels, and the bendamustine dose must be delayed or modified as specified in Table 5 (Arm A) or Table 6 (Arm B). Once a subject has undergone dose modification, subsequent cycles will give the modified dose of bendamustine.

If continued bendamustine-related toxicities occur beyond reasonable delay for recovery in either arm, study treatment will be discontinued (See Table 5 and Table 6). In this event, subjects in Arm B will continue to come to the clinic for scheduled visits and CT scans (to complete all scheduled visits including CT scan, assessment for lymphoma symptoms, and response assessments on Days 84, 168, 252 [+7 days]) and subjects in Arm A will stop

bendamustine and will continue to complete 12 doses of ofatumumab or enter follow-up if the 12 doses of ofatumumab are completed, as described in Appendix 1 and Appendix 2.

Table 5 Bendamustine Dose Reduction Schedule for Arm A

Bendamustine Dose and Schedule	**If Grade 4 Hematologic Toxicity**		**If Grades 3,4 Non-hematologic Toxicity**	
	Dose	**Schedule**	**Dose**	**Schedule**
90 mg/m^2, days 1,2 every 21 days	90 mg/m^2	Days 1,2 every 28 days	90 mg/m^2	Days 1,2 every 28 days
90 mg/m^2, days 1,2 every 28 days	70 mg/m^2	Days 1,2 every 28 days	70 mg/m^2	Days 1,2 every 28 days
70 mg/m^2, days 1,2 every 28 days	Discontinue treatment	Discontinue treatment	Discontinue treatment	Discontinue treatment

Table 6 Bendamustine Dose Reduction Schedule for Arm B

Bendamustine Dose and Schedule	**If Grade 4 Hematologic Toxicity**		**If Grades 3,4 Non-hematologic Toxicity**	
	Dose	**Schedule**	**Dose**	**Schedule**
120 mg/m^2, days 1,2 every 21 days	90 mg/m^2	Days 1,2 every 21 days	90 mg/m^2	Days 1,2 every 21 days
90 mg/m^2, days 1,2 every 21 days	60 mg/m^2	Days 1,2 every 21 days	60 mg/m^2	Days 1,2 every 21 days
60 mg/m^2, days 1,2 every 21 days	Discontinue treatment	Discontinue treatment	Discontinue treatment	Discontinue treatment

General Dosing Considerations for Arm A and Arm B:

- Delay treatment for Grade 4 hematologic toxicity or clinically significant ≥Grade 3 non-hematologic toxicity.
- Toxicities must recover to Grade 1 or baseline before the next administration of treatment. If recovery is not met within 2 weeks after the prescribed start of the treatment cycle (i.e., after a 2 week delay), a decision will be made about continuation in the study following consultation with Medical Lead.
- Bendamustine dosage will be delayed in subjects with a serum creatinine > 1.5 ULN if the calculated creatinine clearance [Cockcroft, 1976] or creatinine clearance from a 24-hour urine collection is ≤40 mL/min.
- Subjects will be monitored for safety as per local practice.

- The protocol must be followed as closely as possible, but if as per local practice, a blood draw for hematology analysis prior to the visit date is required, it would be acceptable for hematology analysis, but the blood draw can be taken no more than 3 days ahead of the visit date. Blood draws performed by local laboratories (e.g. for quicker pre-dose response assessment or assessment of toxicity) of protocol-required lab assessments are acceptable; however, it is important that the sample for the central laboratory analysis is taken at the same time. The local laboratory results of ANC, platelet count, peripheral blood lymphocytes, and hemoglobin must also be entered into the eCRF if it is used to manage a dose delay or reduction. Central Laboratory information will also be entered into the eCRF.

5.2 Treatment Assignment

Subjects will be assigned to study treatment in accordance with the randomization schedule (See Section 3.1.2). Please refer to the SPM for detailed instruction.

5.3 Permitted Medications

Subjects will receive supportive care during the study, including growth factors (e.g. G-CSF), transfusion of blood and blood products, and treatment with antibiotics, antiemetics, antidiarrheals, and analgesics, as appropriate. Please refer to the SPM for details.

5.4 Product Accountability

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of bendamustine and Novartis investigational product administered to study subjects and the amount received from and returned to Novartis, when applicable. Product accountability records must be maintained throughout the course of the study.

5.5 Prohibited Concomitant Medication or Therapies

The following medications are prohibited during this study:

- Anti-cancer medication not part of the protocol treatment (e.g., alkylating agents, anti-metabolites, purine analogues, monoclonal antibodies, radioimmunotherapy, and others)
- Glucocorticoids greater than 10 mg prednisone daily or equivalent, unless given to treat allergy or asthma exacerbations or unless given as pre-medication for or during ofatumumab infusions
- Any non-marketed drug substance or experimental therapy

Therapeutic alternatives to cytochrome P450 1A2 (CYP1A2) inhibitors or inducers must be considered with bendamustine. Please refer to the SPM for a list of CYP1A2 inhibitors and inducers.

6 Study Assessments and Procedures

6.1 Clinical Assessments

6.1.1 Demographics

At screening, date of birth, sex, and race/ethnicity is collected.

6.1.2 Disease Characteristics and Medical History

At screening, relevant medical history is collected including:

- Date of initial indolent lymphoma diagnosis
- Ann Arbor staging at diagnosis and screening
- ECOG Performance Status
- Listing of relevant past and current diseases
- Follicular Lymphoma Prognostic Index Score at screening (FLIPI-1, FLIPI-2)
- Dates and results of bone marrow biopsy and/or aspirate at or prior to screening (if appropriate, prior bone marrow sample provided per guidance in Section 3.1.1)

6.1.3 Previous Indolent Lymphoma Therapy

Prior treatment of indolent lymphoma will be recorded including name of therapy or regimen, start and end date, dosing information, response and duration of response.

6.1.4 Follicular Lymphoma International Prognostic Index (FLIPI)

The Follicular Lymphoma International Prognostic Index (FLIPI) will be assessed at screening. The FLIPI is a prognostic tool that may be used to evaluate and select treatments based on differences in survival between risk groups (low, medium, high). This index includes parameters related to subject characteristics; such as, age, tumor burden (Ann Arbor stage, number of nodal sites), tumor aggressiveness (serum LDH level), and consequences of the lymphoma on the host (hemoglobin level).

FLIPI-2 incorporates beta-2-microglobulin in the prognostic score. Both FLIPI-1 and FLIPI-2 at time of study entry will be calculated for subjects in this study.

See Appendix 6 and [Solal-Celigny, 2004].

6.1.5 Height and Weight

Height (without shoes) will be measured at screening and recorded in the eCRF. Body weight (without shoes) will be measured at each visit and recorded on the eCRF.

6.1.6 Concomitant Medication

Any medication other than the trial drug is considered concomitant medication apart from protocol defined pre-medication given prior to the infusions of ofatumumab combination therapy will be documented, including the following information:

- Indication
- Dose information
- Start date
- Stop date of administration or ongoing at study termination

6.1.7 Physical Examination

A general physical examination is required at the screening visit and as shown in Appendix 1 and Appendix 3. This physical examination will include general appearance including examination of the following: skin, extremities, abdomen, respiratory, cardiovascular, musculoskeletal, and neurological systems.

6.1.8 Electrocardiogram

A standard pre-treatment 12-lead electrocardiogram (ECG) is required at screening. The investigator will perform an overall interpretation of the ECG or may delegate this task to a cardiologist, if applicable. This screening ECG will be retained as part of the subject's source documentation.

6.1.9 Vital Signs

Vital signs including temperature, blood pressure (BP), and pulse are documented per Appendix 1 and Appendix 3, at screening and for the remainder of the study in both treatment arms. Temperatures for individual subjects must be measured using the same method at all visits.

All subjects must be monitored as per standard of care for changes in BP, heart rate, and temperature and for Adverse Events. All recorded values must be documented in the subject's source documentation.

If the subject suffers an AE (Grade ≥1) during the infusion (including asymptomatic fever, hypotension or tachycardia), which is determined by the investigator to be related to either the study procedures or study treatment, vital sign measurements (BP, heart rate and temperature) must be recorded in appropriate source documentation AND the BP and heart rate recorded in the eCRF , for the following time-points:

- At the time of event onset.
- Then every 30 minutes, or more frequently if clinically indicated if in the investigator's opinion the vital sign results at the time of event onset are clinically significant. The subject's vital sign measurements must continue to be recorded until they have returned to normal or pre-infusion levels.

6.1.10 ECOG Performance Status

An Eastern Cooperative Oncology Group (ECOG) Performance Status value [Oken, 1982] is required at screening, and throughout treatment and follow-up phases, to evaluate daily living abilities.

0 = Fully active, able to carry on all pre-disease performance without restriction

1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work

2 = Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours

3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours

4 = Completely disabled; cannot carry on any self care. Totally confined to bed or chair

5 = Dead

6.1.11 Constitutional Symptoms:

Assessment for the presence of the following symptoms (done as per Appendix 1 and Appendix 3):

- night sweats without signs of infection
- unintentional weight loss ≥ 10% within the previous 6 months
- recurrent, unexplained fever of greater than 100.5°F (38°C) for 2 weeks without signs of infection
- extreme fatigue

6.1.12 Pre-treatment Computed Tomography (CT) Scans and/or Imaging

All subjects must have CT scan (with contrast of the neck when lesions are palpable, thorax, abdomen, and pelvis). CT scan may be whole body or per local practice during screening if a CT scan was not done within 1 month (+ 7 days) prior to randomization. If a CT scan was done within 1 month prior to randomization, a copy of the image along with an image report (if available) must be provided prior to randomization. The copy of the CT scan must be adequate to allow comparison to subsequent CT scans for response assessment. This will be considered the baseline CT scan.

In addition to the CT scan required at screening, rituximab-refractory indolent lymphoma must be confirmed as described in Section 3.1.1.1.

6.1.13 Pre-treatment Bone Marrow Examination

See Section 3.1.1 for details on the timing and types of acceptable bone marrow examinations. Further details regarding collection of bone marrow samples are provided in SPM. A pathologist at a central laboratory will evaluate the biopsy.

6.2 Efficacy Assessments

6.2.1 Disease Responses

Complete remission (CR), partial remission (PR), stable disease (SD) or progressive disease (PD) will be based upon the criteria defined in the RRCML guidelines [Cheson, 2007]. Responses will be documented at visits as outlined in Appendix 1 and Appendix 3.

The same physician will evaluate the subject's response and corresponding assessments that are part of the response, wherever possible. Response imaging will be subject to a retrospective blinded independent review by an IRC and the final determination of progression will be based on the evaluations from the independent review and will be used for the study's efficacy analysis and submission to regulatory agencies.

Please refer to SPM for details of submission of imaging for review.

6.2.2 CT Scans

CT scans (with contrast of the neck when lesion is palpable, thorax, abdomen, and pelvis; may be whole body CT scan or according to standard of care) will be done as part of the efficacy evaluation and after treatment has been completed. The scans must be implemented according to a CT scan manual to be provided to Novartis (Imaging Acquisition Guidelines) as mentioned in the SPM.

In situations where PD is apparent through physical examination (such as massive lymphadenopathy), only the body area where PD is apparent must be scanned to confirm PD.

All subjects (Arm A and Arm B) must have a CT scan done on Days 84, 168, and 252 (+7 days). In the event subjects in Arm A or Arm B cannot complete 8 cycles of therapy with bendamustine, then subjects must come to the clinic for all scheduled Day 1 assessments. Subjects will have CT scans at each follow-up visit as described in Table 1, Appendix 1, and Appendix 3. Survival Follow-up visits will begin 2 months after PD is confirmed by CT scan. CT scans will be done to confirm any clinical signs or suspicion of PD. CT scans which are unscheduled and are performed to confirm PD in event of clinical signs or suspicion of progression may be done only of the suspected body area with progression. In the event that an unscheduled CT scan does NOT show PD, the subject will resume the planned CT scan schedule (i.e. the next CT scan will be done based on the date of the last scheduled CT scan and not the day of the unscheduled CT scan). For all other responses, follow-up visits will begin on Day 336 (this is 3 months after Day 252) for both arms and continue until initiation of alternative indolent lymphoma treatment, PD, or withdrawal (WD), See Appendix 1 and Appendix 2 and Appendix 3 for details.

CT scans will be assessed according to an independent review. The independent review will be described in an independent review charter. See Section 6.2.6 for a description of this independent review.

6.2.3 Bone Marrow Examination

Bone marrow examination (both aspirate smear and core, if possible) to confirm CR, as determined by the clinical and laboratory results listed in Section 6.2.5.2 is required no later than ≤ 8 weeks following onset of CR if there was disease involvement in the bone marrow at baseline. Samples are to be reviewed in conjunction with the prior pathology.

6.2.4 Lymphoma Disease-Related Symptoms:

Assessment for the presence of the following symptoms (done as per Appendix 1 and Appendix 3):

- Night sweats due to lymphoma (not due to infection or treatment)

- Fever due to lymphoma (not due to infection or treatment)
- Loss of appetite due to lymphoma (not due to treatment)
- Clinically significant weight loss, since the previous disease assessment, which is due to lymphoma (not due to treatment)
- Fatigue due to lymphoma (not due to treatment)
- Other symptoms due to lymphoma (not due to treatment)

6.2.5 Documentation of Target and Non-target Lesions

Eligibility Criterion

CT scan showing at least:

- 2 or more clearly demarcated lesions/nodes with a long axis >1.5 cm and short axis ≥ 1.0 cm

OR

- 1 clearly demarcated lesion/node with a long axis >2.0 cm and short axis ≥1.0cm

BASELINE DOCUMENTATION OF TARGET AND NON-TARGET LESIONS

Target lesions will be identified from each of the following categories at baseline and followed throughout the study:

1. lymph nodes/masses (maximum 6)
2. hepatic & splenic nodules (maximum 6)
3. Other extranodal lesions (excludes hepatic & splenic nodules) (maximum 6)

The target lesions will be selected according to the following criteria:

- Clearly measurable in two perpendicular dimensions by CT scan with a long axis >1.5 cm and short axis ≥1.0 cm
- The largest lesion from different regions of the body
- Lesions in mediastinal and retroperitoneal areas will be included if these sites have measurable lesions

The longest and perpendicular short diameter (cm) of each lesion will be measured and the product of the perpendicular diameters (PPD) calculated. The sum of the products of the diameters (SPD) will be calculated for each category of target lesions when there are multiple target lesions present in the category. For guidance on calculation of the SPD refer to SPM and Table 7.

During follow-up, with the exception of lesions that regress to >0 cm x >0 cm and ≤0.5 cm x ≤0.5 cm the best estimate of the lesion dimensions must be reported even if necrosis, fibrosis or cavitation are present. If a lesion is present but has regressed to between >0 cm x >0 cm and ≤0.5cm x ≤0.5cm, 'too small to measure' will be assigned and a default size of 0.5 cm x 0.5 cm will be used for calculation purposes. A lesion that is absent would be recorded as >0 cm x >0 cm.

All other lesions (measurable or non-measurable) will be identified as non-target lesions and recorded at baseline. Measurements of non-target lesions are not required, but the presence/absence or unequivocal progression of each will be noted throughout follow-up.

Liver and spleen size will be reported as normal, enlarged not due to lymphoma, enlarged due to lymphoma (nodules must be present for this to be reported), or unequivocal progression (nodules must be present for this to be reported).

The definition of unequivocal progression of non-target disease is based on the definition applied in RECIST 1.1 [Eisenhauer, 2009] as an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased significantly to merit discontinuation of therapy, or if therapy has already been completed, commencement of anti-cancer therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

6.2.5.1 Calculation of SPD

Increase or decrease of SPD of target lesions will be calculated based on the formula as seen in Table 7.

Table 7 Sum of Products Greatest Diameter Measurements (SPD)

Decrease rate=	**SPD before treatment – SPD at assessment / SPD before treatment**	**X100%**
Increase rate=	**SPD at assessment – smallest SPD during the study / Smallest SPD during the study**	**X100%**

6.2.5.2 Complete Remission (CR)

The designation of CR requires the following:

1. Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy. All target nodes must have regressed to ≤1.5cm in the longest diameter (non-measured nodes 1.1-1.5cm in the longest diameter and >1cm in the short axis at baseline, must regress to ≤1cm in the short axis by visual estimation).
2. The spleen and/or liver, if considered enlarged due to lymphoma (nodules must be present) before therapy based on a CT scan and must be considered normal size by imaging studies, and nodules related to lymphoma must disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.
3. If the bone marrow was involved by lymphoma before treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it must be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but that demonstrates a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in subject outcome.

6.2.5.3 Partial Remission (PR)

The designation of PR requires all of the following:

1. At least a 50% decrease from baseline in sum of the SPD of target nodes.
2. The categories of target splenic/hepatic nodules and other extranodal lesions must each regress by ≥50% in their SPD compared to baseline. If the category only contains a single nodule/lesion, it must regress by ≥50% in the greatest transverse diameter compared to baseline.
3. No unequivocal progression must be observed in non-target lesions, liver, or spleen size.

4. Bone marrow assessment is irrelevant for determination of a PR if the sample was positive before treatment. However, if positive, the cell type must be specified (e.g., large-cell lymphoma or small neoplastic B cells). Subjects who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders. When the bone marrow was involved before therapy and a clinical CR was achieved, but with no bone marrow assessment after treatment, subjects must be considered partial responders.
5. No new sites of disease must be observed.

6.2.5.4 Stable Disease (SD)

A subject is considered to have SD when he or she fails to attain the criteria needed for a CR or PR, but does not fulfill those for PD [Cheson, 2007].

6.2.5.5 Relapsed Disease (after CR)/Progressive Disease (after PR, SD)

Criteria for determining PD for new lesions and target lesions are shown in Table 8.

Table 8 Criteria for determining PD for new lesions and target lesions

	Nodes	**Extranodal ('liver/spleen' & 'other' categories)**
New node/lesion[a]	A previously normal node (≤1.5 x ≤1.0 cm), including nodes that were not previously visible, must increase to >2.0 x ≥1.5 cm.	An unequivocal new lesion at a site where there was no disease at baseline, provided the lesion cannot be attributed to non-lymphoma-related causes.
Single node/lesion		
Increase in PPD	≥ 50% increase from nadir in the PPD of any target node. The long axis must increase by at least 5 mm and to >2.0cm.	≥50% increase from nadir in the PPD of any target lesion, and at least a 5 mm increase in either of the axes, and the lesion must be >1.5cm x ≥1.5 cm.
Increase in long axis	≥50% increase from nadir in the long axis of any target node. The long axis must increase by at least 5 mm and to >2.0 cm.	≥ 50% increase from nadir in the long axis of any target lesion, and at least a 5 mm increase in the long axis, and the lesion must be >1.5 cm x ≥1.5 cm.
Multiple nodes/lesions		
Increase in SPD	≥50% increase from nadir in the SPD of target nodes **and at least one node must have a long axis >1.5cm.**	≥50% increase from nadir in the SPD of target lesions **and at least one lesion must have a long axis >1.5cm[b].**

Abbreviations: PPD= product of perpendicular diameters; SPD= sum of the products of the greatest diameter.

a. Abnormal nodes/extranodal lesions present at baseline that normalize/resolve and then subsequently enlarge/relapse are not to be classified as new lesions.

b. Requiring that one node is > 1.5 cm minimizes the risk of declaring PD based on small artifactual changes.

Unequivocal progression, as defined in Section 6.2.5, at a site of non-target disease, or unequivocal progression of the liver or spleen size (nodules must be present in the organ for unequivocal progression to be reported) will fulfill the criteria for PD.

If the subject achieved a CR on protocol, histological confirmation of relapse is strongly recommended.

6.2.6 Independent Review of Disease Response

The study's primary endpoint is to determine PFS as assessed through an independent review of the data based on the RRCML guidelines [Cheson, 2007]. These response criteria are described in Section 6.2. The operation and responsibilities for members that are part of the independent review is described in a separate charter. The final determination of progression will be based on the evaluations by the independent reviewer(s) and will be used for the study's efficacy analysis and submission to regulatory agencies.

- Imaging confirmed CR must show specified changes as described in Section 6.2.5.2
- Imaging to confirm PR has to show specified changes as described in Section 6.2.5.3

6.3 Laboratory Assessments

A detailed description of the procedures for sampling, handling, storage, and shipment of the laboratory samples and all material such as test tubes and labels is provided in the SPM or in the central laboratory manual.

6.3.1 Flow Cytometry for B Lymphocytes

The number of $CD19^+$ and $CD20^+$ B cells will be assessed by flow cytometry. This will be done in Arm A and in Arm B subjects who receive subsequent ofatumumab monotherapy only. Blood samples for B-cell monitoring will be collected during treatment and during follow-up, as defined in Appendix 2 and Appendix 3. See SPM for details.

6.3.2 Peripheral Blood Sampling for Hematology and Biochemistry

Blood samples will be drawn for analysis inclusive but not limited to the following parameters per Appendix 2 and Appendix 3:

- Hepatitis B (HBV) and Hepatitis C (HCV) at screening
  - For subjects that are HBsAg negative, HBcAb positive and HBV DNA negative (see Section 4.3) blood samples will be collected for monthly HBV DNA testing on Day 1 of each cycle depending on the number of cycles administered and samples will be collected during FU. See SPM, and for collection times.
- Japan only: Instructions are in Appendix 8.
- Hematology: Complete blood count with differential counts
  - Biochemistry: sodium, potassium, chloride, bicarbonate, calcium, blood urea nitrogen (BUN), creatinine, uric acid, total bilirubin*, alkaline phosphatase (ALP), aspartate transaminase (AST), alanine transaminase (ALT), lactic acid dehydrogenase (LDH), albumin, glucose (random), and haptoglobulin.

*Bilirubin fractionation is recommended if total bilirubin >2 x ULN

- A creatinine clearance will be calculated prior to bendamustine administration as shown in Appendix 2. Calculated creatinine clearance will be done at screening and can be repeated at the physician's discretion if there is a significant rise in serum creatinine during the treatment phase of the study. The Cockcroft-Gault formula [Cockcroft, 1976] will be used to determine a calculated creatinine clearance:
  - In men: (140 – age [years]) x weight (kg) / (72 x serum creatinine [mg/dL])
  - In women: multiply this result by 0.85

6.3.3 Prognostic Factors

Whole blood will be collected at time points defined in Appendix 1 Appendix 2 for later analysis of the following prognostic factors:

- Follicular lymphoma International Prognostic Index (FLIPI-1, FLIPI-2) See Appendix 6 and [Solal-Celigny, 2004; Federico, 2009]
- Absolute Lymphocyte Count (expressed in % and in absolute numbers)
- Genetic variation in the FcR gamma 3A
- For all patients, Human Anti-Chimeric Antibody (HACA) will be taken at Cycle 1 Day 1 as defined in Appendix 2. If receiving ofatumumab following PD in Arm B, HACA will be taken as defined in Appendix 3.

6.3.4 Peripheral Blood Sampling for Safety and Disease Status

Peripheral samples will be collected for the analysis of:

- Subjects receiving ofatumumab that are Hepatitis B core positive at screening, Hepatitis B DNA will be obtained at each cycle visit while on treatment and collected during F/U. See SPM, Appendix 2, and Appendix 3 for more details
- Screening pregnancy test (HCG) for women of childbearing potential, unless they have had a hysterectomy, have undergone tubal ligation within one year before the screening visit, or have been postmenopausal for at least one year
- Subsequent pregnancy testing in women of child bearing potential will be done as defined in Appendix 2 and Appendix 3
- Human Anti-Human Antibody (HAHA) will be taken in Arm A as defined in Appendix 2. If receiving ofatumumab following PD in bendamustine monotherapy arm, HAHA will be taken as defined in Appendix 3
- IgA, IgG and IgM will be taken in Arm A as defined in Appendix 2 and Appendix 3

6.4 Safety Assessments

6.4.1 Liver Interruption/Stopping and Follow- up Criteria

Liver chemistry stopping and follow up criteria are a mandatory part of Novartis studies and have been designed to assure subject safety and evaluate liver event etiology.

NOTE: if serum bilirubin fractionation is not immediately available, study drug should be discontinued if ALT > 3xULN **and** bilirubin > 2xULN. Serum bilirubin fractionation must be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

The Novartis Safety Monitoring Team will review all events which meet liver chemistry stopping criteria and determine if the event was due to tumor lysis and to exclude drug induced liver injury (DILI) due to ofatumumab.

6.4.1.1 Liver Chemistry Stopping Criteria

The stopping criteria for all subjects are based upon the FDA July 2009 Guidance for Industry, Drug-Induced Liver Injury: Pre-marketing Clinical Evaluation, Section 5, Decision to Stop Drug Administration. The FDA guidance was adapted for oncology ofatumumab protocols such that the criteria for stopping dosing are:

- ALT>3 times upper limit of normal (ULN) **and** bilirubin >2 times ULN (>35% direct bilirubin; bilirubin fractionation required‡)
- ALT >8 times ULN
- ALT >5 times ULN for more than 2 weeks

Compared with the FDA guidance, please note:

- International normalized ratio (INR)>1.5 was not included as in an oncology patient there may be other valid reasons for this value such as poor nutritional status (due to nausea & vomiting).
- Criteria 4 was not considered appropriate for an oncology patient as the symptoms described may also be attributed to the disease status, concomitant therapies or B-cell depletion and cytokine release.
- ALT and fractionated bilirubin (if possible) are selected as more specific laboratory assessments of liver injury.

6.4.1.2 Liver Chemistry Interruption/Stopping and Follow-up Criteria

Liver chemistry stopping and follow up criteria have been designed to assure subject safety and evaluate liver event etiology.

The Novartis Medical Lead and Global Clinical Safety and Pharmacovigilance (GCSP) physician in conjunction with the investigator will review all events which meet liver chemistry stopping criteria to determine if the event was due to tumor lysis, disease related liver involvement, concomitant chemotherapy or other identified cause and to

exclude drug induced liver injury (DILI) due to ofatumumab. If the event is determined to be due to causes other than ofatumumab DILI and improvement is observed after withdrawal of ofatumumab, rechallenge may be attempted if deemed appropriate by the Novartis Medical Lead and investigator and in addition to consent of the subject.

‡ ***NOTE****: If serum bilirubin fractionation not immediately available, study drug must be discontinued if ALT > 3xULN* ***and bilirubin >2xULN pending the results of review by the Medical Lead, GCSP physician and the investigator.*** *Serum bilirubin fractionation must be performed if testing is available. If testing unavailable,* ***record presence of detectable urinary bilirubin on dipstick,*** *indicating direct bilirubin elevations and suggesting liver injury.*

When any of the liver chemistry stopping criteria is met, do the following:

- Immediately stop study treatment
- Report the event to Novartis within 24 hours of learning its occurrence
- Hold ofatumumab for two weeks, repeat liver chemistry testing at least twice weekly, and call the Medical Lead to discuss the possibility of re-challenging with ofatumumab. Note: The 2 week time point for stopping medication was chosen because it will distinguish from liver function test elevations due to tumor lysis which must have resolved within this time period. Medication is interrupted and it is a clinical and patient decision if ofatumumab may be re-started. The risk:benefit ratio is different in an oncology setting and an efficacious therapy may be life-saving.
- Complete the liver event eCRF and SAE data collection tool if the event also meets the criteria for an SAE
    - All events of ALT > 3xULN **and** bilirubin > 2xULN (>35% direct bilirubin) (or ALT>3xULN and INR>1.5, if INR measured; INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants), termed 'Hy's Law', **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**.
    - NOTE: if serum bilirubin fractionation is not immediately available, study treatment must be discontinued if ALT > 3xULN **and** bilirubin > 2xULN. Serum bilirubin fractionation must be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
- Complete liver imaging and/or biopsy eCRF(s) if these tests are performed.
- Perform liver chemistry follow-up assessments (see Section 6.4.1.3) and monitor the subject until liver chemistries resolve, stabilize or return to baseline values as described below.
- In addition, for subject meeting liver stopping criteria 1:
    - Make every reasonable attempt to have subjects return to clinical within 24 hours for repeat liver chemistries, liver event follow-up assessments (See Section 6.4.1.3) and close monitoring

- A specialist or hepatology consultation is recommended
- Monitor subjects twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

- For subjects meeting criteria 2 or 3:
  - Make every reasonable attempt to have subjects return to clinic **within 24 to 72 hours** for repeat liver chemistries and liver event follow-up assessments (See Section 6.4.1.3)
  - Monitor subjects weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.
- After holding ofatumumab for two weeks:
  - If the treatment is exhibiting efficacy **and** the subject wants to continue therapy after being informed of the results of liver chemistry testing, then the ofatumumab may be re-started.
  - Liver chemistries and the signs and symptoms listed in liver chemistry follow-up assessments must be monitored at a minimum of every 2 weeks until resolution, stabilization, or a return to baseline values, at which point monitoring must be continued per protocol.

Subjects with ALT >3xULN **but** <5xULN **and** bilirubin <2xULN without hepatitis symptoms or rash, and who may be monitored weekly for at least 4 weeks, then the following actions must be taken:

- Subjects can continue ofatumumab.
- Return weekly for repeat liver chemistries until they resolve, stabilize, or return to baseline values, then monitor liver chemistries as per protocol assessment schedule.
- If at any time the subject meets any of the liver chemistry stopping criteria, then proceed as described above.
- If after 4 weeks of monitoring, ALT<3xULN and bilirubin<2xULN, monitor twice monthly until liver chemistries normalize or return to within baseline values.
- Hepatic events should be documented as an AE or an SAE as appropriate (See Section 6.5 and Section 6.5.2).

6.4.1.3 Liver Chemistry Follow-up Assessments

For subjects meeting any of the liver chemistry stopping/interruption criteria, make every attempt to carry out the liver event follow up assessments described below:
Viral hepatitis serology including:

1. Hepatitis A IgM antibody
2. HBsAg and HBcAb (IgM);
3. Hepatitis C RNA;

4. Cytomegalovirus IgM antibody;
5. Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing);
6. Hepatitis E IgM antibody
7. Blood sample for PK analysis of ofatumumab (if an Arm A subject), obtained as soon as possible but no later than 5 months of last dose (approximately 5 half-lives of the drug). Record the date/time of the PK sample draw and the date/time of the last dose of ofatumumab prior to blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the best approximation. If a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SPM.
8. Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH)
9. Fractionate bilirubin, if total bilirubin >2xULN
10. Obtain complete blood count with differential to assess eosinophilia
11. Record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, fatigue, decreased appetite, nausea, vomiting, abdominal pain, jaundice, fever, or rash as relevant on the AE report form
12. Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins, on the concomitant medications report form.
13. Record alcohol use on the liver event alcohol intake form

The following assessments are required for subjects with ALT>3xULN and bilirubin>2xULN (.35% direct) but are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies
- Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009].
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.

Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen): quantitative hepatitis B DNA and hepatitis delta antibody. . NOTE: if hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of hepatitis D RNA virus (where needed) – as outlined in: Adverse Events

The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE (Section 6.5 and Section 6.5.2).

6.5 Adverse Events

The investigator or site staff will be responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE (Appendix 1 and Appendix 3).

6.5.1 Definition of an AE

Any untoward medical occurrence in a subject or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Note: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e., lack of efficacy), abuse or misuse.

Events meeting the definition of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after investigational product administration even though it may have been present prior to the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either investigational product or a concomitant medication (overdose per se will not be reported as an AE/SAE).
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the definition of an AE or SAE.

Events that do not meet the definition of an AE include:

- Any clinically significant abnormal laboratory finding or other abnormal safety assessments that is associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition
- Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen
- B cell depletion due to ofatumumab treatment

- Events related to the underlying lymphoma and unrelated to the study therapy, unless more severe than expected for the condition

6.5.2 Definition of a SAE

6.5.3 Toxicity Assessment of AEs and SAEs

The investigator is required to make an assessment of the toxicity grade of each AE or SAE reported. In this protocol, the maximum toxicity grade of each non-hematologic AE/SAEs will be evaluated according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [NCI-CTCAE, 2009].

6.5.4 Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

Any abnormal laboratory test results (hematology, clinical chemistry, or urine analysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgment of the investigator are to be recorded as AEs or SAEs.

ALT levels of greater than 3 times the ULN and simultaneous bilirubin levels of greater than 2 times ULN (>35% direct bilirubin; bilirubin fractionation required) are to be recorded as SAEs.

However, any clinically significant safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition, are not to be reported as AEs or SAEs.

B cell depletion due to treatment with ofatumumab not to be reported as an AE or SAE.

Infusion related AEs may lead to a prolonged infusion time. Overnight stay at the hospital due to slow infusion rate is not to be reported as a SAE.

6.5.4.1 Detection and Management of AEs and SAEs of Special Interest

Specific attention will be paid to monitor events of special interest such as infusion reactions, tumor lysis syndrome, infections and progressive multifocal leukoencephalopathy (PML). Please refer to the SPM and/or the following text for more details.

6.5.4.1.1 Handling Infusion Reactions

Infusion reactions are commonly associated with anti-CD20 antibody therapy. Ofatumumab can cause serious infusion reactions manifesting as bronchospasm, dyspnea, laryngeal edema, pulmonary edema, flushing, hypertension, hypotension, syncope, cardiac ischemia/infarction, back pain, abdominal pain, pyrexia, rash, urticaria, and angioedema. Infusion reactions occur more frequently with the first 2 infusions.

The site staff must be prepared to intervene if an infusion reaction occurs. Special caution should be taken during the first infusion for each subject and during the infusion for any subject who did not tolerate a previous infusion well. It is recommended that a resuscitation

or crash cart/trolley is readily accessible in the event of an emergency. Infusion reactions should be treated according to the investigators judgment and best clinical practice.

Interruption, restart and increasing the rate of the infusion depending on the severity of the AE must be according to the description below. An increase of the infusion rate after an interruption must not exceed the scheduled amount as described in Table 3 and Table 4 (i.e. not more than doubled rate and no earlier than every 30 minutes).

Mild and Moderate Intensity Adverse Events (Grade 1 and 2)

If the investigator judges the AE to be related to the infusion, the infusion must be temporarily slowed or interrupted. When the subject's condition is stable, the infusion can be restarted according to the judgment of the investigator. Upon restart, the infusion rate should be half of the infusion rate at the time the infusion was paused. If, however, the infusion rate was 12mL/hr before the pause, the infusion should be restarted at 12mL/hr.

6.5.4.1.2 Severe Intensity Adverse Events (Grade ≥ 3)

If the investigator judges a grade ≥3 AE to be related to the infusion, the infusion must be interrupted and the appropriate clinical intervention commenced. When the AE decreases to grade <3, the investigator may restart the infusion. Upon restarting the infusion, the infusion rate must be 12mL/hr for the first infusion or 25mL/hr for subsequent infusions, and may subsequently be increased according to the judgment of the investigator, as described in Section 5.1.2.1 of the protocol (i.e. not more than doubled and no earlier than every 30 minutes).

If the severity of the AE does not resolve to grade <3 despite adequate clinical intervention, or the same AE increases to grade =3 on three occasions during one infusion, the subject should be withdrawn from treatment.

6.5.4.1.3 Handling Tumor Lysis Syndrome

Monitoring and treatment of potential Tumor Lysis Syndrome (TLS) should be performed as per oncology standard of care.

Symptoms of TLS include:

- Hyperkalemia, potentially leading to cardiac conduction abnormalities, muscle weakness or paralysis
- Hyperphosphatemia, potentially leading to renal failure
- Hypocalcemia. Symptoms include (but are not limited to): tetany, seizures, mental retardation / dementia, parkinsonian (extrapyramidal) movement disorders, papilledema, emotional instability / agitation / anxiety, myopathy

- Hyperuricemia, potentially leading to renal failure

Risk factors for TLS include a high tumor burden, high concentrations of circulating cells (≥ 25,000/mm3), hypovolemia, renal insufficiency, elevated pre-treatment uric acid levels and elevated lactate dehydrogenase levels. Thus TLS should be suspected in subjects with large tumor burden who develop acute renal failure along with hyperuricemia (> 15 mg/dL) or hyperphosphatemia (> 8 mg/dL). Acute uric acid nephropathy is associated with little or no urine output. The urinalysis may show uric acid crystals or amorphous urates. The hypersecretion of uric acid can be detected with a high urine uric acid:creatinine ratio > 1.0, compared to a value of 0.6-0.7 for most other causes of acute renal failure.

In those patients considered to be at risk for TLS, management of TLS includes correction of electrolyte abnormalities, monitoring of renal function, maintenance of fluid balance (consider aggressive hydration i.e. ~3,000 ml/m^2/day fluid administered parenterally) and supportive care. If signs of TLS occur the investigator can administer rasburicase, allopurinol (e.g. Zyloprim, Allohexal, Allosig, Progout, Zyloric), or other drugs used to treat hyperuricemia, per prescribing information, if deemed appropriate.

6.5.4.1.4 Handling Progressive multifocal leukoencephalopathy (PML)

PML is a viral-induced demyelinating disease of the central nervous system usually occurring in the immunocompromised individual and has been reported with ofatumumab. JC virus (JCV) infection resulting in PML and death has been reported in rituximab-treated subjects with hematologic malignancies or with systemic lupus erythematosus, an indication for which rituximab has not been approved. Investigators and nurses should pay careful attention for signs and symptoms consistent with a diagnosis of PML. Signs and symptoms of PML include visual disturbances, ocular movements, ataxia, and changes in mental status such as disorientation or confusion. These symptoms are not an exhaustive list, and the investigator should exercise judgment in deciding to report signs and symptoms to sponsor promptly.

If a subject develops neurological signs or symptoms consistent with PML, treatment should be halted and the subject referred to a neurologist for evaluation. At a minimum, blood JCV PCR and/or MRI should be performed; if either test is positive, Cerebrospinal Fluid (CSF) JCV PCR should be performed. If blood JCV PCR and MRI are negative, the investigator should contact the Sponsor for appropriate action to be taken. If blood JCV PCR and/or MRI are positive, the subject should be withdrawn from treatment, proceed to the Follow-Up Period, and be followed until resolution. There are no known tests that can reliably determine who is at increased risk for developing PML. There are no known interventions that can reliably prevent PML or adequately treat PML if it occurs.

The investigator will do the following when reporting a serious infection (including PML) or sign/symptom consistent with PML.

- Refer to Section 6.5.8 of this document for further information and detailed guidance for completing and transmitting these and other SAE reports for subjects who experience a serious infection, malignancy, death, or sign or symptom of PML.
- Provide key source documentation for the Sponsor to assist with the safety evaluation process.

Examples of key source documents include but are not limited to: hospitalization records, discharge summaries, laboratory evaluations, biopsy results, culture/sensitivity results, death certificates, and autopsy reports.

If the subject has not otherwise been withdrawn from the study, then the investigator should contact the Sponsor to discuss the appropriate course of action regarding study continuation.

6.5.4.1.5 Monitoring of Hepatitis in patients

In subjects receiving ofatumumab that are Hepatitis B core positive, HBsAg negative, and HBV DNA negative (Section 6.3.2 and Section 6.5.7.1), Hepatitis B DNA must be obtained on Day 1 of each cycle visit while on treatment and then 1,3,6 months post treatment.

For subjects who require hepatitis monitoring, extra visits outside those defined in the protocol may be required.

If a subject converts to HBV DNA positive during the study, Hepatitis B treatment may be initiated by the site investigator after consultation with a physician experienced in the care and management of subjects with Hepatitis B and the Novartis Medical Lead. The risks and benefits of continuing ofatumumab or discontinuing ofatumumab must be discussed with the Medical Lead before appropriate treatment decisions are made for that individual subject.

For subjects randomized to the study in Japan, please see Appendix 8 of the protocol for additional guidance.

6.5.5 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

An event which is part of the natural course of the disease under study (i.e. disease progression) is not to be reported as a SAE. Death from disease progression is also not to be reported as an SAE. However, if the progression of the underlying disease is greater than that which would normally be expected for the subject or if the investigator considers that there was a causal relationship between treatment with investigational product or protocol design/procedures and the disease progression, then this must be reported as a SAE.

6.5.6 Pregnancy

Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form. To ensure subject safety, each pregnancy must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy must be followed up to determine outcome (including premature termination) and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as an AE or SAE. Spontaneous abortions must be reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the investigational product, must be promptly reported to Novartis.

The investigator must attempt to collect pregnancy information about a partner of a male study subject, who becomes pregnant by a male study subject while he is enrolled in the study. Pregnancy information must be reported to Novartis as described above.

6.5.7 Time Period and Frequency of Detecting AEs and SAEs

All SAEs and AEs regardless of relationship to investigational product will be collected from the first dose of investigational product to 60 days after the last dose of investigational product and will be documented on the eCRF. All SAEs regardless of causalitywill be reported from 61 days after the last dose of investigational product to the end of the follow-up period or until initiation of subsequent anti-lymphoma therapy is initiated. Any SAE brought to the investigator's attention after the start of subsequent anti-lymphoma therapy and considered by the investigator as possibly related to either ofatumumab or bendamustine must be reported to Novartis.

From the time a subject consents to participate in and completes the study (See Section 4.4), all SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) will be reported promptly to Novartis as indicated in Table 9.

From the time a subject consents to participate in and completes the study or withdraws from the study (Section 4.4), all SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) will be recorded.

Discontinuation of ofatumumab is not mandated; however the investigator must consult the Novartis Medical Lead to analyze the risk-benefit and determine if appropriate to continue ofatumumab therapy in that individual subject.

Any pre-existing condition or signs and symptoms present prior to investigational product will be recorded as medical history.

Any SAE brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to investigational product must be reported to Novartis.

6.5.7.1 Monitoring subjects with Hepatitis B

Subjects that are HBsAG negative, HBcAb positive and HBV DNA negative may be included in the study but must undergo HBV DNA monitoring per Appendix 2, Appendix 3, or Appendix 8 (for Japan) from the start of treatment during the treatment course and through F/U. Consult with a physician experienced in care & management of subjects with hepatitis B to manage/treat subjects who are anti-HBc positive. Initiate anti-viral therapy if required. If a subject's HBV DNA becomes positive during the study, notify the Novartis Medical Lead. For subjects who have not completed planned ofatumumab therapy, discuss with the Medical Lead the risks and benefits of continuing or discontinuing ofatumumab before appropriate treatment decisions are made for that individual subject.

6.5.8 Prompt Reporting of Serious Adverse Events and Other Events to Novartis

SAEs and pregnancies and liver chemistries meeting pre-defined stopping criteria will be reported promptly to Novartis as described in the following table once the investigator determines that the event meets the protocol definition for that event.

Table 9 SAE reporting

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hours	"SAE" data collection tool	24 hours	Updated "SAE" data collection tool
Pregnancy	24 hours	Pregnancy Notification Form	2 Weeks	Pregnancy Follow up Form
Liver chemistry stopping criteria (See Section 6.4.1)	24 to 72 hours	Liver event CRFs and "SAE" data collection tool	24 hours	Updated Liver Event CRF and SAE form and updated "SAE" data collection tool

The method of detecting, recording, evaluating and follow-up of AEs and SAEs plus procedures for completing and transmitting SAE reports to Novartis are provided in the SPM. Procedures for post-study AEs/SAEs are provided in the SPM.

6.5.9 Regulatory reporting requirements for SAEs

Prompt notification of SAEs by the investigator to Novartis is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

Novartis has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Novartis will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/ IEC and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and Novartis policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from Novartis will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

6.6 PRO Measures

Subjects will be asked to complete PRO measures in a standardized manner (see description below) at baseline, and during treatment or evaluation visits throughout the trial as indicated in Appendix 1. Following completion of questionnaires, site staff will transcribe information into eCRFs. The purpose is to document changes in symptoms and functioning that are

important for subjects with indolent lymphoma. The PRO questionnaires for this study are the FACT-Lym, EQ-5D and an HCQ. Examples of all PRO questionnaires are included in Appendix 5.

For all subjects:

- The FACT-Lym and EQ-5D questionnaires will be administered at baseline (screening visit) and as described in Appendix 1. The HCQ is not administered at the baseline (screening visit), but administered on all other visits as described in Appendix 1.
- Subjects will have all the PROs administered at all quarterly evaluations until PD
- 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

The importance of completing the PRO questionnaires as fully as possible must be stressed to the subjects.

6.6.1 Functional Assessment of Cancer Therapy - Lymphoma (FACT-Lym) Subscale

The FACT-Lym was developed by the FACIT research group and is intended as a lymphoma specific additional concerns subscale that is designed to supplement the FACT-G. The subscale consists of 15 items. Subjects respond to the items on a five point Likert scale ranging from 0 *'Not at all'* to 4 *'Very much'*. Subjects are asked to think back over the past week when responding. The FACT-Lym has been validated for reliability, validity and sensitivity [Webster, 2005] and it has been shown to have strong internal consistency across five different languages [Eremenco, 2004]. The FACT-Lym has recently been shown to be sensitive to indolent lymphoma disease activity [Pettengel, 2008].

6.6.2 EuroQoL Five-Dimension (EQ-5D)

The EQ-5D is a self-administered, generic, indirect utility measure [EuroQoL, 1990] and will be used for health economic analysis. The EQ-5D consists of a 0-100 Visual Analogue Scale (VAS) on which subjects are asked to rate their current overall health status and five single-item dimensions which ask subjects to rate their health in terms of mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The five single items can be summed and expressed as a single global index of health-related quality of life. For each of the five items subjects must choose between three levels of difficulty in accomplishing tasks in that dimension. The VAS is then used in combination with the dimension scores to generate a subject profile.

One response exists per dimension, such that:

- Level 1 (no problem) is coded as "1"
- Level 2 (some or moderate problems) is coded as "2"

- Level 3 (unable, or extreme problems) is coded as “3”

The health states are described in terms of five-digit numbers based on the answers to each of the five questions. The states can then be converted to a single score using a table that contains health utility values for the 243 different possible health states. Thus a health utility score is created that can be incorporated into analyses of cost effectiveness. Additionally, a three-digit number between 0 and 100 is read off the VAS, from the exact point where the subject has marked the scale. The EQ-5D takes less than five minutes to complete. The EQ-5D has been validated in NHL subjects [Pickard, 2007; Doorduijn, 2005; Van Agthoven, 2001], and has been previously used to study the impact of FL on subject quality of life [Cheung, 2009].

6.6.3 Health Change Questionnaire

The HCQ used here is a nine item scale that asks the subject to rate change in the health status since beginning treatment on this study [Cella, 2002]. Subject response provides an ongoing evaluation of perceived progress and satisfaction with treatment services [Juniper, 1994]. The HCQ is valuable to estimate how meaningful change in health status is to subjects, and to anchor the scores from the remaining PRO instruments.

6.7 Ofatumumab Pharmacokinetic Sample Collection

6.7.1 Sample Collection for Subjects in Arm A

Blood samples for the quantification of ofatumumab plasma concentrations will be collected at the same time as the HAHA samples in subjects receiving ofatumumab in order to determine the ofatumumab plasma concentration at that time. For subjects in Arm A (ofatumumab and bendamustine combination), samples will be collected according to Appendix 2. Sample collection, processing, and shipping instructions are provided in the SPM.

6.7.2 Sample Collection for Subjects in Arm B Who Receive Ofatumumab Monotherapy after Disease Progression

Table 10 provides the pharmacokinetic sample collection schedule for subjects that progress on Arm B and select ofatumumab monotherapy (Appendix 3). The actual date and time of each sample collection will be recorded in the eCRF. Sample collection, processing, and shipping instructions are provided in the SPM.

Table 10 Pharmacokinetic sample collection schedule for subjects that progress in Arm B and select ofatumumab monotherapy

Time	Ofatumumab Dose	Sampling time relative to ofatumumab infusion
Week 1	1	Predose
Week 4	4	Predose, EOI
1st monthly dose	5	Predose
5th monthly dose	9	Predose, EOI
6th monthly dose	10	Predose
8th monthly dose	12	Predose, EOI
		1 month after last ofatumumab infusion[1,2]
		6 months after last ofatumumab infusion[1,2]
		12 months after last ofatumumab infusion[1,2]

Abbreviation: EOI: end of infusion . Note: EOI is within 15 minutes prior to stopping infusion.

1. Collect sample relative to last dose of ofatumumab regardless of number of doses
2. Collect sample at any convenient time on study day.

[redacted]

7 data management

Data Management will identify and implement the most effective data acquisition and management strategy for each clinical trial protocol and deliver datasets that support the protocol objectives.

For this study, subject data will be entered into the eCRFs, transmitted electronically to Novartis and be combined with data provided from other sources (e.g. laboratory data) in a validated data system.

Clinical data management will be performed in accordance with applicable standards and data cleaning procedures with the objective of resolving errors and inconsistencies in the data which would otherwise impact the analysis and reporting objectives, or the credibility of the Clinical Study Report. Adverse events and concomitant medications terms will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and medication custom drug dictionary. In all cases, subject initials will not be collected nor transmitted to Novartis according to Novartis policy.

[An appropriate medical dictionary that covers all approved drugs in studies

where Japan is participating will be referenced]. (1 - eDM) "eCRFs (including queries and audit trails) will be retained by Novartis, and

copies will be sent to the investigator to maintain as the investigator copy". In

all cases, subject initials will not be collected or transmitted to Novartis according to Novartis policy.

8 Data Analysis and Statistical Considerations

8.1 Hypotheses

The primary endpoint is PFS. The null and alternative hypotheses are designed with the goal of demonstrating the superiority of ofatumumab and bendamustine combination therapy over bendamustine monotherapy. Superiority will be determined using the following hypotheses:

H_0: PFS curves for ofatumumab + bendamustine and for bendamustine are the same

H_1: PFS curves for ofatumumab + bendamustine and for bendamustine are not the same

8.2 Study Design Considerations

An ‘adaptive-like’ study design is being implemented for this study to take into consideration the possibility of a dosing-change recommendation after an independent review for safety and tolerability. Primary efficacy and safety analyses will be conducted on the ‘final’ stage data set. Supplementary efficacy and safety analyses will also be conducted on the cumulative data set if a dosing-change recommendation occurs.

- Stage 1 will consist of 20 subjects from Arm A and any available data from Arm B to be included in the Dose Confirmation Cohort and any additional subjects randomized prior to the implementation of an IDMC recommended dosing change.

- If no IDMC dosing change is implemented, Stage 1 will continue through the remainder of the study and will comprise the primary analysis set.
- If an IDMC dosing change is implemented, Stage 2 will begin with subjects randomized thereafter. The sample size and event count will restart at this point. If no further dosing change is implemented, subjects enrolled in Stage 2 will comprise the primary analysis set. Analysis of the cumulative set (subjects from Stage 1 and Stage 2) will be supplementary.
- If an additional IDMC dosing change is implemented, Stage 3 will begin with subjects randomized thereafter. The sample size and event count will restart at this point. Subjects enrolled in stage 3 will comprise the primary analysis set. Analysis of the cumulative set (subjects from Stages 1-3) will be supplementary.

The IDMC met after the first 20 subjects in Arm A received at least 3 cycles of OB. Based on the review of the data available as well as the IDMC charter-defined criteria to alter the dose in Arm A, the IDMC recommended that the study can continue without any changes to the dosage of Arm A in the study. Consequently, there will be no further IDMC meetings to assess dose safety and no further dose modifications other than the protocol-directed dose reductions and delays already described. The safety of subjects enrolled into the study will continue to be monitored by Novartis.

Since no IDMC dosing change was implemented, Stage 1 will continue through the remainder of the study and will comprise the primary analysis set.

INTERIM ANALYSIS

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, 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 tothe 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.

PRIMARY ANALYSIS

As of Amendment 9, the primary analysis will be performed after approximately 215 PFS events 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.

Final Analysis

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. All available data from all patients up to this cutoff date will be analyzed and final clinical study report will be produced.

8.2.1 Sample Size Assumptions

The primary endpoint is PFS and the analysis will be conducted using stratified log-rank test. The following assumptions were 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 **Amendment 9**, the primary analysis will take place after approximately 215 PFS events by IRC have been reported which will correspond to approximately 84% power. The other assumptions are not modified. See Section 8.2 - Primary Analysis for details.

As stated, this trial is an event-driven study design with an event-driven sample size of 215 total events and the primary analysis will take place approximately at the time of occurrence of the 215th event.

8.2.2 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.

Table 11 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

8.2.3 Sample Size Re-estimation

Sample size re-estimation will not be performed.

8.3 Data Analysis Considerations

8.3.1 Analysis Populations

8.3.1.1 Four populations are defined for the analyses:

1. The Intent-to-Treat (ITT) Population will include subjects in the primary analysis stage who are randomized to the study drugs. This will be the primary population used for all efficacy assessments. In the analyses, subjects will be grouped based on how they are randomized regardless of which treatment they received. The ITT population will be used for all PRO analyses. The ITT population will also be utilized for the Interim Analysis(IA) for efficacy and futility based on the number of subjects randomized at the time of the IA.
2. The Safety Population will include subjects in the primary analysis stage who receive at least one dose of a study drug. This population will be used for all safety measurements. In the analyses, subjects will be grouped based on the treatment they receive regardless of how they are randomized.
3. The Safety Population (Dose Confirmation Cohort) will include the first 20 subjects in Arm A who receive at least 3 cycles of bendamustine or complete bendamustine therapy (if less than 3 cycles are given). This population will be used to assess the safety and tolerability in the Dose Confirmation Cohort analysis of the study by the IDMC. In the analyses, subjects will be grouped based on the treatment they receive regardless of how they are randomized.
4. The Per Protocol (PP) Population will exclude subjects with major protocol deviation that will impact the efficacy outcome. The Per Protocol Population will be used in the primary endpoint analysis to check the robustness of the result when using the ITT

population. However, if the number of subjects in the PP population is not more than 10% smaller than the ITT population, the analysis will not be performed.

8.3.2 Analysis Data Sets

The primary data set for efficacy will be based on the PFS and ORR assessments. The primary data set for safety will be the AEs and the laboratory data sets.

The efficacy response will be assessed by the investigators and by the independent reviewers. Data will be summarized for investigator assessed response as well as for independent reviewer assessed response. Statistical inference for efficacy claim(s) will be based on the PFS and ORR data assessed by the independent reviewers.

8.3.3 Treatment Comparisons

8.3.3.1 Primary Comparisons of Interest

The primary comparison is performed at IA and at the time of primary analysis. The primary treatment comparison of interest will be ofatumumab + bendamustine vs. bendamustine. This will be based on comparing the overall PFS using the ITT population. Refer to Section 8.2 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 8.2, the significance levels for the interim and final analysis will be adjusted as appropriate using the O'Brien-Fleming spending function.

8.3.3.2 Secondary and Other Comparisons of Interest

The secondary comparisons of interest will include ofatumumab + bendamustine vs. bendamustine, based on the PFS in patient 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 is 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 the other secondary endpoints. No multiplicity adjustment will be considered for the other secondary endpoints.

Per Amendment 9, the primary analysis will be performed after approximately 215 PFS events by IRC have been reported. See Section 8.2 - Primary Analysis for details.

8.3.4 Interim Analysis for Safety

A safety and tolerability analysis was planned after 20 subjects completed 3 cycles (or completion of bendamustine therapy) of treatment in Arm A. This process is described in Section 3.1.3 and was further detailed in a charter for the IDMC.

8.3.5 Interim Analysis for Efficacy and Futility

An Interim Analysis (IA) for efficacy was planned when approximately two thirds (or approximately 172) of the initial total 259 IRC events is achieved. The interim analysis for PFS was planned to be performed by an IDMC utilizing an O'Brien-Fleming spending function with significance level of 0.012 (with 172 events). Performing this interim analysis with an IDMC was planned to allow for an earlier detection of clinical benefit to patients with ofatumumab+bendamustine. The interim analysis of the primary endpoint, PFS, was conducted as described in Section 8.2, and further details of the interim analysis was 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. Per Amendment 9 (See Section 8.2 - Primary Analysis for details), 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. This process is further detailed in a charter for the IDMC.

8.3.6 Key Elements of Analysis Plan

The primary analysis will take place when the target number of events is reached in the study. An event is defined as a subject who either has PD or death due to any cause during the study. All available data will be analyzed and the results will be presented in a report.

Released data that are available from later visits will be included as supportive analyses.

Withdrawal

Subjects will be treated until disease progression or withdrawal from study treatment due to unacceptable AE(s), consent withdrawal or other reasons. All data up to time of withdrawal will be included in the analysis.

Subjects who are withdrawn prematurely from study treatment, but who are not withdrawn from the study at the time of analysis, will be included in the analysis, regardless of treatment duration.

Missing Data

Since the duration of treatment for a given subject will depend on the efficacy and safety of the study drug, the duration of follow-up will vary among subjects. Consequently, there will be no imputation for missing data, with the exception of overall response and PRO scores, for which some imputation might be necessary. Details will be given in the Reporting and Analysis Plan (RAP).

The appropriate available data will be summarized over specified intervals using suitable summary statistics.

For PFS endpoint, subjects who are alive and have not progressed at the time of analysis will be censored at the date associated with the last visit with adequate assessment. If a progression event occurs after an extensive lost-to-follow-up time (12 weeks or greater), the primary analysis will censor those subjects at the date of their last visit with an adequate assessment even if subsequent information is available regarding progression or date of death. Sensitivity analyses, described in Section 8.3.6.1 will be examined to evaluate the impact of the missing assessments.

Derived and Transformed Data

The overall response will be evaluated by the IRC in addition to being evaluated by the investigators. All analyses will be based on the IRC assessments. Details for the evaluation of objective response will be provided in RAP.

Details of the assignments of progression and censoring dates will be provided in the RAP.

Other Issues

Data from all participating centers will be pooled for the analyses. It is anticipated that subject accrual will be spread thinly across centers and summary of data by center would be unlikely to be informative, and therefore, will not be conducted.

Subgroup analyses will be provided by stratification factors and the important baseline covariates for supportive purpose.

Subjects that are treated with ofatumumab following PD in the bendamustine monotherapy arm will be analyzed as subjects that have a 'new anti-cancer therapy started' for efficacy analyses. For safety analyses, subjects will be analyzed based on the treatment course received and additional summaries may be required to explore the safety profile for rescued subjects.

Any deviations from, or additions to, the original analysis plan described in this protocol will be documented in the RAP and final study report.

8.3.6.1 Efficacy Analyses

Primary Analysis:

Progression-free survival is defined as the time from randomization until progression or death. The progression events will be defined by well-documented and verifiable data. Details of censoring will be provided in the RAP.

An interim analysis of the primary endpoint, PFS, was performed with 180 PFS events by IRC . The interim analysis for PFS was performed by an IDMC. The interim analysis of PFS was conducted in the same manner as described for the primary analysis, and further details of the interim analysis areprovided in the IDMC Charter.

Per **Amendment 9**, the primary analysis will take place after approximately 215 PFS events by IRC. The primary analysis of PFS will be tested based on a two-sided test, with a significance level of 0.0483 (See Section 8.2 - Primary Analysis for details). Survival distributions will be estimated using the Kaplan-Meier method, and survival curves will be compared using a stratified log-rank test.

In addition to the stratified log-rank test, a Cox regression model will be used and will include covariates for treatment, stratification factors (type of last prior rituximab: R-chemo or Rituximab alone and by prior exposure to bendamustine: exposed or not exposed) age, gender, race, pathology (based on inclusion criteria), FLIPI and ECOG. Analytical results will include the estimated hazard ratios along with 95% confidence intervals, and associated probabilities for the effect of treatment, stratification factors and the covariates. The hazard ratio for treatment will express the risk of experiencing disease progression or death for 'ofatumumab + bendamustine' vs. 'bendamustine'.

The sensitivity analysis of PFS will be conducted to confirm the robustness of the primary PFS analysis. The assignments of progression and date of censoring for sensitivity analysis of PFS are the same as those of the primary PFS, with the following difference: if a clinical progression is proclaimed by the investigator, the outcome is 'Progressed', and the date of the progression is the date of the claim or the next scheduled visit (if between visits).

Analyses of PFS (as well as sensitivity analysis of PFS) will be conducted for the independent reviewer assessed data. The statistical inference will be based on the independent reviewer assessed data.

The PP population will only be used for the primary endpoint if the difference of total number of subjects is greater than 10% of the ITT population.

Subgroup analyses will be conducted for PFS for the stratification factors.

Inferential Secondary Analyses:

- Progression-free survival in patients with follicular lymphoma
- Overall response rate in the overall population
- Overall response rate in patients with follicular lymphoma

Responders include subjects with CR, PR. Non-responders include subjects with SD, and PD. Subjects with unknown or missing responses will be considered as non-responders.

The number and proportion of subjects with ORR for CR, PR, SD and PD will also be provided.

The exact Cochran-Mantel-Haenszel (CMH) test will be used to compare the proportion of subjects with overall response for ofatumumab in combination with bendamustine vs. bendamustine, adjusting for stratification factors (type of last prior rituximab: R-chemotherapy or Rituximab alone and by prior exposure to bendamustine: exposed or not exposed).

- Overall survival in overall population

- Overall survival in patients with follicular lymphoma

OS is defined as the time from randomization until death. Analysis methods will be similar to those described for the PFS analysis and details of censoring will be provided in the RAP.

Survival distributions will be estimated using the Kaplan-Meier method, and survival curves will be compared using a stratified log-rank test.

Efficacy analyses on PFS, ORR and OS will also be performed in the non-FL patients to allow an accurate interpretation of the results.

Other Secondary Analyses

Clinical:

- Time to response
  - Time to response is defined as time from randomization to the first response (CR/ PR). Kaplan-Meier curves will be provided for the treatment arms over time. The median time to response along with the associated 95% confidence will be provided for ofatumumab in combination with bendamustine and for bendamustine. Time to response will be analysed in all patients, as well as in patients with and without follicular lymphoma.
- Duration of response
  - The duration of response is defined as the time from the initial response (CR/ PR) to progression or death. The same analysis will be performed as described for time to response analysis. Duration of response will be analysed in all patients, as well as in patients with and without follicular lymphoma.
- Time to progression
  - Time to progression (TTP) is defined as the time from randomization until disease progression. The same analysis will be performed as described for time to response analysis. Time to progression will be analysed in all patients, as well as in patients with and without follicular lymphoma.
- Time to next therapy
  - Time to next therapy is defined as the time from randomization until next line treatment. The same analysis will be performed as described for time to response analysis. Time to next therapy will be analysed in all patients, as well as in patients with and without follicular lymphoma.
- 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.
- Improvement of ECOG performance status

  - Improvement is defined as a decrease from baseline by at least one step on the ECOG performance status scale (yes/no). The same analysis will be performed as described for ORR analysis.

- Incidence of grade 3 and 4 infections
  - The frequency and rate of subjects with grade 3 and 4 infections at the scheduled visits will be provided. A summary by responders and non-responders will also be provided.
- Human Anti-Chimeric Antibodies (HACA)
  - The number of subjects with positive HACA in the predose samples will be reported.
  - HACA results prior to ofatumumab administration will be listed.
- Human Anti-Human Antibodies (HAHA)
  - The number of positive and negative results at each visit will be provided in subjects who receive ofatumumab. HAHA results and associated ofatumumab plasma concentration at each time point will be listed.
- Evaluation of myelosuppression (anemia, neutropenia, thrombocytopenia)
  - Frequency and percent of subjects with myelosuppression will be provided by responders and non-responders.
- IgG, IgA, IgM
  - Summaries of IgG, IgA, IgM will be provided at scheduled visits.

Disease and Prognostic Markers:

- B-cell monitoring
  - The change of $CD19^+$ or $CD20^+$ from baseline (absolute and percentage) will be summarized to assess the treatment effect and to monitor the normal B-cell population. In addition, frequency and percentage with complete B-cell depletion will be summarized by responders and non-responders.
- Known and exploratory prognostic markers correlating with clinical response
  - Cox regression may be used to explore the relationship between PFS and the following explanatory variables: treatment group, FLIPI-1, FLIPI-2, genetic variants in FcR, cytogenetics (analyzed by FISH) at baseline, Absolute Lymphocyte Count (ALC), thymidine kinase, soluble CD20 at baseline, Human anti-chimeric antibodies (HACA) to rituximab.
  - Logistic regression will be conducted to explore the relationship between objective response and the same set of explanatory variables.

[redacted]

8.3.6.2 Safety Analyses

The Safety population will be used for the safety analyses. For continuous variables, the mean, median, standard deviation, minimum, and maximum will be provided in the summary tables. For categorical variables, the frequency and percentage will be provided in the summary tables.

Extent of Exposure

The number of subjects administered to each treatment group will be summarized according to the duration of treatment.

Adverse Events

AEs will be coded using the standard MedDRA dictionary, and grouped by system organ class.

Events will be summarized by frequency and proportion of subjects by system organ class and preferred terms.

If the AE is listed in the NCI CTCAE (version 4.0) table, the maximum grade will be summarized.

The incidence of AEs, severity of AE, deaths and the primary cause of death will also be provided.

Clinical Laboratory Evaluations

Hematology and clinical chemistry data will be summarized at each scheduled visit according to NCI CTCAE grade (version 4.0). The proportion of values outside the reference range will also be presented.

Safety Evaluation

After 20 subjects have been treated for 3 cycles (or completion of bendamustine therapy), an analysis to assess safety and tolerability will be conducted. A charter will detail the types of analyses, rules for modifying treatment course, and the membership and conduct of the IDMC.

8.3.6.3 PRO Analyses

All PRO measures will be scored as per the developers instructions, with scores created for each pre-specified domain. Details of the scoring methods will be provided in the statistical analysis plan. Each PRO domain will be summarized for each treatment group and the total PRO sample at each time point and presented in tabular format as mean, standard deviation, median, minimum and maximum. Methods for imputation of missing data will be detailed in the RAP.

Mixed effect model for repeated measures may be used to compare the two treatment arms in terms of change from baseline in PRO measures. Details will be specified in the RAP. PRO analysis will be performed in all patients and patients with follicular lymphoma.

8.3.6.4 Pharmacokinetic Analyses

The plasma concentrations for individual subjects will be determined using validated analytical methods for ofatumumab. Plasma ofatumumab concentration-time data will be summarized and displayed in tabular and graphical form separately for subjects in Arm A and for subjects in Arm B who receive ofatumumab following PD. Individual plasma concentrations of ofatumumab will be listed.

Population PK modeling, using non-linear mixed effects modeling will be performed on the data for subjects in Arm B who receive ofatumumab following PD using validated software such as the computer program NONMEM, if data permit. Data from this study may be combined with data from other studies for analysis. The aims of this modeling approach are to:

- Define the structural PK model that characterizes the population time course of plasma levels of ofatumumab in this subject population
- Describe between-subject variability for PK parameter estimates
- Estimate intra-subject variability on predicted concentrations

If possible, the effects of subject characteristics (such as gender, weight, height, disease status, etc.) will be investigated in order to account for potential sources of inter-individual variability in systemic exposure. If there are sufficient data for analysis, the details of the population PK analyses will be provided in a reporting and analysis plan.

[redacted]

9 Study CONDUCT CONSIDERATIONS

9.1 Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a study site, Novartis will obtain approval from the appropriate regulatory authority to conduct the study in accordance with applicable country-specific regulatory requirements, including those required under a US Investigational New Drug (IND).

The study will be conducted in accordance with all applicable regulatory requirements, IND Number 11,465.

The study will be conducted in accordance with Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the declaration of Helsinki, including, but not limited to:

- IRB)/IEC review and approval of study protocol and any subsequent amendments.

- Subject informed consent.
- Investigator reporting requirements.
- Novartis will provide full details of the above procedures, either verbally, in writing, or both.
- Written informed consent must be obtained from each subject prior to participation in the study.

9.2 Quality Control (Study Monitoring)

In accordance with applicable regulations, GCP, and Novartis procedures, Novartis (or designated Clinical Research Organization) personnel will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and Novartis requirements. When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the eCRF will serve as the source document. Novartis will monitor the study to ensure that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.
- The investigator and the head of the medical institution (where applicable) agrees to allow the Novartis (or designated Clinical Research Organization) personnel direct access to all relevant documents.

9.3 Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, Novartis may conduct a quality assurance audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study. In the event of an audit or inspection, the investigator (and institution) must agree to grant the auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss any findings/relevant issues.

9.4 Study and Site Closure

Upon completion or termination of the study, the Novartis (or designated Contract Research Organization) personnel will conduct site closure activities with the investigator or site staff (as appropriate), in accordance with applicable regulations, GCP, and Novartis Standard Operating Procedures.

Novartis reserves the right to temporarily suspend or terminate the study at any time for reasons including (but not limited to) safety issues, ethical issues, or severe noncompliance. If Novartis determines that such action is required, Novartis will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When

feasible, Novartis will provide advance notice to the investigator or head of the medical institution of the impending action.

If a study is suspended or terminated for safety reasons, Novartis will promptly inform all investigators, heads of the medical institutions (where applicable), and/or institutions conducting the study. Novartis will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination.

9.5 Records Retention

Following closure of the study, the investigator or head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed (e.g., for a Novartis audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless the Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

The investigator must notify Novartis of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that the investigator is no longer associated with the site.

9.6 Provision of Study Results and Information to Investigators

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a Novartis site or other mutually-agreeable location.

Upon completion of the clinical study report, Novartis will ensure public disclosure of the clinical trial research results via the Novartis Clinical Trials Register according to the Novartis Standard Operating Procedure and provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study

subjects, as appropriate. In addition, upon study completion and finalization of study report, Novartis aims to submit results of the study for publication.

When publication is not feasible, please refer to the Novartis Clinical Trial Results website (.novartisclinicaltrials.com) for a summary of the trial results.

9.7 Independent Data Monitoring Committee (IDMC)

9.7.1 Dose Confirmation for Safety and Tolerability

An IDMC will be utilized to ensure external objective medical and/or statistical review of safety issues in order to protect the ethical and safety interests of subjects and to protect the scientific validity of the study. The schedule of any planned interim analysis and the analysis plan for IDMC review is described in the charter, which is available upon request.

The intended meeting schedule is outlined below:

Twenty subjects in Arm A will comprise an initial dose confirmation cohort. In addition, available data from Arm B will be provided. The IDMC will assess Arm A (O+B) for the safety and tolerability of ofatumumab (1000 mg Day 1; q21 days) and bendamustine (90 mg/m^2 Days 1, 2; q21 days) after completion of 3 cycles (or until completion of bendamustine if less than 3 cycles are administered).

The IDMC will confirm or reject the notion that the Arm A utilizes a safe bendamustine dose and schedule. They will base this decision on a rule described in the IDMC charter. The IDMC will have a primary option (in Stage 1) to lengthen the cycle duration from 21 to 28 days and have a secondary option (Stage 2) to decrease the bendamustine dose in Arm A for improved safety and tolerability.

Stage 1:

- If the safety and tolerability of Arm A is confirmed by the IDMC (Stage 1), Stage 1 will continue throughout the remainder of the study and will comprise the primary analysis set.
- If the IDMC decides to modify the bendamustine dosing schedule in Arm A, Stage 2 will begin and this modified treatment schedule (bendamustine 90 mg/m^2 Days 1 and 2, every 28 days, up to 8 cycles) will be used in Arm A for the remainder of the study.

Stage 2:

- If an IDMC cycle change is implemented, the sample size and event count will restart at this point, and subjects enrolled in Stage 2 will comprise the primary analysis set. Analysis of the cumulative set (subjects from Stage 1 and Stage 2) will be supplementary.
- If the IDMC modifies the treatment schedule in Arm A, the IDMC will assess the modified treatment schedule (bendamustine 90 mg/m^2 Days 1 and 2, every 28 days, up to 8 cycles) after 10 subjects in Arm A are treated at this schedule for 3 cycles (or until bendamustine completion, if less than 3 cycles). If the IDMC confirms the safety of bendamustine 90 mg/m^2 Days 1 and 2, every 28 days, in Arm A, then Stage 2 will proceed without further dose modification in Arm A.
- If the IDMC deems that toxicity remains excessive, the IDMC will have the option to reduce the bendamustine dose in Arm A to 70 mg/m^2; Days 1 and 2, every 28 days (up to 8 cycles). This will be Stage 3.

Stage 3:

- The IDMC will then assess the modified treatment schedule (bendamustine 70 mg/m^2 Days 1 and 2, every 28 days, up to 8 cycles) after 10 subjects in Arm A are treated at this schedule for 3 cycles (or until completion of bendamustine therapy if less than 3 cycles).
- If the IDMC deems that bendamustine 70 mg/m^2 Days 1 and 2, every 28 days, up to 8 cycles in Arm A is safe, then no further dose modification in Arm A will occur.
- If the IDMC decides that bendamustine 70 mg/m^2 Days 1 and 2, every 28 days, up to 8 cycles, in Arm A is excessively toxic, the IDMC will have the option to close this study.

STAGE 1 RESULTS FROM IDMC DATA REVIEW

The IDMC met after the first 20 subjects in Arm A received at least 3 cycles of OB. Based on their review of the data as well as the IDMC charter defined criteria to alter the dose in Arm A, the final recommendation from IDMC was to not change the current dose regimen and therefore to allow the study to proceed unchanged [IDMC communication, 2011]. There will be no further dose modifications other than the protocol-directed dose reductions and delays already described in Section 5.1.3.1 of this protocol. The safety of subjects enrolled in the study will continue to be monitored by Novartis.

9.7.2 Interim Analysis

An IDMC was utilised to review the primary endpoint, progression free survival when approximately two thirds of the initial total IRC events has been reached. The IDMC reviewed data from the interim analysis and the futility analysis.

The IDMC met once to review the data and will recommend that the study continue without any changes.

Further details can be found in the IDMC charter.

9.8 Publication Policy

Publications and oral presentations of any results from the study shall be in accordance with accepted scientific practice, academic standards and customs and in accordance with the specific policy developed for the study. This policy shall be made available to all investigators/sites and groups participating in the study.

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11 Appendices

11.1 Appendix 1: Time and Events Table for Treatment and Follow-Up

	SCR[1]	TREATMENT PERIOD[25]																				1M FU Arm A[27]	Follow Up		Survival/PD F/U[23]	WD[24]
Treatment Cycle[2]		**1**		**2**		**3**		**4**		**5**		**6**		**7**		**8**		**Ofatumumab for Arm A (12 total infusions) Every 1M**[19]					F/U1[21]	F/U2[22]		
Days within Cycle		**1**	**2**	**1**	**2**	**1**	**2**	**1**	**2**	**1**	**2**	**1**	**2**	**1**	**2**	**1**	**2**	**1M**	**1M**	**1M**	**1M**					
Visit		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20					
TREATMENT																										
Ofatumumab		X[2]		X[2]		X[2]		X[2]		X[2]		X[2]		X[2]		X[2]		X[3]	X[3]	X[3]	X[3]					
Bendamustine[4]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X									
Pre-medication		X[5]		X[6]		X[6]		X[6]		X[6]		X[6]		X[6]		X[6]		X[6]	X[6]	X[6]	X[6]					
CLINICAL ASSESSMENTS																										
Informed Consent	X[7]																									
Eligibility Criteria	X[8]																									
Demographics	X																									
Physical Exam.	X																									X
ECG	X																									
Height	X																									
Body Wt, Constitutional	X	X		X		X		X		X		X		X		X		X	X	X	X		X	X		X

	SCR[1]	TREATMENT PERIOD[25]																				1M FU Arm A[27]	Follow Up		Survival/PD F/U[23]	WD[24]
Treatment Cycle[2]		**1**		**2**		**3**		**4**		**5**		**6**		**7**		**8**		**Ofatumumab for Arm A (12 total infusions) Every 1M**[19]					F/U1[21]	F/U2[22]		
Days within Cycle		**1**	**2**	**1**	**2**	**1**	**2**	**1**	**2**	**1**	**2**	**1**	**2**	**1**	**2**	**1**	**2**	**1M**	**1M**	**1M**	**1M**					
Visit		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20					
Symptoms																										
Medical History	X[9]																									
BM/tissue biopsy[13]	X[13]																									
Survival Assessment		X		X		X		X		X		X		X		X		X	X	X	X		X	X	X	X
Next NHL Tx and response																									X	
ECOG PS	X	X		X		X		X		X		X		X		X		X	X	X	X		X	X		X
Vitals Signs[14]	X	X		X		X		X		X		X		X		X		X	X	X	X		X	X		X
AEs	X[15]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[16]	X[16]	X[16]	X[16]	X[16]
Concomitant Med.	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[17]	X[17]	X[17]	X[17]
PRO[18]	X	X				X				X				X				X		X			X	X	X[18]	X
CT Scan[12]	X[10,11]	**Days 84, 168, and 252[12,20]** (+7 days)																					X	X		X[25]
Disease Response.		**Days 84, 168, and 252[12,20]** (+7 days)																					X	X		X
Lymphoma disease symptom assessment[26]		**Days 84, 168, and 252[12,20]** (+7 days)																					X[26]	X[26]		X[26]

Appendix 1: Time and Events Table for Treatment and Follow-Up (Continued)

Abbreviations: AE= Adverse Events; Assess.= Assessments; B=bendamustine; BM= bone marrow; BP= Blood Pressure; CT= Computed Tomography; ECG= Electrocardiogram; Eval.= Evaluation; FLIPI= Follicular lymphoma International Prognostic Index; F/U= Follow-up; IV= intravenous; LN= lymph node; Med.= Medication; M=Months; NHL= Non-Hodgkins Lymphoma; ECOG= Eastern Cooperative Oncology Group; O= ofatumumab; PO= Oral; PD=Progressive Disease; PRO= Patient Reported Outcomes; PS= Performance Status; SAE= Severe adverse event; SCR= Screening; Tx= Therapy; SPM= Study procedures manual; WD= Withdrawal; Wt= Weight; YR=Years

1. Screening is ≤21 days of dosing for Cycle 1, Day 1, per Section 3.1.1.
2. During treatment phase, Arm A (OB) will receive: ofatumumab 1000 mg given on the first day of each cycle and bendamustine (90 mg/m2) given on Days 1, 2 of each cycle. If bendamustine cannot be given on the Day 1, the day of ofatumumab infusion, bendamustine may be administered on Days 2 and 3 of each cycle (see SPM for procedures). In the event the 1st infusion of bendamustine is on Day 2 of a cycle, then assessments required for Day 1 (except HAHA, ofatumumab concentration, Ig, and flow cytometry) will be done on Day 2 and the assessments required for Day 2 will now be done on Day 3. See SPM for more details. Day 1 of each cycle occurs every 21 days (on or 3 days after). See Section 5.1.3.1 and Table 5 for instructions on cycle length in the event of dose reduction. There are a maximum of 8 cycles of OB treatment. If dose delays last longer than 2 weeks, See Section 5.1.3.1. In the event a subject cannot complete all scheduled treatments, subjects are expected to come to the clinic for all scheduled assessments until study completion.
3. Ofatumumab monotherapy (1000 mg, q28 days with a +3 day window). A total of 12 infusions of ofatumumab (1000 mg), including any doses given with bendamustine, will be administered in Arm A regardless of the number of OB cycles completed. In the event a subject in Arm A cannot complete 8 cycles of therapy with bendamustine, subjects must come for all scheduled Day 1 assessments (Visits 1-20).
4. During the treatment phase, Arm B will receive bendamustine 120 mg/m2 (Days 1, 2 of each cycle). Day 1 of each cycle occurs every 21 days (on or within 3 days after Day 1 of each cycle). There are a maximum of 8 cycles of B. If dose delays last longer than 2 weeks, See Section 5.1.3.1. In the event a subject in Arm B cannot complete 8 cycles of therapy with bednamustine, subjects in Arm B must come for all scheduled Day 1 visits (Visits 1-20) that have assessments without treatment (if it is not tolerated). Following Visit 16, subjects will come to the clinic every 28 days, for 4 times and complete scheduled assessments with no treatment.
5. Administer pre-medication (acetaminophen approximately 1000 mg PO, diphenhydramine or equivalent approximately 50 mg IV, and glucocorticoid approximately 50 mg IV prednisolone equivalent) 30 minutes-2 hours before each ofatumumab dose in Arm A. For Arm B, administration of premedication is not required, but can be administered at the investigator's discretion, per prescribing information.
6. Administration of premedication in Arm A (OB) will be at investigator discretion if severe infusion reactions did not occur during first infusion. For Arm B, administration of premedication is not required, but can be administered at the investigator's discretion per the bendamustine prescribing information.
7. Informed consent can be obtained outside the screening visit window i.e. prior to screening date.
8. Criteria specified in inclusion and exclusion criteria must be met. Criteria also include completion of the rituximab refractory worksheet (See Section 3.1.1.1 in protocol for details). Subjects will not be enrolled until Novartis verifies this worksheet. Imaging or documentation verifying rituximab refractory disease requested 30 days following randomization. In the event a CT scan will be used as a baseline CT scan, the CT scan must be submitted per the instructions in Section 6.1.12.
9. Includes date of initial indolent NHL diagnosis, Ann Arbor stage, FLIPI-1 and FLIPI-2 scores, and medical history. See Section 6.1.2 in protocol for more details.
10. Documentation worksheet showing dates of CT showing rituximab refractory status while on rituximab are required for inclusion. See Section 3.1.1.1 in protocol for details.
11. A CT scan is required at screening if it was not done ≤1 month (+ 7 days) prior to randomization (Section 6.1.12). If CT scan done >1 month (+ 7 days), investigator may contact Medical Lead to determine whether scan may be used.

12. All scheduled visit days requiring a CT scan (+7 days for Days 84, 168, 252) must be completed regardless of the number of completed cycles. Pertains to both Arm A and Arm B.
13. A sample (further details in Section 3.1.1 and lab manual) will be required at screening unless an appropriate previous sample is available. A bone marrow biopsy will be performed no later than ≤8 weeks following CR (as judged by investigator) if the BM sample were positive at the start of the study.
14. Includes BP, temperature, and pulse. Documented at screening and during treatment for both treatment arms, See Section 6.1.9.
15. Only SAEs relating to study procedures or Novartis concomitant medication should be reported. See Section 6.5
16. All SAEs regardless of causality will be reported from 61 days after the last dose of investigational product to the end of the follow-up period or withdrawal or until initiation of subsequent anti-lymphoma therapy is initiated. Any SAE brought to the investigator's attention after the start of subsequent anti-lymphoma therapy and considered by the investigator as possibly related to either ofatumumab or bendamustine must be reported to Novartis. See Section 6.5 for more details.
17. Only steroids, growth factors, transfusions, anticancer, and anti-infectious treatments will be followed from 61 days after the last dose of investigational product to the end of the follow-up period or withdrawal or until initiation of subsequent anti-lymphoma therapy..
18. FACT-Lym, EQ-5D, and HCQ (except at screening) paper questionnaires are to be completed at all specified visits. Sites will transcribe completed questionnaires into eCRFs.If PD, then complete on Day 1 of progression determination and once post PD.
19. Monthly ofatumumab dosing begins 28 days after Day 1 of the previous cycle. Arm B will not receive ofatumumab every 1M, but must come into the clinic for scheduled visits and procedures as if they were on the every 1 month (q28 day) schedule following 8 cycles of bendamustine.
20. Subjects in both arms must come for scheduled Day 84, Day 168, and Day 252 visits (+7 days). See SPM.
21. This is follow-up schedule #1. The F/U 1 schedule, in both arms, begins on Day 336 (this is 3 months following Day 252) and will continue every 3 months until Month 18 of the F/U phase (Table 1). There will be a ±7 day visit window around each visit.
22. This is follow-up schedule #2 (Table 1). The F/U 2 schedule comes after the end of F/U 1 and continues until Month 60 in the F/U phase. Visits will occur at least every 12 months until Month 54 or earlier if clinical symptoms of progression are suspected. CT scans must occur every 12 months (but may occur more frequently if clinical symptoms of progression are suspected). The last required yearly CT scan will be done on Month 54 of F/U2. Following Month 54, subjects will be followed until Month 60 of the F/U phase. CT scans will be done to confirm any clinical signs or suspicion of PD throughout the study. There will be a ±14 day visit window around each day.
23. Subjects that progress in Arm B (bendamustine alone) will have the option to receive ofatumumab monotherapy. If Arm B subjects select ofatumumab monotherapy, they must have PD confirmed by independent radiology review. If PD confirmed, Appendix 3 assessments will be followed. They must not continue with Appendix 2 survival assessments. See Section 3.1.6 and for more details. Subjects with PD, as confirmed by CT scan, will be followed for survival. Survival follow-up visits begin 2 months after PD is confirmed by CT scan or start of non-protocol treatment.. Additionally, subjects without PD who stop protocol treatment and begin non-protocol treatment will go into Survival Follow-Up. Survival follow-up visits will occur every 3 months (± 7 days) until Month 18 of the F/U phase then every 12 months (± 14 days) until Month 54 of the F/U phase. Refer to Section 3.1.5. Following Month 54, subjects will be followed until Month 60. Table 1 describes this F/U schedule. Subjects in Arm B with PD may select optional ofatumumab monotherapy and are followed up according to Appendix 3. PD must be confirmed by an independent review prior to receiving ofatumumab monotherapy. Survival follow-up visits may be phone-calls instead of physician office visits.
24. There are 2 types of withdrawal (WD): WD from investigational product and WD from study. See Section 4.4 for details on withdrawal criteria. If a subject, without PD, discontinues or withdraws from treatment (for any reason), the subject remains in the study and completes all scheduled visits that have assessments, but without study drug. In the event a subject WD consent from study, the WD visit must be completed. CT scan done at WD from study if last CT was >91 days. One month is 28 days when being treated in this study.

25. Treatment is expected to be given on the scheduled days. A visit window of 3 days following the scheduled day will be allowed between cycles but there is no visit window once the subject has entered the cycle (except bendamustine may be administered on either Days 1,2 or Days 2,3 if needed). There is a minimum 21 day interval between cycles (See Section 9.7).
26. Assess disease symptoms as defined in Section 6.2.4 of protocol on Days 84, 168, and 252 (+7 days), F/U 1, F/U 2 or withdrawal. Assess disease symptoms during follow-up visits.
27. One month following treatment completion in Arm A, regardless of response and regardless of when treatment ended in the study.

11.2 Appendix 2: Time and Events Table for Laboratory Assessments

	SCR[1]	TREATMENT PERIOD[5,19]																1M FU Arm A[20]	Follow Up		Survival/PD F/U[15,17]	WD[16]
Treatment Cycle		1		2		3		4		5		6		7		8		Ofatumumab for Arm A (12 total infusions) Every 1M[5,12]					F/U1[13]	F/U2[14]		
Days within Cycle		1	2	1	2	1	2	1	2	1	2	1	2	1	2	1	2	1M	1M	1M	1M					
Visit		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20					
Hematology	X	X		X		X		X		X		X		X		X		X	X	X	X		X	X		X
Biochemistry	X	X		X		X		X		X		X		X		X		X	X	X	X					X
Calculated Creatinine Clearance[2]	X[2]																									
Flow Cytometry	X[1]	X[3]		X[3]						X[3]		X[3]				X[3]		X[3]				X[8]	X[8]			
HAHA		X[4,18]												X[4]							X[4]		X[4]		X[4]	X[4]
HACA[11]		X[18]																								
Ofatumumab PK samples		X[9]												X[9]							X[9]		X[9]		X[9]	X[9]
HBV[6] & HCV, Pregnancy Test[7]	X[6,7]	X[7]																				X[6]	X[7]			
IgG, IgA, IgM		X[3,18]										X[3]										X[8]	X[8]	X[8]		
[redacted]																										
Prognostic Markers[11,18]		X[11,18]																								
ß2 micro.[11]		X[18]																								

APPENDIX 2: TIME AND EVENTS TABLE FOR LABORATORY ASSESSMENTS (CONTINUED)

Abbreviations: ALC= absolute lymphocyte count; D=Days; DNA= deoxyribonucleic acid; M=Months; FcR= Fc Gamma Receptor; FLIPI= Follicular lymphoma international prognostic index; F/U= Follow -up; PD=Progressive Disease; HAHA= Human anti-Human Antibodies; HACA= Human anti-Chimeric Antibodies; HBV= hepatitis B virus; HBC= Hepatitis C virus; Ig= immunoglobulin; micro.= microglobulin; [redacted]; PK= pharmacokinetics; SCR= Screening; SPM= study procedures manual; SLL= Small lymphocytic lymphoma; Tx= Therapy; WD= Withdrawal; YR=Years

1. Screening is ≤21 days of dosing for Cycle 1, Day 1, per Section 3.1.1. If subjects have SLL, they must have a lymphocyte count of <5000/μL. If subjects with SLL have a lymphocyte count of ≥5000/μL, then flow cytometry must be done. Subjects with SLL are not eligible if they have a B lymphocyte count of ≥5000/μL according to the Central Laboratory results (Section 4.2).
2. Calculated creatinine clearance will be done at screening and can be repeated at the physician's discretion if there is a significant rise in serum creatinine during the treatment phase of the study. See Section 6.3 and Section 6.4 for details on laboratory tests.
3. Flow cytometry and IgG, IgA, IgM done in Arm A only. During treatment, collect immunoglobulins (Ig) no later than every 6 months (collection to correspond with a scheduled visit). B-cell flow cytometry for CD19, CD20 (See Section 6.3.1).
4. HAHA done in Arm A only. HAHA samples must be collected prior to the start of the ofatumumab infusion on dosing days. During treatment, collect every 6 months. During first year of follow-up, collect every 6 months for the first year after last ofatumumab infusion. A HAHA sample must be collected for subjects who withdraw (see footnote 16) or on one occasion post-PD for subjects with PD.
5. In the event a subject in Arm A or Arm B cannot complete 8 cycles of therapy, subjects must come for all scheduled visits (Visits 1-20) that have assessments without treatment (i.e., if it is not tolerated). Following Visit 16, subjects will come to the clinic every 28 days, 4 times, and complete scheduled assessments with no treatment. One month is 28 days when being treated in this study.
6. In subjects receiving ofatumumab that are Hepatitis B core positive, HBsAg negative, and HBV DNA negative (Section 6.3.2 and Section 6.5.7.1), Hepatitis B DNA must be obtained on Day 1 of each cycle visit while on treatment and then 1,3,6 months post treatment. If a subject converts to HBV DNA positive during the study, Hepatitis B treatment may be initiated by the site investigator after consultation with a physician experienced in the care and management of subjects with Hepatitis B and the Novartis Medical Lead. The risks and benefits of continuing ofatumumab or discontinuing ofatumumab must be discussed with the Medical Lead before appropriate treatment decisions are made for that individual subject. Instructions for Japanese subjects are in Appendix 8.
7. Women of childbearing potential must agree to use a method of birth control approved by the study doctor while during study and for one year after the last dose of treatment. Pregnancy testing in women of child bearing potential will be done at Screening then prior to dosing if last test >30 days ago and again 6 months after last dose of ofatumumab.
8. B-cells and Immunoglobulins (Ig) will be monitored for a period of 2 years after the last ofatumumab infusion in Arm A or until the number of B-cells and circulating IgG, IgM and IgA have returned to normal or to within baseline values (according to the central laboratory), whichever is earlier. Monitoring will be done during scheduled F/U visits. F/U will be discontinued in the event the subject is treated with another anti-CD20 therapy, e.g., rituximab or B-cell modifying or depleting agent.
9. Ofatumumab PK sample collection done for Arm A only. Pharmacokinetic samples must be collected at the time of HAHA sample collection(refer to Footnote 4 in Appendix 2).

[redacted]

11. Prognostic markers include: ALC, FLIPI-1, FLIPI-2 (includes ß2-microglobulin), FcR gamma 3A, and HACA.

12. Ofatumumab monotherapy (1000 mg once every 1 month). A total of 12 infusions of ofatumumab (1000 mg) will be administered in Arm A regardless of the number of OB cycles completed. Arm B will not receive ofatumumab q1M (this is q28 days), but must come into the clinic for scheduled visits and procedures as if they were on the q1 month schedule following 8 cycles of bendamustine.

13. Follow-up #1, in both arms, will begin on Day 336 (this is 3 months following Day 252) and will continue every 3 months until Month 18 of the F/U phase (Table 1). There will be a ±7 day visit window around each day.
14. The follow-up #2 schedule comes after the end of F/U 1 and continues until Month 60 in the entire F/U phase (Table 1). Visits will occur at least every 12 months until Month 54 or earlier if clinical symptoms of progression are suspected. Following Month 54, subjects will be followed until Month 60 of the F/U phase. The last required yearly CT scan will be done on Month 54 of F/U2. CT scans will be done to confirm any clinical signs or suspicion of PD throughout the study. There will be a ±14 day visit window around each day.
15. Subjects with PD, as confirmed by CT scan, will be followed for survival. Survival follow-up visits begin 2 months after PD is confirmed by CT scan for both arms Subjects who stop protocol treatment and begin non-protocol treatment will go into Survival Follow-Up. Survival follow-up visits will occur every 3 months (± 7 day) until Month 18 of the F/U phase following PD confirmation by CT scan. After Month 18 of the F/U phase, visits will be at least every 12 months (± 14 day) until Month 54. Following Month 54, subjects will have one more survival F/U on Month 60 of the entire F/U phase. Table 1 describes this F/U visit schedule. Subjects in Arm B with PD may select optional ofatumumab monotherapy. PD must be confirmed by an independent review prior to receiving ofatumumab monotherapy. Survival follow-up visits may be phone-calls instead of physician office visits See Section 3.1.6 for more details. Subjects with PD or are no longer receiving treatment will be followed for survival.
16. There are 2 types of withdrawal (WD): WD from investigational product and WD from study. See Section 4.4 for details on withdrawal criteria. If a subject, without PD discontinues or withdraws from treatment (for any reason) the subject remains in the study and completes all scheduled visits without study drug. In the event a subject withdraws consent from study, the WD visit must be completed. CT scan done at WD from study if last CT was >91 days.
17. Subjects that progress in Arm B (bendamustine alone) will have the option to receive fatumumab monotherapy. If Arm B subjects decide to receive ofatumumab monotherapy then they must follow Appendix 3 and must not continue with Appendix 2 survival assessments. See Section 3.1.6 and Appendix 3 for more details.
18. Sample taken prior to first infusion.
19. A visit window of 3 days following the scheduled day will be allowed between cycles but there is no visit window once the subject has entered the cycle (except bendamustine may be administered on either Days 1,2 or Days 2,3 if needed). There is a minimum 21 day interval between cycles. In the event the 1st infusion of bendamustine is on Day 2 of a cycle, then assessments required for Day 1 (except HAHA, ofatumumab plasma concentration, Ig, and flow cytometry) will be done on Day 2 and the assessments required for Day 2 will now be done on Day 3. See SPM for more details. The protocol must be followed as closely as possible. If as per local practice, a blood draw for hematology analysis prior to the visit date is required, it would be acceptable for hematology analysis, but the blood draw can be taken no more than 3 days ahead of the visit date. Blood draws performed by local laboratories (e.g. for quicker pre-dose response assessment or assessment of toxicity) of protocol-required lab assessments are acceptable; however, it is important that the sample for the central laboratory analysis is taken at the same time. Since absolute neutrophil count, platelet count, peripheral blood lymphocytes, and hemoglobin results are required to establish if a bendamustine dose reduction and/or treatment delay is required, the results of each of these local laboratory tests must also be entered into the eCRF if it is used to manage a dose delay or dose reduction . Central Laboratory information will also be entered into the eCRF.
20. One month following treatment completion in Arm A, regardless of response and regardless of when treatment ended in the study

11.3 Appendix 3: Time and Events: Ofatumumab Following PD for Bendamustine Monotherapy Arm

Phase	TREATMENT PERIOD[24]					Follow-up			Survival/PD confirmation[21]	WD[18]
Visit	1	2	3	4	5-12					
	Week 1	Week 2	Week 3	Week 4	Every1M x8 doses[17]	1M F/U[11]	F/U1[19]	F/U2[20]		
Visit Window (Days)		+1	+1	+1	±3	±3	±7	±14		
Pre-medication	X[1]	X[2]	X[2]	X[2]	X[2]					
Ofatumumab	X[3]	X[4]	X[4]	X[4]	X[4]					
Physical examination	X									X
Body weight & Constitutional Symptoms	X									X
CT Scan[5]						X				X
Response evaluation[5]						X[5]				X
Lymphoma disease symptom assessment[5]						X[5]				X
Bone marrow biopsy[6]						X[6]				
Survival assessment	X	X	X	X	X	X	X	X	X	X
ECOG Performance Status				X[7]						X
Vital signs (BP, Pulse, temp.)	X	X	X	X	X	X	X	X		X
AE	X	X	X	X	X	X	X, X[8]	X[8]	X[8]	X
Concomitant Medication	X	X	X	X	X	X	X[9]	X[9]	X[9]	X
Hematology[10]	X[25]			X	X		X	X		X
Biochemistry[10]	X[25]			X	X	X	X[23]			X
Flow Cytometry[12]	X[12]				X[12]	X[12]	X[12]			
HACA	X[13]									
HAHA[14]	X[13,14]				X[14]		X[14]		X[14]	X[14]
Ofatumumab PK sample[15]	X[15]			X[15]	X[15]	X[15]	X[15]		X[15]	X[15]

Phase	TREATMENT PERIOD[24]					Follow-up			Survival/PD confirmation[21]	WD[18]
Visit	1	2	3	4	5-12					
	Week 1	Week 2	Week 3	Week 4	Every1M x8 doses[17]	1M F/U[11]	F/U1[19]	F/U2[20]		
Visit Window (Days)		+1	+1	+1	±3	±3	±7	±14		
IgG, IgA, IgM	X[13,14]				X[12,14]	X[12,14]	X[12,14]	X[12,14]		
Hepatitis B[16]				X[16]		X[16]	X[16]			
Pregnancy[22]							X[22]			
[redacted]										

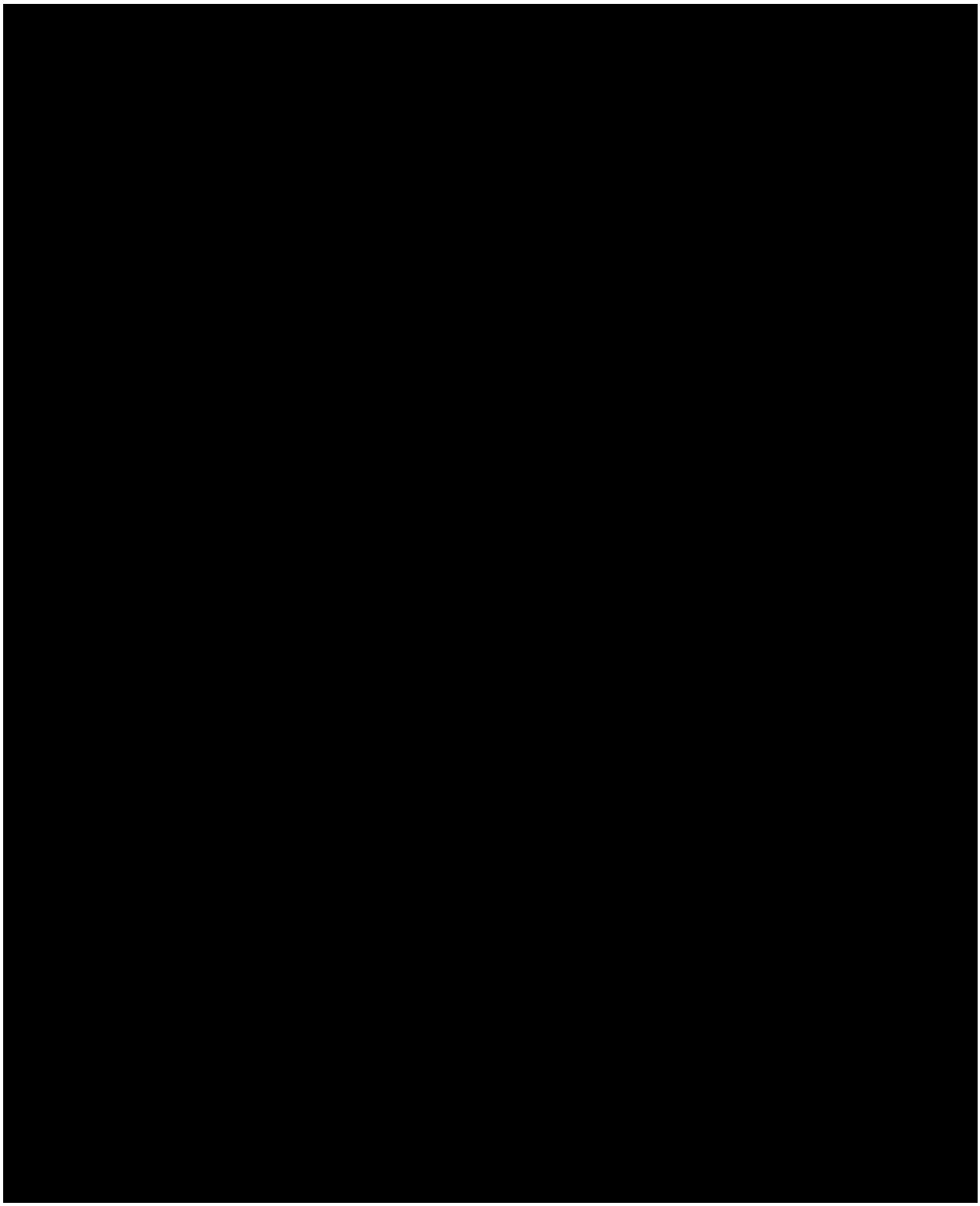
APPENDIX 3: TIME AND EVENTS: OFATUMUMAB FOLLOWING PD FOR BENDAMUSTINE MONOTHERAPY ARM (CONTINUED)

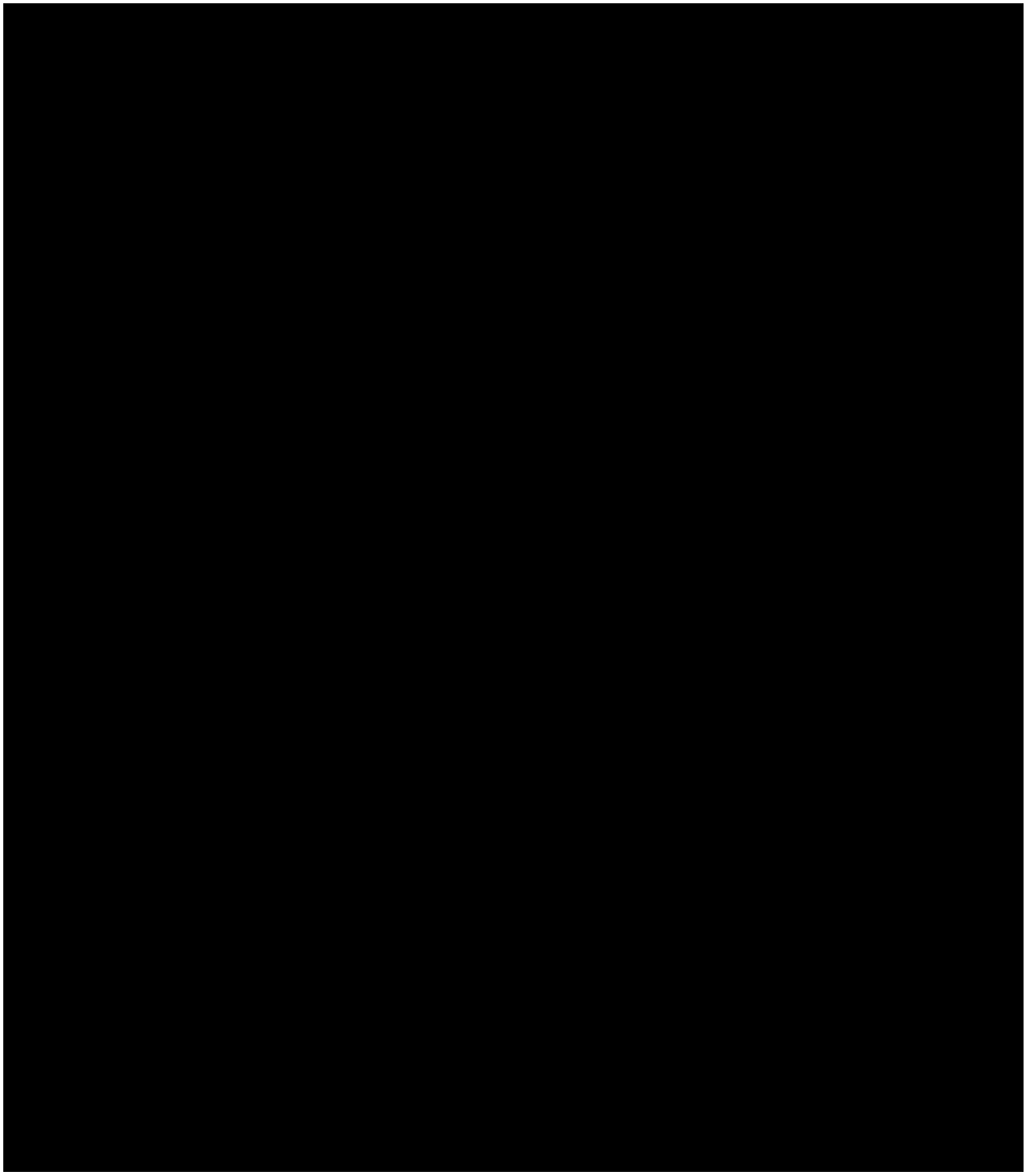
Abbreviations: AE= Adverse Events; CR= Complete Remission; CT= Computed Tomography; DNA= deoxyribonucleic acid ; ECOG= Eastern Cooperative Oncology Group; F/U= Follow-Up; HBV= Hepatitis B Virus; Ig= immunoglobulin; PD= Progressive Disease; PO= oral; M=Months; HAHA= Human anti-Human Antibodies; HACA= Human anti-Chimeric Antibodies;IRC=Independent Review Committee; IV= intravenous; SPM= study procedures manual; WD= Withdrawal

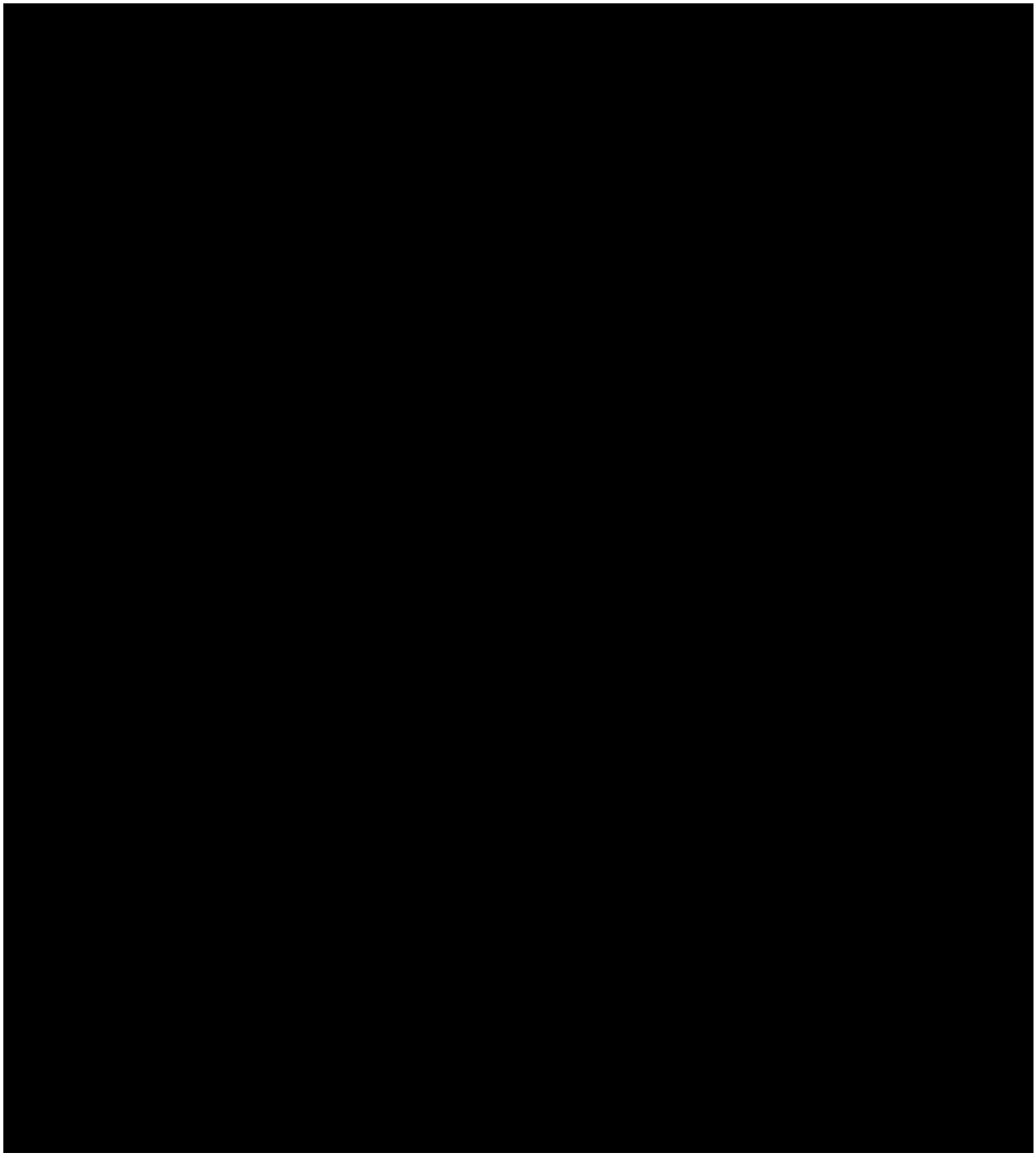
1. Administer pre-medication (acetaminophen approximately 1000 mg PO, diphenhydramine or equivalent approximately 50 mg IV, and glucocorticoid approximately 50 mg IV prednisolone equivalent) 30 minutes-2 hours before each Ofatumumab dose.
2. Administration of premedication as indicated (Section 5.1.1) at investigator discretion. Premedication is administered in conjunction with ofatumumab.
3. Ofatumumab (1000 mg)
4. Ofatumumab (2000 mg)
5. PD must be confirmed by an IRR before receiving ofatumumab. The CT scan data confirmed by IRR (or may be a CT scan done after IRR confirmation if available) will be used for baseline CT assessments in Appendix 3 . CT scan, response assessment, and assessment of lymphoma-related disease symptoms are done once (+3 days during 1 month following last ofatumumab infusion). Lymphoma-related symptoms are described in Section 6.2.4.
6. A bone marrow biopsy will be performed no later than 8 weeks following CR (as judged by investigator) if bone marrow was positive for lymphoma at baseline.
7. ECOG performance status done once (on last weekly visit for fourth ofatumumab infusion) or withdrawal
8. All SAEs regardless of causality will be reported from 61 days after the last dose of investigational product to the end of the follow-up period or until initiation of subsequent anti-lymphoma therapy is initiated. Any SAE brought to the investigator's attention after the start of subsequent anti-lymphoma therapy and considered by the investigator as possibly related to either ofatumumab or bendamustine must be reported to Novartis. See Section 6.5 for more details.
9. Only steroids, growth factors, transfusions, anticancer, and anti-infectious treatments will be followed from 61 days after the last dose of investigational product to the end of the follow-up period or until initiation of subsequent anti-lymphoma therapy .
10. See Section 6.3 and Section 6.4 for details on Appendix 3 laboratory tests. The protocol must be followed as closely as possible, but if as per local practice, a blood draw for hematology analysis prior to the visit date is required, it would be acceptable for hematology analysis, but the blood draw can be taken no more than 3 days ahead of the visit date. Blood draws performed by local laboratories (e.g. for quicker pre-dose response assessment or assessment of toxicity) of protocol-required lab assessments are acceptable; however, it is important that the sample for the central laboratory analysis is taken at the same time. The local laboratory results of absolute neutrophil count, platelet count, peripheral blood lymphocytes, and hemoglobin must also be entered into the eCRF if it is used for a treatment decision. Central Laboratory information will also be entered into the eCRF.
11. One month following treatment completion, regardless of response and regardless of when treatment ended in the study.
12. B cell flow cytometry for CD19, CD20 (See Section 6.3.1). B-cells and immunoglobulins (Ig) will be monitored for a period of 2 years after the last ofatumumab infusion or until the number of B-cells and circulating IgG, IgM and IgA have returned to normal or to within baseline values (according to the central laboratory), whichever is earlier. Monitoring will be done during scheduled F/U visits. F/U will be discontinued in the event the subject is treated with another anti-CD20 therapy, e.g., rituximab or B-cell modifying or depleting agent.
13. Table 1 Collect HAHA, HACA, and Immunoglobulin (Ig) samples prior to start of ofatumumab infusion at first dose (Dose 1).
14. During treatment, collect HAHA and Ig no later than every 6 months (collection to correspond with a scheduled visit). During first year of F/U, collect no later than every 6 months (corresponding with a scheduled visit) for the first year after the last ofatumumab infusion. Collect HAHA at withdrawal (see footnote 18 of Appendix 3) or on one occasion post-PD for subjects with PD.
15. Collect ofatumumab PK samples according to Table 10 in Section 6.7.2 and at the time of each HAHA sample.

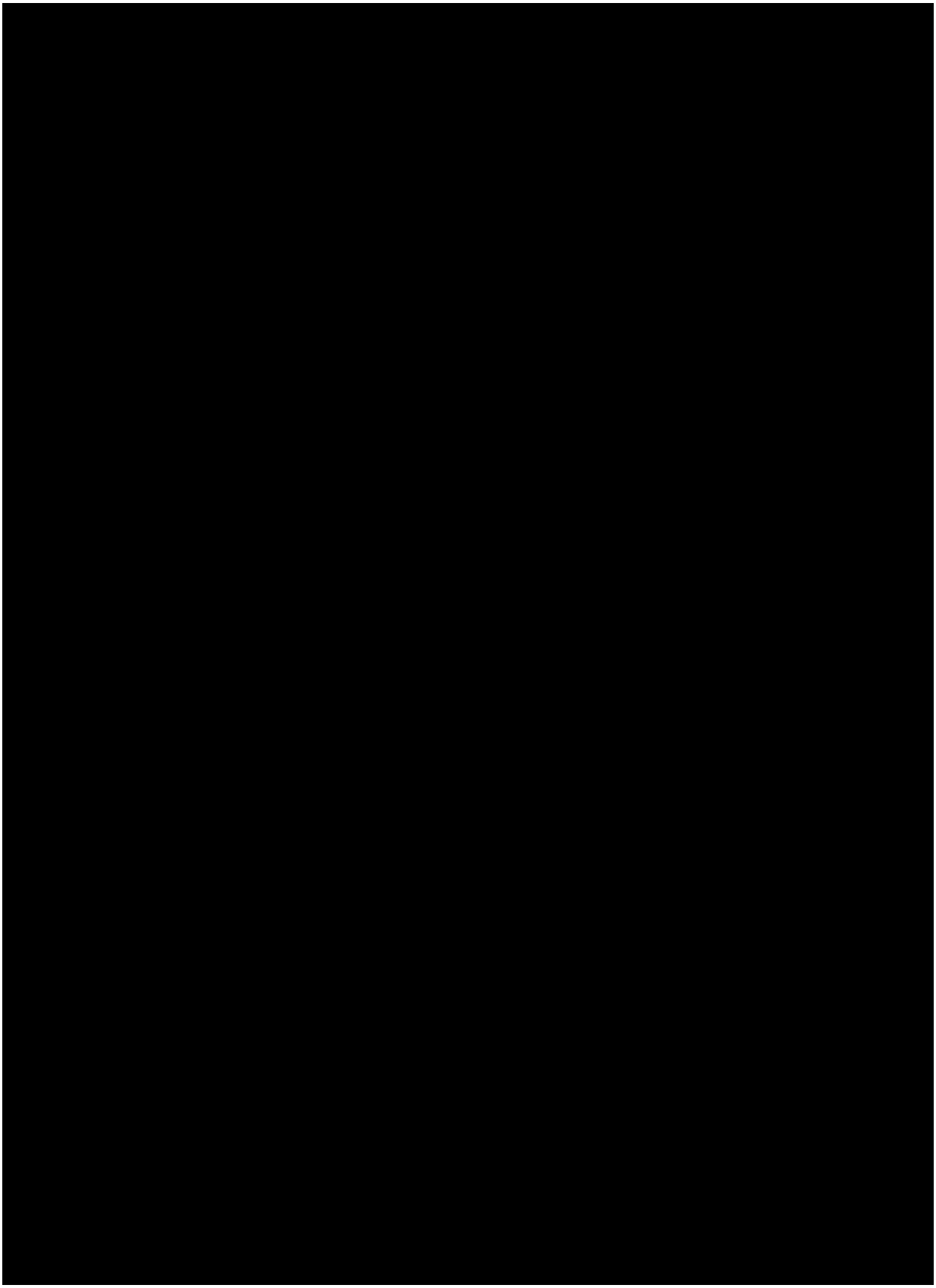
APPENDIX 3: TIME AND EVENTS: OFATUMUMAB FOLLOWING PD FOR BENDAMUSTINE MONOTHERAPY ARM (CONTINUED

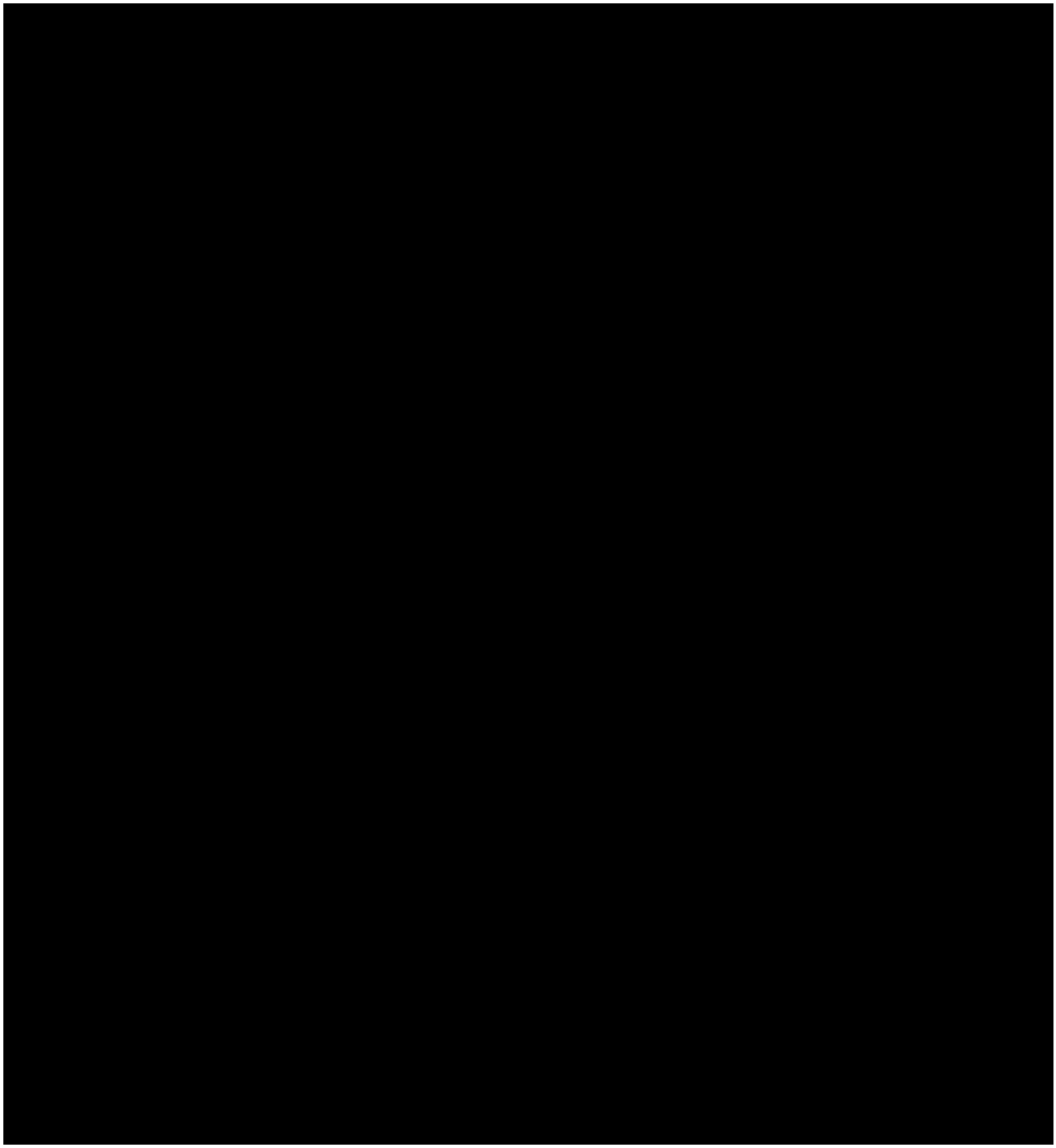
16. In subjects receiving ofatumumab that are Hepatitis B core positive, HBsAg negative, and HBV DNA negative (Section 6.3.2 and Section 6.5.7.1), Hepatits B DNA must be obtained while on treatment and then 1,3, 6 months post treatment. If a subject converts to HBV DNA positive during the study, Hepatitis B treatment may be initiated by the site investigator after consultation with a physician experienced in the care and management of subjects with Hepatitis B and the Novartis Medical Lead. The risks and benefits of continuing ofatumumab or discontinuing ofatumumab must be discussed with the Medical Lead before appropriate treatment decisions are made for that individual subject. Instructions for Japanese subjects are in Appendix 8.
17. First monthly (q28 days) ofatumumab dose (2000 mg) begins 1 month (q28 days) after Week 4 ofatumumab infusion. Subsequent ofatumumab infusions occur every 1 month (q28 days) for 8 doses. There will be a ±3 day visit window around each day
18. There are 2 types of withdrawal (WD): WD from investigational product and WD from study. See Section 4.4 for details on withdrawal criteria (exception: no PRO will be done in Appendix 3). If a subject, without PD, discontinues or withdraws from treatment (for any reason) the subject remains in the study and completes all scheduled visits without study drug. In the event a subject withdraws from study, the WD visit must be completed. CT scan done at WD from study if last CT was >91 days.
19. This is follow-up schedule #1 (schedule frequency shown in Table 1). F/U 1, in both arms, begins 1 month following last infusion of ofatumumab. Follow-up will continue every 3 months until Month 18 of the F/U phase. There will be a ±7 day visit window around each visit.
20. The follow-up #2 schedule comes after the end of F/U 1 and continues until Month 60 of the entire F/U phase (schedule frequency shown in Table 1). Visits will occur every 12 months until Month 54 or earlier if clinical symptoms of progression are seen. Following Month 54, subjects will be followed until Month 60 of the F/U phase. There will be a ±14 day visit window around each day.
21. Subjects with PD, as confirmed by CT scan, will be followed for survival. Additionally, subjects without PD who stop protocol treatment and begin non-protocol treatment will go into Survival Follow-Up. Survival follow-up visits occur every 3 until Month 18 of F/U 1 then every 12 months until Month 54 of the F/U 2 phase. Following Month 54, there will be one more visit at Month 60 of the F/U phase. There will be a ± 7 day visit window around visit in F/U 1. Survival follow-up visits begin 2 months after PD is confirmed by CT scan or start of non-protocol treatment. There will be a ±14 day visit window around each visit in F/U 2.
22. Women of childbearing potential must agree to use a method of birth control approved by the study doctor while during study and for one year after the last dose of treatment. Pregnancy testing in women of child bearing potential will be done prior to dosing if last test >30 days ago and again 6 months after last dose of ofatumumab.
23. Only for Month 3.
24. One month is 28 days when being treated in this study.
25. To be done prior to first ofatumumab dose only if central laboratory results are not available to confirm eligibility for ofatumumab monotherapy following PD in Arm B per Section 3.1.6

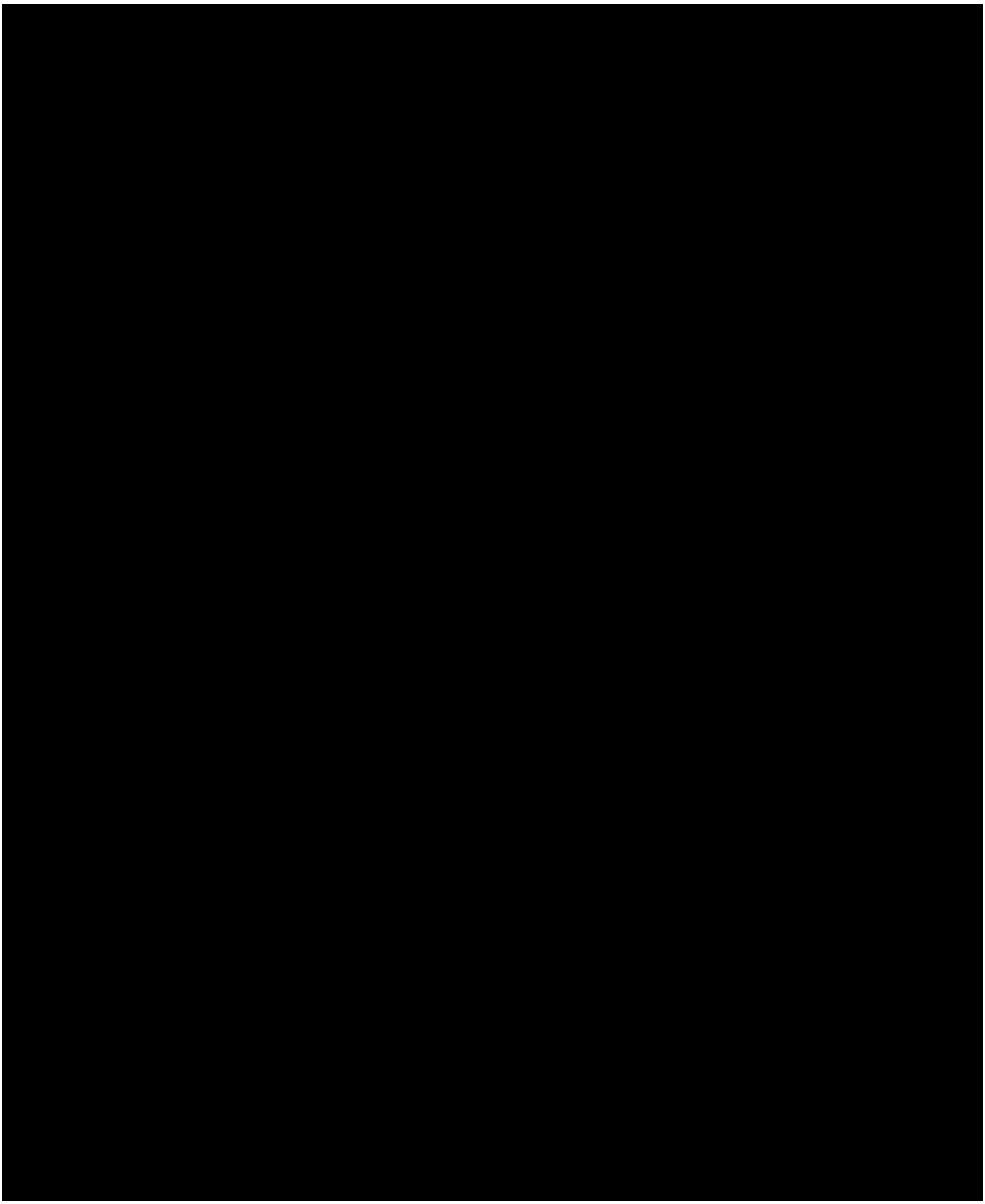












11.5 Appendix 5: Patient Reported Outcome Measures

11.5.1 Functional Assessment of Cancer Therapy - Lymphoma (FACT-Lym, version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-Lym (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-Lym (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
P2	I have certain parts of my body where I experience pain	0	1	2	3	4
LEU1	I am bothered by lumps or swelling in certain parts of my body (e.g., neck, armpits, or groin)	0	1	2	3	4
BRM3	I am bothered by fevers (episodes of high body temperature)	0	1	2	3	4
ES3	I have night sweats	0	1	2	3	4
LYM1	I am bothered by itching	0	1	2	3	4
LYM2	I have trouble sleeping at night	0	1	2	3	4
BMT6	I get tired easily	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
Ga1	I have a loss of appetite	0	1	2	3	4
HI8	I have trouble concentrating	0	1	2	3	4
N3	I worry about getting infections	0	1	2	3	4
LEU6	I worry that I might get new symptoms of my illness	0	1	2	3	4
LEU7	I feel isolated from others because of my illness or treatment	0	1	2	3	4
BRM9	I have emotional ups and downs	0	1	2	3	4
LEU4	Because of my illness, I have difficulty planning for the future	0	1	2	3	4

11.5.2 EuorQoL Five-Dimension (EQ-5D)

By placing a checkmark in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

- I have no problems in walking about ☐
- I have some problems in walking about ☐
- I am confined to bed ☐

Self-Care

- I have no problems with self-care ☐
- I have some problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

Usual Activities (e.g., work, study, housework, family, or leisure activities)

- I have no problems with performing my usual activities ☐
- I have some problems with performing my usual activities ☐
- I am unable to perform my usual activities ☐

Pain/Discomfort

- I have no pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have extreme pain or discomfort ☐

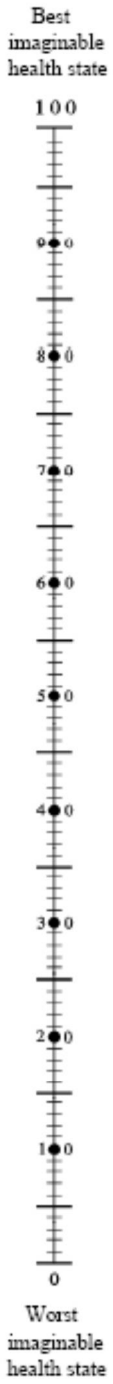
Anxiety/Depression

- I am not anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am extremely anxious or depressed ☐

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



11.5.3 Health Change Questionnaire

HEALTH CHANGE QUESTIONNAIRE

Please answer the following question:

1. Since you began the study, has there been any change in your overall health? (Please mark only one box.)

My health is:

- ❒ 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

11.6 Appendix 6: Follicular Lymphoma International Prognostic Index-1 (FLIPI-1)

TABLE I: THE FIVE PARAMETERS RETAINED FOR BUILDING THE FLIPI

Parameter	Adverse Factor
Age	≥60 years
Ann Arbor Stage	III-IV
Hemoglobin Level	< 120 g/L
Serum LDH Level	> ULN
Number of Nodal Sites	> 4

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

1. See [Solal-Celigny, 2004]

TABLE II: OUTCOME AND RELATIVE RISK OF DEATH ACCORDING TO RISK GROUP AS

Risk Group	Number of Factors	Distribution of Patients, %	5-year OS, %(SE)	10-year OS, %(SE)	RR	95% CI
Low	0-1	36	90.6 (1.2)	70.7 (2.7)	1.0	NA
Intermediate	2	37	77.6 (1.6)	50.9 (2.7)	2.3	1.9-2.8
High	≥3	27	52.5 (2.3)	35.5 (2.8)	4.3	3.5-5.3

1. N= 1795.
2. Abbreviations: OS indicates overall survival; SE, standard error; CI, confidence interval; RR, relative risk (of death) and NA, not applicable.
3. *Factors adversely affecting survival in the FLIPI include age greater than 60 years; Ann Arbor stage III-IV; number of nodal sites greater than 4; serum LDH level greater than the upper limit of normal; and hemoglobin level less than 120 g/L.
4. Table II Abbreviations: OS indicates overall survival; SE, standard error; CI, confidence interval; RR, relative risk (of death), and NA, not applicable.
5. FLIPI, N=1795 [Solal-Celigny, 2004]
6. FLIPI2, N= 832 [Federico, 2009]

11.7 Appendix 7: Follicular Lymphoma International Prognostic Index-2 (FLIPI-2)

TABLE III: THE FIVE PARAMETERS RETAINED FOR BUILDING THE FLIPI

Parameter	Adverse Factor
Beta-2-microglobulin	> ULN
LoDLIN	>6cm
Bone marrow involvement presence	yes
Hemoglobin	<120 g/L
Age	>60 years

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

TABLE IV: OUTCOME AND RELATIVE RISK OF DEATH ACCORDING TO RISK GROUP AS DEFINED BY THE FLIPI-2

Risk Group	Number of Factors	Distribution of Patients, %	3-year PFS, %(SE)	5-year OS, %(SE)	RR	95% CI
Low	0	20	90.9 (2.4)	79.5 (5.0)	1.0	NA
Intermediate	1-2	53	69.3 (2.4)	51.2 (5.7)	3.19	2.0-5.15
High	3-5	27	51.3 (3.7)	18.8 (13)	5.76	3.53-9.4

1. N= 1795.
2. Abbreviations: PFS= indicates Progression Free Survival; SE, standard error; CI, confidence interval; RR, relative risk (of death), and NA, not applicable.

[Federico, 2009]

11.8 Appendix 8: Instructions for Japanese Hepatitis Testing

These instructions are for patients who enroll on this study in Japan only.

For HBcAb and/or HBsAb positive subjects, to prevent hepatitis B reactivation it is recommended that the guidance in the following report be applied: 'Prevention of immunosuppressive therapy or chemotherapy-induced reactivation of hepatitis B virus infection -Joint Report of the Intractable Liver Diseases Study Group of Japan and the Japanese Study Group of the Standard Antiviral Therapy for Viral Hepatitis' (Ministry of Health, Labour and Welfare in Japan). The report states:

- *In subjects who are HBV-DNA positive, it is recommended that a nucleoside analogue be administered prophylactically.*
- *In subjects who are HBV-DNA negative, but HBsAb and/or HBcAb positive, it is recommended that monthly monitoring of HBV-DNA be conducted until 12 months after the completion of study drug administration*.

11.9 Appendix 9: General Protocol Changes for Amendment 1 (16-November-2009) from Protocol (dated 7-AUG-2009)

WHERE THE AMENDMENT APPLIES

Amendment 1 is applicable to all study sites.

SUMMARY AND RATIONALE FOR AMENDMENT CHANGES

ADMINISTRATIVE CHANGES

Due to administrative changes within GSK, appropriate revisions were made to the Medical Monitor contact information to reflect personnel updates and organizational restructuring.

NUMBER OF CYCLES CHANGED FROM 6 TO UP TO 8 CYCLES IN BOTH ARMS

Up to 8 cycles of ofatumumab (O) + bendamustine (B) or B monotherapy will be allowed in each study arm. This reflects the Treanda label [TREANDA, 2008].

OFATUMUMAB DOSING FREQUENCY: 12 INFUSIONS OF OFATUMUMAB IN ARM A

A total of 12 ofatumumab infusions will be administered in Arm A (OB) regardless of the total number of completed OB therapy cycles.

Several randomized studies have indicated that extended or maintenance rituximab therapy prolongs PFS in relapsed FL, whether after rituximab monotherapy or combination chemotherapy [Ghielmini, 2004; Hainsworth, 2003; Hoechster, 2009; van Van Oers, 2006]. Several schedules have been examined for extended or maintenance dosing of rituximab. A recent meta-analysis, which examined a variety of dosing schedules, suggested that maintenance rituximab therapy may improve overall survival (OS) [Vidal, 2009]. Most recently, the PRIMA study reportedly showed a significant benefit for rituximab maintenance therapy after induction therapy with a rituximab combination regiment in previously untreated FL. Therefore, maintenance monotherapy with rituximab has a role after induction therapy with combination chemotherapy in FL.

Study OMB110918 study will examine the role of extended or maintenance ofatumumab monotherapy after OB combination therapy in rituximab-refractory FL. Two points must be considered. First, clearance of ofatumumab may be faster in rituximab-refractory FL patients, as they presumably will have greater tumor volume after completing induction therapy than patients with more sensitive disease. Study OMB110918 will enroll rituximab-refractory FL patients who are expected to have more disease following OB therapy (and thus, faster ofatumumab clearance) and have shorter PFS than the rituximab-sensitive, relapsed FL patients in the 920 study. Thus, more frequent dosing of ofatumumab may be necessary for extended dosing in this patient population, similar to the monthly maintenance dosing in CLL in the 406 study.

Recently, Study Hx-CD20-405 reported the results of ofatumumab monotherapy in a rituximab refractory patient population. Study Hx-CD20-405 study indicated a median PFS

of 6 months when 500-1000 mg was used. This suggested that it may be prudent to give the maintenance doses more frequently than every 8 weeks to ensure that patients will actually be able to receive extended dosing before their FL progresses. To date, we have no evidence that 2000 mg is more effective than 1000 mg in FL. Therefore, we will use 1000 mg as the maintenance dose in Study OMB110918 study. However, we will administer the maintenance doses every 4 weeks in anticipation of faster antibody clearance and faster disease progression.

OFATUMUMAB MONOTHERAPY FOR PATIENTS WHO PROGRESS IN ARM B

A study a regimen of ofatumumab 2000 mg weekly for 4 weeks followed by 2000 mg every 4 weeks for 4 additional doses (total: 8 doses) in rituximab-refractory FL patients who progress during or following single agent bendamustine will be offered to subjects with PD in Arm B. This study design will allow us to study 1) ofatumumab monotherapy using the 2000 mg dose and 2) extended dosing using a monthly schedule in the context of an existing study in rituximab-refractory FL. This is a change from dosing ofatumumab (1000 mg), weekly for 8 doses.

To gain information about higher doses of ofatumumab monotherapy in refractory FL, patients who progress during or after therapy in Arm B (bendamustine alone) will be offered ofatumumab monotherapy. The only data regarding the dose-response relationship of anti-CD20 antibody monotherapy in this poor patient population was obtained in Study Hx-CD20-405, in which patients with rituximab-refractory FL were randomized to single agent ofatumumab 500 mg or 1000 mg weekly for 8 doses. The response rate was approximately 10%, and median PFS was 6 months, with no difference between the treatment arms. While the study indicated that administering ofatumumab monotherapy at 500-1000 mg weekly was not highly effective in rituximab-refractory FL patients, the role of dose intensification is unknown in this patient population. Our experience in chronic lymphocytic leukemia (CLL) indicated that increasing the dose intensity of rituximab was able to significantly improve the overall response rate from 10-15% to 45%. Furthermore, ofatumumab showed significant clinical activity with an acceptable safety profile in Study Hx-CD20-406 study in fludarabine-refractory CLL when administered at a dose of 2000 mg. Therefore, it is reasonable to examine the 2000 mg dose in refractory FL. The optimal duration of therapy in this setting is unclear. The 406 study administered 8 weekly doses of ofatumumab 2000 mg (first dose 300 mg) followed by 4 monthly doses of 2000 mg. However, the standard length of weekly rituximab therapy in FL is 4 weeks, and there are no convincing data that increasing the number of weekly ritxuimab infusions from 4 to 8 is of benefit.

We will study extended dosing of ofatumumab monotherapy in this patient group, similar to our plan in Study OMB113676. However, Study OMB110918 will enroll rituximab-refractory, indolent NHL patients who are expected to have more disease following 4 weeks of ofatumumab monotherapy (and thus, faster ofatumumab clearance) and have shorter PFS than the rituximab-sensitive relapsed FL patients in the 676 study. Thus, more frequent dosing of ofatumumab may be necessary for extended dosing in this patient population, similar to the monthly maintenance dosing in CLL in Study Hx-CD20-406. Therefore, the extended dosing will consist of 2000 mg given monthly for 4 doses.

OFATUMUMAB DOSING FREQUENCY: 12 INFUSIONS OF OFATUMUMAB IN ARM A

Clarification in response criteria (Section 6.2.4, Section 6.2.4.2, Section 6.2.4.3, and Section 6.2.4.5).

RESPONSE CRITERIA

Section 6.2 (Efficacy Assessments) updated for clarity

SPECIFIC PROTOCOL CHANGES FOR AMENDMENT 1 (16-NOVEMBER-2009) FROM PROTOCOL (DATED 7-AUG-2009)

LIST OF SPECIFIC CHANGES

Note: deleted language is presented with a ~~strikethrough~~ and added language is printed in **bold**.

EXAMPLE:

Section: Throughout Document

Original text:

~~Patient~~

Text changed to:

Subject

Rationale for Change:

For consistent use of terminology throughout the document. Amended in appropriate document sections.

Section: Sponsor Information Page

Original text:

Medical Monitor Contact Information:

[redacted] MD, Ph.D

[redacted] ~~– ofatumumab~~

[redacted]

[redacted]

~~United Kingdom~~

Tel: [redacted]

Mob: [redacted]

Fax: [redacted]

Email: [redacted]

Text changed to:

Medical Monitor Contact Information:

[redacted] MD

[redacted] USA

Telephone: [redacted]

Fax: [redacted]

Email: [redacted] Contact Information:

Same as above

Rationale for Change:

Information Update.

Section 1.3: Ofatumumab

Original text:

A Phase I/II dose escalation study of ofatumumab in subjects with relapsed or refractory follicular lymphoma tested four weekly doses of ofatumumab at 300, 500, 700, or 1000 mg [Study Hx-CD20-001; Hagenbeek, 2008]. Results demonstrated clinical activity with reversible Grade 3, 4 adverse events occurring on the day of initial infusion. Those adverse events included dyspnea, hypoxia, laryngeal edema, throat tightness, pruritus, and rash. Median time to progression (TTP) was 8.8 and 32.6 months, respectively. Median duration of response was 29.9 months. Median and maximum follow-up was 9.2 and 38.6 months, respectively. Response did not correlate with ofatumumab dose.

Text changed to:

The Food and Drug Administration (FDA) recently approved ofatumumab (ARZERRA) for chronic lymphocytic leukemia (CLL) refractory to fludarabine and alemtuzumab.

A Phase I/II dose escalation study of ofatumumab in subjects with relapsed or refractory follicular lymphoma tested four weekly doses of ofatumumab at 300, 500, 700, or 1000 mg [Study Hx-CD20-001; Hagenbeek, 2008]. Results demonstrated clinical activity with reversible Grade 3, 4 adverse events occurring on the day of initial infusion. Those adverse events included dyspnea, hypoxia, laryngeal edema, throat tightness, pruritus, and rash. Median time to progression (TTP) was 8.8 and 32.6 months, respectively. Median duration of response was 29.9 months. Median and maximum follow-up was 9.2 and 38.6 months, respectively. Response did not correlate with ofatumumab dose.

A Phase II, open label study in patients with previously-untreated FL compared ofatumumab in combination with CHOP vs CHOP. Patients were randomized into two dose groups (N= 29 per group): 300 mg of ofatumumab at the first infusion, followed by 5 infusions of either 500 or 1000 mg of ofatumumab every 3 weeks in combination with 6 cycles of CHOP. Results demonstrated an ORR of 90%, CR of 24%, and 45% Cru (500 mg of ofatumumab, N=29). In patients treated with 1000 mg of ofatumumab (n=29), the ORR was 100% including 38% CR, and 17% Cru. There were no unexpected safety findings reported during treatment and within 30 days after last infusion. The most common adverse events of grade 3 or 4 (> 10%) were leukopenia and neutropenia.

In a single-arm, double-blind study of single-agent ofatumumab, a total of 116 patients were treated with two doses of ofatumumab. The ORR in the total population was 11%. This group of patients was highly refractory with 49% refractory to their last chemotherapy. Patients in the study had previously received a median of 4 prior treatment regimens. The 1000 mg dose group (N=86) demonstrated an ORR of 10% (included 1 CR, 8 PR). In addition, 50% (43) of patients in the 1000 mg treatment arm had stable disease. The ORR among patients who were refractory to prior rituximab monotherapy (n=27) was 22%. For patients considered refractory to rituximab in combination with chemotherapy the RR was 7% and among patients considered refractory to rituximab maintenance the RR was 9%. The median duration of response in the 1000 mg treatment arm was 6 months and the PFS was 6 months. There were no unexpected safety findings reported during treatment and within 30 days after last infusion. The most common adverse events (> 10%) were rash, urticaria, pruritus, fatigue, nausea, pyrexia and cough.

Section 2: Objectives

Original text:

Secondary objectives:

- To compare overall response rate, overall survival, time to and duration of response, and time to progression in subjects treated with ofatumumab and bendamustine combination therapy to those treated with bendamustine monotherapy
- 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 ofatumumab pharmacokinetics when given with bendamustine
- To evaluate and compare the two treatment arms with respect to changes in subjects' health-related quality of life
- To evaluate and compare prognostic markers and their correlation with clinical responses in subjects treated with ofatumumab and bendamustine compared to those treated with bendamustine monotherapy (i.e. ALC, FcR gamma 3, IgVH gene rearrangement)

Text changed to:

Secondary objectives:

- To compare overall response rate, overall survival, time to and duration of response, and time to progression in subjects treated with ofatumumab and bendamustine combination therapy to those treated with bendamustine monotherapy
- 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 ofatumumab pharmacokinetics when given with bendamustine
- To evaluate and compare the two treatment arms with respect to changes in subjects' health-related quality of life
- To evaluate and compare prognostic markers and their correlation with clinical responses in subjects treated with ofatumumab and bendamustine compared to those treated with bendamustine monotherapy (i.e. ALC, FcR gamma 3)
- To evaluate the overall response rate to optional ofatumumab monotherapy in subjects who are unresponsive to rituximab during or within 6 months of a rituximab-containing regimen who progress during or following single-agent bendamustine

Section 3.1: Study Design

Original text:

The study will evaluate, in the first 20 subjects (Stage 1), the safety and tolerability of ofatumumab added to bendamustine at 90 mg/m^2 bendamustine (Days 1, 2; q21D) ~~after 6~~ cycles. An independent data safety monitoring board (IDMC) will determine the bendamustine ~~dose~~ for the remainder of the trial. If the bendamustine dose in Arm A is not changed by the IDMC, Stage 1 will continue throughout the remainder of the study and will comprise the final analysis set. If an IDMC ~~dosing~~ change is implemented, the sample size and event count will restart at this point, and subjects enrolled in Stage 2 will comprise the final analysis set. Analysis of the cumulative set (subjects from Stage 1 and Stage 2) will be supplementary.

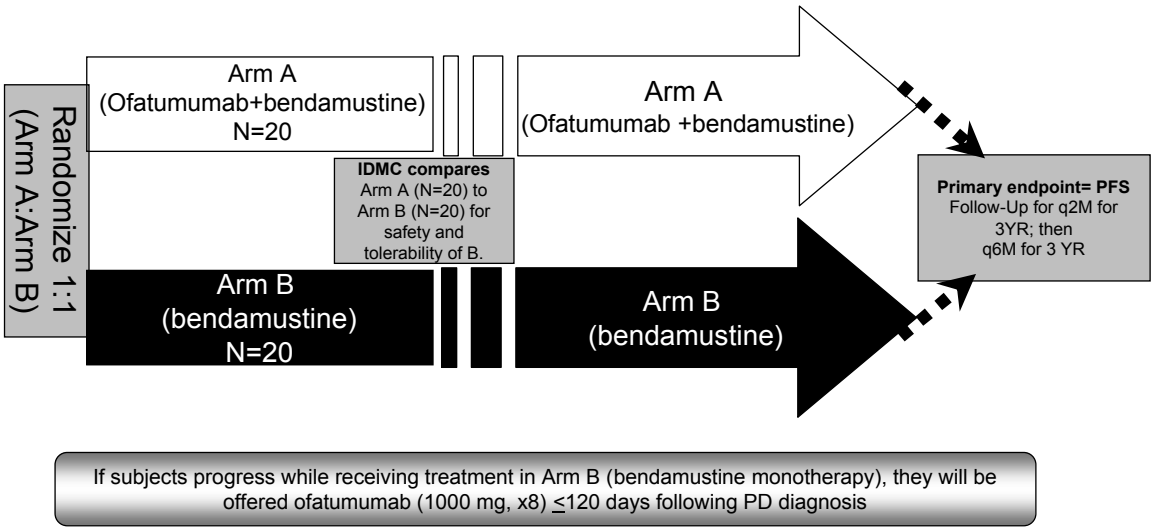
Text changed to:

The study will evaluate, in the first 20 subjects **who complete 3 cycles (or complete bendamustine therapy with fewer than 3 cycles) cycles in Arm A** (Stage 1), the safety and tolerability of ofatumumab added to bendamustine at 90 mg/m^2 bendamustine (Days 1, 2; q21 **days**). **Data from Arm B will be made available for review.** An independent data safety monitoring board (IDMC) will determine **if** the bendamustine **cycle length should be changed to q28 days (Arm A)** for the remainder of the trial. If the bendamustine **cycle length** in Arm A is not changed by the IDMC, Stage 1 will continue throughout the remainder of the study and will comprise the final analysis set. If an IDMC **cycle** change is implemented, the sample size and event count will restart at this point, and subjects enrolled in Stage 2 will comprise the final analysis set. Analysis of the cumulative set (subjects from Stage 1 and Stage 2) will be supplementary.

If toxicity remains excessive despite the reduction of the bendamustine dose to 90 mg/m^2, Days 1, 2, q28 days, the IDMC will assess the next 10 subjects in Arm A who complete 3 cycles (or complete bendamustine therapy) and have the option to reduce the bendamustine dose to 70 mg/m^2 (Stage 3), Days 1, 2; q28 days in Arm A in a similar way as was done for Stage 1 and Stage 2. Data from Arm B will be made available each time the IDMC assesses Arm A.

Section 3.1: Figure 1, Figure 2

Original Figure 1:



Figures changed to:

Figure 1:

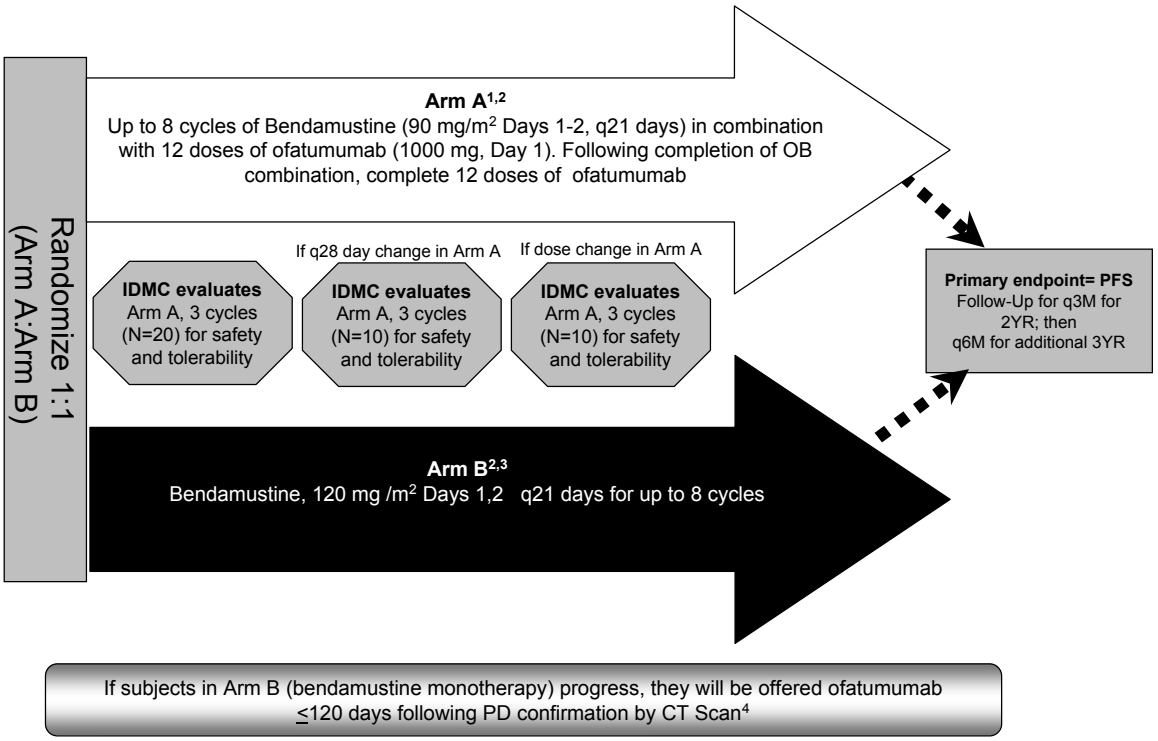
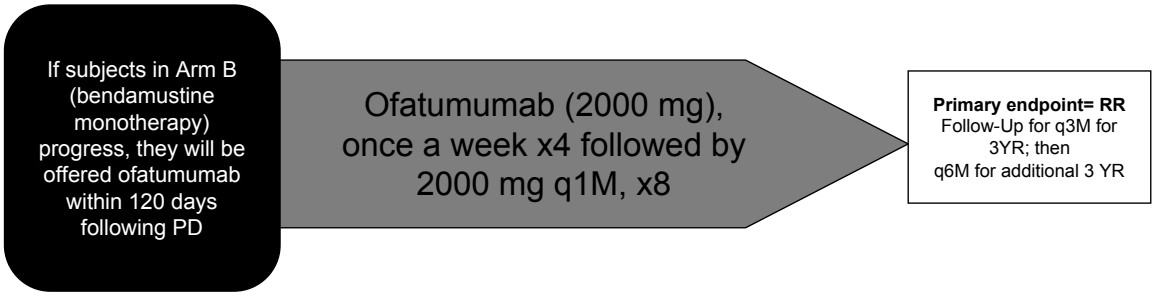


Figure 2 added:



Section 3.1.3: Dose Confirmation for Safety and Tolerability

Original text:

~~Forty subjects (20 per treatment arm) who enter this study will be part of a dose confirmation cohort for evaluation of safety and tolerability of ofatumumab and bendamustine combination therapy. Subjects in Arm A will receive ofatumumab, 1000 mg Day 1 followed by bendamustine, 90 mg/m2, Days 1,2; every 21 days. The combination will be given in 21-day cycles up to 6 cycles. Subjects in Arm B will receive bendamustine, 120 mg/m2, Days 1,2; every 21 days. Bendamustine monotherapy will be given in 21-day cycles up to 6 cycles. The independent data monitoring committee (IDMC) involved in this study will follow a decision rule, described in the IDMC charter, to decide whether the dose of bendamustine, in Arm A, should remain at 90 mg/ m2, Days 1, 2; every 21 days, or change. When administered along with ofatumumab, the bendamustine dose will not exceed 90 mg/m2 (administered on Days~~

~~1,2; every 21 days) in this study. The IDMC decision rule will take into account and compare the nature and severity of serious adverse events and dose-limiting toxicities between Arm A and Arm B. The IDMC will have the option to decrease the bendamustine dose and/or lengthen the cycle duration from 21 to 28 days in Arm A for improved safety and tolerability. Should the IDMC decide to reduce the dose of bendamustine if the nature and severity of serious adverse events or dose-limiting toxicities in Arm A exceed those found in Arm B (monotherapy bendamustine), then the dose and dose reduction schedule found in the IDMC charter will be followed for the remainder of the study. Also see Section 9.7 for further details.~~

Text changed to:

The IDMC will review safety and tolerability data for Arm A at specific points throughout the study as specified in the IDMC charter and summarized in Section 9.7. The IDMC will initially review data from the first 20 subjects who complete 3 cycles (or complete bendamustine therapy with fewer than 3 cycles) in Arm A to determine whether the bendamustine cycle length should be lengthened in to q28 days Arm A or if the cycle length should remain as it is. If cycle length of bendamustine is lengthened in Arm A, the IDMC will then review the data to determine whether the dose of bendamustine in Arm A should be reduced or if it is appropriate for the dose to remain as it is. If the dose of bendamustine in Arm A is reduced, the IDMC will once more review the data to determine if it is appropriate for the study to continue. For each decision the IDMC will follow a decision rule that will be defined in the IDMC charter. Arm B data will be made available to the IDMC each time they assess Arm A.

Section 3.1.4: Treatment Phase

Original text:

Subjects will be followed as described in Appendix 1. Subjects will be randomized 1:1 to receive either:

Arm A: Ofatumumab (1000 mg starting on Day 1 q21 days, Cycles 1-6) followed by bendamustine (90 mg/m2, Days 1,2; q21 days, Cycles 1-6)

Arm B: Bendamustine (120 mg/m^2, Days 1, 2; q21 days, Cycles 1~~-6~~)

An IDMC will ~~compare~~ the safety and toxicity ~~between~~ Arm A ~~and Arm B~~. In the event the toxicity in Arm A ~~exceeds Arm B,~~ the IDMC will follow a decision rule for bendamustine regimen modification as described in the IDMC charter. Please see Section 9.7.

Assessments to determine subject response or progression will be performed for both arms including:

- Physical examination including examination of lymph nodes, spleen and liver
- Peripheral blood sample evaluation for complete blood count (CBC) and differential with both percent and absolute number of lymphocytes
- CT scans for confirmation of response are required (within ~~10~~ days) after a subject fulfils the Revised Response Criteria for Malignant Lymphoma (RRCML) requirements for CR or PR

Text changed to:

Subjects will be followed as described in Appendix 1. Subjects will be randomized 1:1 to receive either:

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

Arm B: Bendamustine (120 mg/m^2, Days 1, 2; q21 days, up to 8 cycles)

Subjects in Arm B who cannot complete 8 cycles of therapy must still come in for all planned visits (Visits 1-20).

An IDMC will **assess** the safety and toxicity **in** Arm A. In the event **of excessive toxicity in** Arm A, the IDMC will follow a decision rule for bendamustine regimen modification as described in the IDMC charter. Please see Section 9.7.

Blood samples are acquired at the start of each cycle, throughout the treatment phase.

Assessments to determine subject response or progression will be performed for both arms including:

- Physical examination including examination of lymph nodes, spleen and liver
- Peripheral blood sample evaluation for complete blood count (CBC) and differential with both percent and absolute number of lymphocytes
- CT scans **will be performed** within **3 days** of the post randomization Days 84, 168, and 252 **to assess clinical response** by the Revised Response Criteria for Malignant Lymphoma (RRCML). **Patients who are unable to complete 8 cycles of therapy must still have CT scans done on post randomization Days 84, 168, and 252.**

Section 3.1.5: Follow-up Phase

Original text:

Following study treatment, subjects who have CR, PR or SD will receive regular follow-up for 5 years. Follow-up visits will begin on 3 months after post randomization Day 252 for Arm A and Arm B and then continue every 3 months for 2 years, then every 6 months for 3 years. Follow-up visits will include survival, and disease status assessments. In addition, subjects will be monitored for safety, efficacy, and pharmacokinetics. See Appendix 1 and Appendix 2 for a complete list of follow-up phase procedures.

Text changed to:

Following study treatment, subjects who have CR, PR or SD will receive regular follow-up for 5 years **in Arm A**. **If Arm B subject do decide to receive optional ofatumumab monotherapy, they will not follow the schedule described in Section 3.1.5, Appendix 1, and Appendix** 2**, but will receive one End of Treatment visit (EOT) as described in Appendix 1, and Appendix** 2 **and will then follow the schedule described in Section 3.1.6 and Appendix 3.**

Follow-up visits will begin on **Day 336 (this** is 3 months after post randomization Day 252) and then continue every 3 months for 2 years, then every 6 months for 3 years. **One month is defined as having 28 days. Each follow-up visit will have a time window of ± 7 days.** Follow-up visits will include survival, **concomitant medications**, and disease status assessments. In addition, subjects will be monitored for safety, efficacy, and pharmacokinetics **as described**. See Appendix 1 and Appendix 2 for a complete list of follow-up phase procedures.

Section 3.1.6: Ofatumumab Following Progressive Disease

Original text:

At the discretion of the physician in consultation with the study subject, ofatumumab may be administered to subjects who develop PD during treatment with bendamustine monotherapy as defined in Section 6.2.4.5 (See Appendix 3 for follow-up procedures). Subjects who receive ofatumumab following diagnosis of PD must fulfill the inclusion criteria found in Section 4.2 and the exclusion criteria found in Section 4.3 (except for exclusion criteria #7: prior bendamustine treatment).

Follow-up will be considered in days post randomization ~~(Day 1).~~

Text changed to:

Follow-up for Progressive Disease

Subjects receiving ofatumumab and bendamustine combination therapy (Arm A) or bendamustine monotherapy (Arm B) who experience disease progression, as defined in Section 6.2.4.5, will be assessed for safety and followed as described in Appendix 1 and Appendix 2 (Survival/PD visits).

Follow-up visits will begin on Day 336 (this is 3 months after Day 252) and continue every 3 months for 2 years and then every 6 months for 3 years. One month is defined as having 28 days. Follow up visits will have a ± 7 day time window.

If an Arm B subject decides to receive optional ofatumumab monotherapy, the subject will not follow the schedule described in Section 3.1.5, Appendix 1, and Appendix 2**, but will receive one End of Treatment visit (EOT) visit as described in Appendix 1, and**

Appendix 2 **and will then follow the treatment and follow-up schedules described in Section 3.1.6 and Appendix 3.**

Section 3.1.6: Ofatumumab Following Progressive Disease for Arm B

Follow-up for Progressive Disease

Subjects receiving ofatumumab and bendamustine combination therapy or bendamustine monotherapy, who experience disease progression, as defined in Section 6.2.4.5, ~~during treatment~~ will be assessed for safety and followed as described in Appendix 1 and Appendix 2.

Text changed to:

At the discretion of the physician in consultation with the study subject, ofatumumab may be administered to subjects who develop PD during **or following** treatment with bendamustine monotherapy **in Arm B** as defined in Section 6.2.4.5 (See Appendix 3 for follow-up procedures). **Subjects with PD in Arm B must have a CT scan done with independent radiology review confirmation of PD. This CT scan will determine measurements of pre-ofatumumab disease before exercising the option to receive ofatumumab.**

Subjects who receive ofatumumab following diagnosis of PD must fulfill the inclusion criteria found in Section 4.2 and the exclusion criteria found in Section 4.3 (except for exclusion criteria #7: prior bendamustine treatment). **Subjects in Arm B who choose to receive optional ofatumumab monotherapy receive ofatumumab 2000 mg weekly (±3 days) for 4 doses followed by 2000 mg every month (±3 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 for 2 years then every 6 months for 3 years as described in Appendix 3.

Section 3.1.7: Study Endpoints

Original text:

Secondary Endpoints

- Overall response rate
- Overall survival
- Time to response and duration of response
- Time to progression and time to next therapy
- Changes in health-related quality of life (HRQL) measures
- Reduction in tumor size
- Improvement in ECOG Performance status
- Incidence and severity of adverse events, serious adverse events and other safety parameters including frequency of transfusions, development of Human Anti-Human Antibodies (HAHA), incidence of 3 and 4 infections, and myelosuppression (anemia, neutropenia, and thrombocytopenia)

- Changes in clinical laboratory values
- Quantitative assessments of IgG, IgA, IgM
- Plasma ofatumumab concentrations
- B-cell monitoring ($CD19^+$, $CD20^+$)

KNOWN AND EXPLORATORY PROGNOSTIC MARKERS CORRELATING WITH RESPONSE

- Baseline FLIPI
- Baseline Absolute Lymphocyte Count (ALC)
- FcR gamma 3
- IgVH gene rearrangement

Text changed to:

Secondary Endpoints

- Overall response rate
- Overall survival
- Time to response and duration of response
- Time to progression and time to next therapy
- Changes in health-related quality of life (HRQL) measures
- Reduction in tumor size
- Improvement in ECOG Performance status
- Incidence and severity of adverse events, serious adverse events and other safety parameters including frequency of transfusions, development of Human Anti-Human Antibodies (HAHA), incidence of 3 and 4 infections, and myelosuppression (anemia, neutropenia, and thrombocytopenia)
- **Overall response rate to optional ofatumumab monotherapy in patients in Arm B who progress during or following single-agent bendamustine**
- Changes in clinical laboratory values
- Quantitative assessments of IgG, IgA, IgM
- Plasma ofatumumab concentrations
- B-cell monitoring ($CD19^+$, $CD20^+$)

KNOWN AND EXPLORATORY PROGNOSTIC MARKERS CORRELATING WITH RESPONSE

- Baseline FLIPI (FLIPI-1 and FLIPI-2)
- Baseline Absolute Lymphocyte Count (ALC)

- FcR gamma 3

Section 3.2.2: Ofatumumab Dosing

Original text:

The ofatumumab dose in this study, 1000 mg, was selected based on several considerations: preclinical data with ofatumumab and clinical population pharmacokinetic modelling and simulation; prior clinical experience with ofatumumab (Study Hx-CD20-001 [Hagenbeek, 2008]); ongoing clinical experience with ofatumumab (Studies Hx-CD20-405 and Hx-CD20-409); and prior clinical experience with rituximab. The proposed schedule is Day 1 of each 21-day or 28-day cycle, depending upon the IDMC dose recommendation for Stage 2 of the study (Section 3.1.3).

Preclinical data suggest that ofatumumab plasma concentrations >10 μg/mL are sufficient to suppress peripheral B-cell recovery in cynomolgus monkeys as well as to suppress tumor cell growth in Daudi tumor-bearing SCID mice [Bleeker, 2008]. SCID mice previously inoculated with Daudi B-cells received ofatumumab at 0.5 and 50 mg/kg and were observed for tumor growth. Tumor growth was delayed 3-4 weeks after ofatumumab administration, with a greater duration of tumor growth inhibition at the higher dose level. Acceleration of tumor growth was observed at the timepoint at which ofatumumab concentrations had dropped below 0.4 μg/mL.

In the Bleeker study, cynomolgus monkeys received ofatumumab at three dose levels: 1.25, 6.25, or 12.5 mg daily for four consecutive days (cumulative doses 5, 25, or 50 mg/kg). A profound B-cell depletion was induced both peripherally and in the lymph nodes, with a longer time to recovery at higher dose levels. Ofatumumab concentrations above 50 μg/mL were sufficient for complete B-cell depletion. Recovery of $CD20^+$ cells in peripheral blood and lymph nodes was detected when plasma ofatumumab concentrations had dropped below 5-10 μg/mL. Thus, a potential ~~clinical~~ target in developing ofatumumab dosing regimens is prolonged maintenance of plasma concentrations >10 μg/mL.

Pharmacokinetic data from the Phase I study in subjects with relapsed or refractory follicular lymphoma (FL) (Study Hx-CD20-001) were analyzed using a two-compartment model with a decrease in clearance after the first dose and assuming a stepped-rate infusion using a nonlinear mixed-effects modeling approach (NONMEM). The resulting model was used to simulate concentration-time data for 500 subjects receiving ofatumumab infusions at 1000 mg on the first day of each 21-day or 28-day cycle for a total of six cycles. Based on the simulations, the probability of maintaining plasma ofatumumab concentrations >10 μg/mL was high with both dosing schedules. With a 21-day cycle length, the probability of maintaining Cp >10 μg/mL was >90% after the first cycle and >95% throughout the remainder of the six-cycle dosing period and for four weeks after the last dose; the probability of Cp >10 μg/mL was approximately 89% at eight weeks after the last dose. With a 28-day cycle length, the probability of maintaining Cp >10 μg/mL was 84% after the first cycle and >95% throughout the remainder of the six-cycle dosing period and for four weeks after the last dose; the probability of Cp >10 μg/mL was approximately 85% at eight weeks after the last dose. Thus, a dosing schedule of 1000 mg infusions on Day 1 of each 21-day or 28-day cycle for ~~six cycles~~ is expected to achieve prolonged maintenance of plasma concentrations >10 μg/mL in a high proportion of subjects with follicular lymphoma.

Prior clinical experience in a Phase I trial of ofatumumab in subjects with relapsed or refractory FL suggests that four weekly infusions of 300 mg to 1000 mg are effective. [Study Hx-CD20-001; Hagenbeek, 2008] Responses were observed in all four dose groups [(300 mg: 5 of 8 subjects (63%); 500 mg: 3 of 10 subjects (30%); 700 mg: 2 of 10 subjects (20%); and 1000 mg: 5 of 10 subjects (50%)]. Thus, a regimen using ~~six~~ 1000 mg doses of ofatumumab at 21-day or 28-day intervals is expected to be effective.

There was no apparent difference in the severity and number of adverse events between patients with FL receiving ofatumumab at doses ranging from 300 mg to 1000 mg, including full ofatumumab doses at first infusion [Study Hx-CD20-001]. Thus, the use of a full ofatumumab dose (i.e., 1000 mg) at first infusion is proposed in this study.

In ongoing studies, 1000 mg of ofatumumab has been administered weekly for seven weeks after an initial infusion of 300 mg in subjects with FL refractory to rituximab in combination with chemotherapy (Study Hx-CD20-405) and administered every three weeks after an initial infusion of 300 mg in combination with CHOP for a total of six cycles in subjects with previously untreated FL (Study Hx-CD20-409). Although no efficacy results are currently available, no major safety issues have been observed to date [OFATUMUMAB Investigator Brochure, 2009].

Prior clinical experience with rituximab suggests that prolonged or maintenance administration schedules enhance response duration in subjects with NHL. [reviewed in Collins-Burow, 2007; Ghielmini, 2004; Cersosimo, 2003]. The proposed ~~six-cycle~~ dosing schedule with doses at 21-day or 28-day intervals increases the duration of ofatumumab exposure, which should maintain chemosensitization of FL to concomitant chemotherapy while enhancing response duration.

Text changed to:

The ofatumumab dose in this study, 1000 mg, was selected based on several considerations: preclinical data with ofatumumab and clinical population pharmacokinetic modelling and simulation; prior clinical experience with ofatumumab (Study Hx-CD20-001 [Hagenbeek, 2008]); ongoing clinical experience with ofatumumab (Studies Hx-CD20-405 and Hx-CD20-409); and prior clinical experience with rituximab.

A total of 12 doses of ofatumumab will be given in Arm A. Ofatumumab will be given on day 1 of each cycle of bendamustine as long as patients in Arm A receive bendamustine (up to 8 cycles). Once patients in Arm A complete bendamustine therapy, additional doses of ofatumumab will be given monthly for a total of 12 ofatumumab doses.

Preclinical data suggest that ofatumumab plasma concentrations >10 μg/mL are sufficient to suppress peripheral B-cell recovery in cynomolgus monkeys as well as to suppress tumor cell growth in Daudi tumor-bearing SCID mice [Bleeker, 2008]. SCID mice previously inoculated with Daudi B-cells received ofatumumab at 0.5 and 50 mg/kg and were observed for tumor growth. Tumor growth was delayed 3-4 weeks after ofatumumab administration, with a greater duration of tumor growth inhibition at the higher dose level. Acceleration of tumor growth was observed at the timepoint at which ofatumumab concentrations had dropped below 0.4 μg/mL.

In the Bleeker study, cynomolgus monkeys received ofatumumab at three dose levels: 1.25, 6.25, or 12.5 mg daily for four consecutive days (cumulative doses 5, 25, or 50 mg/kg). A

profound B-cell depletion was induced both peripherally and in the lymph nodes, with a longer time to recovery at higher dose levels. Ofatumumab concentrations above 50 μg/mL were sufficient for complete B-cell depletion. Recovery of $CD20^+$ cells in peripheral blood and lymph nodes was detected when plasma ofatumumab concentrations had dropped below 5-10 μg/mL. Thus, a potential target in developing ofatumumab dosing regimens is prolonged maintenance of plasma concentrations >10 μg/mL.

Pharmacokinetic data from the Phase I study in subjects with relapsed or refractory follicular lymphoma (FL) (Study Hx-CD20-001) were analyzed using a two-compartment model with a decrease in clearance after the first dose and assuming a stepped-rate infusion using a nonlinear mixed-effects modeling approach (NONMEM). The resulting model was used to simulate concentration-time data for 500 subjects receiving ofatumumab infusions at 1000 mg on the first day of each 21-day or 28-day cycle for a total of six cycles. Based on the simulations, the probability of maintaining plasma ofatumumab concentrations >10 μg/mL was high with both dosing schedules. With a 21-day cycle length, the probability of maintaining Cp >10 μg/mL was >90% after the first cycle and >95% throughout the remainder of the six-cycle dosing period and for four weeks after the last dose; the probability of Cp >10 μg/mL was approximately 89% at eight weeks after the last dose. With a 28-day cycle length, the probability of maintaining Cp >10 μg/mL was 84% after the first cycle and >95% throughout the remainder of the six-cycle dosing period and for four weeks after the last dose; the probability of Cp >10 μg/mL was approximately 85% at eight weeks after the last dose. Thus, a dosing schedule of 1000 mg infusions on Day 1 of each 21-day or 28-day cycle for **12 doses** is expected to achieve prolonged maintenance of plasma concentrations >10 μg/mL in a high proportion of subjects with follicular lymphoma.

Prior clinical experience in a Phase I trial of ofatumumab in subjects with relapsed or refractory FL suggests that four weekly infusions of 300 mg to 1000 mg are effective. [Study Hx-CD20-001; Hagenbeek, 2008] Responses were observed in all four dose groups (300 mg: 5 of 8 subjects (63%); 500 mg: 3 of 10 subjects (30%); 700 mg: 2 of 10 subjects (20%); and 1000 mg: 5 of 10 subjects (50%). Thus, a regimen using **twelve** 1000 mg doses of ofatumumab at 21-day or 28-day intervals is expected to be effective.

There was no apparent difference in the severity and number of adverse events between patients with FL receiving ofatumumab at doses ranging from 300 mg to 1000 mg, including full ofatumumab doses at first infusion [Hagenbeek, 2008]. Thus, the use of a full ofatumumab dose (i.e., 1000 mg) at first infusion is proposed in this study.

In ongoing **studies in subjects with FL**, repeated doses of 500 mg or 1000 mg of ofatumumab have been administered. **In Study Hx-CD20-405, ofatumumab was administered at 500 mg or 1000 mg** weekly for seven weeks after an initial infusion of 300 mg in subjects with FL refractory to rituximab in combination with chemotherapy; in **Study Hx-CD20-409, ofatumumab doses of 500 mg** or 1000 mg were administered every three weeks after an initial infusion of 300 mg in combination with CHOP for a total of six cycles in subjects with previously untreated FL**. In these two studies, there were no unexpected safety findings reported during treatment and within 30 days of last infusion. The results from these studies suggest that administration of 1000 mg at 21- or 28-day intervals is expected to be well tolerated.**

Prior clinical experience with rituximab suggests that prolonged or maintenance administration schedules enhance response duration in subjects with NHL. [reviewed in Collins-Burow, 2007; **Ghielmini, 2004**; Cersosimo, 2003]. **Prior clinical experience with ofatumumab demonstrated longer median duration of response with the addition of four infusions at four-week intervals after the end of weekly ofatumumab treatment in subjects with fludarabine-refractory CLL (Study Hx-CD20-406). The proposed regimen of twelve ofatumumab six-cycle dosing schedule with doses administered**. The proposed **ofatumumab regimen of 12 doses administered** at 21-day or 28-day intervals increases the duration of ofatumumab exposure, which should maintain chemosensitization of FL to concomitant chemotherapy while enhancing response duration.

OFATUMUMAB MONOTHERAPY FOR SUBJECTS WHO PROGRESS IN ARM B

Subjects who progress during or after therapy in Arm B (bendamustine alone) will be offered ofatumumab monotherapy. Data regarding ofatumumab monotherapy in this population were obtained in Study Hx-CD20-405, in which subjects with rituximab-refractory FL were randomized to single agent ofatumumab at 500 mg or 1000 mg weekly for 7 doses after a 300 mg initial dose (total of 8 doses). The response rate was approximately 10%, and median progression-free survival (PFS) was 6 months, with no difference between the dose groups. Experience in CLL indicates that increasing the dose intensity of rituximab was able to mprove the overall response rate significantly from 10-15% to 45% (add references); in addition, ofatumumab at a dose of 2000 mg showed significant clinical activity with an acceptable safety profile in subjects with fludarabine-refractory CLL in Study Hx-CD20-406. Therefore, it is reasonable to examine the 2000 mg dose in refractory FL.

The optimal duration of therapy in this setting is unclear. Study Hx-CD20-406 administered eight weekly doses of ofatumumab 2000 mg (first dose 300 mg) followed by four monthly doses of 2000 mg; however, the standard length of weekly rituximab therapy in FL is four weeks, and there are no convincing data that increasing the number of weekly rituximab infusions from 4 to 8 is of benefit.

The rituximab-refractory FL population in this study may have more disease (and thus, faster clearance) and shorter PFS following four weeks of ofatumumab monotherapy than subjects with rituximab-sensitive FL. Thus, more frequent administration may be necessary for extended dosing in this refractory population, similar to the subjects with fludarabine-refractory CLL in Study Hx-CD20-406, who received monthly extended doses.

Thus, a regimen of 2000 mg ofatumumab for four weekly doses followed by 2000 mg ofatumumab every 4 weeks for four additional doses (for a total of 8 doses) will be offered to the subjects in Arm B who have progressive disease during or after bendamustine monotherapy.

Section 4.1: Number of Subjects

Original text:

Subjects who meet all the following inclusion and exclusion criteria will be eligible for enrollment into the study. Approximately ~~296~~ subjects will be screened to randomize ~~266~~ subjects. See Section 8.2 for further details on assumptions for subject numbers.

Text changed to:

Subjects who meet all the following inclusion and exclusion criteria will be eligible for enrollment into the study. Approximately **376** subjects will be screened to randomize **338** subjects. See Section 8.2 for further details on assumptions for subject numbers.

Rationale for change:

Increased study power from 80% to 90%.

Section 4.3: Exclusion Criteria

Original text:

- Previous autologous stem cell transplant, ~~fludaranine~~ therapy, or Radioimmunotherapy in the past 12 months

Text changed to:

- Exclusion criterion 3. Previous autologous stem cell transplant, **fludarabine** therapy, or radioimmunotherapy in the past 12 months
- Exclusion criterion 7. Treatment with anti-CD20 monoclonal antibody within 3 months of randomization
- Exclusion criterion 14. Positive serology for Hepatitis B (HB) defined as a positive test for HBsAg. In addition, if negative for HBsAg but HBcAb positive (regardless of HBsAb status), a HB DNA test will be performed and if positive the subject will be excluded.**
    - Treatment with anti-CD20 monoclonal antibody or with alemtuzumab within 3 months of randomization
    - ****Subjects can participate in the study if in the opinion of the investigator and medical monitor it is thought not to affect the subject's safety, the conduct of the study or the interpretation of the data.***
    - ***** If HBV DNA is negative, subject may be included but must undergo HBV DNA monitoring (see Section 6.5.7). Prophylactic antiviral therapy may be initiated at the discretion of the investigator.***

Section 5.1.1: Ofatumumab

Original text:

Ofatumumab will be infused intravenously on day 1 (1000 mg) of each cycle~~, followed by five more infusions of 1000 mg every 21 or 28 days. Subjects developing progressive disease in the bendamustine monotherapy arm will have the option to receive ofatumumab 1000 mg once weekly for a maximum of eight infusions. This treatment option will be available within 120 days following diagnosis of progressive disease.~~

Text changed to:

In Arm A, ofatumumab 1000 mg will be given on day 1 of each cycle of bendamustine as long as patients in Arm A receive bendamustine. Once patients in Arm A complete bendamustine therapy, the remaining doses of ofatumumab will be given monthly until

all 12 doses have been administered. A total of 12 ofatumumab infusion will be administered in Arm A regardless of the number of ofatumumab and bendamustine cycles completed.

Subjects developing progressive disease in the bendamustine monotherapy arm (Arm B) will have the option to receive ofatumumab. Subjects who choose this option will receive ofatumumab 2000 mg once a week for 4 infusions followed by an additional ofatumumab (2000 mg) infusions once every month for 8 doses (total: 12 doses). Patients in Arm B who choose this option must begin ofatumumab therapy within 120 days following diagnosis of progressive disease, which can occur at any time during treatment or follow-up.

Rational for change:

To reflect updated ofatumumab schedule and randomization post PD.

Section 5.1.2: Bendamustine

Original text:

Bendamustine (IV) is available as a single-use vial containing 100 mg of bendamustine HCl as lyophilized powder. In the monotherapy arm, the bendamustine dose is 120 mg/m^2, given on days 1 and 2, every 21 days for ~~6~~ cycles. In the experimental arm, the bendamustine dose is 90 mg/m^2, given on days 1 and 2, every 21 days for ~~6~~ cycles. Investigators will follow the label dose reduction schedule if subjects require lower doses as they advance through treatment. The initial dose of bendamustine in Arm A may be lowered on recommendation of the IDMC after evaluation of data from the dose confirmation cohort (up to the first 40 patients). Detailed instructions for dose reduction and subsequent dose reductions will be in the IDMC charter and in Section 9.7

Bendamustine may be initiated within 1 day of scheduled start for logistical reasons. The start of Cycles 2-~~6~~ may be delayed due to toxicity by up to 2 weeks for medical reasons at the investigator's discretion. If the subject is medically unable to receive a subsequent cycle of treatment after 2 weeks' delay, a decision will be made about whether the subject will withdraw from treatment. Please see Section 5.1.2.1.

Text changed to:

Bendamustine (IV) is available as a single-use vial containing 100 mg of bendamustine HCl as lyophilized powder. In the monotherapy arm, the bendamustine dose is 120 mg/m^2, given on days 1 and 2, every 21 days for **up to 8** cycles. In the experimental arm, the bendamustine dose is 90 mg/m^2, given on days 1 and 2, every 21 days for up to **8** cycles. Investigators will follow the label dose reduction schedule if subjects require lower doses as they advance through treatment. The initial cycle **length and** dose of bendamustine in Arm A may be lowered on recommendation of the IDMC after evaluation of data from the dose confirmation cohort**s** (up to the first 40 patients). Detailed instructions for dose reduction and subsequent dose reductions will be in the IDMC charter and in Section 9.7

Bendamustine may be initiated within 1 day of scheduled start for logistical reasons. The start of Cycles 2-**8** may be delayed due to toxicity by up to 2 weeks for medical reasons at the investigator's discretion. If the subject is medically unable to receive a subsequent cycle of treatment after 2 weeks' delay, a decision will be made about whether the subject will withdraw from treatment. Please see Section 5.1.2.1.

Rationale for changes:

Reflects changes to number of cycles from 6 to 8.

Section 5.1.2.1: Bendamustine Dose Reduction

Original text:

The dose of bendamustine will be reduced if, with any cycle, a subject develops grade 4 hematologic or grade 3/4 non-hematologic toxicities, according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version ~~3.0~~ [NCI-CTCAE, ~~2006~~]. This labeled dose reduction will be followed for ~~both arms of the study, See Table 4~~ [TREANDA Prescribing Information, 2007].

Toxicities must be resolved to grade 1 or baseline before beginning the next cycle. Absolute neutrophil count (ANC) must have recovered to at least 1,000 cells/mm^3 (1.0 x 10^9 cells/L) and platelets to at least 75,000 cells/mm^3 (75 x 10^9 cells/L) by the start of the next cycle.

If continued toxicities occur beyond reasonable delay for recovery when subjects are ~~dosed with 60 mg/m^2 of bendamustine~~ in either arm, study treatment will be discontinued (See Table 4). Subjects in Arm A will stop both ofatumumab and bendamustine and will enter follow up as described in Appendix 1 and Appendix 2.

TABLE 4 BENDAMUSTINE DOSE REDUCTION SCHEDULE

Bendamustine Dose and Schedule	If Grade 4 Hematologic Toxicity		If Grades 3,4 Nonhematologic Toxicity	
	Dose	Schedule	Dose	Schedule
120 mg/m^2, days 1,2 every 21 days	90 mg/m^2	Days 1,2 every 21 days	90 mg/m^2	Days 1,2 every 21 days
90 mg/m^2, days 1,2 every 21 days	60 mg/m^2	Days 1,2 every 21 days	60 mg/m^2	Days 1,2 every 21 days
60 mg/m^2, days 1,2 every 21 days	Discontinue treatment	Discontinue treatment	Discontinue treatment	Discontinue treatment

General Dosing Considerations for ~~both arms~~:

Delay treatment for Grade 4 hematologic toxicity or clinically significant ≥Grade 2 non-hematologic toxicity

Toxicities must recover to Grade 1 or baseline before the next administration of treatment. If recovery is not met within 2 weeks after the prescribed start of the treatment cycle (i.e., after a 2 week delay), a decision will be made about continuation in the study.

If the IDMC decides to reduce the starting dose of bendamustine (in Arm A) from 90 mg/m^2, Days 1,2; every 21 days to a lower dose or longer treatment cycle, then the dose and dose reduction schedule found in the IDMC charter will be followed for the remainder of the study. See Section 9.7 for details on the IDMC.

Text changed to:

The dose of bendamustine will be reduced if, with any cycle, a subject develops grade 4 hematologic or grade 3/4 non-hematologic toxicities, according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE) version **4.0** [NCI-CTCAE v4, **2009**]. This labelled dose reduction will be followed for **bendamustine in Arm B** of the study, See Table **5** [TREANDA Prescribing Information, 2007]. **Arm A will follow the bendamustine dose reduction described in Table 4.**

Toxicities must be resolved to grade 1 or baseline before beginning the next cycle. Absolute neutrophil count (ANC) must have recovered to at least 1,000 cells/mm^3 (1.0 x 10^9 cells/L) and platelets to at least 75,000 cells/mm^3 (75 x 10^9 cells/L) by the start of the next cycle.

If continued toxicities occur beyond reasonable delay for recovery**, study treatment will be discontinued (See Table 4 and Table 5). In this event, subjects in Arm B will continue to come to the clinic for scheduled visits and CT scans (to complete all scheduled visits and CT scan Days 84, 168, 252) and subjects in Arm A will stop bendamustine and will continue to complete 12 doses of ofatumumab or enter follow-up if the 12 doses of ofatumumab are completed, as described in Appendix 1 and Appendix** 2**.**

TABLE 4 BENDAMUSTINE DOSE REDUCTION SCHEDULE FOR ARM A

Bendamustine Dose and Schedule	If Grade 4 Hematologic Toxicity		If Grades 3,4 Nonhematologic Toxicity	
	Dose	Schedule	Dose	Schedule
90 mg/m^2, days 1,2 every 21 days	90 mg/m^2	Days 1,2 every 28 days	90 mg/m^2	Days 1,2 every 28 days
90 mg/m^2, days 1,2 every 28 days	70 mg/m^2	Days 1,2 every 28 days	70 mg/m^2	Days 1,2 every 28 days
70 mg/m^2, days 1,2 every 28 days	Discontinue treatment	Discontinue treatment	Discontinue treatment	Discontinue treatment

TABLE 5 BENDAMUSTINE DOSE REDUCTION SCHEDULE FOR ARM B

Bendamustine Dose and Schedule	If Grade 4 Hematologic Toxicity		If Grades 3,4 Nonhematologic Toxicity	
	Dose	Schedule	Dose	Schedule
120 mg/m^2, days 1,2 every 21 days	90 mg/m^2	Days 1,2 every 21 days	90 mg/m^2	Days 1,2 every 21 days
90 mg/m^2, days 1,2 every 21 days	60 mg/m^2	Days 1,2 every 21 days	60 mg/m^2	Days 1,2 every 21 days
60 mg/m^2, days 1,2 every 21 days	Discontinue treatment	Discontinue treatment	Discontinue treatment	Discontinue treatment

General Dosing Considerations for **Arm A and Arm B:**

- Delay treatment for Grade 4 hematologic toxicity or clinically significant ≥Grade 3 non-hematologic toxicity
- Toxicities must recover to Grade 1 or baseline before the next administration of treatment. If recovery is not met within 2 weeks after the prescribed start of the treatment cycle (i.e., after a 2 week delay), a decision will be made about continuation in the study.

If the IDMC decides to **change the cycle length in Arm A from q21 days to q28 days or** reduce the starting dose of bendamustine (in Arm A) from 90 mg/m^2, Days 1,2; every 21 days to a lower dose or longer treatment cycle, then the dose and dose reduction schedule found in the IDMC charter will be followed for the remainder of the study. See Section 9.7 for details on the IDMC.

Rationale for change:

To clarify that this bendamustine dose reduction schedule should be followed for bendamustine dose reductions that occur in Arm A and Arm B. Also updates the remit of the IDMC to first alter cycle length then consider altering starting bendamustine dose.

Section 6.1.12: Lymph Node and Organ Examination

Original text:

A physical lymph node and organ (spleen and liver) examination will be performed at screening ~~and throughout the trial as part of physical examination.~~

~~Lymph nodes evaluation requires physical exam recording the diameter in two planes of the largest palpable node in each of the following sites: cervical, axillary, supraclavicular, inguinal and femoral.~~ Lymphadenopathy is defined as lymph nodes with the largest diameter ≥ 1.5 cm.

Original text:

A complete physical lymph node and organ (spleen and liver) examination will be performed at screening.

Lymphadenopathy is defined as lymph nodes with the largest diameter ≥ 1.5 cm.

Liver and spleen size is assessed by physical exam and documented as 'cm' below the costal margin.

Section 6.1.13: Pre-treatment Computed Tomography (CT) Scans

Original text:

All subjects must have a CT-scan with contrast of the thorax, abdomen, and pelvis performed during screening. This will be considered the baseline, CT scan.

Text changed to:

All subjects must have a CT-scan with contrast of the thorax, abdomen, and pelvis performed during screening **if a CT scan was not done within 1 month prior to randomization. The copy of the CT scan must be adequate to allow comparison to subsequent CT scans for response assessment.** This will be considered the baseline CT scan.

Rationale for change:

We will now allow a CT scan done within 1 month prior to randomization as the baseline CT scan.

Section 6.1.2: Disease Characteristics and Medical History

Original text:

- Follicular Lymphoma Prognostic Index Score (FLIPI) at screening

Text changed to:

- Follicular Lymphoma Prognostic Index Score at screening **(FLIPI-1, FLIPI-2)**

Section 6.2.2: CT Scans

Original text:

All subjects must have a CT scan performed before Day 1 of study. Baseline CT scans will be done during the screening period according to the defined standard.

~~All subjects must have a CT scan performed within 10 days of both Visit 10 (Day 84) and Visit 16 (Day 168) during the treatment period (for both arms) and~~ during follow-up visits, or until initiation of alternative indolent lymphoma treatment, See Appendix 1.

Text changed to:

All subjects must have a CT scan performed before Day 1 of study. Baseline CT scans will be done during the screening period according to the defined standard**; however, a CT scan done within 1 month prior to randomization will be accepted as the baseline CT scan if images (which are sufficient for comparison to subsequent CT scans for response assessment) are provided.**

All subjects must have a CT scan **performed within 3 days of Days 84, 168, and 252 post-randomization, for both arms. Subjects must come to the clinic for all scheduled visits regardless of dose delays. In the event subjects cannot complete 8 cycles of therapy then subjects must come to the clinic for all scheduled visits. Follow-up visits will begin 3 months after Day 252, for both arms and continue** during follow-up visits, or until initiation of alternative indolent lymphoma treatment or **WD**, See Appendix 1.

Rationale for changes:

To accommodate ofatumumab schedule and administration of B up to 8 cycles.

Section 6.2.4.5: Relapsed Disease (after CR)/Progressive Disease (after PR, SD)

Original text:

Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is only assessable (e.g., pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative.

Text changed to:

Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. **Because extranodal disease is uncommon in follicular lymphoma and can be difficult to measure accurately after treatment, measurable extranodal disease is considered a nontarget lesion.** For these recommendations, the spleen is considered nodal disease. Disease that is only assessable (e.g., pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative.

Section 6.3.2: Peripheral Blood Sampling for Hematology and Biochemistry

Original text:

Blood samples will be drawn for analysis inclusive but not limited to the following parameters per Appendix 2 and Appendix 3.

Text changed to:

Blood samples will be drawn for analysis inclusive but not limited to the following parameters per Appendix 2 and Appendix 3.

- Hepatitis B (HBV) and Hepatitis C (HCV) at screening
- For subjects that are HBsAg negative, HBcAb positive and HBV DNA negative (see Section 4.3) blood samples will be collected for monthly HBV DNA testing on day 1 of each cycle depending on the number of cycles administered and during FU at the 1M, 3M and 6M post drug visit

Section 6.5.7: Time Frequency of Detecting AEs and SAEs

Original text:

From the time a subject consents to participate in and completes the study (See Section 4.4), all SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to GSK concomitant medication, will be reported promptly to GSK as indicated in Table 7.

SAEs will not be reported after subsequent anti-NHL therapy is initiated.

Specific attention will be paid to monitor infusion reactions, tumor lysis syndrome, infections and progressive multifocal leukoencephalopathy (PML) (please refer to the SPM for more detail).

If a subject converts to HBV DNA positive during the study, Hepatitis B treatment may be initiated by the site investigator after consultation with the GSK medical monitor.

Text changed to:

From the time a subject consents to participate in and completes the study (See Section 4.4), all SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to GSK concomitant medication, will be reported promptly to GSK **as indicated in Table** 7.

SAEs will not be reported after subsequent anti-NHL therapy is initiated.

Specific attention will be paid to monitor infusion reactions, tumor lysis syndrome, infections and progressive multifocal leukoencephalopathy (PML) (please refer to the SPM for more detail).

Subjects that are HBsAG negative, HBcAb positive and HBV DNA negative may be included in the study but must undergo HBV DNA monitoring. Prophylactic antiviral therapy may be initiated at the discretion of the investigator. If a subjects' HBV DNA becomes positive during the study, the investigator should manage the clinical situation as per the standard of care of that institution, and the GSK medical monitor should be notified. The risks and benefits of continuing ofatumumab or discontinuing ofatumumab should be discussed with the medical monitor before appropriate treatment decisions are made for that individual subject.

Rationale for change: Hepatitis B reactivation may be associated with anti-CD20 mAb infusion.

Section 6.7: Pharmacokinetics (PK)

Original text:

Blood samples will be collected from subjects receiving ofatumumab and bendamustine combination therapy predose and ~~0.5~~ h after the end of the ofatumumab infusion and prior to bendamustine administration on Day 2 in treatment Cycle 1 and Cycle 4, if bendamustine is administered on Days 2 and 3 in Cycle 1 or Cycle 4, an additional sample should be collected prior to bendamustine administration on Day 3. In addition, predose samples will be collected prior to ofatumumab administration at Cycles 2, 3, 5, and 6. Samples will also be collected at 1, 3, and 6 months post-treatment. The actual date and time of each sample collection will be recorded in the eCRF.

Table 7 provides the pharmacokinetic sample collection schedule.

TABLE 7 OFATUMUMAB PHARMACOKINETIC SAMPLE COLLECTION SCHEDULE (FOR SUBJECTS IN THE OFATUMUMAB-BENDAMUSTINE ARM ONLY)

Cycle	Cycle Day	Sampling time relative to ofatumumab infusion
1	1	Predose, 0.5 h post-end of infusion (EOI)
1	2	Prior to bendamustine administration
1	3	Prior to bendamustine administration[1]
2	1	Predose
3	1	Predose
4	1	Predose, 0.5 h post-EOI
4	2	Prior to bendamustine administration
4	3	Prior to bendamustine administration[1]
5	1	Predose
6	1	Predose
		1 month after last dose[2,3]
		3 months after last dose[2,3]
		6 months after last dose[2,3]

1. Collect sample only if subject receives bendamustine on Day 3 of the cycle
2. Collect sample at any convenient time on study day.
3. Collect sample relative to last dose of ofatumumab regardless of number of cycles~~.~~

Sample collection, processing, and shipping instructions are provided in the study procedures manual.

Text changed to:

Blood samples will be collected from subjects receiving ofatumumab and bendamustine combination therapy predose, **at the end of the ofatumumab infusion (immediately prior to stopping the infusion,** and **1** h after the end of the ofatumumab infusion and prior to bendamustine administration on Day 2 in treatment Cycle 1, Cycle 4, **and Cycle 7; if bendamustine is not administered in Cycle 4 or Cycle 7, the Day 2 ofatumumab pharmacokinetic sample may be omitted.** If bendamustine is administered on Days 2 and 3 in Cycle 1, Cycle 4 or Cycle 7, an additional sample should be collected prior to bendamustine administration on Day 3. In addition, predose samples will be collected prior to ofatumumab administration at Cycles 2, 3, 5, 6, **8,9, 10, and 11. Samples will be collected prior to and at the end of the ofatumumab infusion at dose 12.** Samples will also be collected at 1, 3, and 6 months post-treatment. Samples will also be collected at 1, 3, and 6 months post-treatment. The actual date and time of each sample collection will be recorded in the eCRF.

Table 7 provides the pharmacokinetic sample collection schedule.

TABLE 7 OFATUMUMAB PHARMACOKINETIC SAMPLE COLLECTION SCHEDULE (FOR SUBJECTS IN THE OFATUMUMAB-BENDAMUSTINE ARM ONLY)

Cycle	Cycle Day	Ofatumumab Dose	Sampling time relative to ofatumumab infusion
1	1	1	Predose, end of infusion (EOI), 1 h post-EOI
1	2		Prior to bendamustine administration
1	3		Prior to bendamustine administration[1]
2	1	2	Predose
3	1	3	Predose
4	1	4	Predose, EOI, 1 h post-EOI
4	2		Prior to bendamustine administration[2]
4	3		Prior to bendamustine administration[1,2]
5	1	5	Predose
6	1	6	Predose
7	1	7	Predose, EOI, 1 h post-EOI
7	2		Prior to bendamustine administration[2]
7	3		Prior to bendamustine administration[1,2]
8	1	8	Predose
		9	Predose
		10	Predose
		11	Predose
		12	Predose, EOI
			1 month after last dose[3,4]
			3 months after last dose[3,4]
			6 months after last dose[3,4]

- **Collect sample only if subject receives bendamustine on Day 3 of the cycle**
- **Collect sample only if bendamustine is administered**
- **Collect sample at any convenient time on study day.**
- **Collect sample relative to last dose of ofatumumab regardless of number of cycles.**

Sample collection, processing, and shipping instructions are provided in the study procedures manual.

Section: 8.2: Study Design Considerations

Original text:

An 'adaptive-like' study design is being implemented for this study to take into consideration the possibility of a dosing-change recommendation after an independent review for safety and tolerability. Primary efficacy and safety analyses will be conducted on the 'final' stage data set. Supplementary efficacy and safety analyses will also be conducted on the cumulative data set if a dosing-change recommendation occurs.

- Stage 1 will consist of the 40 subjects included in the Dose Confirmation Cohort and any additional subjects randomized prior to the implementation of an IDMC recommended dosing change.
- If no IDMC dosing change is implemented, Stage 1 will continue through the remainder of the study and will comprise the final analysis set.
- If an IDMC dosing change is implemented, Stage 2 will begin with subjects randomized thereafter. The sample size and event count will restart at this point. Subjects enrolled in stage 2 will comprise the final analysis set. Analysis of the cumulative set (subjects from Stage 1 and Stage 2) will be supplementary.

Text changed to:

An 'adaptive-like' study design is being implemented for this study to take into consideration the possibility of a dosing-change recommendation after an independent review for safety and tolerability. Primary efficacy and safety analyses will be conducted on the 'final' stage data set. Supplementary efficacy and safety analyses will also be conducted on the cumulative data set if a dosing-change recommendation occurs.

- Stage 1 will consist of the 40 subjects included in the Dose Confirmation Cohort and any additional subjects randomized prior to the implementation of an IDMC recommended dosing change.
- If no IDMC dosing change is implemented, Stage 1 will continue through the remainder of the study and will comprise the final analysis set.
- If an IDMC dosing change is implemented, Stage 2 will begin with subjects randomized thereafter. The sample size and event count will restart at this point. **If no further dosing change is implemented,** subjects enrolled in stage 2 will comprise the final analysis set. Analysis of the cumulative set (subjects from Stage 1 and Stage 2) will be supplementary.
- If an additional IDMC dosing change is implemented, Stage 3 will begin with subjects randomized thereafter. The sample size and event count will restart at this point. Subjects enrolled in stage 3 will comprise the final analysis set. Analysis of the cumulative set (subjects from Stages 1-3) will be supplementary.

Section: 8.2.1: Sample Size Assumptions

Original text:

The primary endpoint is PFS 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

A median PFS for bendamustine is 9 months.

A median PFS for ofatumumab + bendamustine is 13.5 months

A 1:1 stratified randomization scheme

A ~~80%~~ 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 6 subjects per month

Under the above assumptions, approximately ~~192~~ total events from both treatment arms combined are needed for the study to have ~~80%~~ power. With a sample size of ~~238~~ subjects, the duration of the study will be about ~~51~~ months (under H_1) to obtain the ~~192~~ total events. Assuming a dropout rate of 10%, the total sample size randomized for both arms combined will be ~~266~~ subjects, with approximate study duration of ~~56~~ months.

Assuming a screening failure rate of 10%, the total number of subjects screened will be approximately ~~296~~.

As stated, this trial is an event-driven study design with an event-driven sample size of ~~192~~ total events and the final analysis will take place at the time of occurrence of the ~~192nd~~ event. The guideline for the study reaching ~~192~~ total events with respect to previously stated assumptions involve screening of ~~296~~ subjects so as to have ~~266~~ subjects randomized and to have a study duration of about ~~56~~ months from the first day of first subject until the time of the ~~192nd~~ event.

Text changed to:

The primary endpoint is PFS 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
- A median PFS for bendamustine is 9 months.
- A 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 6 subjects per month

Under the above assumptions, approximately **256** total events from both treatment arms combined are needed for the study to have **90%** power. With a sample size of **304** subjects, the duration of the study will be about **6**2 months (under H_1) to obtain the **256** total events. Assuming a dropout rate of 10%, the total sample size randomized for both arms combined will be **338** subjects, with approximate study duration of 68 months.

Assuming a screening failure rate of 10%, the total number of subjects screened will be approximately **376.**

As stated, this trial is an event-driven study design with an event-driven sample size of **256** total events and the final analysis will take place at the time of occurrence of the **256**th event. The guideline for the study reaching **256** total events with respect to previously stated assumptions involve screening of **37**6 subjects so as to have **338** subjects randomized and to have a study duration of about 68 months from the first day of first subject until the time of the **256**th event.

Rationale for change: Reflects increase from 80% to 90% power in study.

Section: 8.2.2: Sample Size Sensitivity

Original text:

The robustness and sensitivity of the above sample size calculation is considered in order to assess the impact on power should the assumed median PFS vary. The following table shows the estimated power for different median values of PFS for ofatumumab + bendamustine. The total number of events is ~~192~~, and the number of subjects is ~~238.~~

TABLE 10 PRIMARY ENDPOINT POWER CALCULATION

Median PFS for Ofatumumab + Bendamustine	Median PFS for Bendamustine	Estimated Power
12	9	~~0.52~~
13	9	~~0.72~~
13.5	9	~~0.80~~
14	9	~~0.86~~
15	9	~~0.93~~

Text changed to:

The robustness and sensitivity of the above sample size calculation is considered in order to assess the impact on power should the assumed median PFS vary. The following table shows the estimated power for different median values of PFS for ofatumumab + bendamustine. The total number of events is **256**, and the number of subjects is **304.**

TABLE 10 PRIMARY ENDPOINT POWER CALCULATION

Median PFS for Ofatumumab + Bendamustine	Median PFS for Bendamustine	Estimated Power
12	9	**0.64**
13	9	**0.83**
13.5	9	**0.90**
14	9	**0.94**
15	9	**0.98**

Rationale for change: Reflects increase from 80% to 90% power in study.

Section: 8.3.1.1: Four populations are defined for the analysis

Original text:

1. The Intent-to-Treat (ITT) Population will include subjects in the final analysis stage who are randomized to the study drugs. This will be the primary population used for all efficacy assessments. In the analyses, subjects will be grouped based on how they are randomized regardless of which treatment they received. The ITT population will also be used for all Patient Reported Outcomes (PRO) analyses.
2. The Safety Population will include subjects in the final analysis stage who receive at least one dose of a study drug. This population will be used for all safety measurements. In the analyses, subjects will be grouped based on the treatment they receive regardless of how they are randomized.
3. The Safety Population (Dose Confirmation Cohort) will include the first 40 subjects who receive at least one dose of study drug. This population will be used to assess the safety and tolerability in the Dose Confirmation Cohort analysis of the study by the IDMC. In the analyses, subjects will be grouped based on the treatment they receive regardless of how they are randomized
4. The Per Protocol (PP) Population will exclude subjects with major protocol deviation that will impact the efficacy outcome. The Per Protocol Population will be used in the primary endpoint analysis to check the robustness of the result when using the ITT population. However, if the number of subjects in the PP population is not more than 10% smaller than the ITT population, the analysis will not be performed.

Text changed to:

1. The Intent-to-Treat (ITT) Population will include subjects in the final analysis stage who are randomized to the study drugs. This will be the primary population used for all efficacy assessments. In the analyses, subjects will be grouped based on how they are randomized regardless of which treatment they received. The ITT population will also be used for all Patient Reported Outcomes (PRO) analyses.
2. The Safety Population will include subjects in the final analysis stage who receive at least one dose of a study drug. This population will be used for all safety measurements. In the analyses, subjects will be grouped based on the treatment they receive regardless of how they are randomized.
3. The Safety Population (Dose Confirmation Cohort) will include the first **20** subjects **in Arm A** who **complete bendamustine therapy or receive at least 3 cycles of bendamustine**. This population will be used to assess the safety and tolerability in the Dose Confirmation Cohort analysis of the study by the IDMC. In the analyses, subjects will be grouped based on the treatment they receive regardless of how they are randomized. **If an additional IDMC review is required, then a second Dose**

Confirmation Cohort will be created to capture the 20 subjects included in the subsequent IDMC review.

4. The Per Protocol (PP) Population will exclude subjects with major protocol deviation that will impact the efficacy outcome. The Per Protocol Population will be used in the primary endpoint analysis to check the robustness of the result when using the ITT population. However, if the number of subjects in the PP population is not more than 10% smaller than the ITT population, the analysis will not be performed.

Section 8.3.3.1: Primary Comparisons of Interest

Original text:

The primary treatment comparison of interest will be ofatumumab + bendamustine vs. bendamustine. This will be based on comparing the overall progression-free survival (PFS) when the total number of events reaches ~~192~~ total events (from both arms) using the ITT population.

Text changed to:

The primary treatment comparison of interest will be ofatumumab + bendamustine vs. bendamustine. This will be based on comparing the overall progression-free survival (PFS) when the total number of events reaches **256** total events (from both arms) using the ITT population.

Rationale for change: Reflects increase from 80% to 90% power in study.

Section 8.3.4: Interim Analysis

Original text:

A safety and tolerability analysis is planned after ~~40~~ subjects have completed ~~6 cycles~~ of treatment ~~and is described in Section 3.1.3~~. If a dosing change is required, an additional review of safety and tolerability may be conducted after ~~20~~ subjects have completed ~~6 cycles~~ of treatment on the new regimen. This process is described in Section 3.1.3 and will be further detailed in a charter for the IDMC.

Text changed to:

A safety and tolerability analysis is planned after **20** subjects have completed **3 cycles (or completion of bendamustine therapy) of treatment in Arm A. If a dosing change is required, an additional review of safety and tolerability may be conducted after 10 subjects in Arm A have completed 3 cycles (or completion of bendamustine therapy) on the new regimen. Available data for Arm B may be provided to the IDMC at the time of their assessments. This process is described in Section 3.1.3 and will be further detailed in a charter for the IDMC.**

Section 8.3.5.2: Safety Evaluation

Original text:

After ~~40~~ subjects have been treated for ~~6 cycles~~, an analysis to assess safety and tolerability will be conducted. A charter will detail the types of analyses, rules for modifying treatment course, and the membership and conduct of the IDMC.

Text changed to:

After **20** subjects have been treated **for 3 cycles (or completion of bendamustine therapy)**, an analysis to assess safety and tolerability will be conducted. A charter will detail the types of analyses, rules for modifying treatment course, and the membership and conduct of the IDMC.

Section 8.3.5.4: Efficacy Analyses

Original text:

[redacted]

Text changed to:

[redacted]

Section 9.7: Independent Data Monitoring Committee (IDMC)

Original text:

An IDMC will be utilized in this study to ensure external objective medical and/or statistical review of safety issues in order to protect the ethical and safety interests of subjects and to protect the scientific validity of the study. The schedule of any planned interim analysis and the analysis plan for IDMC review is described in the in the charter, which is available upon request.

~~Forty subjects (20 per treatment arm)~~ will comprise an initial dose confirmation cohort. The IDMC will ~~compare~~ Arm A (O+B) ~~and Arm B (B)~~ to assess the safety and tolerability of ofatumumab (1000 mg Day 1; q21 days) and bendamustine (90 mg/m^2 Days 1, 2; q21 days). The IDMC will confirm or reject the notion that the Arm A utilizes a safe bendamustine dose. They will base this decision on a rule described in the IDMC charter. ~~This rule will take into account observed toxicities associated with bendamustine monotherapy in Arm B.~~ The IDMC will have the option to decrease the bendamustine dose and/or lengthen the cycle duration from 21 to 28 days in Arm A for improved safety and tolerability.

Text changed to:

An IDMC will be utilized in this study to ensure external objective medical and/or statistical review of safety issues in order to protect the ethical and safety interests of subjects and to protect the scientific validity of the study. The schedule of any planned interim analysis and the analysis plan for IDMC review is described in the charter, which is available upon request.

Twenty subjects in Arm A will comprise an initial dose confirmation cohort. **In addition, available data from Arm B will be provided.** The IDMC will assess Arm A (O+B) **for** the safety and tolerability of ofatumumab (1000 mg Day 1; q21 days) and bendamustine (90

mg/m^2 Days 1, 2; q21 days), **3 cycles (or completion of bendamustine therapy)**. The IDMC will confirm or reject the notion that the Arm A utilizes a safe bendamustine dose. They will base this decision on a rule described in the IDMC charter. The IDMC will have the option to decrease the bendamustine dose and/or lengthen the cycle duration from 21 to 28 days in Arm A for improved safety and tolerability.

STAGE 1:

- **If the safety and tolerability of Arm A is confirmed by the IDMC (Stage 1), the study will continue to enrol until completion in order to compare progression-free survival between Arm A and Arm B.**
- **If the IDMC decides to modify the bendamustine dosing schedule in Arm A, Stage 2 will begin and this modified treatment schedule (bendamustine 90 mg/m^2 Days 1 and 2, every 28 days, up to 8 cycles) will be used in Arm A for the remainder of the study.**

STAGE 2:

a. If an IDMC cycle change is implemented, the sample size and event count will restart at this point, and subjects enrolled in Stage 2 will comprise the final analysis set. Analysis of the cumulative set (subjects from Stage 1 and Stage 2) will be supplementary.

b. If the IDMC modifies the treatment schedule in Arm A, the IDMC will assess the modified treatment schedule (bendamustine 90 mg/m^2 Days 1 and 2, every 28 days, up to 8 cycles) after 10 subjects in Arm A are treated at this schedule for 3 cycles (or until bendamustine completion if less than 3 cycles). If the IDMC confirms the safety of bendamustine 90 mg/m^2 Days 1 and 2, every 28 days, in Arm A then, Stage 2 will proceed without further dose modification in Arm A.

- If the IDMC deems that toxicity remains excessive, the IDMC will have the option to reduce the bendamustine dose in Arm A to 70 mg/m2; Days 1 and 2, every 28 days (up to 8 cycles). This will be Stage 3.

STAGE 3:

- **The IDMC will then assess the modified treatment schedule (bendamustine 70 mg/m^2 Days 1 and 2, every 28 days, up to 8 cycles) after 10 subjects in Arm A are treated at this schedule for 3 cycles (or until completion of bendamustine therapy if less than 3 cycles).**
    - If the IDMC deems that bendamustine 70 mg/m^2 Days 1 and 2, every 28 days, up to 8 cycles in Arm A is safe, then no further dose modification in Arm A will occur.
    - If the IDMC decides that bendamustine 70 mg/m^2 Days 1 and 2, every 28 days, up to 8 cycles, in Arm A is excessively toxic, the IDMC will have the option to close this study.

Rationale for change:

Reflects change to using up to 8 cycles of therapy.

11.10 Appendix 10: General Protocol Changes for Amendment 2 (12-May-2010) from Amendment 1 (dated 16-NOV-2009)

WHERE THE AMENDMENT APPLIES

Amendment 2 is applicable to all study sites.

SUMMARY AND RATIONALE FOR AMENDMENT CHANGES IMPLEMENTED THROUGHOUT AMENDMENT 2

ADMINISTRATIVE CHANGES

Due to administrative changes within GSK, appropriate revisions were made to the Medical Monitor contact information to reflect personnel updates and organizational restructuring.

INITIAL INFUSION FOR OPTIONAL OFATUMUMAB

Subjects in Arm B who choose to receive optional ofatumumab monotherapy will receive ofatumumab 1000 mg for the first dose.

VISIT WINDOWS

On Days 84, 168, 252 (±7 days).

Visit window between cycles specified: ofatumumab and bendamustine must be given consecutively. A visit window of "on or within 7 days after" will be allowed between cycles

In Appendix 3, weekly intervals will be a minimum of 7 days with a ±1 day window around each visit.

CT SCANS

CT scans (contrast imaging of neck (when lesion is palpable), thorax, abdomen, pelvis; may be whole body CT scan or according to SOC). Only in the event when whole body CT scan is not available, then contrast imaging of neck, thorax, abdomen, pelvis, and any areas with new lesions may be done.

COMPLETE REMISSION

Physical exam of spleen and liver will not be part of this response assessment.

PRO

FACT-G was removed since the questions are incorporated into Version 4 of FACT-Lym. FACT-Lym TOI was removed. This is an analysis that combines 2 different PRO questionnaires and does not require a separate questionnaire. Therefore, it was removed.

HACA

Test is done at before initial ofatumumab infusion in Arm A and for subjects that select optional ofatumumab. HACA is considered an exploratory prognostic marker.

PK

Additional samples for subjects that select optional ofatumumab. Reflected in time and events table in Appendix 3 and in Section 6.7.

[redacted]

Time and Events Tables, Appendix 1, Appendix 2, and Appendix 3:

Entire tables were updated. Updated to reflect study changes (HAHA, PK) and to add clarify items such as frequency of pregnancy testing, time windows around CT scans, and time window between cycles.

Major changes include:

In Appendix 1 and Appendix 2: If bendamustine cannot be given on the Day 1, the day of ofatumumab infusion, bendamustine may be administered on Days 2 and 3 of each cycle. In the event the 1st infusion of bendamustine is on Day 2 of a cycle, then PK (see Table 9 for details) and assessments required for Day 1 (except i.e. HAHA, Ig, flow cytometry, etc) will be done on Day 2 and the assessments required for Day 2 will now be done on Day 3.

- Appendix 1:
- 1 month follow-up column added. Provide more clarity than before where it was merely mentioned in a footnote
- Time window changes reflected in table
- Addition of lymphoma disease symptoms when CT scans are done
- Appendix 2:
- Addition of HACA test before the 1st dose of ofatumumab. Will be a prognostic marker
- ß2 microglobulin row added. Provides more clarity than before where it was merely mentioned in a footnote and in the protocol text as being part of the FLIPI-2 prognostic marker
- 1 month follow-up column added. Provides more clarity than before where it was merely mentioned in a footnote
- Frequency of pregnancy testing updated for those with child bearing capacity
- Time windows reflected in table
- PK and HAHA added at withdraw and PD
- Appendix 3:
- Time windows changes reflected in table

- Addition of PK sampling
- Addition of HACA test before the 1st dose of ofatumumab.
- Initial dose of ofatumumab is 1000 mg and not 2000 mg
- Frequency of pregnancy testing updated for those with child bearing capacity
- PK and HAHA added at withdraw and PD

STUDY SCHEMATICS UPDATED TO REFLECT PROTOCOL UPDATES

Figure 2 specifies that PD must be confirmed by an IRR before receiving ofatumumab following PD in Arm B and 1000 mg will be administered as the first ofatumumab monotherapy infusion.

REFERENCES UPDATED

Investigator Brochure update (28 April 2010); Kahl, 2010; Byrd 2001, and Weirda, 2010 references added. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues updated to 4rth edition, 2008.

SPECIFIC PROTOCOL CHANGES FOR AMENDMENT 2 (12-MAY-2010) FROM AMENDMENT 1 (DATED 16-NOV-2009)

LIST OF SPECIFIC CHANGES

Note: deleted language is presented with a ~~strikethrough~~ and added language is printed in **bold**.

EXAMPLE:

Section: Throughout Document

Original text:

~~Patient~~

Text changed to:

Subject

Rationale for Change:

For consistent use of terminology throughout the document. Amended in appropriate document sections.

Section: Sponsor Information Page

Original text:

Medical Monitor Contact Information:
Telephone: [redacted]

Text changed to:

Medical Monitor Contact Information:
Telephone: [redacted]

Section 1.3: Ofatumumab

Additional text:

The pivotal trial Study Hx-CD20-406 in subjects with fludarabine-refractory CLL [refractory to both fludarabine and alemtuzumab (n=59) or refractory to fludarabine and with bulky lymphadenopathy for whom alemtuzumab is not suitable (n=79)] evaluated 300 mg + 7 x 2000 mg for eight weekly doses, followed by four monthly 2000 mg doses. An objective response rate of 58% consisting of partial responses (PR) was achieved in the fludarabine and alemtuzumab refractory group with a median progression-free survival of 5.7 months. Similarly, in the bulky fludarabine refractory group with a similar unmet medical need, an objective response rate of 47% was achieved, including 1 complete response (CR), with all other responses being partial responses (PR). The median PFS in the bulky fludarabine refractory group was 5.9 months. In this study, ofatumumab was generally well tolerated. The most frequently reported adverse events (>15% frequency) were pyrexia, diarrhea, fatigue, cough, neutropenia, anemia and pneumonia. There were no unexpected safety findings [Wierda, 2010]. The results of this pivotal study served as the basis for the grant of accelerated approval by the FDA for ofatumumab (ARZERRA) for the treatment of patients with CLL refractory to fludarabine and alemtuzumab (DR population) in October 2009.

Rationale: To explain the rationale of using 2000 mg ofatumumab for subjects developing progressive disease in the bendamustine monotherapy arm (Arm B)

Deleted text:

~~Only two subject were treated in the 500 mg group.~~

Rationale: deleted repeated information.

Section 2: Objectives

Original Text and Text changed to:

Secondary objectives:

- 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. ALC, FcR gamma 3A, **HACA**)

[redacted]

Section 3.1.1: Screening Phase

Original Text and Text changed to:

- A bone marrow aspirate and biopsy will be required at screening if results are not available from a prior bone marrow aspirate and biopsy performed within 8 weeks prior to randomization. **Results may be provided in the form of a bone marrow biopsy report when a previous aspirate and biopsy are not available as long as the report was based on the biopsy done within 8 weeks prior to randomization.** To confirm that disease has not transformed to a Diffuse Large B-cell Lymphoma, an incisional or excisional lymph node biopsy of accessible adenopathy is highly recommended. In less accessible lymph nodes, 4 to 8 core biopsies are recommended, but not required. If the investigator has clinical suspicion that the protocol candidate has transformed disease, the investigator should not consider that subject for the trial.
- Bone marrow aspirate, biopsy, and lymph node pathology report including details confirming $CD20^+$ tumor status will be sent to GSK along with tissue or slides for central review. Please see SPM for details.
- Blood samples, physical examination, and **whole body** CT imaging **(with contrast imaging of the neck, thorax, abdomen, and pelvis)** ~~(with contrast imaging of thorax, abdomen, and pelvis)~~ will be provided to determine baseline disease and study eligibility
- Rationale: To provide clarity.

Section 3.17: Study Endpoints

Additional Text:

Secondary Endpoints

Known and Exploratory Prognostic markers Correlating with Response

- Baseline FLIPI (FLIPI-1 and FLIPI-2)
- Baseline Absolute Lymphocyte Count (ALC)
- FcR gamma 3A
- Human Anti-Chimeric Antibodies (HACA),

[redacted]

SECTION 3.2.2: OFATUMUMAB DOSING WHEN ADMINISTERED WITH BENDAMUSTINE

Text Added:

An important safety factor of any antibody therapy concerns infusion reaction, particularly following intravenous administration. Both the proportion of patients experiencing infusion reactions to rituximab and the severity of the reactions are higher for the first infusion than for subsequent infusions [Chung, 2008]. Early experience with ofatumumab showed a similar pattern of infusion reactions [Coiffier, 2008; Hagenbeek, 2008], and a first infusion dose of 300 mg was therefore adopted in all studies in the ofatumumab development program to minimise first dose infusion reaction. However, upon further review of the data collected in the phase I/II study of ofatumumab in patients with relapsed or refractory follicular lymphoma grade I-II (Study Hx-CD20-001), no clinically significant differences in the severity or frequency of adverse events were observed. As a result, the median duration of the first infusion and the number of infusion reactions between patients with FL receiving ofatumumab at doses of 300 mg, 500 mg, 700 mg, or 1000 mg, including ofatumumab doses of up to 1000 mg did not differ significantly. [OFATUMUMAB, 2011; Hagenbeek, 2008]. Thus, the use of 1000 mg at first infusion is proposed in study OMB110918.

Rationale: Provides additional rationale for 1000 mg initial infusion. Also clarifies there was little difference between dose cohorts regarding infusion time and infusion reactions upon initial infusion.

Section 3.2.2.1: Ofatumumab monotherapy for subjects who progress in Arm B

Text Added:

Infusion reactions occur more frequently at the initial infusion. Patients with indolent NHL are less likely to have severe infusion toxicity than CLL patients because they do not have circulating peripheral blood tumor cells which react with antibody.

To date, no subjects have received 2000 mg as the initial dose, while subjects with follicular lymphoma received an initial infusion of 1000 mg in Study Hx-CD20-001. Thus, a first dose of 1000 mg will be used in Arm A (Appendix 1, Section 3.1.4) and for subjects that progress on Arm B and select optional ofatumumab (Appendix 3, Section 3.1.6). Study Hx-CD20-001 infused a 2 mg/mL concentration of ofatumumab at an initial rate of 25 mL/hr. Due to the observed tolerability associated with this concentration and rate, Study OMB110918 will infuse ofatumumab (2 mg/mL) at a starting rate of 25 mL/hr for infusions that follow the initial infusion for subjects that select ofatumumab following PD in Arm B (Appendix 3, Section 3.1.6).

Rationale: Clarifies rationale for infusion of 2000 mg (2 mg/mL) at 25 mL/hr.

Section 4.2: Inclusion Criteria

Original Text

Inclusion criteria 1: Indolent lymphoma including grades 1-3a follicular, small lymphocytic, lymphoplasmacytic, and marginal zone lymphoma; stages III-IV, ~~or bulky disease stage II (i.e. as any single mass > 5 cm in any direction) defined according to WHO guidelines [WHO, 2001]~~

Text Changes:

Inclusion criteria 1: Small lymphocytic, lymphoplasmacytic, marginal zone lymphoma, and follicular lymphoma (FL); grades 1, 2 and 3A, defined according to WHO guidelines.

- Rationale: Expands patient population.

Section 4.2: Inclusion Criteria

Inclusion criteria 2: Indolent B-cell NHL that remains stable or unresponsive during or within 6 months of treatment with rituximab or a rituximab-containing regimen (See Section 6.2.5.5):

- Maintaining stable disease or failure to achieve PR to rituximab-based therapy. (CT imaging will support this finding, and will be performed at least ~~30~~ **60**days after the last dose of rituximab-based therapy)
- or,
- disease progression while on rituximab-based therapy (e.g., includes 4 weekly courses of rituximab given at 6-~~week~~ **month** intervals [Hainsworth, 2005])
- or,
- disease progression in subjects with stable disease or better response to rituximab-based therapy <6 months of the last dose of rituximab

Note: Subjects must have received ~~at least 4 infusions of rituximab (either as monotherapy or in combination with any chemotherapy)~~ **a minimum of 4 rituximab infusions as monotherapy or 3 infusions as part of a rituximab-containing combination regimens.**

Rationale: Expands patient population.

Section 4.3: Exclusion Criteria

Original Text and Text Change:

Exclusion criteria 3: Previous autologous stem cell transplant, or fludarabine therapy, or radioimmunotherapy in the past 12 last 6 months

Exclusion criteria 5: High dose steroids ≥ 60 100 mg prednisone/day (or equivalent) for 7 consecutive days, given as concomitant medication, within 3 months of prior to randomization. No more than 10 mg prednisone daily at the time of randomization

Exclusion criteria 7: Treatment with anti-CD20 monoclonal antibody within 3 months of randomization. Prior treatment with anti-CD20 monoclonal antibody, if 1st dose was administered within 60 days prior to randomization. Prior use of any monoclonal antibody (other than anti-CD20) within 3 months prior to randomization.

Exclusion criteria 20: Treatment with anti-CD20 monoclonal antibody within 3 months of randomization

Exclusion criteria 15: Current active liver or biliary disease (subjects with Gilbert's syndrome or asymptomatic gallstones, liver metastases related to indolent NHL or otherwise stable chronic liver disease per investigator assessment)

Exclusion criteria 17: Screening laboratory values:

- platelets < 100 x 10^9/L (unless due to indolent lymphoma involvement of the bone marrow)
- neutrophils < 1.5 x 10^9/L (unless due to indolent lymphoma involvement of the bone marrow)
- Serum creatinine > 1.5 times the institution's upper limit of normal (ULN)**;** subjects with a serum creatinine > 1.5 ULN will be eligible if the calculated creatinine clearance [Cockcroft, 1976] **or** creatinine clearance from a 24-hour urine collection is ≥ 40 mL/min.
- Total bilirubin > 1.5 times ULN (unless due to liver involvement by FL or Gilbert's disease)
- Transaminases > 3 times ULN.

Exclusion criteria 18: Previous treatment or known or suspected hypersensitivity to ofatumumab, bendamustine, or mannitol

Exclusion criteria 21: 21 "as per local acceptable standards"

Rationale: Expands patient population.

For #3, the 12 month interval was overly cautious and would limit population. The original intention of 12 months was to allow for bone marrow recovery. Six months is sufficient for this to occur.

For #5: 30 mg may be administered as part of standard chemotherapy in this population. We should not limit enrollment for those getting standard treatment.

For #7: All of the subjects in this study will have rituximab prior to study entry. A three month interval between last rituximab and first ofatumumab infusion would severely limit accrual. Further evidence from a previous ofatumumab study (Hx-CD20-405) suggested that

the interval between last rituximab and first ofatumumab infusion did not correlate with response or lack of response.

For #20: This criterion repeated #7.

For #15: Clarification.

For #18: There may be subjects with known bendamustine and mannitol sensitivity (per bendamustine product label). Bendamustine vials contain mannitol. We want to limit them into our study to minimize subjects who are hypersensitive to these agents.

For#21: To ensure that local acceptable standards are followed.

Section 4.4: Withdrawal Criteria

- Additional Text:
- HAHA and PK (as indicated in Appendix 2 and Appendix 3)

Rationale: HAHA and PK were added at these time points to determine if HAHA is present and to assess if it potentially interfered with ofatumumab therapy.

- Section 5.1.1: Pre-medication
- Allows this guidance for subjects receiving bendamustine, in addition to those receiving ofatumumab.

Section 5.1.2.1: Ofatumumab Treatment Schedule

- Original Text and Text Change:
- The starting rate of the initial infusion of 1000 mg (Section 3.1.4), ~~or 2000 mg~~ (~~Section 3.1.6~~ ~~and~~ ~~Appendix 3~~) ofatumumab (1.0 mg/mL) should be 12 mL/hour (hr). If no infusion reactions occur the infusion rate should be increased every 30 minutes, to a maximum of 400 mL/hr, according to Table 2. If this schedule is followed, the 1000 mg infusion duration will be approximately 4.5 hours ~~and the 2000 mg infusion duration will be approximately 6.5 hours.~~

Subsequent infusions of ofatumumab

If the previous infusion has been completed without grade ≥ 3 infusion-associated AEs, the subsequent infusion 1000 mg (Section 3.1.4, Appendix 1) or 2000 mg (Section 3.1.6 and Appendix 3) ofatumumab (1.0 mg/mL **or 2.0 mg/mL**) can start at a rate of 25 mL/hr and should be doubled every 30 minutes up to a maximum of 400 mL/hr.

Rationale: 2000 mg dose no longer being used as initial infusion. The 2000 mg dose will be utilized for subsequent infusions if Arm B subjects with PD select optional ofatumumab.

Section 6.2.2: CT Scans

Original Text and Text Change:

Whole body CT scans **(with contrast of the neck (when lesion is palpable), thorax, abdomen, and pelvis)** ~~(with contrast of the thorax, abdomen, and pelvis)~~ will be ~~performed~~ **done** as part of the efficacy evaluation and after treatment has been completed. The scans must be ~~performed~~ **implemented** according to a CT scan manual to be provided to GSK as mentioned in the SPM.

In situations where progressive disease is apparent through physical examination (such as massive lymphadenopathy), only the body area where progressive disease is apparent will need to be scanned to confirm progressive disease.

~~An Independent Radiology Review (IRR) will review the~~ CT scans **will be assessed** according to **an independent review**. The independent review will be described in an independent review charter ~~an independent radiology review charter, as described.~~ See Section 6.2.6 for a description of this **independent** review.

Follow-up visits will begin on Day 336 (this is 3 months after Day 252) for both arms and continue during follow-up visits, or until initiation of alternative indolent lymphoma treatment **or withdrawal (WD)**

Rationale: Specify preference for whole body CT scans with contrast of particular areas. Edited text for independent review for clarity.

Section 6.2.4: Lymphoma Disease-Related Symptoms:

Entire Section Added:

- Assessment for the presence of the following symptoms (done as per Appendix 1 and Appendix 3):
- Night sweats due to lymphoma (not due to infection or treatment)
- Fever due to lymphoma (not due to infection or treatment)
- Loss of appetite due to lymphoma (not due to treatment)
- Clinically significant weight loss, since the previous disease assessment, which is due to lymphoma (not due to treatment)
- Fatigue due to lymphoma (not due to treatment)
- Other symptoms due to lymphoma (not due to treatment)

Rationale: Assessment of lymphoma-related symptoms is necessary for CR. Therefore, these assessments must be done when response assessments are done. These differ from constitutional symptoms assessments taken during the study. Lymphoma disease-related symptoms must specifically be due to the lymphoma and cannot be due to infection or therapy.

Section 6.2.5: Documentation of Target and Non-target Lesions

Added Text:

The definition of unequivocal progression of non-target disease is based on the definition applied in RECIST 1.1 [Eisenhauer, 2009] as an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased significantly to merit discontinuation of therapy, or if therapy has already been completed, commencement of anti-cancer therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

Rationale: Adds clarity by defining "unequivocal progression".

Section 6.2.5.2: Complete Remission (CR)

Original Text and Text Change:

1. The spleen and/or liver, if considered enlarged due to lymphoma (nodules must be present) before therapy on the basis of a ~~physical examination or~~ CT scan ~~should not be palpable on physical examination~~ and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.

Rationale: Spleen and lymph nodes will be assessed by CT scan and not by physical exam.

Section 6.2.5.5: Relapsed Disease (after CR)/Progressive Disease (after PR, SD)

Original Text and Text Change:

Criteria for determining PD for new lesions and target lesions are shown n Table 7

TABLE 7 CRITERIA FOR DETERMINING PD FOR NEW LESIONS AND TARGET LESIONS

	Nodes	**Extranodal ('liver/spleen' & 'other' categories)**
New node/lesion[a]	A previously normal node (≤1.5 x ≤1.0 cm), including nodes that were not previously visible, must increase to >2.0 x ≥1.5 cm.	~~Any new lesion, irrespective of size, will be considered PD~~ **An unequivocal new lesion at a site where there was no disease at baseline, provided the** lesion cannot be attributed to non-lymphoma-related causes.
Single node/lesion		
Increase in PPD	≥ 50% increase from nadir ~~of any previously involved node > 1.5 cm in the long axis at baseline~~ **in the PPD of any target node.** The long axis must increase by at least 5 mm and to >2.0cm.	≥50% increase from nadir in the PPD of any target lesion, and at least a 5 mm increase in either of the axes, and the lesion must be >1.5cm x ≥1.5 cm.
Increase in long axis	≥50% increase from nadir in the long axis ~~of any previously involved node > 1.5 cm in the long axis at baseline~~ **of any target node.** The long axis must increase by at least 5 mm and to >2.0 cm.	≥ 50% increase from nadir in the long axis of any target lesion, and at least a 5 mm increase in the long axis, and the lesion must be >1.5 cm x ≥1.5 cm.
Multiple nodes/lesions		
Increase in SPD	≥50% increase from nadir in the SPD of target nodes and at least one node should have a long axis >1.5cm.	≥50% increase from nadir in the SPD of target lesions and at least one lesion should have a long axis >1.5cm[b].

- Table abbreviations: PPD= product of perpendicular diameters; SPD= sum of the products of the greatest diameter.

1. **Abnormal nodes/extranodal lesions present at baseline that normalize/resolve and then subsequently enlarge/relapse are not to be classified as new lesions.**
2. **Requiring that one node is > 1.5 cm minimizes the risk of declaring PD based on small artifactual changes.**

Rationale: Provides further details.

Unequivocal progression, as defined in Section 6.2.5, at a site of non-target disease, or unequivocal progression of the liver or spleen size (nodules must be present in the organ for unequivocal progression to be reported) will fulfill the criteria for PD.

If the subject achieved a CR on protocol, histological confirmation of relapse is strongly recommended.

Section 6.2.6: Independent Review of Disease Response Committee (IRC)

The study's primary endpoint is to determine PFS as assessed **through an independent review of the data based on the** ~~by the IRC according to~~ the RRCML guidelines [Cheson, 2007]. **These response criteria are described in Section 6.2.** The operation and responsibilities **for members** ~~of~~ **that are part of the** ~~IRC~~ **independent review** is described in a separate charter. The final determination of progression will be based on the evaluations by the independent reviewer(s) and will be used for the study's efficacy analysis and submission to regulatory agencies.

Rationale: Clarification.

Section 6.3.2: Peripheral Blood Sampling for Hematology and Biochemistry

- Original Text and Text Change:
- A creatinine clearance will be calculated prior to ~~drug~~ **bendamustine** administration ~~on Day 1 of each bendamustine cycle. (If a measured creatinine clearance is available, the measured creatinine clearance may be used).~~**as shown in Appendix 2**. The Cockcroft-Gault formula will be used to determine a calculated creatinine clearance:

- Rationale: Clarification when a calculated creatinine clearance will be done.

Section 6.3.4: Peripheral Blood Sampling for Safety and Disease Status

Original Text and Text Changes:

- Hepatitis B (HBV) and Hepatitis C (HCV) at screening. Subjects receiving ofatumumab that are Hepatitis B core positive, Hepatitis B DNA should be obtained at each cycle visit while on treatment and then at 1,3,6 months post treatment. See SPM for more details.
- Screening pregnancy test (HCG) for women of childbearing potential, unless they have had a hysterectomy, have undergone tubal ligation within one year before the screening visit, or have been postmenopausal for at least one year.
- Subsequent pregnancy testing in women of child bearing potential will be done as defined in Appendix 2
- Human Anti-Human Antibody (HAHA) will be taken as defined in Appendix 2. If receiving ofatumumab following PD in bendamustine monotherapy arm, HAHA will be taken as defined in Appendix 3

- Human Anti-Chimeric Antibody (HACA) will be taken as defined in Appendix 2. If receiving ofatumumab following PD in Arm B, HACA will be taken as defined in Appendix 3

Rationale: HACA testing added as part of amendment 2. Pregnancy test requirements clarified.

Section 6.5.4: Laboratory and Other Safety Assessment Abnormalities Reported as AEs and SAEs

Original Text and Text Changes:

B cell depletion~~, IgG below LLN, low CD19+ count, and hypogammaglobulinemia~~ due to treatment with ofatumumab are not to be reported **as an** AE or SAE.

Rationale: Ofatumumab mechanism is based on successful B cell depletion with expected B cell recovery.

Section 6.6.1: Functional Assessment of Cancer Therapy – ~~General~~ Lymphoma ~~(FACT-G)~~ (FACT-Lym) Subscale

~~The FACT-G has previously been used to identify quality of life in other studies of indolent lymphoma subjects [~~Witzig~~, 2002a; ~~Witzig~~, 2002b]. The FACT-G (FACT-General) was developed by the FACIT group for use in adults in a wide range of oncology clinical trial populations. The 27 items of the FACT-G are scored in the following domains: Physical Well-being (7 items), Social/Family Well-being (7 items), Emotional Well-being (6 items) and Functional Well-being (7 items).~~

~~Subjects respond to the items on a five point Likert scale ranging from 0 '*Not at all*' to 4 '*Very much*'. Possible ranges of score are from 0 to 108. Subjects are asked to think back over the past week when responding to the items. The FACT-G is designed to be self-administered but has also been validated in an interview format. It has been widely used in various oncology populations. It is available in over 50 languages and higher scores indicate better PRO. The FACT-G is widely used and has been well validated in a number of different cancer indications [Overcash, 2001; Winstead, 1997; Cella 1995].~~

Rationale: FACT-G was integrated into FACT-Lym questions as part of FACT-Lym version 4.

Section 6.7:

Added Text:

Section 6.7.1: Sample Collection for Subjects in Arm A

A pharmacokinetic sample (and a HAHA sample) will be collected with other withdrawalwithdraw assessments for subjects who withdraw from treatment. For subjects who experience progressive disease, a pharmacokinetic sample (and a HAHA sample) will be collected on one occasion after disease progression.

Section 6.7.2: Sample Collection for Subjects in Arm B With Disease Progression and Who Receive Ofatumumab Monotherapy

A pharmacokinetic sample (and a HAHA sample) will be collected with other withdrawal assessments for subjects who withdraw from treatment. For subjects who experience progressive disease, a pharmacokinetic sample (and a HAHA sample) will be collected on one occasion after disease progression. Table 10 provides a summary of the pharmacokinetic sample collection schedule for subjects that progress on Arm B and select ofatumumab monotherapy.

TABLE 10 PHARMACOKINETIC SAMPLE COLLECTION SCHEDULE FOR SUBJECTS THAT PROGRESS IN ARM B AND SELECT OFATUMUMAB MONOTHERAPY

Time	Ofatumumab Dose	Sampling time relative to ofatumumab infusion
Week 1	1	Predose
Week 4	4	Predose, EOI
1st monthly dose	5	Predose
6th monthly dose	10	Predose, EOI
		1 month after last ofatumumab infusion[1,2]
		6 months after last ofatumumab infusion[1,2]

- Note: EOI is within 15 minutes prior to stopping infusion.

3. Collect sample relative to last dose of ofatumumab regardless of number of cycles
4. Collect sample at any convenient time on study day.

Rationale: Additional HAHA and PK samples will be done at time of PD to determine if HAHA may be one potential reason for ofatumumab failure. These tests will also be done at time of withdrawal so that an adequate number of subjects may be assessed for safety and PK of ofatumumab.

[redacted]

[redacted]

Section 8.3.5.1: Efficacy Analysis

Original Text and Updated Text:

- Known and exploratory **p**rognostic markers correlating with clinical response

Cox regression will be used to explore the relationship between PFS and the following explanatory variables: treatment group, cytogenetics (analyzed by FISH) at baseline, Absolute Lymphocyte Count (ALC), thymidine kinase, soluble CD20 at baseline, **Human anti-chimeric antibodies (HACA) to rituximab.**

- **Human Anti-Chimeric Antibodies (HACA)**

HACA results prior to ofatumumab administration will be listed.

- Human Anti Human Antibodies (HAHA)
- **The change in HAHA titers from predose to post-baseline visits and the number and proportion of positive and negative results at each visit will be provided in patients who receive ofatumumab. HAHA results and associated ofatumumab plasma concentration at each timepoint will be listed.** ~~The change in HAHA titers from screening to post-baseline visits will be provided. ANCOVA analysis will be conducted.~~

Rationale: HACA testing added to this amendment.

11.11 Appendix 11: Protocol Changes for Amendment 3 (19 JANUARY 2012) from Amendment 2 (dated 12 MAY 2010)

General Protocol Changes for Amendment 3 (19-January-2012) from Amendment 2 (dated 12-May-2010)

Note: Appendix 11 is meant to emphasize areas where major changes occurred. You must refer to the final protocol in its entirety to see all final changes in Amendment 3. The information in the protocol will always supercede information presented in Appendix 11.

Where the Amendment Applies

Amendment 3 is applicable to all study sites.

Summary and Rationale for Amendment Changes

Administrative Changes

Bendamustine (LEVACT) was approved in EU. This trade name is reflected in document along with the European Medicines Agency (EMA) approval.

Minor changes have been made throughout the protocol and the time and events tables for spelling, punctuation, general administrative changes, and consistency between sections.

List of Abbreviations

Changed to reflect proper abbreviation spelling.

Recruitment, Screen Failure Rate, and Drop-out Rate

The guideline for the study reaching 256 total events with respect to previously stated assumptions involve screening of 408 subjects so as to have 346 subjects randomized and to have a study duration of about 69 months from the first day of first subject until the time of the 256^{th} event.

This change is reflected throughout the updated protocol.

Study Schematics

Updated to reflect change in study design, including follow-up frequency.

IDMC Decision on Dose Alteration in Arm A

Updates on this decision were made in Section: 3.1, Section 3.1.3, Section 8.2, and Section 9.7. Updates were made to reflect output of meeting.

The IDMC met after the first 20 subjects in Arm A received at least 3 cycles of OB. Based on their review of the data as well as the IDMC charter defined criteria to alter the dose in Arm A, the final recommendation from IDMC was to not change the current dose regimen and therefore to allow the study to proceed unchanged. Consequently, there will be no further IDMC meetings and no further dose modifications other than the protocol-directed dose reductions and delays already described in Section 5.1.3.1 of this protocol. The safety of subjects enrolled in the study will continue to be monitored by GSK.

CT Scan Time Window

Updated to be + 7 days not ± 7 days.

Screening Time Window

Updated to be ≤21 days not ≤14 days.

Follow-Up Schedule

Follow up (F/U) 1 begins on Day 336 post randomization and occurs every 3 months until Month 18 of the F/U phase. F/U 2 follows F/U 1 and occurs every 12 months until Month 54 of the F/U phase with one more visit on Month 60 of the F/U phase. The last required CT scan will be done on Month 54 of the F/U phase. Following Month 54, there will be a Month 60 F/U visit without a required CT scan. Outside the required CT scans within F/U, unscheduled CT scans will be done to confirm clinical signs or suspicion of progression.

This change was made throught the protocol.

References

Updated to reflect current Summary of Product Characteristics (SPC) and Prescribing Information (PI)

Clarification text

Clarification of "recommendations" versus "requirements" made throughout protocol. The word "should" has been replaced in protocol to offer clarity where needed.

Time and Events Tables (Appendix 1, Appendix 2 and Appendix 3) and other General Study Updates throughout Amendment 3

- Tables and footnotes updated to reflect changes in protocol:
- CT scan time window
- No bone marrow aspirate
- Screening is ≤21 days of dosing for Cycle 1, Day 1
- Ofatumumab concentration assessed rather than pharmacokinetics (PK)
- After 61 days of last treatment, all SAEs, regardless of causality, should be reported until the end of follow-up
- Monthly ofatumumab dosing begins 28 days after Day 1 of the previous cycle in Arm A
- CT scan may be whole body or per local practice
- The F/U1 schedule, in both arms, begins on Day 336 (this is 3 months following Day 252) and will continue every 3 months until Month 18 of the F/U phase. There will be a ±7 day visit window around each visit.
- The follow-up #2 schedule comes after the end of follow-up schedule #1 and continues until Month 54 of F/U phase. The last required CT scan will be done on Month 54 of the F/U phase. Following Month 54, there will be a Month 60 F/U visit without a required CT scan. Outside the required CT scans within F/U, unscheduled CT scans will be done to confirm clinical signs or suspicion of progression
- Subjects with PD, as confirmed by CT scan, will be followed for survival. Additionally, subjects without PD who stop protocol treatment and begin non-protocol treatment will go into Survival Follow-Up. Survival follow-up visits will occur every 3 months until Month 18 of F/U 1. Following F/U 1, survival visits for F/U 2 will occur q12 months until Month 54, then one final visit at Month 60 of the F/U phase. Survival follow-up visits begin 2 months after PD is confirmed by CT scan or start of non-protocol treatment. Subjects in Arm B with PD may select optional ofatumumab

monotherapy. PD must be confirmed by an independent review prior to receiving ofatumumab monotherapy. There will be a ±7 day visit window around each F/U 1 visit and a ±14 day visit window around each F/U 2 visit.

- If a subject, without PD, discontinues or withdraws (WD) from treatment (for any reason) the subject remains in the study and completes all scheduled visits without study drug. In the event a subject WD from study, the WD visit (as noted in time and events tables) must be completed. CT scan done at WD from study if last CT was >91 days.
- Treatment is expected to be given on the scheduled days. A visit window of 3 days following the scheduled day will be allowed between cycles but there is no visit window once the subject has entered the cycle (except bendamustine may be administered on either Days 1,2 or Days 2,3 if needed). There is a minimum 21 day interval between cycles.
- One month follow-up occurs following treatment completion in Arm A, regardless of response.
- HAHA and ofatumumab concentration (PK sample) sample frequency changed. During treatment, collect every 6 months. During first year of follow-up, collect every 6 months for the first year after last ofatumumab infusion. Collect a HAHA sample at withdrawal or on one occasion post-PD for subjects with PD.
- Ig and vital sign schedules altered in time and events tables

[redacted]

- Ofatumumab concentration (PK) only for subjects receiving ofatumumab.
- The protocol should be followed as closely as possible. If as per local practice, a blood withdrawal for hematology and biochemistry analysis prior to the visit date is required, it would be acceptable for hematology and biochemistry analysis, but the blood draw can be taken no more than 3 days ahead of the visit date. Blood draws performed by local laboratories (e.g. for quicker pre-dose response assessment or assessment of toxicity) of protocol-required lab assessments are acceptable; however it is important that the sample for the central laboratory analysis is taken at the same time. Since absolute neutrophil count, platelet count, peripheral blood lymphocytes, and hemoglobin results are required to establish if a bendamustine dose reduction and/or treatment delay is required, the results of each of these local laboratory tests must also be entered into the eCRF if it is used to manage a dose delay or dose reduction. Central Laboratory information will also be entered into the eCRF.
- Appendix 3: visit window now + 1 day

SPECIFIC PROTOCOL CHANGES FOR AMENDMENT 3 (19-JAN.-2012) FROM AMENDMENT 2 (DATED 12-MAY-2010)

List of Specific Changes

Note: deleted language is presented with a ~~strikethrough~~ and added language is printed in **bold**. Specific changes do not replicate the entire section that was changed, but merely show sentences and/or paragraphs were most of the changes occurred. Some paragraphs were truncated in the following examples. Specific changes are not shown for every section. Specific changes are shown for some sections to highlight extent of change. These specific changes were implemented throughout the protocol even though not shown in this section. *The final protocol and not this appendix must always be followed when implementing the protocol rather these appendices.*

Example:

Section: Throughout Document

Original text:

~~Patient~~

Text changed to:

Subject

Rationale for Change:

For consistent use of terminology throughout the document. Amended in appropriate document sections.

Sections: Protocol Summary

Text changed to:

Objectives

The primary objective of the study is to test whether the ofatumumab and bendamustine combination therapy will improve disease progression-free survival in subjects with indolent B-cell NHL**who had stable disease to, or progressed during or within 6 months of the end of a rituximab or rituximab-containing regimen** ~~that did not respond (stable disease or progressive disease) to rituximab or a rituximab-containing regimen during or within 6 months of the last rituximab treatment.~~

Secondary objectives evaluate clinical benefit, changes in health-related quality of life (HRQL) measures, safety, tolerability, ~~pharmacokinetics~~, ~~and~~ exploratory prognostic markers in subjects treated with ofatumumab and bendamustine, **and ofatumumab pharmacokinetics in subjects receiving ofatumumab alone after disease progression.**

Study Design

Screening assessments include physical exam, vital signs, biochemistry, and blood samples. Blood samples (hematology), vital signs, and biochemistry samples are taken throughout the treatment phase. Follow-up assessments begin on Day 336 (3 months after Day 252), then ~~every 3 months for 2 years, and every 6 months for 3 years~~ **according to Appendix 1 and Appendix 2**. **In the event of PD, Survival Follow-Up visits begin 2 months after PD is confirmed by CT scan**. A bone marrow examination is required to confirm Complete Remission (CR) when a subject fulfills the **complete** response criteria, based on the Revised Response Criteria for Malignant Lymphoma definition of a CR **if the subject had bone marrow involvement at baseline.** CT imaging is required for confirmation of all responses (CR, PR, SD, PD). During this study, CT imaging of the neck (when lesion is palpable), thorax, abdomen, and pelvis will be performed at baseline, and on Days 84, 168, and 252 (+7 days), regardless of the number of completed cycles of therapy in Arm A and Arm B.

A total of 256 events in a sample size of 304 evaluable subjects (152 subjects per arm) are needed for the study to have a 90% power to detect a 50% improvement in progression-free survival (PFS) between study arms. Assuming a dropout rate of ~~10~~ **12**%, the total sample size randomized for both arms combined will be ~~338~~ **346** subjects, with approximate study

duration of ~~68~~ **69** months. Assuming a screening failure rate of ~~10~~**15**%, the total number of subjects screened will be approximately ~~376~~ **408**.

Section 3.1.7

Text changed to:

Known and Exploratory Prognostic Markers Correlating with Response

- Baseline FLIPI-1 and FLIPI-2 scoresBaseline Absolute Lymphocyte Count (ALC)
- **Genetic variation in** FcR gamma 3A
- Human Anti-Chimeric Antibodies (HACA)

[redacted]

Rationale for Change:

Summary updated to reflect changes in the document.

Section 1.2: Frontline Treatment

Text changed to:

Bendamustine hydrochloride (RIBOMUSTIN) is currently approved in Germany **(i.e., 60 mg/m² I.V. on days 1-5, vincristine 2 mg I.V. on day 1, prednisone 100 mg/m² I.V. on days 1-5; cycle repeated after 3 weeks)** for the primary treatment of advanced, indolent NHL in combination regimens and as a single agent or combination therapy for multiple myeloma and chronic lymphocytic leukemia (CLL) [RIBOMUSTIN **Prescribing Information** ~~Package Insert~~, 2009; **LEVACT SPC, 2010**]. ~~Approval for indolent NHL that relapsed during or within 6 months of receiving a rituximab-containing regimen is pending in Europe and Japan.~~ **Bendamustine is approved for indolent NHL that relapsed during or within 6 months of receiving a rituximab-containing regimen.** In the US, bendamustine hydrochloride (TREANDA) as a single agent is also approved for the treatment of CLL and rituximab-refractory indolent NHL [TREANDA Package Insert, 2010].

Rationale for Change:

Levact approved in EU.

Section 1.3: Ofatumumab

Text changed to:

The pivotal trial Study Hx-CD20-406 in subjects with fludarabine-refractory CLL [refractory to both fludarabine and alemtuzumab (n=59) or refractory to fludarabine and with bulky lymphadenopathy for whom alemtuzumab is not suitable (n=79)] evaluated 300 mg + 7 x 2000 mg for eight weekly doses, followed by four monthly 2000 mg doses. ~~An~~ **The investigator-determined overall** objective response rate of **patients refractory to fludarabine and alemtuzumab was** ~~58~~ **42% with a median duration of response of 6.5 months** ~~consisting of partial responses (PR) was achieved in the fludarabine and alemtuzumab refractory group with a median progression-free survival of 5.7 months.~~ **The best response was PR.** ~~Similarly, in the bulky fludarabine refractory group with a similar unmet medical need, an objective response rate of 47% was achieved, including 1 complete response (CR), with all other responses being partial responses (PR). The median PFS in the bulky fludarabine refractory group was 5.9 months.~~ In this study, ofatumumab was generally well tolerated. **Specifically, in the DR group**, ~~T~~the most frequently reported adverse events (>15% frequency) were pyrexia, diarrhea, fatigue, cough, neutropenia, anemia and pneumonia.

Rationale for Change:

Results updated.

Section 2 Objectives:

Secondary objectives:

Text changed to:

- To evaluate ofatumumab pharmacokinetics when ~~ofatumumab is~~ given ~~with~~ **as monotherapy to subjects who progress during or following single-agent** bendamustine

Rationale for change:

Pharmacokinetic objective is removed from the main body of the study; this objective is being addressed appropriately in another study. This study will assess ofatumumab pharmacokinetics in subjects in Arm B who receive ofatumumab monotherapy after disease progression.

Section 3.1: Study Design

Text changed to:

The primary analysis of progression-free survival will use 90% power to detect a 50% treatment effect; a 13.5 vs. 9 month improvement in Arm A (ofatumumab and bendamustine combination therapy) vs. Arm B (bendamustine monotherapy~~). A total of 256 events will be required in a sample size approximately 304 subjects (152 subjects per arm). With an estimated accrural rate of 6 subjects per month, the study treatment duration wil be approximately 62 months. However, to meet an assumed 10% drop out rate, 338 subjet will be randomized to the study. The study duration increases to approximately 68 months. It is also estimated that approximately 10 % of subjects screened may fail screening criteria; therefore, approximately 376 subjects may be screened for this study to obtain 338 randomized subjects.~~ **This trial is an event-driven study design with an event-driven sample size of 256 total events and the final analysis will take place at the time of**

occurrence of the 256th event. The guideline for the study reaching 256 total events with respect to previously stated assumptions involve screening of ~~376~~ 408 subjects so as to have ~~338~~ 346 subjects randomized and to have a study duration of about ~~62~~ 69 months from the first day of first subject until the time of the 256th event.

Rationale for Change:

Screen failure rate and dropout rate updated to reflect current study status.

Section 3.1.1: Screening Phase

Text changed to:

Baseline Bone Marrow Sample:

Two types of bone marrow samples will be accepted:

1. **An historical bone marrow biopsy sample (obtained at any time prior to study entry) may be used to fulfill the study's needs if:**
   - **The bone marrow biopsy showed involvement by lymphoma and**
   - **The subject has received no lymphoma therapy in the intervening time period.**
2. **A study specific (screening) sample will be required if any of the following points are met:**
   1. **The subject has no previous bone marrow biopsy, or**
   2. **The bone marrow biopsy was taken >1 month prior to randomization and showed no involvement by lymphoma, or**
   3. **The subject has received lymphoma therapy in the intervening time period since the prior bone marrow biopsy.**

~~A screening bone marrow biopsy and aspirate will be required if a prior bone marrow biopsy and aspirate results from the previous ≤8 weeks cannot be provided.~~

~~4. A bone marrow aspirate and biopsy will be required at screening if results are not available from a prior bone marrow aspirate and biopsy performed within 8 weeks prior to randomization. Results may be provided in the form of a bone marrow biopsy report when a previous aspirate and biopsy are not available as long as the report was based on the biopsy done within 8 weeks prior to randomization. Results may be provided in the form of a bone marrow biopsy report when a previous aspirate and biopsy are not available as long as the report was based on the biopsy done within 8 weeks prior to randomization. If the investigator has clinical suspicion that the protocol candidate has transformed to Diffuse Large B-cell Lymphoma (DLBCL), the investigator should not consider that subject for the trial unless a lymph node biopsy is performed. To confirm that disease has not transformed to a DLBCL, an incisional or excisional lymph node biopsy of accessible adenopathy is highly recommended. In less accessible lymph nodes, 4 to 8 core biopsies are recommended, but not required.~~

Lymph Node Biopsy if Transformation to DLBCL Is Suspected:

If the investigator has clinical suspicion that the protocol candidate has transformed to Diffuse Large B-cell Lymphoma (DLBCL), the investigator should not consider that subject for the trial unless a lymph node biopsy is performed. To confirm that disease has not transformed to

a DLBCL, an incisional or excisional lymph node biopsy of accessible adenopathy is highly recommended. In less accessible lymph nodes, 4 to 8 core biopsies are recommended, but not required.

- ~~Bone marrow aspirate, biopsy and lymph node pathology report including details confirming $CD20^+$ tumor status will be sent along with tissue or slides for central review. Please see SPM for more details.~~

Review of Materials:

Bone marrow biopsy and tissue pathology report (including details on core and aspirate, core alone, or aspirate only) including details confirming $CD20^+$ tumor status will be sent along with tissue or slides for central review. Please see SPM for more details.
Blood samples, physical examination, and ~~whole body~~ CT imaging (with contrast imaging of the neck when lesion is palpable, thorax, abdomen, and pelvis; **may be whole body CT scan or according to standard of care)** will be provided to determine baseline disease and study eligibility **(See Imaging Acquisition Guidelines).** All examinations ~~should be~~ **must** be performed ≤ ~~14~~ **21** days prior to randomization with the exception of the CT imaging and bone marrow biopsy and aspirate as mentioned above. CT imaging done ≤1 month prior to randomization may be used as the baseline CT scan. If the investigator ~~would~~ want**s** to use a CT scan done >1 month prior to randomization, the medical monitor may be contacted to determine if CT scan can be accepted.

Rationale for Change:

Clarification.

Section 3.1.1.1 Documentation of Indolent B-cell NHL that is stable or has progressed during or within six month of the end of treatment with rituximab or a rituximab-containing regimen

Text changed to:

A documentation worksheet verifying the investigator's diagnosis of stable disease **following**, or progression ~~of indolent B-cell NHL~~ during or within 6 months of treatment with rituximab or a rituximab-containing regimen will be required at screening. This documentation worksheet must be sent to GSK prior to randomization and will ask for:

Information about last rituximab therapy:

- Dates before and dates after last rituximab-containing regimen
- Type of rituximab therapy and regimen (examples: weekly, monthly):
    - Rituximab (includes monotherapy and maintenance), or
    - Rituximab added to chemotherapy
- Date and type of response associated with last rituximab-containing regimen
- *Information regarding imaging:*
- Copy of the imaging report prior to last rituximab-containing regimen **is** required **(if available)**
- Copy of **documentation confirming PD (for example, an** imaging report, **clinical documentation)** after subject deemed unresponsive or relapsed to rituximab-based regimen is required

Rationale for Change:

Obvious progression could be documented using methods other than imaging. As long as these other methods/documentation can show progression, they may be used to confirm rituximab refractory disease.

Section 3.1.4: Treatment Phase

Text changed to:

- Arm A: Up to 8 cycles of bendamustine (90 mg/m^2, Days 1, 2; q21 days) in combination with 12 doses of ofatumumab (1000 mg). **Beginning in Cycle 2, o**fatumumab will be given on Day 1 (or within 3 days after 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 **o**fatumumab will be given monthly, q28 days (on or 3 days after Day 1 of each month) until all 12 doses are completed. **Administer the first dose of ofatumumab monotherapy 28 days after Day 1 of the last cycle where combination (ofatumumab+bendamustine) was scheduled to be given.**
- Arm B: Up to 8 cycles of bendamustine (120 mg/m^2, on or 3 days after Days 1, 2; q21 days.).

Subjects ~~in Arm B~~ who cannot complete ~~8 cycles~~ **the planned** therapy (**in Arm A and Arm B**) must still come in for all planned visits and assessments (Visits 1-20) according to the schedule presented in Appendix 1 and Appendix 2. Also see SPM for more details. Subjects in Arm A and Arm B are required to come for all planned CT scans with corresponding assessments for these days (Days 84, 168, 252; ~~±7~~ **+7** days).

Rationale for Change:

Clarification**.**

Section 3.1.5: Follow-up Phase

Text changed to:

Following study treatment, subjects who have CR, PR or SD will receive regular follow-up for 5 years in Arm A. **The last required CT scan will be done on Month 54 (Table 1). Unscheduled CT scans will be required in addition to the scheduled CT scans if there are clinical signs or suspicion of progression throughout the study.** Arm B will also follow this schedule if Arm B subjects do not select ofatumumab monotherapy.

Table 1 Follow-up visit schedule and CT scan requirements

F/U phase[1]	CT scan[3]
3 M F/U 1[2]	Required
6 M F/U 1	Required
9 M F/U 1	Required
12 M F/U 1	Required
15 M F/U 1	Required
18 M F/U 1	Required
30 M F/U 2	Required
42 M F/U 2	Required
54 M F/U 2	Required
60 M F/U 2	Not required[3]

Abbreviations: Follow-Up 1= F/U 1; Follow-Up 2= F/U 2; Month= M

7. **This schedule is for F/U 1, F/U 2, and the Survival F/U.**
8. **The 3 M F/U 1 visit occurs 336 days after randomization (or 3 months after Day 252) in Arm A and Arm B (Appendix 1, Appendix 2). This 3 M F/U 1 visit occurs 3 months after last ofatumumab monotherapy dose for subjects with PD in Arm B who select ofatumumab monotherapy (Appendix 3).**
9. **CT scans are required during scheduled F/U 1 and F/U 2 visits with the last required CT scan on Month 54. CT scans will be required to confirm clinical signs or suspicion of progression if observed outside scheduled F/U 1 and F/U 2 visits. CT scans are not required for Survival F/U.**

Follow-up assessments begin on Day 336 (3 months after Day 252), then according to Appendix 1 and Appendix 2 (also see SPM). In the event of PD, Survival Follow-Up visits begin 2 months after PD is confirmed by CT scan~~. Follow-up visits will begin on Day 336 (this is 3 months after Day 252) and then continue every 3 months for 2 years, then every 6 months for 3 years~~.Each follow-up visit and assessment will have a time window of ±7 days for Follow-Up Visit #1 and a time window of ±14 days for Follow-Up Visit #2. Follow-up visits will include **collection of** survival **status**, concomitant medications, and response assessments, based on RRCML. **Survival follow-up visits may be phone calls instead of physician office visits.** In addition, subjects will be monitored for safety, efficacy, and ~~pharmacokinetics~~ as described. See Appendix 1 and Appendix 2 for a complete list of follow-up procedures.

If a subject in Arm B decides to receive ofatumumab monotherapy following PD, they will not follow the schedule described in Section 3.1.5, Appendix 1 and Appendix 2, but will be monitored according to the follow-up schedule described in Section 3.1.6, Appendix 3, **and Table 1 (where 3 month F/U begins 3 months after last dose of ofatumumab).**

Rationale for Change:

Follow -up frequency (including CT scans required within these visits) were reduced to addresss UK Ethics feedback on the protocol. The UK Ethics Committee asked that we reduce the number of CT scans in this study. As long as subjects remain on a consistent follow up schedule, there is no risk for this new schedule to interfere with data analysis.

Section 3.1.5: Follow-up for Progressive Disease

Text changed to:

A PD Worksheet will be completed following the CT scan. Instructions for this worksheet are found in the SPM.

Survival ~~F~~follow-up visits will begin ~~on Day 336 (this is 3 months after Day 252)~~ **2 months after PD is confirmed by CT scan as described in Appendix 1 and Appendix 2 and Table 1** ~~and continue every 3 months for 2 years and then every 6 months for 3 years~~. **Each follow-up visit will have a time window of ±7 days for Follow-Up Visit #1 and a time window of ±14 days for Follow-Up Visit #2**.~~One month is defined as having 28 days. Each follow up visit and assessment will have a time window of ±7 days~~. **Survival follow-up visits may be a phone call instead of physician office visit.**

Rationale for Change:

To synchronize follow-up visits after the date of progression in all subjects.

Section 3.1.6: Ofatumumab Following Progressive Disease for Arm B

Text changed to:

A PD Worksheet must be completed once the decision to begin ofatumumab monotherapy following PD in Arm B is taken (See SPM for details).

The first follow-up visit will occur one month following the last infusion of ofatumumab monotherapy and continue ~~every 3 months for 2 years then every 6 months for 3 years~~ as described in Appendix 3 **and Table 1.**

Text changed to:

Clarification and reflects change in documentation requirements.

Section 4.2: Inclusion Criteria

Text changed to:

Inclusion #1: Small lymphocytic, lymphoplasmacytic, marginal zone lymphoma, and follicular lymphoma (FL); grades 1, 2 and 3A, defined according to WHO guidelines.

- Tumor verified to be $CD20^+$ positive from a previous or current ~~lymph node~~ **tissue** biopsy. ~~A bone marrow biopsy is not sufficient for tissue diagnosis.~~
- CT imaging in screening phase (based on local evaluation) showing 2 or more clearly demarcated lesions with a largest diameter ~~≥~~ >1.5 cm **and short axis ≥ 1.0 cm**, or 1 clearly demarcated lesion/**node** with a **long axis** ~~largest diameter ≥~~ >2.0 cm **and short axis ≥ 1.0 cm**. CT imaging performed at screening as baseline image.

Inclusion #2: Indolent B-cell NHL **with failure to achieve at least a partial response lasting 6 months beyond the of treatment with** ~~that remains stable or unresponsive during~~

~~or within 6 months of treatment with~~ rituximab or a rituximab-containing regimen (See Section 6.2.5.4~~-~~ **Section 6.2.5.5** for details on response criteria), **i.e**.:

- **Stable disease after rituximab or a rituximab-containing regimen (imaging will support this finding. NOTE: in cases of stable disease after rituximab monotherapy as induction treatment, the minimum time to confirm stable disease by imaging is 60 days from start of first rituximab infusion)**

  or,

- **·Disease progression during or within 6 months of treatment with rituximab or a rituximab-containing regimen. Imaging must support this finding and will be done ≤ 6 months after the last infusion of rituximab.**

- ~~Maintaining stable disease or failure to achieve PR to rituximab-based therapy. (Imaging will support this finding, and will be performed at least 60 days after the last dose of rituximab-based therapy)~~

- ~~or,~~

- ~~disease progression while on rituximab-based therapy (e.g., includes 4 weekly courses of rituximab given at 6-month intervals [Hainsworth, 2005])~~

- ~~or,~~

- ~~disease progression in subjects with stable disease or better response to rituximab-based therapy <6 months of the last dose of rituximab~~

Note: Subjects must have received a minimum of 4 rituximab infusions as monotherapy or 3 infusions as part of rituximab-containing combination regimens

Rationale for Change:

Inclusion Criterion #1: CD20 staining can be accurately determined from non-lymph node tissue (such as bone marrow or splenic tissue). Some patients with splenic marginal zone lymphoma may have disease which is primarily non-nodal (or have nodes which are not easily accessed), and this change allows such patients to be considered for this study.

Inclusion Criterion #2: Clarification to accommodate local practices. Extra examples were unnecessary to convey criterion.

Section 4.3: Exclusion Criteria

Text changed to:

Exclusion Criterion #2: Previous autologous stem cell transplant ~~or fludarabine therapy, or radioimmunotherapy~~ in the last 6 months **or previous allogeneic stem cell transplant at any time**

Prior Exclusion Criterion #4: ~~Previous external beam radiation therapy to the pelvis. Previous external beam radiation therapy for bony disease to the cranium, mediastinum, and axilla or to more than 3 vertebral bodies~~

Exclusion Criterion #3: **High dose steroids ≥ 100 mg prednisone/day (or equivalent) for 7 consecutive days, given as concomitant medication, within 3 months prior to randomization. No more than 10 mg prednisone daily at the time of randomization**

Exclusion Criterion #4: **Prior bendamustine treatment within 1 year of randomization not resulting in a CR or PR for at least 6 months**

Exclusion Criterion #5: **Prior use of any monoclonal antibody (other than CD20) within 3 months prior to randomization**

Prior Exclusion Criterion #7: ~~Prior treatment with anti-CD20 monoclonal antibody, if 1st dose was administered within 60 days prior to randomization. Prior use of any monoclonal antibody (other than anti-CD20) within 3 months prior to randomization~~

Rationale for Changes:

No longer excludes fludarabine and radioimmunotherapy:

- Previous concern was that prior fludarabine and RI would deplete BM reserve. We wanted BM reserve to recover from these prior therapies before subjects entered the OMB110918 study, since bendamustine is myelosuppressive. Since the inclusion and exclusion criteria already require minimum hematological values to safeguard against subjects at increased risk of hematologic toxicity from bendamustine, exclusion of prior fludarabine and radioimmunotherapy is not necessary.

No longer exclude previous external beam radiation therapy to the pelvis, previous external beam radiation therapy for bony disease to the cranium, mediastinum, and axilla or to more than 3 vertebral bodies:

- Previous concern was that extensive radiation therapy would reduce marrow reserve. We want adequate BM reserve for subjects in the OMB110918 study, since bendamustine is myelosuppressive. Since the I/E criteria already require minimum hematological values to safeguard against subjects at increased risk of hematologic toxicity from bendamustine, exclusion of patients based on the amount of prior radiation is not necessary.

Removed Exclusion criterion restricting anti-CD20 antibody within the last 60 days:

- Since rituximab is included in virtually all treatment regimens for indolent B-NHL and refractory patients often have clinically aggressive disease that requires treatment, it is not medically feasible to require patients to wait 60 days to begin new therapy if they do not respond to their last therapy.

Section 4.4: Withdrawal Criteria

Text added:

Entire section updated.

Rationale for Change:

Clarification: text added to explain the difference between “Withdrawal from Investigational Product” vs “Withdrawal from study”.

Section 5.1.1: Pre-Medication, Table footnote

Text changed to:

Pre-Medication Schedule

Infusion Number	30 minutes to 2 hours prior to treatment		
	Acetaminophen (PO) ~1000 mg or equivalent	Antihistamine (IV or PO) equivalent to ~50 mg diphenhydramine	Glucocorticoid (IV) equivalent to ~50 mg prednisolone
1st	X	X	X
>1[1]	X[1]	X[1]	X[1]

5. Administration of ~~steroid~~ premedication in Arm A (and in Arm B, as applicable) will be at investigator discretion if severe infusion reactions did not occur during first infusion.

Rationale for Change:

Correction.

Section 5.1.3: Bendamustine

Text added:

Bendamustine will be given for up to 8 cycles in both Arm A and Arm B. However, in the following instances, bendamustine may be given for fewer than 8 cycles:

- **If a subject cannot tolerate bendamustine and is unable to receive further treatment with bendamustine, the subject may stop bendamustine treatment.**
- **If this occurs in Arm A: the subject will continue to receive all 12 doses of ofatumumab and continue to attend all scheduled visits on Day 1. Day 2 visits are not required unless the investigator requires additional tests.**
- **If this occurs in Arm B: the subject will continue to attend all scheduled visits. Note: Subjects will only be required to attend the equivalent of the Day 1 visit. The Day 2 visit is not required unless assessed as necessary by the Investigator**.

6. The number of cycles will be contingent upon the response to the first 4 cycles. Subjects achieving CR after 4 cycles in either Arm will be treated with a total of 6 cycles only, whereas, all other subjects will receive 8 courses of bendamustine as monotherapy (Arm B) or in combination with ofatumumab (Arm A).

   2. If this occurs in Arm A: the subject should continue to receive all 12 doses of ofatumumab and continue to attend all scheduled visits

   3. If this occurs in Arm B: the subject should continue to attend all scheduled visits on Day 1 of each cycle

7. Subjects with progressive disease at any time during bendamustine monotherapy (Arm B) or OB combination therapy (Arm A) will be taken off treatment and will continue with survival follow-up (Section 3.1.6 describes subjects with PD in Arm B that continue on to ofatumumab monotherapy).

~~The initial cycle length or dose of bendamustine in Arm A may be lowered on recommendation of the IDMC after evaluation of data from the dose confirmation cohorts. Detailed instructions for dose reduction and subsequent dose reductions will be in the IDMC charter and summarized in Section 9.7.~~

Bendamustine may be initiated within 1 day of scheduled start for logistical reasons. Once the first infusion occurs, the second infusion should occur the following day. The start of Cycles 2-8 may be delayed due to toxicity by up to 2 weeks for medical reasons at the investigator's discretion.

Rationale for Change:

Clarification.

Section 5.1.3.1: Bendamustine Dose Reduction

Text added:

General Dosing Considerations for Arm A and Arm B:

- Delay treatment for Grade 4 hematologic toxicity or clinically significant ≥Grade 3 non-hematologic toxicity.
- Toxicities must recover to Grade 1 or baseline before the next administration of treatment. If recovery is not met within 2 weeks after the prescribed start of the treatment cycle (i.e., after a 2 week delay), a decision will be made about continuation in the study following consultation with medical monitor.
    - **Bendamustine dosage will be delayed in subjects with a serum creatinine > 1.5 ULN if the calculated creatinine clearance [Cockcroft, 1976] or creatinine clearance from a 24-hour urine collection is ≤40 mL/min.**
- Subjects should be monitored for safety as per local practice.
    - **The protocol should be followed as closely as possible, but if as per local practice, a blood draw for hematology analysis prior to the visit date is required, it would be acceptable for hematology analysis, but the blood draw can be taken no more than 3 days ahead of the visit date. Blood draws performed by local laboratories (e.g. for quicker pre-dose response assessment or assessment of toxicity) of protocol-required lab assessments are acceptable; however, it is important that the sample for the central laboratory analysis is taken at the same time. The local laboratory results of absolute neutrophil count, platelet count, peripheral blood lymphocytes, and hemoglobin must also be entered into the eCRF if it is used for a treatment decision. Central Laboratory data will also be entered into the eCRF.**

Rationale for Changes:

Taken from Treanda Prescribing Information and added to protocol for clarity. Also added clarification of when and how local laboratory tests may be used in this study.

Section 6.1.9: Vital Signs

Text added:

Vital signs including temperature, blood pressure (BP), and pulse are documented per Appendix 1 and Appendix 3, at screening and for the remainder of the study in both arms. Temperatures for individual subjects must be measured using the same method at all visits.

All subjects must be monitored as per standard of care for changes in blood pressure, heart rate, and temperature and for Adverse Events. All recorded values should be documented in the subject's source documentation.

If the subject suffers an adverse event (Grade ≥1) during the infusion (including asymptomatic fever, hypotension or tachycardia), which is determined by the Investigator to be related to either the study procedures or study treatment, vital sign measurements (blood pressure, heart rate and temperature) should be recorded in appropriate source documentation AND the blood pressure and heart rate recorded in the INFORM eCRF system, for the following time-points:

- **At the time of event onset.**
- **Then every 30 minutes, or more frequently if clinically indicated, if in the Investigator's opinion the vital sign results at the time of event onset are clinically significant. The subject's vital sign measurements should continue to be recorded until they have returned to normal or pre-infusion levels.**

Rationale for Change:

Simplification of instructions.

Section 6.2.2: CT Scans

Text changed to:

~~Whole body~~ CT scans (with contrast of the neck when lesion is palpable, thorax, abdomen, pelvis, **may be whole body CT scan or according to standard of care**) will be done as part of the efficacy evaluation and after treatment has been completed. The scans must be implemented according to a CT scan manual to be provided to GSK (**Imaging Acquisition Guidelines**) as mentioned in the SPM.

In situations where progressive disease is apparent through physical examination (such as massive lymphadenopathy), only the body area where progressive disease is apparent must be scanned to confirm progressive disease.

All subjects (Arm A and Arm B) must have a CT scan done on Days 84, 168, and 252 (~~±7~~ +7 days). In the event subjects in Arm B cannot complete 8 cycles of therapy then subjects must come to the clinic for all scheduled visits. Subjects will have CT scans at each follow-up visit **as described in Table 1, Appendix 1, and Appendix 3. Survival Follow-up visits will begin 2 months after PD is confirmed by CT scan. CT scans will be done to confirm any clinical signs or suspicion of PD. CT scans which are unscheduled and are performed to confirm PD in event of clinical signs or suspicion of progression may be done only of the suspected body area with progression. In the event that an unscheduled CT scan does NOT show PD, the subject will resume the planned CT scan schedule (i.e. the next CT scan will be done based on the date of the last scheduled CT scan and not the day of the unscheduled CT scan). For all other responses, f**ollow-up visits will begin on Day 336 (this is 3 months after Day 252) for both arms and continue ~~during follow-up visits~~, ~~or~~ until

initiation of alternative indolent lymphoma treatment**, PD,** or withdrawal (WD), See Appendix 1 and Appendix 2 **and Appendix 3** for details. ~~One month is defined as having 28 days~~.

CT scans will be assessed according to an independent review. The independent review will be described in an independent review charter. See Section 6.2.6 for a description of this independent review.

Rationale for Change:

Whole body CT imaging is not done at all sites. All change were made to accommodate different global local practices. Instructions for CT scans in the event of clinical signs of progression were added.

Section 6.2.3: Bone Marrow Examination

Text changed to:

Bone marrow examination (**both aspirate** smear and ~~biopsy~~ **core, if possible**) to confirm CR, as determined by the clinical and laboratory results listed in Section 6.2.5.2 is required no later than ≤ 8 weeks following onset of CR **if there was disease involvement in the bone marrow at baseline**. Samples are to be reviewed in conjunction with the prior pathology.

Rationale for Change:

Clarification on what is needed for study.

Section 6.2.5: Documentation of Target and Non-target Lesions

Text changed to:

Eligibility Criterion

CT scan showing at least:

- 2 or more clearly demarcated lesions/nodes with a long axis >1.5 cm and short axis ≥1.0cm ~~and not previously irradiated~~

OR

- 1 clearly demarcated lesion/node with a long axis >2.0 cm and short axis ≥1.0cm ~~and not previously irradiated.~~

Rationale for Change:

If a patient who failed radiation therapy and a lesion which has been previously irradiated is the primary site of disease progression, an investigator should be allowed to use that lesion to measure response to study therapy without compromising study response.

Section 6.3.2: Peripheral Blood Sampling for Hematology and Biochemistry

Text changed to:

- Biochemistry: sodium, potassium, chloride, bicarbonate, calcium, blood urea nitrogen (BUN), creatinine, uric acid, total bilirubin*, alkaline phosphatase (ALP), aspartate transaminase (AST), alanine transaminase (ALT), lactic acid dehydrogenase (LDH), albumin, glucose (random), and haptoglobulin.
    - *~~b~~**B**ilirubin fractionation is recommended if total bilirubin >2 x ULN

- A creatinine clearance will be calculated prior to bendamustine administration as shown in Appendix 2. **Calculated creatinine clearance will be done at screening and can be repeated at the physician's discretion if there is a significant rise in serum creatinine during the treatment phase of the study.** The Cockcroft-Gault formula **[Cockcroft, 1976]** will be used to determine a calculated creatinine clearance:

Rationale for Change:
Clarification.

Section 6.3.3: Prognostic Factors

Text changed to:

- **Genetic variation in the** FcR gamma 3A
- **Human Anti-Chimeric Antibody (HACA) will be taken as defined in Appendix 2. If receiving ofatumumab following PD in Arm B, HACA will be taken as defined in Appendix 3**
- ~~HACA~~

Rationale for Change:

Clarification on the type of FcR gamma 3 A test.

Section 6.3.4: Peripheral Blood Sampling for Safety and Disease Status

Text changed to:

- ~~Hepatitis B (HBV) and Hepatitis C (HCV) at screening.~~ Subjects receiving ofatumumab that are Hepatitis B core positive **at screening**, Hepatitis B DNA ~~should~~ **will** be obtained at each cycle visit while on treatment and then at 1,3,6 months post treatment. See SPM for more details.
- ~~Human Anti-Chimeric Antibody (HACA) will be taken as defined in Appendix 2. If receiving ofatumumab following PD in Arm B, HACA will be taken as defined in Appendix 3~~

Rationale for Change:

HACA schedule changed and clarification of hepatitis testing.

Section 6.4.1: Liver Chemistry/Stopping and Follow-up Criteria

This entire section was updated. See protocol text.

Rationale for Change:

Modified to align to the stopping criteria which has been adopted for all ofatumumab studies based upon the FDA July 2009 Guidance for Industry, Drug-Induced Liver Injury: Pre-marketing Clinical Evaluation, Section 5, Decision to Stop Drug Administration. Because transient elevations in LFTs may be due to tumor lysis which is of clinical benefit, disease related liver involvement or due to other chemotherapy rather than drug induced liver injury from ofatumumab, the protocol was modified to allow re-challenge with investigational

product. Any decision to restart therapy after interruption must be determined by the investigator in consultation with the GSK Medical Monitor and the GCSP assigned physician.

Section 6.5.1: Definition of an AE

Text added:

Events that do not meet the definition of an AE include:

- **Events related to the underlying lymphoma and unrelated to the study therapy, unless more severe than expected for the condition**

Rationale for Change:

Clarification.

Section 6.5.7: Time Period and Frequency of Detecting AEs and SAEs

Text changed to:

All SAEs and AEs regardless of relationship to investigational product will be collected from the first dose of investigational product to 60 days after the last dose of investigational product and will be documented on the eCRF. Only SAEs**, regardless of causality,** will be reported from ~~60 days~~ **61 Days** after the last dose of treatment to the end of the follow-up period

From the time a subject consents to participate in and completes the study (See Section 4.4), all SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to GSK concomitant medication, will be reported promptly to GSK as indicated in Table **8**.

~~SAEs will not be reported after subsequent anti-NHL therapy is initiated.~~

Rationale for Change:

Clarification and instructions on SAE reporting after NHL therapy.

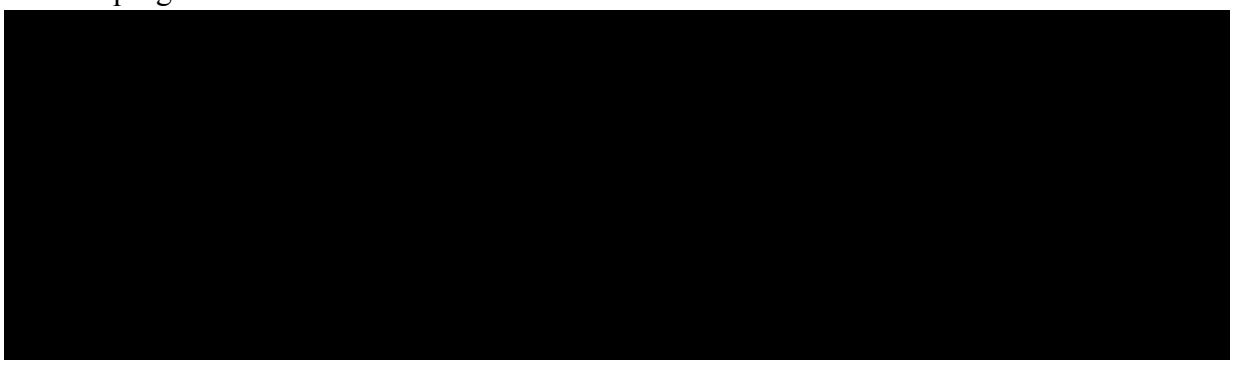
Section 6.7: Ofatumumab Pharmacokinetic Sample Collection

Entire section updated.

Rationale for Change:

Removal of the pharmacokinetic objective in the main body of the study resulted in the removal of the ofatumumab sample collection in subjects in Arm A related to the assessment of ofatumumab pharmacokinetics. The rationale for the removal of the objective is that it is being addressed appropriately in another study.

Addition of more extensive HAHA surveillance resulted in the addition of ofatumumab sample collection in both Arm A subjects and Arm B subjects who received ofatumumab after disease progression related to that surveillance.



Section 8.3.5.1: Efficacy Analyses
Other Secondary Analyses

Text changed to:

- Human Anti-Chimeric Antibodies (HACA)
  - ~~HACA results prior to ofatumumab administration will be listed.~~ The number of patients with positive HACA in the predose samples will be reported
- Human Anti-Human Antibodies (HAHA)
  - The ~~change in HAHA titers from predose to post-baseline visits and the~~ number ~~and proportion~~ of positive and negative results at each visit will be provided in patients who receive ofatumumab. HAHA results and associated ofatumumab plasma concentration at each time point will be listed.

Rationale for Change:

Reflects updates in HACA sampling and assessments and planned reporting of HAHA results.

Section 8.3.5.4: Pharmacokinetic Analyses

The plasma concentrations for individual subjects will be determined using validated analytical methods for ofatumumab. Plasma ofatumumab concentration-time data will be summarized and displayed in tabular and graphical form separately for subjects in Arm A and for subjects in Arm B who receive ofatumumab following progressive disease. Individual plasma concentrations of ofatumumab will be listed.

Population pharmacokinetic modeling, using non-linear mixed effects modeling will be performed **on the data for subjects in Arm B who receive ofatumumab following progressive disease** using validated software such as the computer program NONMEM, if data permit. Data from this study may be combined with data from other studies for analysis. The aims of this modeling approach are to:

- Define the structural pharmacokinetic model that characterizes the population time course of plasma levels of ofatumumab in this patient population
- Describe between-subject variability for pharmacokinetic parameter estimates
- Estimate intra-subject variability on predicted concentrations

If possible, the effects of subject characteristics (such as gender, weight, height, disease status, etc.) will be investigated in order to account for potential sources of inter-individual variability in systemic exposure. If there are sufficient data for analysis, the details of the population pharmacokinetic analyses will be provided in a reporting and analysis plan.

Rationale for change:

Removal of the pharmacokinetic objective from the main body of the study.

Section 8.3.5.5: Pharmacokinetic Analyses

Section removed:

~~[redacted] analyses will be performed to determine any potential relationships between ofatumumab pharmacokinetics or exposure and B-cell monitoring results or other clinical [redacted] endpoints, data permitting. If appropriate, data from all subjects will be pooled and analyzed using a population approach. If there are sufficient data for analysis, the details of the PK/PD analyses will be provided in a separate reporting and analysis plan.~~

Rationale for Change:

Removal of the pharmacokinetic objective from the main body of the study.

[redacted]

11.12 Appendix 12: Protocol Changes for Amendment 4 (09-April-2012) from Amendment 3 (dated 19-Jan-2012)

Where the Amendment Applies

Amendment 4 is applicable to all study sites.

Important Note"

Appendix 12 describes general, major changes in the protocol and is not all-inclusive of all changes. The protocol Amendment 4 will always supercede items presented in Appendix 12; therefore, the protocol Amendment 4 must be consulted for all final guidance.

General Protocol Changes for Amendment 4 (09-April-2012) from Amendment 3 (dated 19-Jan-2012)

- Correction in footnotes to Time and Event Table (Appendix 1): baseline CT scans required ≤1 month of randomization. Correct to footnotes in time and events tables so that premedication reflects text of protocol.
- Abbreviations added to abbreviation table.
- Clarifications made throughout document specifying subjects who cannot complete 8 cycles of therapy with bendamustine must still have all planned Day 1 assessments including scheduled CT scans on Days 84, 168, 252.
- Section 1.3 updated with most recent results for ofatumumab studies.
- Removed all references to baseline bone marrow being required within 8 weeks prior to randomization. Refer to Section 3.1.1 for updated details.
- Section 3.1.1: To be consistent with protocol, removed any requirement for a lymph node biopsy and require a biopsy if suitable per the instructions in Section 3.1.1
- Section 3.1.1.1: Clarified this section refers to the "qualifying" rituximab regimen and when imaging and/or other documentation are required.
- Section 3.1.5 Table 1: Clarified when Survival Follow Up begins and that Survival Follow Up timings may not follow Table 1 exactly, but will follow the Table 1 schedule (i.e. F/U 1 is every 3 months until Month 18 of F/U and F/U 2 is every 12 months until approximately Month 54 of F/U and then Month 60).
- Section 3.1.6: Clarified that the PD Worksheet is required upon diagnosis of PD.
- Section 3.2.2 and Section 3.2.2.1: Upated results based on updated study data.
- Inclusion Criterion #1 now specifies that subjects with a diagnosis of SLL who have a peripheral blood monoclonal B lymphocyte count of 5,000/μL are considered to have CLL and are not eligible for this study.
- Exclusion Criteria #3: high dose steroids ≥ 25 mg prednisolone/day (or equivalent) for 7 consecutive days. Updated from ≥ 100 mg to ≥ 25 mg.
- Section 5.1.3: Added an example to clarify that subjects in Arm A may have first cycle dose of bendamustine initiated on Day 1 or Day 2 of the cycle.

- Section 5.1.3.1: Clarified that local laboratory data must be entered into eCRF when a dose delay or reduction decision is made based on local laboratory data.
- Section 6.3.1: Clarified the number of $CD19^+$ and $CD20^+$ B cells will be assessed by flow cytometry rather than the "surface expression".
- Section 6.3.2, Section 6.3.4, and Time and Events tables (Appendix 2, Appendix 3) footnotes: made consistent to indicate Hepatitis B DNA (if required) will be obtained at each cycle and 1,3,6 months after last ofatumumab dose.
- Section 6.5.7: Clarified that subjects that are HBsAG negative, HBcAb positive and HBV DNA negative may be included in the study but must undergo HBV DNA monitoring per the time and events tables..
- For Japan only: additional directions for Hepatitis monitoring added to Appendix 8
- Section 6.5.7: Table 9 is the correct reference.
- Section 6.5.7: Added text: All SAEs regardless of causality will be reported from 61 days after the last dose of investigational product to the end of the follow-up period or until initiation of subsequent anti-lymphoma therapy is initiated. Any SAE brought to the investigator's attention after the start of subsequent anti-lymphoma therapy and considered by the investigator as possibly related to either ofatumumab or bendamustine must be reported to GSK.
- Follow up for concomitant medications: after 2 years, only steroids, growth factors, transfusions, anticancer, and anti-infectious treatments will be followed from 61 days after the last dose of investigational product to the end of the follow-up period or until initiation of subsequent anti-lymphoma therapy is initiated
- Study Schematic specifies that the IDMC met.
- Time and Events Tables updated to be consistent with protocol text and to clarify timepoints when needed (example: clarified that B cells tracking will be done in accordance with scheduled follow up visits and no extra visits are required).
- Appendix 3: additional biochemistry testing added for 1, 2, 3, 4, 5, 6, 7, and 8 months post-Week 4 of treatment, added for the 1 month follow-up visit, and added for the Month 3 follow-up visit.
- Appendix 3: A 3 day window rather than a ± 3 day window allowed for CT scans.
- For immunoglobulin collection (Appendix 2 and Appendix 3): Flow cytometry and IgG, IgA, IgM done in Arm A only. During treatment, collect immunoglobulins (Ig) no later than every 6 months (collection to correspond with a scheduled visit). B-cells and Immunoglobulins (Ig) will be monitored for a period of 2 years after the last ofatumumab infusion in Arm A or until the number of B-cells and circulating IgG, IgM and IgA have returned to normal or to within baseline values (according to the central laboratory), whichever is earlier. Monitoring will be done during scheduled F/U visits/ F/U will be discontinued in the event the subject is treated with another anti-CD20 therapy

- Appendix 10: updates made to keep this appendix consistent with changes made in Amendment 3.
- Minor changes in Time and Events footnotes for protocol consistency.

Administrative Changes

1. Minor changes have been made throughout the protocol for spelling, grammar, punctuation, and for consistency between sections.
2. Investigator Brochure updated in references
3. Author list edited.
4. Reference to IDMC decision letter included.
5. Title for sponsor signature

11.13 Appendix 13: Protocol Changes for Amendment 5 (07-Feb.-2013) from Amendment 4 (dated 09-April-2012)

Where the Amendment Applies

Amendment 5 is applicable to all study sites that are required to include information from the Study Procedures Manual into Section 6.5.4 of the protocol.

General Protocol Changes for Amendment 5 (07-Feb.-2013) from Amendment 4 (dated 09-April-2012)

6. Specific details on how to handle AEs and SAEs such as infusion reactions, tumor lysis syndrome, progressive multifocal leukoencephalopathyand hepatitis described in Section 6.5.4 of the protocol.

11.14 Appendix 14: Protocol Changes for Amendment 6 (02-DEC.-2013) from Amendment 4 (dated 09-April-2012)

Where the Amendment Applies

Amendment 6 is applicable to all study sites.

Due to country specific requests, some countries were using Amendment 5; whereas, the rest of the world were using Amendment 4. Amendment 6 incorporated changes made in Amendment 5.

General Protocol Changes for Amendment 6 (02-DEC.2013) compared to Amendment 4 (dated 09-April-2012)

If your country was using Amendment 4

7. Exclusion criteria now specifies that physician experienced in care and management of subjects with Hepatitis B to manage/treat subjects who are anti-HBc positive must be consulted
8. Specific details on how to manage AEs and SAEs such as infusion reactions, tumor lysis syndrome, progressive multifocal leukoencephalopathyand hepatitis are described.
9. Instructions for monitoring subjects with Hepatitis B
10. Universal Trial Number added per country request
11. Minor grammer, spelling, and administrative edits

If your country was using Amendment 5:

12. Exclusion criteria now specifies that physician experienced in care and management of subjects with Hepatitis B to manage/treat subjects who are anti-HBc positive must be consulted
13. Instructions for monitoring subjects with Hepatitis B
14. Universal Trial Number added per country request
15. Minor grammer, spelling, and administrative edits

11.15 Appendix 15: Protocol Changes for Amendment 7 (07-JUL-2015) from Amendment 6 (dated 02-Dec-2013)

Where the Amendment Applies

Amendment 7 is applicable to all study sites.

List of Specific Changes

Note: deleted language is presented with a ~~strikethrough~~ and added language is printed in **bold**.

Section: Title Page,Sponsor Information Page and Sponsor Signatory Page

Authors, contacts and sponsor signatory updated to reflect current team members and contact details.

Section: List of Abbreviations

Text changed to include:

FA: Futility Analysis

IA: Interim Analysis

Section: Protocol Summary: Study Design

Original Text:

A total of 256 events in a sample size of 304 evaluable subjects (152 subjects per arm) are needed for the study to have a 90% power to detect a 50% improvement in PFS (PFS) between study arms. Assuming a dropout rate of 12%, the total sample size randomized for both arms combined will be 346 subjects, with approximate study duration of 69 months. Assuming a screening failure rate of 15%, the total number of subjects screened will be approximately 408.

Text changed to:

A total of ~~256~~ **259** events in a sample size of 304 evaluable subjects (152 subjects per arm) are needed for the study to have a 90% power to detect a 50% improvement in PFS (PFS) between study arms. Assuming a dropout rate of 12%, the total sample size randomized for both arms combined will be 346 subjects, with approximate study duration of ~~69~~ **77** months. Assuming a screening failure rate of 15%, the total number of subjects screened will be approximately 408.

Rationale for Change:

Event count increased slightly from 256 to 259 events to allowfor adding an interim analysis and maintaining the overall study alpha-level of 0.05 and 90% power. The approximate duration of the study was increased from 69 months to 77 months as enrollment for the study has declined due to the changes in the current management of patients with rituximab-

refractory iNHL. The original assumption of 6 patients randomized per month has decreased to 4 patients per month over the past year

Section: Protocol Summary: Study Design

Text added:

INTERIM ANALYSIS

An Interim Analysis (IA) for efficacy of the primary endpoint, progression free survival, will occur when approximately two thirds of the total Independent Radiology Review (IRR) events is achieved. At the same time as the IA, a Futility Analysis (FA) will also occur and an Independent Data Monitoring Committee (IDMC) will review the data. Based on the IDMC review of the data available the IDMC will recommend that the study continue without any changes, be stopped to further enrollment, or be terminated.

Rationale for Change:

An IA and a futility analysis have been added. The IA may also allow for an earlier detection of clinical benefit to patients with the ofatumumab and bendamustine combination. The purpose the IA is to review accumulating safety and efficacy data and to also provide an opportunity to terminate the study if there is strong evidence that the ofatumumab and bendamustine combination will fail to show superiority if the study is allowed to run to its planned completion (stopping for futility).

Section 3.1: INVESTIGATIONAL PLAN - Study Design

Original Text:

Primary Analysis

The primary analysis of PFS will use 90% power to detect a 50% treatment effect; a 13.5 vs. 9 month improvement in Arm A (ofatumumab and bendamustine combination therapy) vs. Arm B (bendamustine monotherapy). This trial is an event-driven study design with an event-driven sample size of 256 total events and the final analysis will take place at the time of occurrence of the 256th event. The guideline for the study reaching 256 total events with respect to previously stated assumptions will require the screening of 408 subjects to ensure 346 subjects are randomized and to have a study duration of approximately 69 months from the first day of first subject until the time of the 256th event.

Text changed to:

The primary analysis of PFS will use 90% power to detect a 50% treatment effect; a 13.5 vs. 9 month improvement in Arm A (ofatumumab and bendamustine combination therapy) vs. Arm B (bendamustine monotherapy). This trial is an event-driven study design with an event-driven sample size of ~~256~~ **259** total events and the final analysis will take place at the time of occurrence of the ~~256th~~ **259th** event. The guideline for the study reaching ~~256~~ **259** total events with respect to previously stated assumptions will require the screening of 408 subjects to ensure 346 subjects are randomized and to have a study duration of approximately ~~69~~**77** months from the first day of first subject until the time of the ~~256th~~ **259th** event.

Rationale for Change:

See rationale above for event count increase and study duration increase.

Section 3.1: Investigational Plan – Study Design

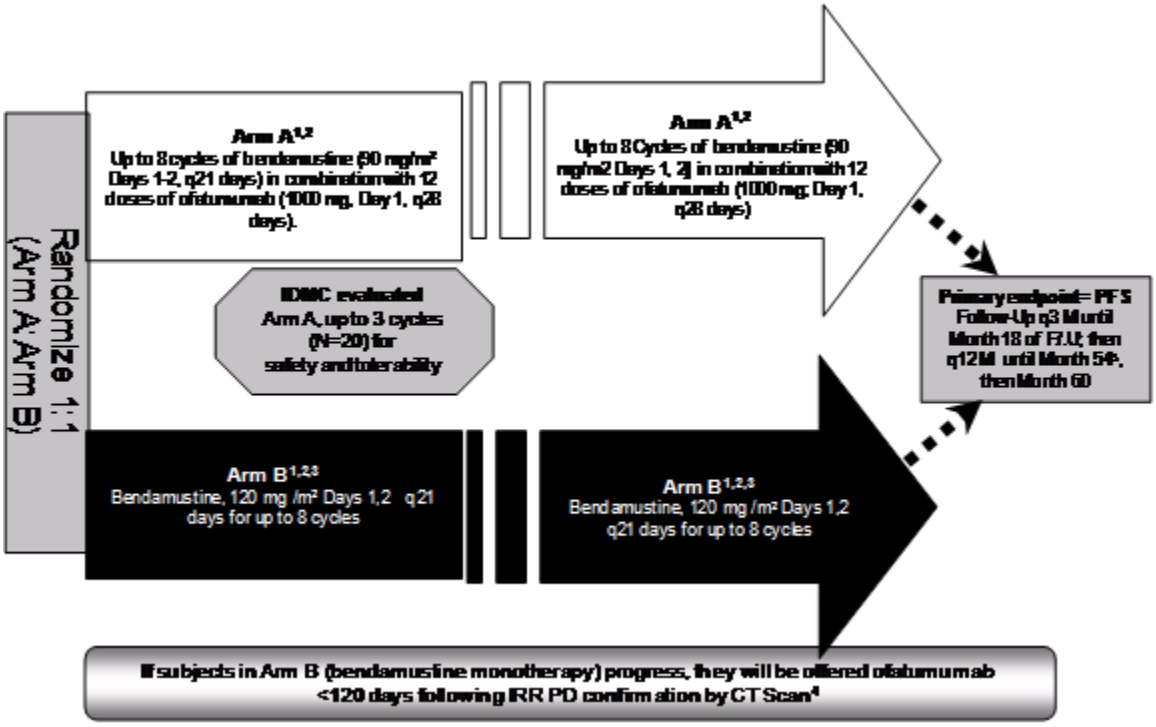
Text added:

Interim Analysis

An Interim Analysis (IA) for efficacy of the primary endpoint, progression free survival, will occur when approximately two thirds (or approximately 172) of the total 259 IRR events is achieved. The IA will be conducted at a significance level of 0.012. At the same time as the IA, a Futility analysis (FA) will also occur. The IDMC will review the efficacy and futility data at this timepoint.

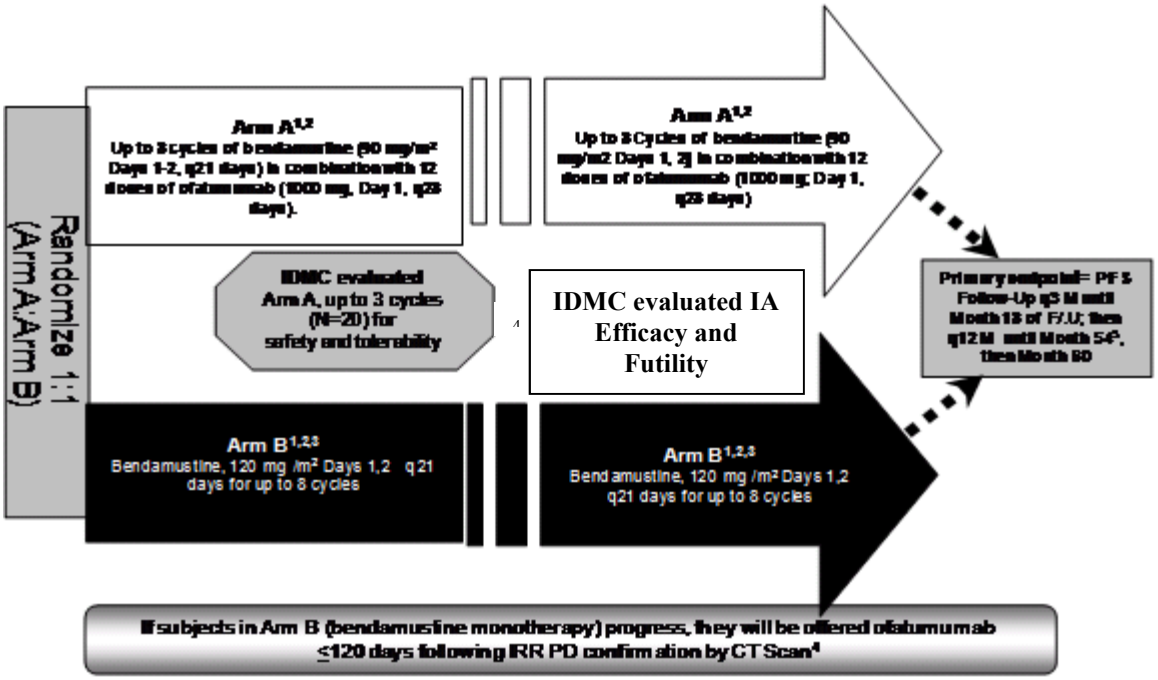
Section 3.1: Investigational Plan - Study Schema

Original Text:



16. The IDMC met and confirmed the safety and tolerability of the Arm A combination therapy. No further IDMC meetings are required.

Text changed to:



1. The IDMC met and confirmed the safety and tolerability of the Arm A combination therapy~~. No further IDMC meetins are required~~. **A further IDMC meeting will review the IA and FA data.**

Rationale for Change:

Inclusion of an interim analysis.

SECTION 3.1.2 RANDOMIZATION AND STRATIFICATION

Original Text:

Centralized randomization numbers within each stratum will be created for treatment assignment using the GSK RandALL randomization system. The investigator will access the GSK Randomization and Medication Ordering System (RAMOS) by telephone to receive the subject's randomization number and initial study medication container number.

Text changed to:

Centralized randomization numbers within each stratum will be 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 **(with randomly permuted blocks within strata).** The investigator will access the GSK Randomization and Medication Ordering System (RAMOS) by telephone to receive the subject's randomization number and initial study medication container number.

Rationale for Change:

Further clarification of the randomisation process.

Section 3.1.5 Follow-Up Phase

Original Text:

TABLE 1 FOLLOW-UP VISIT SCHEDULE AND CT SCAN REQUIREMENTS FOR ARM A AND ARM B

F/U phase[1]	CT scan[3]
3 M F/U 1[2]	Required
6 M F/U 1	Required
9 M F/U 1	Required
12 M F/U 1	Required
15 M F/U 1	Required
18 M F/U 1	Required
30 M F/U 2	Required
42 M F/U 2	Required
54 M F/U 2	Required
60 M F/U 2	Not required[3]

Abbreviations: Follow-Up 1= F/U 1; Follow-Up 2= F/U 2; Month= M

1. This time schedule is for F/U 1, F/U 2, and the Survival F/U (begins 2 months after PD, see footnote 2).
2. The 3 M F/U 1 visit occurs 336 days after randomization (or 3 months after Day 252) in Arm A and Arm B (Appendix 1, Appendix 2). For subjects with PD in Arm B who select ofatumumab monotherapy (these are subjects who enter), this 3 M F/U 1 visit begins 3 months after last ofatumumab monotherapy doseAppendix 3. Note: unlike F/U1 and F/U 2, the Survival F/U begins 2 months after PD then continues every 3 months until Month 18 of F/U then every 12 months until approximately Month 54 of F/U (or 36 months after Month 18 of F/U) and a final visit on Month 60 of F/U.
3. CT scans are required during scheduled F/U 1 and F/U 2 visits in Arm A and Arm B (Appendix 1) with the last required CT scan on Month 54. CT scans for ofatumumab monotherapy following PD in Arm B will be done according to the schedule presented in Appendix 1. CT scans will be required to confirm clinical signs or suspicion of progression if observed outside all scheduled F/U 1 and F/U 2 visits. CT scans are not required for Survival F/U.

Follow-up assessments begin on Day 336 (3 months after Day 252), then according to Appendix 1 and Appendix 2 (also see SPM). In the event of PD, Survival Follow-Up visits begin 2 months after PD is confirmed by CT scan and will follow the time intervals described in Appendix 1. and Appendix 3. Survival F/U begins 2 months after PD then follows the F/U 1 and F/U 2 time intervals described in . Each follow-up visit and assessment will have a time window of ±7 days for Follow-Up Visit #1 and a time window of ±14 days for Follow-Up Visit #2. Follow-up visits will include collection of survival status, concomitant medications, and response assessments, based on RRCML. Survival follow-up visits may be phone calls instead of physician office visits. In addition, subjects will be monitored for safety and efficacy as described. See Appendix 1 and Appendix 2 for a complete list of follow-up procedures.

Text changed to:

TABLE 1 FOLLOW-UP VISIT SCHEDULE AND CT SCAN REQUIREMENTS FOR ARM A AND ARM B

F/U phase[1]	CT scan[1]
3 M F/U 1[2]	Required
6 M F/U 1	Required
9 M F/U 1	Required
12 M F/U 1	Required
15 M F/U 1	Required
18 M F/U 1	Required
30 M F/U 2	Required
42 M F/U 2	Required
54 M F/U 2	Required
60 M F/U 2	Not required[1]

Abbreviations: Follow-Up 1= F/U 1; Follow-Up 2= F/U 2; Month= M

- ~~This time schedule is for F/U 1, F/U 2, and the Survival F/U (begins 2 months after PD, see footnote 2).~~
- ~~The 3 M F/U 1 visit occurs 336 days after randomization (or 3 months after Day 252) in Arm A and Arm B (Appendix 1, Appendix 2). For subjects with PD in Arm B who select ofatumumab monotherapy (these are subjects who enter), this 3 M F/U 1 visit begins 3 months after last ofatumumab monotherapy doseAppendix 3. Note: unlike F/U1 and F/U 2, the Survival F/U begins 2 months after PD then continues every 3 months until Month 18 of F/U then every 12 months until approximately Month 54 of F/U (or 36 months after Month 18 of F/U) and a final visit on Month 60 of F/U.~~

1. CT scans are required during scheduled F/U 1 and F/U 2 visits in Arm A and Arm B (Appendix 1) with the last required CT scan on Month 54. CT scans for ofatumumab monotherapy following PD in Arm B will be done according to the schedule presented in Appendix 1. CT scans will be required to confirm clinical signs or suspicion of progression if observed outside all scheduled F/U 1 and F/U 2 visits. CT scans are not required for Survival F/U.

For patients with SD, PR, or CR, follow-up assessments begin on Day 336 (3 months after Day 252), then **continue** according to Appendix 1, ~~and~~ Appendix 2**, and Table 1** (also see SPM).

For patients with ~~In the event of~~ PD **during the treatment period**, Survival Follow-Up visits begin 2 months after PD is confirmed by CT scan and will follow the time intervals described in Appendix 1, ~~and~~ Appendix 3 and Table 1**, beginning with the 3M F/U visit one month after the 2 M F/U visit**. ~~Survival F/U begins 2 months after PD then follows the F/U 1 and F/U 2 time intervals described in .~~

For patients with PD during the follow up period, Survival Follow-Up visits begin 2 months after PD is confirmed by CT scan. After the 2M F/U visit they will continue on their current follow up schedule according to Appendix 1, Appendix 2 and Table 1.

Each follow-up visit and assessment will have a time window of ±7 days for Follow-Up Visit #1 and a time window of ±14 days for Follow-Up Visit #2. Follow-up visits will include collection of survival status, concomitant medications, and response assessments, based on RRCML. Survival follow-up visits may be phone calls instead of physician office visits. In addition, subjects will be monitored for safety and efficacy as described. See Appendix 1 and Appendix 2 for a complete list of follow-up procedures.

Rationale for Change:

Clarification of instructions for patients moving into Survival Follow-Up

Section 6.4.1: Safety Assessments: Ofatumumab Liver Interruption/Stopping and Follow-up Criteria

Original Text:

Title: **Ofatumumab Liver Interruption/Stopping and Follow-up Criteria**

Text changed to:

Title: ~~**Ofatumumab**~~ **Liver Interruption/Stopping and Follow-up Criteria**

Rationale for Change:

Liver stopping criteria should apply to all patients on study, and not just ofatumumab patients only (Arm A). This will assure the safety of all subjects, and the need to evaluate liver event etiology.

Section 6.4.1.1: Safety Assessments: Liver Chemistry Stopping Criteria

Original Text:

The stopping criteria for ofatumumab are based upon the FDA July 2009 Guidance for Industry, Drug-Induced Liver Injury: Pre-marketing Clinical Evaluation, Section 5, Decision to Stop Drug Administration. The FDA guidance was adapted for oncology ofatumumab protocols such that the criteria for stopping dosing are:

Text changed to:

The stopping criteria for ~~ofatumumab~~ **all subjects** are based upon the FDA July 2009 Guidance for Industry, Drug-Induced Liver Injury: Pre-marketing Clinical Evaluation, Section 5, Decision to Stop Drug Administration. The FDA guidance was adapted for oncology ofatumumab protocols such that the criteria for stopping dosing are:

Rationale for Change:

See rationale above for liver stopping criteria.

Section 6.4.1.3: Safety Assessments: Liver Chemistry Follow-up Assessments

Original Text:

- Blood sample for PK analysis of ofatumumab, obtained as soon as possible but no later than 5 months of last dose (approximately 5 half-lives of the drug). Record the date/time of the PK sample draw and the date/time of the last dose of ofatumumab prior to blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the best approximation. If a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SPM.

Text changed to:

- Blood sample for PK analysis of ofatumumab **(if an Arm A subject),** obtained as soon as possible but no later than 5 months of last dose (approximately 5 half-lives of the drug). Record the date/time of the PK sample draw and the date/time of the last dose of ofatumumab prior to blood sample draw on the eCRF. If the date or time of the last dose is unclear, provide the best approximation. If a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SPM.

Rationale for Change:

Clarification added as PK analysis of ofatumumab if only required per protocol requirements for Arm A patients.

Section 8.2: Study Design Considerations

Text added to include:

INTERIM ANALYSIS

An Interim Analysis (IA) for efficacy of the primary endpoint, progression free survival, will occur when approximately two thirds (or approximately 172) of the total 259 IRR events is achieved. The interim analysis will be conducted at a significance level of 0.012. At the same time as the IA, a Futlity Analysis (FA) will also occur. The Independent Data Monitoring Committee (IDMC) will review the efficacy and futility data at this timepoint. Based on the IDMC review of the data available, as well as the IDMC charter-defined criteria, the IDMC will recommend that the study continue without any changes, be stopped to further enrollment, or be terminated. Further details are specified in the IDMC charter.

The actual significance level at the interim and the final analysis will depend on the actual number of events at the time of analysis - utilizing the O'Brien-Fleming boundary. Should the interim occur at 172 events then the corresponding significance level is 0.012. Additionally, the final analysis (at 259 events) would be tested against 0.046 to maintain the overall type I error rate at 5% two-sided. If the actual event counts differ for the analysis, modification to the significance levels (0.012 for the interim and 0.046 for the

final analysis) would be adjusted as appropriate according to the O'Brien-Fleming spending function.

Rationale for Change:

Inclusion of an interim analysis

Section 8.2.1: Sample Size Assumptions

Original Text:

- Accrual rate is 6 subjects per month

Under the above assumptions, approximately 256 total events from both treatment arms combined are needed for the study to have 90% power. With a sample size of 304 subjects, the duration of the study will be about 62 months (under H_1) to obtain the 256 total events. Assuming a dropout rate of 12%, the total sample size randomized for both arms combined will be 346 subjects, with approximate study duration of 69-months.

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

As stated, this trial is an event-driven study design with an event-driven sample size of 256 total events and the final analysis will take place at the time of occurrence of the 256th event. The guideline for the study reaching 256 total events with respect to previously stated assumptions involve screening of 408 subjects so as to have 346 subjects randomized and to have a study duration of about 69 months from the first day of first subject until the time of the 256th event.

Text changed to:

- Accrual rate is ~~6~~ **5.1** subjects per month

Under the above assumptions, approximately ~~256~~ **259** total events from both treatment arms combined are needed for the study to have 90% power. With a sample size of 304 subjects, the duration of the study will be about ~~62~~ **70** months (under H_1) to obtain the ~~256~~ **259** total events. Assuming a dropout rate of 12%, the total sample size randomized for both arms combined will be 346 subjects, with approximate study duration of ~~69~~ **77** months.

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

As stated, this trial is an event-driven study design with an event-driven sample size of ~~256~~ **259** total events and the final analysis will take place at the time of occurrence of the ~~256th~~ **259th** event. The guideline for the study reaching ~~256~~ **259** total events with respect to previously stated assumptions involve screening of 408 subjects so as to have 346 subjects randomized and to have a study duration of about ~~69~~ **77** months from the first day of first subject until the time of the ~~256th~~ **259th** event.

Rationale for Change:

See rationale above for event count increase and study duration increase.

Section 8.2.2: Sample Size Sensitivity

Original Text:

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 256, and the number of subjects is 304.

Text changed to:

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 ~~256~~ **259**, and the number of subjects is 304.

Rationale for Change:

See rationale above for event count increase.

Section 8.3.1.1 Analysis Population - Four Populations are determined for the analyses:

Original Text:

- The Intent-to-Treat (ITT) Population will include subjects in the final analysis stage who are randomized to the study drugs. This will be the primary population used for all efficacy assessments. In the analyses, subjects will be grouped based on how they are randomized regardless of which treatment they received. The ITT population will also be used for all PRO analyses.

Text changed to:

- The Intent-to-Treat (ITT) Population will include subjects in the final analysis stage who are randomized to the study drugs. This will be the primary population used for all efficacy assessments. In the analyses, subjects will be grouped based on how they are randomized regardless of which treatment they received. The ITT population will ~~also~~ be used for all PRO analyses. **The ITT population will also be utilized for the Interim Analysis(IA) for efficacy and futility based on the number of subjects randomized at the time of the IA.**

Rationale for Change:

Updated due to addition of the Interim Analysis. IA will be conducted using an ITT population as defined.

Section 8.3.3.1 Treatment Comparisons - Primary Comparisons of Interest

Original Text:

The primary treatment comparison of interest will be ofatumumab + bendamustine vs. bendamustine. This will be based on comparing the overall PFS when the total number of events reaches 256 total events (from both arms) using the ITT population.

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 at the 0.05 level, 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.

Text Changed to:

The primary treatment comparison of interest will be ofatumumab + bendamustine vs. bendamustine. This will be based on comparing the overall PFS when the total number of events reaches ~~256 events (from both arms)~~ **172 events for the interim analysis or 259 events for the final analysis** using the ITT population.

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 at the ~~0.05~~ **0.012 level for the interim analysis or 0.046 level for the final analysis**, 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 8.2, the significance levels for the interim and final analysis will be adjusted as appropriate using the O'Brien-Fleming spending function.

Rationale for Change:

Inclusion of an interim analysis.

Section 8.3.3.2 Treatment Comparisons Secondary and Other Comparisons of Interest

Original Text:

The secondary comparisons of interest will be ofatumumab + bendamustine vs. bendamustine, based on the ORR and OS. The ORR and OS will be considered as "inferential secondary endpoints" and will be tested hierarchically only if the primary endpoint, PFS, is significant. Each hypothesis will be tested at alpha level 0.05. If the PFS is significant then the ORR will be tested and if significant, then the OS will be tested.

The other comparisons of interest will be ofatumumab + bendamustine vs. bendamustine, based on the other secondary endpoints at alpha level 0.05. No multiplicity will be considered in the other secondary endpoints and any p-value that is ≤ 0.05 will be identified as nominally significant.

Text Changed to:

The secondary comparisons of interest will be ofatumumab + bendamustine vs. bendamustine, based on the ORR and OS. The ORR and OS will be considered as "inferential secondary endpoints" and will be tested hierarchically only if the primary endpoint, PFS, is significant. Each hypothesis will be tested at alpha level ~~0.05~~ **0.012 for the interim analysis or 0.046 for**

the final analysis. If the PFS is significant then the ORR will be tested and if significant, then the OS will be tested.

The other comparisons of interest will be ofatumumab + bendamustine vs. bendamustine, based on the other secondary endpoints at alpha level ~~0.05~~ **0.012 for the interim analysis or 0.046 for the final analysis**. No multiplicity will be considered in the other secondary endpoints and any p-value that is ~~≤ 0.05~~ ≤ **0.012 for the interim analysis and ≤ 0.046 for the final analysis** will be identified as nominally significant.

Rationale for Change:

Inclusion of an interim analysis

Section 8.3. Data Analysis Considerations:

Text added:

8.3.5 INTERIM ANALYSIS FOR EFFICACY AND FUTILITY

An Interim Analysis (IA) for efficacy will occur when approximately two thirds (or approximately 172) of the total 259 IRR events is achieved. The interim analysis for PFS will be performed by an IDMC utilizing an O'Brien-Fleming spending function with significance level of 0.012 (with 172 events). Performing this interim analysis with an IDMC may allow for an earlier detection of clinical benefit to patients with ofatumumab+bendamustine and if this analysis is positive, may support a submission that enables earlier access to patients. The interim analysis of the primary endpoint, PFS, will be conducted as described in Section 5.1.3.1, and further details of the interim analysis will be provided in the IDMC Charter. The final analysis will be conducted at a significance level of 0.046 (with 259 events) to maintain an overall study significance level of 0.05. At the same time as the IA, a Futlity Analysis (FA) will also occur. This process is further detailed in a charter for the IDMC.

Rationale for Change:

Inclusionof an interim analysis.

Section 8.3.6.1 Efficacy Analyses

Primary Analysis

Original text:

Progression-free survival is defined as the time from randomization until progression or death. The progression events will be defined by well-documented and verifiable data. Details of censoring will be provided in the RAP.

PFS will be tested based on a two-sided test, with a significance level of 0.05. Survival distributions will be estimated using the Kaplan-Meier method, and survival curves will be compared using a stratified log-rank test.

Text changed to:

Progression-free survival is defined as the time from randomization until progression or death. The progression events will be defined by well-documented and verifiable data. Details of censoring will be provided in the RAP.

An interim analysis of the primary endpoint, PFS, will be performed when two thirds of the total number of events have occurred (172 events). The interim analysis for PFS will be performed by an IDMC utilizing a significance level of 0.012. The interim analysis of PFS will be conducted in the same manner as described for the final analysis, and further details of the interim analysis will be provided in the IDMC Charter.

The final analysis of PFS will be tested based on a two-sided test, with a significance level of ~~0.05~~ **0.046**. Survival distributions will be estimated using the Kaplan-Meier method, and survival curves will be compared using a stratified log-rank test.

Rationale for change:

Inclusion of an interim analysis

Section 8.3.6.1 Efficacy Analyses

Original text:

Inferential Secondary Analyses:

- Overall survival

OS is defined as the time from randomization until death. Analysis methods will be similar to those described for the PFS analysis and details of censoring will be provided in the RAP.

OS will be tested on a two sided test, with a significance level of 0.05.- Survival distributions will be estimated using the Kaplan-Meier method, and survival curves will be compared using a stratified log-rank test.

Text changed to:

Inferential Secondary Analyses:

- Overall survival

OS is defined as the time from randomization until death. Analysis methods will be similar to those described for the PFS analysis and details of censoring will be provided in the RAP.

~~OS will be tested on a two sided test, with a significance level of 0.05.~~ Survival distributions will be estimated using the Kaplan-Meier method, and survival curves will be compared using a stratified log-rank test.

Rationale:

Updated to avoid duplication with other sections.

Section 9.7 Independent Data Monitoring Committee (IDMC):

Sub-headings added:

9.7.1 Dose Confirmation for Safety and Tolerability

9.7.2 Interim Analysis

Section 9.7 Independent Data Monitoring Committee (IDMC):

Original text:

STAGE 1 RESULTS FROM IDMC DATA REVIEW

The IDMC met after the first 20 subjects in Arm A received at least 3 cycles of OB. Based on their review of the data as well as the IDMC charter defined criteria to alter the dose in Arm A, the final recommendation from IDMC was to not change the current dose regimen and therefore to allow the study to proceed unchanged [IDMC communication, 2011]. Consequently, there will be no further IDMC meetings and no further dose modifications other than the protocol-directed dose reductions and delays already described in Section 5.1.3.1of this protocol. The safety of subjects enrolled in the study will continue to be monitored by GSK.

Text changed to:

STAGE 1 RESULTS FROM IDMC DATA REVIEW

The IDMC met after the first 20 subjects in Arm A received at least 3 cycles of OB. Based on their review of the data as well as the IDMC charter defined criteria to alter the dose in Arm A, the final recommendation from IDMC was to not change the current dose regimen and therefore to allow the study to proceed unchanged [IDMC communication, 2011]. ~~Consequently~~ **T**here will be~~ no further IDMC meetings and~~ no further dose modifications other than the protocol-directed dose reductions and delays already described in Section 5.1.3.1of this protocol. The safety of subjects enrolled in the study will continue to be monitored by GSK.

Rationale for Change:

Inclusion of an interim analysis.

Section 9.7 Independent Data Monitoring Committee (IDMC):

Text added:

9.7.2 Interim Analysis

An IDMC will be utilised to review the primary endpoint, progression free survival when approximately two thirds of the total IRR events has been reached. The IDMC will review data from the interim analysis and the futility analysis.

The IDMC will meet once to review the data and will recommend that the study continue without any changes, be stopped to further enrolment, or be terminated.

Further details can be found in the IDMC charter.

Rationale for Change:

Inclusion of an interim analysis

11.16 Appendix 16: Protocol Changes for Amendment 8 (18-MAR-2016) from Amendment 7 (dated 07-JUL-2015)

Where the Amendment applies:

Ammendment 8 is applicable to all study sites.

Global Changes:

Section(s)	Change	Rationale
Header/Footer	Changed as per Novartis requirements	Change in study sponsorship from GSK to Novartis
Title Page	Title page replaced as per Novartis requirements	Change in study sponsorship from GSK to Novartis
Sponsor Information Page	The GSK contact information replaced with Novartis contact information	Change in study sponsorship from GSK to Novartis
Sponsor signatory	Change of sponsor signatory	Change in study sponsorship from GSK to Novartis
Multiple	The term 'medical monitor' replaced with 'Medical Lead'	Change in study sponsorship from GSK to Novartis
Multiple	References to GSK or its staff replaced with that of Novartis and its authorized agents	To align with the change of sponsorship from GSK to Novartis
Multiple	References to GSK tools, departments, and concomitant medication deleted	To align with the change of sponsorship from GSK to Novartis
Appendices	References to GSK in figures changed to Novartis	To align with the change of sponsorship from GSK to Novartis
In addition, several typographical and format changes have been made throughout the protocol, but not listed individually.		

List of Specific Changes

Note: deleted language is presented with a ~~strikethrough~~ and added language is printed in **bold**.

Section: Title Page, Sponsor Information Page, and Sponsor Signatory Page

Authors, contacts and sponsor signatory updated to reflect the curren team members and contact details. Also, necessary changes are made to reflect the study transfer from GSK to Novartis.

Section: List of Abbreviations

List has been updated as required.

Trademark information deleted to align with Novartis processes and procedures.

Protocol Summary:

Study Design: Dose Confirmation Cohort

Original text:

The safety of subjects enrolled into the study will continue to be monitored by GlaxosmithKline (GSK).

Text changed to:

The safety of subjects enrolled into the study will continue to be monitored by ~~GlaxosmithKline (GSK)~~ **Novartis**.

Rationale for change:

The rationale for the change is deletion or replacement of all references to GSK or its staff with that of Novartis and its authorized agents to align with the change of sponsorship and make administrative changes to align with Novartis processes and procedures.

Section 3.1: Study Design

Original text:

The safety of subjects enrolled into the study will continue to be monitored by GlaxosmithKline (GSK).

Text changed to:

The safety of subjects enrolled into the study will continue to be monitored by ~~GlaxosmithKline (GSK)~~ **Novartis**.

Rationale for change:

The rationale for the change is deletion or replacement of all references to GSK or its staff with that of Novartis and its authorized agents to align with the change of sponsorship and make administrative changes to align with Novartis processes and procedures.

Section 3.1.1: Screening Phase

Original text:

Review of Materials:

If the investigator wants to use a CT scan done >1 month (+7 days) prior to randomization, the medical monitor must be contacted to determine if CT scan can be accepted.

Text changed to:

If the investigator wants to use a CT scan done >1 month (+7 days) prior to randomization, the ~~medical monitor~~ **Medical Lead** must be contacted to determine if CT scan can be accepted.

Rationale for change:

The rationale for the change is deletion or replacement of all references to GSK or its staff with that of Novartis and its authorized agents to align with the change of sponsorship and make administrative changes to align with Novartis processes and procedures.

Section 3.1.1.1: Documentation of indolent B-cell NHL that is stable or has progressed during or within six months of the end of treatment with rituximab or a rituximab–containing regimen

Original text:

A documentation worksheet verifying the investigator's diagnosis of SD following, or progression during or within 6 months of treatment with rituximab or a rituximab-containing regimen will be required at screening. This documentation worksheet must be sent to GSK prior to randomization and will ask for:

Information about last qualifying rituximab therapy:

- Dates before and dates after last qualifying rituximab-containing regimen
- Type of rituximab therapy and regimen (examples: weekly, monthly):
  - Rituximab (includes monotherapy and maintenance), or
  - Rituximab added to chemotherapy
- Date and type of response associated with last qualifying rituximab-containing regimen

Information regarding imaging:

- Copy of documentation (for example, an imaging report, clinical documentation) prior to last qualifying rituximab-containing regimen is required (if available)
- Copy of documentation confirming PD (for example, an imaging report, clinical documentation) after subject deemed unresponsive or relapsed to rituximab-based regimen is requiredAssurance of an ability to submit, for each subject
  - imaging or other documentation showing disease status before the start of the last qualifying rituximab-containing regimen is requested
  - imaging or other documentation confirming unresponsive or relapse following the last qualifying rituximab regimen is required
  - CT imaging is performed at screening

Subjects will not be enrolled in the study unless the investigator or designate verifies SD following, or progression during or within six months of treatment with rituximab or a rituximab–containing regimen. Submission of the subject's imaging is expected be sent to GSK within one month following randomization.

Text changed to:

A documentation worksheet verifying the investigator's diagnosis of SD following, or progression during or within 6 months of treatment with rituximab or a rituximab-containing regimen will be required at screening. This documentation worksheet must be sent to ~~GSK~~ **Novartis** prior to randomization and will ask for:

Information about last qualifying rituximab therapy:

- Dates before and dates after last qualifying rituximab-containing regimen
- Type of rituximab therapy and regimen (examples: weekly, monthly):
  - Rituximab (includes monotherapy and maintenance), or

- Rituximab added to chemotherapy

- Date and type of response associated with last qualifying rituximab-containing regimen

Information regarding imaging:

- Copy of documentation (for example, an imaging report, clinical documentation) prior to last qualifying rituximab-containing regimen is required (if available)
- Copy of documentation confirming PD (for example, an imaging report, clinical documentation) after subject deemed unresponsive or relapsed to rituximab-based regimen is required
- Assurance of an ability to submit, for each subject
  - imaging or other documentation showing disease status before the start of the last qualifying rituximab-containing regimen is requested
  - imaging or other documentation confirming unresponsive or relapse following the last qualifying rituximab regimen is required
  - CT imaging is performed at screening

Subjects will not be enrolled in the study unless the investigator or designate verifies SD following, or progression during or within six months of treatment with rituximab or a rituximab–containing regimen. Submission of the subject's imaging is expected be sent to ~~GSK~~ **Novartis** within one month following randomization.

Rationale for change:

The rationale for the change is deletion or replacement of all references to GSK or its staff with that of Novartis and its authorized agents to align with the change of sponsorship and make administrative changes to align with Novartis processes and procedures.

Section 3.1.2: Randomization and Stratification

Original text:

Centralized randomization numbers within each stratum will be 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 (with randomly permuted blocks within strata). The investigator will access the GSK Randomization and Medication Ordering System (RAMOS) by telephone to receive the subject's randomization number and initial study medication container number.

Text changed to:

Centralized randomization numbers within each stratum will be 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~~ **a** randomization system (with randomly permuted blocks within strata). The investigator will access the ~~GSK Randomization and Medication Ordering System (RAMOS)~~ **Interactive Voice Response System** by telephone to receive the subject's randomization number and initial study medication container number.

Rationale for change:

The rationale for the change is deletion or replacement of all references to GSK or its staff with that of Novartis and its authorized agents to align with the change of sponsorship and make administrative changes to align with Novartis processes and procedures.

Section 3.1.3: Dose Confirmation for Safety and Tolerability

Original text:

Update: Decision from IDMC Meeting (Stage 1):

The safety of subjects enrolled into the study will continue to be monitored by GSK.

Text changed to:

The safety of subjects enrolled into the study will continue to be monitored by ~~GSK~~ **Novartis**.

Rationale for change:

The rationale for the change is deletion or replacement of all references to GSK or its staff with that of Novartis and its authorized agents to align with the change of sponsorship and make administrative changes to align with Novartis processes and procedures.

Section 4.3: Exclusion Criteria

Original text:

11. Significant concurrent, uncontrolled medical condition that in the opinion of the investigator or GSK medical monitor contraindicates participation this study

Subjects can participate in the study if in the opinion of the investigator and medical monitor it is thought not to affect the subject's safety, the conduct of the study or the interpretation of the data

Text changed to:

11. Significant concurrent, uncontrolled medical condition that in the opinion of the investigator or ~~GSK medical monitor~~ **Novartis Medical Lead** contraindicates participation this study

*Subjects can participate in the study if in the opinion of the investigator and ~~medical monitor~~ **Medical Lead** it is thought not to affect the subject's safety, the conduct of the study or the interpretation of the data*

Rationale for change:

The rationale for the change is deletion or replacement of all references to GSK or its staff with that of Novartis and its authorized agents to align with the change of sponsorship and make administrative changes to align with Novartis processes and procedures.

Section 5.1: Investigational Product and Reference Therapy

Original text:

A Material Safety Data Sheet (MSDS) describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from GSK upon request.

Text changed to:

A Material Safety Data Sheet (MSDS) describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from ~~GSK~~ **Novartis** upon request.

Rationale for change:

The rationale for the change is deletion or replacement of all references to GSK or its staff with that of Novartis and its authorized agents to align with the change of sponsorship and make administrative changes to align with Novartis processes and procedures.

Section 5.1.3.1: Bendamustine Dose Reduction

Original text:

Toxicities must recover to Grade 1 or baseline before the next administration of treatment. If recovery is not met within 2 weeks after the prescribed start of the treatment cycle (i.e., after a 2 week delay), a decision will be made about continuation in the study following consultation with medical monitor.

Text changed to:

Toxicities must recover to Grade 1 or baseline before the next administration of treatment. If recovery is not met within 2 weeks after the prescribed start of the treatment cycle (i.e., after a 2 week delay), a decision will be made about continuation in the study following consultation with ~~medical monitor~~ **Medical Lead**.

Rationale for change:

The rationale for the change is deletion or replacement of all references to GSK or its staff with that of Novartis and its authorized agents to align with the change of sponsorship and make administrative changes to align with Novartis processes and procedures.

Section 5.4: Product Accountability

Original text:

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of bendamustine and GSK investigational product administered to study subjects and the amount received from and returned to GSK, when applicable. Product accountability records must be maintained throughout the course of the study.

Text changed to:

In accordance with local regulatory requirements, the investigator, designated site staff, or head of the medical institution (where applicable) must document the amount of bendamustine and ~~GSK~~ **Novartis** investigational product administered to study subjects and the amount received from and returned to ~~GSK~~ **Novartis**, when applicable. Product accountability records must be maintained throughout the course of the study.

Rationale for change:

The rationale for the change is deletion or replacement of all references to GSK or its staff with that of Novartis and its authorized agents to align with the change of sponsorship and make administrative changes to align with Novartis processes and procedures.

Section 6.2.2: CT Scans

Original text:

The scans must be implemented according to a CT scan manual to be provided to GSK (Imaging Acquisition Guidelines) as mentioned in the SPM.

Text changed to:

The scans must be implemented according to a CT scan manual to be provided to ~~GSK~~ **Novartis** (Imaging Acquisition Guidelines) as mentioned in the SPM.

Rationale for change:

The rationale for the change is deletion or replacement of all references to GSK or its staff with that of Novartis and its authorized agents to align with the change of sponsorship and make administrative changes to align with Novartis processes and procedures.

Section 6.4.1: Liver Interruption/Stopping and Follow-up Criteria

Original text:

Liver chemistry stopping and follow up criteria are a mandatory part of GSK studies and have been designed to assure subject safety and evaluate liver event etiology.

The GSK Safety Review Team will review all events which meet liver chemistry stopping criteria and determine if the event was due to tumor lysis and to exclude drug induced liver injury (DILI) due to ofatumumab.

Text changed to:

Liver chemistry stopping and follow up criteria are a mandatory part of ~~GSK~~ **Novartis** studies and have been designed to assure subject safety and evaluate liver event etiology.

The ~~GSK~~ Novartis Safety ~~Review~~ Monitoring Team will review all events which meet liver chemistry stopping criteria and determine if the event was due to tumor lysis and to exclude drug induced liver injury (DILI) due to ofatumumab.

Rationale for change:

The rationale for the change is deletion or replacement of all references to GSK or its staff with that of Novartis and its authorized agents to align with the change of sponsorship and make administrative changes to align with Novartis processes and procedures.

Section 6.4.1.2: Liver Chemistry Interruption/Stopping and Follow-up Criteria

Original text:

The GSK Medical Monitor and Global Clinical Safety and Pharmacovigilance (GCSP) physician in conjunction with the investigator will review all events which meet liver chemistry stopping criteria to determine if the event was due to tumor lysis, disease related liver involvement, concomitant chemotherapy or other identified cause and to exclude drug induced liver injury (DILI) due to ofatumumab. If the event is determined to be due to causes other than ofatumumab DILI and improvement is observed after withdrawal of ofatumumab, rechallenge may be attempted if deemed appropriate by the GSK Medical Monitor and investigator and in addition to consent of the subject.

‡ ***NOTE****: If serum bilirubin fractionation not immediately available, study drug must be discontinued if ALT > 3xULN* ***and bilirubin >2xULN pending the results of review by the Medical Monitor, GCSP physician and the investigator.*** *Serum bilirubin fractionation must be performed if testing is available. If testing unavailable,* ***record presence of detectable urinary bilirubin on dipstick,*** *indicating direct bilirubin elevations and suggesting liver injury.*

When any of the liver chemistry stopping criteria is met, do the following:

- Immediately stop study treatment
- Report the event to GSK within 24 hours of learning its occurrence

Hold ofatumumab for two weeks, repeat liver chemistry testing at least twice weekly, and call the Medical Monitor to discuss the possibility of re-challenging with ofatumumab.

Text changed to:

The ~~GSK~~ Novartis Medical ~~Monitor~~ Lead and Global Clinical Safety and Pharmacovigilance (GCSP) physician in conjunction with the investigator will review all events which meet liver chemistry stopping criteria to determine if the event was due to tumor lysis, disease related liver involvement, concomitant chemotherapy or other identified cause and to exclude drug induced liver injury (DILI) due to ofatumumab. If the event is determined to be due to causes other than ofatumumab DILI and improvement is observed after withdrawal of ofatumumab, rechallenge may be attempted if deemed appropriate by the ~~GSK~~ Novartis Medical ~~Monitor~~ Lead and investigator and in addition to consent of the subject.

‡ ***NOTE**: If serum bilirubin fractionation not immediately available, study drug must be discontinued if ALT > 3xULN **and bilirubin >2xULN pending the results of review by the Medical ~~Monitor~~ Lead, GCSP physician and the investigator.** Serum bilirubin fractionation must be performed if testing is available. If testing unavailable, **record presence of detectable urinary bilirubin on dipstick,** indicating direct bilirubin elevations and suggesting liver injury.*

When any of the liver chemistry stopping criteria is met, do the following:

- Immediately stop study treatment
- Report the event to ~~GSK~~ **Novartis** within 24 hours of learning its occurrence

Hold ofatumumab for two weeks, repeat liver chemistry testing at least twice weekly, and call the Medical ~~Monitor~~ **Lead** to discuss the possibility of re-challenging with ofatumumab.

Rationale for change:

The rationale for the change is deletion or replacement of all references to GSK or its staff with that of Novartis and its authorized agents to align with the change of sponsorship and make administrative changes to align with Novartis processes and procedures.

Section 6.5.4.1.5: Monitoring of Hepatitis in patients

Original text:

If a subject converts to HBV DNA positive during the study, Hepatitis B treatment may be initiated by the site investigator after consultation with a physician experienced in the care and management of subjects with Hepatitis B and the GSK medical monitor. The risks and benefits of continuing ofatumumab or discontinuing ofatumumab must be discussed with the medical monitor before appropriate treatment decisions are made for that individual subject.

Text changed to:

If a subject converts to HBV DNA positive during the study, Hepatitis B treatment may be initiated by the site investigator after consultation with a physician experienced in the care and management of subjects with Hepatitis B and the ~~GSK medical monitor~~ **Novartis Medical Lead**. The risks and benefits of continuing ofatumumab or discontinuing ofatumumab must be discussed with the ~~medical monitor~~ **Medical Lead** before appropriate treatment decisions are made for that individual subject.

Rationale for change:

The rationale for the change is deletion or replacement of all references to GSK or its staff with that of Novartis and its authorized agents to align with the change of sponsorship and make administrative changes to align with Novartis processes and procedures.

Section 6.5.6: Pregnancy

Original text:

To ensure subject safety, each pregnancy must be reported to GSK within 2 weeks of learning of its occurrence.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the investigational product, must be promptly reported to GSK.

The investigator must attempt to collect pregnancy information about a partner of a male study subject, who becomes pregnant by a male study subject while he is enrolled in the study. Pregnancy information must be reported to GSK as described above.

Text changed to:

To ensure subject safety, each pregnancy must be reported to ~~GSK~~ **Novartis** within ~~2 weeks~~ **24 hours** of learning of its occurrence.

Any SAE occurring in association with a pregnancy brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the investigational product, must be promptly reported to ~~GSK~~ **Novartis**.

The investigator must attempt to collect pregnancy information about a partner of a male study subject, who becomes pregnant by a male study subject while he is enrolled in the study. Pregnancy information must be reported to ~~GSK~~ **Novartis** as described above.

Rationale for change:

The rationale for the change is deletion or replacement of all references to GSK or its staff with that of Novartis and its authorized agents to align with the change of sponsorship and make administrative changes to align with Novartis processes and procedures.

Section 6.5.7: Time Period and Frequency of Detecting AEs and SAEs

Original text:

Any SAE brought to the investigator's attention after the start of subsequent anti-lymphoma therapy and considered by the investigator as possibly related to either ofatumumab or bendamustine must be reported to GSK.

From the time a subject consents to participate in and completes the study (See Section 4.4), all SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to GSK concomitant medication, will be reported promptly to GSK as indicated in Table 9.

From the time a subject consents to participate in and completes the study or withdraws from the study (Section 4.4), all SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to concomitant medication, will be recorded.

Discontinuation of ofatumumab is not mandated; however the investigator must consult the GSK medical monitor to analyze the risk-benefit and determine if appropriate to continue ofatumumab therapy in that individual subject.

Any pre-existing condition or signs and symptoms present prior to investigational product will be recorded as medical history.

Any SAE brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to investigational product must be reported to GSK.

Text changed to:

Any SAE brought to the investigator's attention after the start of subsequent anti-lymphoma therapy and considered by the investigator as possibly related to either ofatumumab or bendamustine must be reported to ~~GSK~~ **Novartis**.

From the time a subject consents to participate in and completes the study (See Section 4.4), all SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) ~~or related to GSK concomitant medication,~~ will be reported promptly to ~~GSK~~ **Novartis** as indicated in Table 9.

From the time a subject consents to participate in and completes the study or withdraws from the study (Section 4.4), all SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) ~~or related to concomitant medication,~~ will be recorded.

Discontinuation of ofatumumab is not mandated; however the investigator must consult the ~~GSK medical monitor~~ **Novartis Medical lead** to analyze the risk-benefit and determine if appropriate to continue ofatumumab therapy in that individual subject.

Any pre-existing condition or signs and symptoms present prior to investigational product will be recorded as medical history.

Any SAE brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to investigational product must be reported to ~~GSK~~ **Novartis**.

Rationale for change:

The rationale for the change is deletion or replacement of all references to GSK or its staff with that of Novartis and its authorized agents to align with the change of sponsorship and make administrative changes to align with Novartis processes and procedures.

Section 6.5.7.1: Monitoring subjects with Hepatitis B

Original text:

If a subject's HBV DNA becomes positive during the study, notify the GSK medical monitor. For subjects who have not completed planned ofatumumab therapy, discuss with the medical monitor the risks and benefits of continuing or discontinuing ofatumumab before appropriate treatment decisions are made for that individual subject.

Text changed to:

If a subject's HBV DNA becomes positive during the study, notify the ~~GSK medical monitor~~ **Novartis Medical Lead**. For subjects who have not completed planned ofatumumab therapy, discuss with the ~~medical monitor~~ **Medical Lead** the risks and benefits of continuing or discontinuing ofatumumab before appropriate treatment decisions are made for that individual subject.

Rationale for change:

The rationale for the change is deletion or replacement of all references to GSK or its staff with that of Novartis and its authorized agents to align with the change of sponsorship and make administrative changes to align with Novartis processes and procedures.

Section 6.5.8: Prompt Reporting of Serious Adverse Events and Other Events to ~~GSK~~ Novartis

Original text:

SAEs and pregnancies and liver chemistries meeting pre-defined stopping criteria will be reported promptly to GSK as described in the following table once the investigator determines that the event meets the protocol definition for that event.

Table 12 SAE reporting

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hours	"SAE" data collection tool	24 hours	Updated "SAE" data collection tool
Pregnancy	2 Weeks	Pregnancy Notification Form	2 Weeks	Pregnancy Follow up Form
Liver chemistry stopping criteria (See Section 6.4.1)	24 to 72 hours	Liver event CRFs and "SAE" data collection tool	24 hours	Updated Liver Event CRF and SAE form and updated "SAE" data collection tool

The method of detecting, recording, evaluating and follow-up of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in the SPM. Procedures for post-study AEs/SAEs are provided in the SPM.

Text changed to:

SAEs and pregnancies and liver chemistries meeting pre-defined stopping criteria will be reported promptly to ~~GSK~~ **Novartis** as described in the following table once the investigator determines that the event meets the protocol definition for that event.

Table 13 SAE reporting

	Initial Reports		Follow-up Information on a Previous Report	
Type of Event	**Time Frame**	**Documents**	**Time Frame**	**Documents**
All SAEs	24 hours	"SAE" data collection tool	24 hours	Updated "SAE" data collection tool
Pregnancy	~~2 Weeks~~ **24 hours**	Pregnancy Notification Form	2 Weeks	Pregnancy Follow up Form
Liver chemistry stopping criteria (See Section 6.4.1)	24 to 72 hours	Liver event CRFs and "SAE" data collection tool	24 hours	Updated Liver Event CRF and SAE form and updated "SAE" data collection tool

The method of detecting, recording, evaluating and follow-up of AEs and SAEs plus procedures for completing and transmitting SAE reports to ~~GSK~~ **Novartis** are provided in the SPM. Procedures for post-study AEs/SAEs are provided in the SPM.

Rationale for change:

The rationale for the change is deletion or replacement of all references to GSK or its staff with that of Novartis and its authorized agents to align with the change of sponsorship and make administrative changes to align with Novartis processes and procedures.

Section 6.5.9: Regulatory reporting requirements for SAEs

Original text:

Prompt notification of SAEs by the investigator to GSK is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/ IEC and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Text changed to:

Prompt notification of SAEs by the investigator to ~~GSK~~ **Novartis** is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

~~GSK~~ **Novartis** has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. ~~GSK~~ **Novartis** will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/ IEC and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and ~~GSK~~ **Novartis** policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from ~~GSK~~ **Novartis** will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Rationale for change:

The rationale for the change is deletion or replacement of all references to GSK or its staff with that of Novartis and its authorized agents to align with the change of sponsorship and make administrative changes to align with Novartis processes and procedures.

Section 7: DATA MANAGEMENT

Original text:

For this study, subject data will be entered into GSK defined eCRFs, transmitted electronically to GSK and combined with data provided from other sources (e.g. laboratory data) in a validated data system.

Clinical data management will be performed in accordance with applicable GSK standards and data cleaning procedures with the objective of removing errors and inconsistencies in the data which would otherwise impact the analysis and reporting objectives, or the credibility of the Clinical Study Report. Adverse events and concomitant medications terms will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and GSKDrug, an internal validated medication dictionary. In all cases, subject initials will not be collected nor transmitted to GSK according to GSK policy.

[An appropriate medical dictionary that covers all approved drugs in studies where Japan is participating will be referenced]. [Select one of the following 2 options: (1 - eDM) "eCRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy" or (2- paper) "Original CRFs will be retained by GSK, while the investigator will retain a copy" .] In all cases, subject initials will not be collected or transmitted to GSK according to GSK policy.

Text changed to:

For this study, subject data will be entered into ~~GSK defined~~ **the** eCRFs, transmitted electronically to ~~GSK~~ **Novartis** and **be** combined with data provided from other sources (e.g. laboratory data) in a validated data system.

Clinical data management will be performed in accordance with applicable ~~GSK~~ standards and data cleaning procedures with the objective of ~~removing~~ **resolving** errors and inconsistencies in the data which would otherwise impact the analysis and reporting objectives, or the credibility of the Clinical Study Report. Adverse events and concomitant medications terms will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and ~~GSKDrug, an internal validated~~ **medication custom drug** dictionary. In all cases, subject initials will not be collected nor transmitted to ~~GSK~~ **Novartis** according to ~~GSK~~ **Novartis** policy.

[An appropriate medical dictionary that covers all approved drugs in studies where Japan is participating will be referenced]. ~~[Select one of the following 2 options:~~ (1 - eDM) "eCRFs (including queries and audit trails) will be retained by ~~GSK~~ **Novartis**, and copies will be sent to the investigator to maintain as the investigator copy"**.** ~~or (2- paper) "Original CRFs will be retained by GSK, while the investigator will retain a copy" .]~~ In all cases, subject initials will not be collected or transmitted to ~~GSK~~ **Novartis** according to ~~GSK~~ **Novartis** policy.

Rationale for change:

The rationale for the change is deletion or replacement of all references to GSK or its staff with that of Novartis and its authorized agents to align with the change of sponsorship and make administrative changes to align with Novartis processes and procedures.

Section 8.2: Study Design Considerations

Original text:

The safety of subjects enrolled into the study will continue to be monitored by GSK.

Text changed to:

The safety of subjects enrolled into the study will continue to be monitored by ~~GSK~~ **Novartis**.

Rationale for change:

The rationale for the change is deletion or replacement of all references to GSK or its staff with that of Novartis and its authorized agents to align with the change of sponsorship and make administrative changes to align with Novartis processes and procedures.

Section 8.3.6.2: Safety Analyses

Original text:

Adverse Events

AEs will be coded using the standard GSK MedDRA dictionary, and grouped by system organ class.

Text changed to:

AEs will be coded using the standard ~~GSK~~ MedDRA dictionary, and grouped by system organ class.

Rationale for change:

The rationale for the change is deletion or replacement of all references to GSK or its staff with that of Novartis and its authorized agents to align with the change of sponsorship and make administrative changes to align with Novartis processes and procedures.

Section 9.1: Regulatory and Ethical Considerations, Including the Informed Consent Process

Original text:

Prior to initiation of a study site, GSK will obtain approval from the appropriate regulatory authority to conduct the study in accordance with applicable country-specific regulatory requirements, including those required under a US Investigational New Drug (IND).

The study will be conducted in accordance with all applicable regulatory requirements, IND Number 11,465.

The study will be conducted in accordance with Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the declaration of Helsinki, including, but not limited to:

- IRB/IEC review and approval of study protocol and any subsequent amendments.
- Subject informed consent.
- Investigator reporting requirements.
- GSK will provide full details of the above procedures, either verbally, in writing, or both.

Text changed to:

Prior to initiation of a study site, ~~GSK~~ **Novartis** will obtain approval from the appropriate regulatory authority to conduct the study in accordance with applicable country-specific regulatory requirements, including those required under a US Investigational New Drug (IND).

The study will be conducted in accordance with all applicable regulatory requirements, IND Number 11,465.

The study will be conducted in accordance with Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the declaration of Helsinki, including, but not limited to:

- IRB/IEC review and approval of study protocol and any subsequent amendments.
- Subject informed consent.
- Investigator reporting requirements.
- ~~GSK~~ **Novartis** will provide full details of the above procedures, either verbally, in writing, or both.

Rationale for change:

The rationale for the change is deletion or replacement of all references to GSK or its staff with that of Novartis and its authorized agents to align with the change of sponsorship and make administrative changes to align with Novartis processes and procedures.

Section 9.2: Quality Control (Study Monitoring)

Original text:

In accordance with applicable regulations, GCP, and GSK procedures, monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements. When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the eCRF will serve as the source document. GSK will monitor the study to ensure that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.
- The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

Text changed to:

In accordance with applicable regulations, GCP, and ~~GSK~~ **Novartis** procedures, **Novartis (or designated Clinical Research Organization) personnel** ~~monitors~~ will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and ~~GSK~~ **Novartis** requirements. When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the eCRF will serve as the source document. ~~GSK~~ **Novartis** will monitor the study to ensure that the:

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

- The investigator and the head of the medical institution (where applicable) agrees to allow the **Novartis (or designated Clinical Research Organization) personnel** ~~monitor~~ direct access to all relevant documents.

Rationale for change:

The rationale for the change is deletion or replacement of all references to GSK or its staff with that of Novartis and its authorized agents to align with the change of sponsorship and make administrative changes to align with Novartis processes and procedures.

Section 9.3: Quality Assurance

Original text:

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.

Text changed to:

To ensure compliance with GCP and all applicable regulatory requirements, ~~GSK~~ **Novartis** may conduct a quality assurance audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.

Rationale for change:

The rationale for the change is deletion or replacement of all references to GSK or its staff with that of Novartis and its authorized agents to align with the change of sponsorship and make administrative changes to align with Novartis processes and procedures.

Section 9.4: Study and Site Closure

Original text:

Upon completion or termination of the study, the GSK monitor will conduct site closure activities with the investigator or site staff (as appropriate), in accordance with applicable regulations, GCP, and GSK Standard Operating Procedures.

GSK reserves the right to temporarily suspend or terminate the study at any time for reasons including (but not limited to) safety issues, ethical issues, or severe noncompliance. If GSK determines that such action is required, GSK will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, GSK will provide advance notice to the investigator or head of the medical institution of the impending action.

If a study is suspended or terminated for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable), and/or institutions conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination.

Text changed to:

Upon completion or termination of the study, the ~~GSK monitor~~ **Novartis (or designated Contract Research Organization) personnel** will conduct site closure activities with the investigator or site staff (as appropriate), in accordance with applicable regulations, GCP, and ~~GSK~~ **Novartis** Standard Operating Procedures.

~~GSK~~ **Novartis** reserves the right to temporarily suspend or terminate the study at any time for reasons including (but not limited to) safety issues, ethical issues, or severe noncompliance. If ~~GSK~~ **Novartis** determines that such action is required, ~~GSK~~ **Novartis** will discuss the reasons for taking such action with the investigator or head of the medical institution (where applicable). When feasible, ~~GSK~~ **Novartis** will provide advance notice to the investigator or head of the medical institution of the impending action.

If a study is suspended or terminated for safety reasons, ~~GSK~~ **Novartis** will promptly inform all investigators, heads of the medical institutions (where applicable), and/or institutions conducting the study. ~~GSK~~ **Novartis** will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination.

Rationale for change:

The rationale for the change is deletion or replacement of all references to GSK or its staff with that of Novartis and its authorized agents to align with the change of sponsorship and make administrative changes to align with Novartis processes and procedures.

Section 9.5: Records Retention

Original text:

Following closure of the study, the investigator or head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

GSK will inform the investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, GSK standard operating procedures, and/or institutional requirements.

The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that the investigator is no longer associated with the site.

Text changed to:

Following closure of the study, the investigator or head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere) in a safe and secure location. The records must be easily accessible when needed (e.g., for a ~~GSK~~ **Novartis** audit or regulatory inspection) and must be

available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of the records may be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution must be exercised before such action is taken. The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original. In addition, they must meet accessibility and retrieval standards, including regeneration of a hard copy, if required. The investigator must also ensure that an acceptable back-up of the reproductions exists and that there is an acceptable quality control procedure in place for creating the reproductions.

~~GSK will inform the investigator of the time period for retaining the site records in order to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to a particular site, as dictated by local laws/regulations, GSK standard operating procedures, and/or institutional requirements.~~

Essential documents (written and electronic) should be retained for a period of not less than fifteen (15) years from the completion of the Clinical Trial unless the Sponsor provides written permission to dispose of them or, requires their retention for an additional period of time because of applicable laws, regulations and/or guidelines.

The investigator must notify ~~GSK~~ **Novartis** of any changes in the archival arrangements, including, but not limited to archival of records at an off-site facility or transfer of ownership of the records in the event that the investigator is no longer associated with the site.

Rationale for change:

The rationale for the change is deletion or replacement of all references to GSK or its staff with that of Novartis and its authorized agents to align with the change of sponsorship and make administrative changes to align with Novartis processes and procedures.

Section 9.6: Provision of Study Results and Information to Investigators

Original text:

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

Upon completion of the clinical study report, GSK will ensure public disclosure of the clinical trial research results via the GSK Clinical Trials Register according to the GSK Standard Operating Procedure and provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

Text changed to:

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a ~~GSK~~ **Novartis** site or other mutually-agreeable location.

Upon completion of the clinical study report, ~~GSK~~ **Novartis** will ensure public disclosure of the clinical trial research results via the ~~GSK~~ **Novartis** Clinical Trials Register according to the ~~GSK~~ **Novartis** Standard Operating Procedure and provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate. **In addition, upon study completion and finalization of study report, Novartis aims to submit results of the study for publication.**

When publication is not feasible, please refer to the Novartis Clinical Trial Results website (...novartisclinicaltrials.com) for a summary of the trial results.

Rationale for change:

The rationale for the change is deletion or replacement of all references to GSK or its staff with that of Novartis and its authorized agents to align with the change of sponsorship and make administrative changes to align with Novartis processes and procedures.

Section 9.7.1: Dose Confirmation for Safety and Tolerability

Original text:

Stage 1 Results from IDMC Data Review

The safety of subjects enrolled in the study will continue to be monitored by GSK.

Text changed to:

The safety of subjects enrolled in the study will continue to be monitored by ~~GSK~~ **Novartis**.

Rationale for change:

The rationale for the change is deletion or replacement of all references to GSK or its staff with that of Novartis and its authorized agents to align with the change of sponsorship and make administrative changes to align with Novartis processes and procedures.

Section 11: Appendices

Text changed to:

All references to GSK and medical monitor has been replaced with Novartis and Medical Lead in the relevant sections, respectively.

Rationale for change:

The rationale for the change is deletion or replacement of all references to GSK or its staff with that of Novartis and its authorized agents to align with the change of sponsorship and make administrative changes to align with Novartis processes and procedures.

Section 11.4: Appendices 1, 2, 3, and 4

Text changed to:

All references to GSK has been replaced with Novartis.

Rationale for change:

The rationale for the change is deletion or replacement of all references to GSK or its staff with that of Novartis and its authorized agents to align with the change of sponsorship and make administrative changes to align with Novartis processes and procedures.