Official Title: A Non-Interventional, Retrospective and Prospective, Multicenter, Single Arm Study Evaluating the Effectiveness and Safety of Obinutuzumab in Patients with Previously Untreated Advanced Follicular Lymphoma

NCT Number: NCT04034056

Document Date: Protocol Amendment Version 2: 23-May-2021

NIS PROTOCOL AMENDMENT

TITLE:	**A NON-INTERVENTIONAL, RETROSPECTIVE AND PROSPECTIVE, MULTICENTER, SINGLE ARM STUDY EVALUATING THE EFFECTIVENESS AND SAFETY OF OBINUTUZUMAB IN PATIENTS WITH PREVIOUSLY UNTREATED ADVANCED FOLLICULAR LYMPHOMA** Short title: **U**ntreated Follicula**R** Lymphoma treated with O**B**inituzum**A**b in a **N**on-interventional study (URBAN)
PROTOCOL NUMBER:	ML41215
VERSION NUMBER:	2.0
STUDIED MEDICINAL PRODUCT	Obinutuzumab
MARKETING AUTHORIZATION HOLDER:	Roche Registration GmbH Emil-Barell-Strasse 1 D-79639 Grenzach-Wyhlen - Germany
DATE FINAL:	Version 1.0: 16-May-2019
DATE AMENDED	Version 2.0: See electronic date stamp below

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	**Title**	**Approver's Name**
23-May-2021 08:54:07	Company Signatory	[redacted]

PROTOCOL AMENDMENT, VERSION 2.0: RATIONALE

Protocol ML41215 has been amended to align the protocol to the protocol template Version 7.0 released on 16 Dec 2019 and to implement other changes.

Changes to protocol to align the protocol to the protocol template Version 7.0 released on 16 Dec 2019 are as follows:

- A new section (Section 6.2.2: Recruitment Procedure) has been added to describe procedures for recruitment.
- Section 6.8.4 (Retention of Records): record retention requirements have been updated.
- Section 7.2 (Informed Consent): details about the accountability of the physician on the ICF administration process.
- Section 7.4 (Confidentiality): a description of any foreseen further use of data has been added.
- A new section (Section 8.3: Reporting of Products Complaints Without Adverse Events) has been added to define procedures for reporting of Roche product complaints without Adverse Events.

Additional changes to the protocol are as follows:

- Synopsis, Section 5.2.3 and Section 6.3.4 – Other objectives and variables updated
- Synopsis - Study design and Appendix 2. Minimum requirements for follow-up data have been added.
- Synopsis – *Data Analysis* , and Section 6.7.4 an additional Interim Analysis has been added
- Synopsis – End of study. Further specifications have been added.
- Section 6.4.2 and Appendix 2. Details on time for administration of PRO questionnaires have been added.
- Section 6.4.3. referral to “appendix 2” has been removed because it is not applicable for this study.
- Section 6.7. The program used for statistical analysis has been changed.
- Section 6.7.3. Text has been removed (“no biomarker analysis is scheduled in the study”), and replaced with other scheduled analyses (use of Obinutuzumab in the real world setting, prescription profile, and impact of COVID-19).
- Section 6.8.5. Details of administrative procedures have been changed.
- Section 8.1.1.2. The list of adverse events of special interest has been changed.
- Section 8.1.2.2. A specification on procedures for recording of adverse events has been added.

- Section 8.1.3.4. The paragraph about Pregnancies in Female Partners of Male Patients has been removed

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

PROTOCOL AMENDMENT, VERSION 2.0: SUMMARY OF CHANGES

PROTOCOL SYNOPSIS (Other Objectives – other Variables of interest) and Section 5.2.3 (Other Objectives) and Section 6.3.4 (Other Variables of Interest)

The following objectives have been added:

- *To explore effectiveness of Obinutuzumab in the real world setting;*
- *To explore prescription profile*
- *To explore COVID-19 impact on therapy adherence*

PROTOCOL SYNOPSIS (Study design, 4th paragraph) and Appendix 2 (Data Collection Overview (as per Standard of Care), item b

The following sentence has been added:

'Follow-up data will include at least tumor assessments*, new anti-lymphoma therapy informations* and safety data'.

PROTOCOL SYNOPSIS (Data Analysis) and SECTION 6.7.4 (Interim and Final Analyses and Timing of Analyses)

The following sentences have been added:

"A second interim analysis will be performed approximately two years after the first patient included in the study in order to evaluate safety and primary and secondary effectiveness data, and the impact of COVID-19 on the patient management.
The results of the first two interim analysis will be compared.
The final Analysis will be performed at the end of the study."

PROTOCOL SYNOPSIS (End of study) and Section 6.1.1 (Overview of Study design), End of Study

The following sentence:

'The end of the study will be the date from which the last information of the last patient is recorded in the study database.'

has been replaced with the following:

'The end of the study will be the date from which the last information of the last patient *still in the study* is recorded in the study database.'

SECTION 4.1 (STUDY RATIONALE)

The following sentence:

“For information on the condition under observation and on the Obinutuzumab please refer to the Investigator's Brochure and to the most recent version of the Summary of Product Characteristics (SmPC) of Gazyvaro®, i.e. the brand name of Obinutuzumab, for further details on nonclinical and clinical studies”.

has been replaced with the following:

“For information on the condition under observation and on the Obinutuzumab please refer ~~to the Investigator's Brochure and~~ to the most recent version of the Summary of Product Characteristics (SmPC) of Gazyvaro®, i.e. the brand name of Obinutuzumab, for further details on nonclinical and clinical studies”.

SECTION 6.2.2 (Recruitment Procedure):

This section has been added to describe procedures for recruitment, to align the protocol to the protocol template Version 7.0 released on 16 Dec 2019.

6.2.2 Recruitment Procedure

‘*No specific procedures for recruitment (e.g. advertisements, published information or other) were used for the study.*

The Principal Investigator or a co-investigator in each investigational site will verify the eligibility of each patient for the participation in the study based on adherence to inclusion/exclusion criteria. Eligible patients who signed the ICF were then included in the study’.

SECTION 6.4.2 (Data Collected During the Observation Period), last paragraph and Appendix 2 (Data Collection Overview (as per Standard of Care), item g:

The following sentence:
‘PRO questionnaires (FACT-Lym, EQ-5D) should be administered prior to any treatment and assessments’.

Has been replaced with the following sentence:

‘PRO questionnaires (FACT-Lym, EQ-5D) should be administered *on Day 1 of alternate cycles during induction treatment period and at each cycle during manteinace treatment period. PRO Questionnaires should be administered on Day 1 of the cycle prior to any treatment and assessments, i.e. PRO questionnaires should be collected only when corresponding to a treatment cycle.* PRO questionnaires should also be administered at first visit after reporting disease progression.

Please see Appendix 2 for the data collection overview (as per standard of care).'

SECTION 6.4.3 (Data Collected at Study Completion):

As no predetermined study completion visit is not scheduled, the following text has been removed:

'*Please see Appendix 2 for the data collection overview at the study completion visit'*.

SECTION 6.7 (STATISTICAL CONSIDERATIONS):

The following text in the second sentence:

'*The statistical analysis will be performed using the SAS System version 9.4 or higher'*.

Has been replaced with the following text to update the program used for statistical analysis:

'*The statistical analysis will be performed using the R System*.

SECTION 6.7.3. (Other Analyses):

As no biomarkers analyses are scheduled in the study, the following sentence has been deleted:

'*The results of biomarker analyses will be presented using descriptive statistics only*.'

Details of other analyses have been added with the following text:
The following other analyses will be performed:

Use of Obinutuzumab in the real world setting

Descriptive statistics for the use of Obinutuzumab in real world setting will be performed.

At least the following conditions will be considered in the analysis:

- *Not performing obinutuzumab administration on Day 8 and Day 15 in Cycle 1 (without safety reasons)*
- *Maintenance period: administration of obinutizumab in an interval superior to 10 days from the expected date (every 2 months per label). NOTE: An analysis will be performed to assess if this condition will have impact on efficacy parameters (PFS/ POD24) and to explore the delay reason (COVID-19 or others)*
- *All the chemotherapy scheme used with Obinutuzumab in the real word setting*

Prescription profile

Obinutuzumab prescription profile and chemotherapy backbone choice by Italian region, age range, patient's profile and site dimension (outlying sites/universities, etc.)

Impact of COVID-19

- *Safety (infections and COVID-19 related events)*
- *Choice of chemotherapy in combination with Obinutuzumab*
- *Maintenance delay or interruption due to pandemic status*
- *Therapy interruption due to patient's complications caused by COVID-19*

SECTION 6.7.4 (Interim and Final Analyses and Timing of Analyses)

The following sentences have been added:

"A second interim analysis will be performed approximately two years after the first patient included in the study in order to evaluate safety and primary and secondary effectiveness data, and the impact of COVID-19 on the patient management.

The results of the first two interim analysis will be compared.

The final Analysis will be performed at the end of the study."

SECTION 6.8.4 (Retention of Records):

The following sentence has been added at the beginning of the section to align the protocol to the protocol template Version 7.0 released on 16 Dec 2019:

Archiving at the study site has to be for 15 years after final study report or first publication of study results, whichever comes later.

SECTION 6.8.4 (Retention of Records):

The following text:
"*Records and documents pertaining to the conduct of this study, including eCRFs and Informed Consent Forms, must be retained by the physician for at least 15 years after completion or discontinuation of the study, or for the length of the time required by relevant national or local health authorities, whichever is longer"*

has been changed with:

"*Records and documents pertaining to the conduct of this study, including eCRFs and Informed Consent Forms, must be retained by the ~~physician~~MAH for at least ~~1~~25 years after completion or discontinuation of the study, or for the length of the time required by relevant national or local health authorities, whichever is longer"*

SECTION 6.8.5 (Administrative Structure):

The following text:

‘*Enrolment will occur through an interactive web response system (IWRS) or similar system to capture electronically enrolled patients.*

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

Has been replaced with:

‘*Enrolment will occur through an eCRF system to capture electronically enrolled patients.*

Local laboratories will be used for routine monitoring; local laboratory ranges will be included in eCRF as applicable’.

SECTION 7.2 (Informed Consent):

To align the protocol to the protocol template Version 7.0 released on 16 Dec 2019, the following text:

‘*It is the accountability of the physician to obtain written informed consent from each patient participating in the study, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study.*’

has been replaced with the following text:

‘*It is the accountability of the physician for ascertaining that the subject has comprehended the information and to obtain written informed consent from each patient participating in the study, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study.*’.
Furthermore, the following sentences have been changed with the added words in italics:

"The sponsor’s sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child’s Assent or Caregiver's Informed Consent Form, if applicable) *and the privacy form* will be provided to each site."

"The Consent *and Privacy Forms* must be signed and dated by the patient or the patient’s legally authorized representative before start of documentation of his or her data in the CRF."

"A copy of each signed *and dated* Consent Form must be provided to the patient or the patient’s legally authorized representative."

SECTION 7.4 (Confidentiality):

The following text has been added (third paragraph) to align the protocol to the protocol template Version 7.0 released on 16 Dec 2019:

‘*The sponsor, including affiliates, collaborators and licensees may use study data labeled with the patient ID numbers. Study data may also be shared with independent researchers or government agencies, but only after personal information that can identify the patient has been removed. Patients’ study data may be combined with other patient’s data and/or linked to other data collected from the patients. Patients’ study data may be used to help better understand why people get diseases, how to best*

prevent, diagnose and treat diseases, and to develop and deliver access to new medicines, medical devices, and healthcare solutions to advance patient care'.

SECTION 8.1.1.2 (Assessment of Serious Adverse Events (Immediately Reportable to the Marketing Authorization Holder), Non-serious Adverse Events of Special Interest (AESI) and Other Non-serious Adverse Events)

The following list of Adverse events of special interest:

- *Serious IRRs;*
- *Tumour lysis syndrome (irrespective of regulatory seriousness criteria);*
- *Serious neutropenia*
- *Serious infections;*
- *Hepatitis B reactivation while receiving the appropriate anti-viral therapy***.**

Has been replaced with the following list of Adverse events of special interest:

- *Tumor lysis syndrome (TLS), irrespective of causality*
- *Second malignancies*
- *Cases of potential medicine-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Appendix 3).*
- *Suspected transmission of an infectious agent by the study medicine, as defined below:*
  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term only applies when a contamination of the study medicine is suspected.

SECTION 8.1.2.2 (Procedures for Recording of Adverse Events):

This specification has been added (8th bullet):

'*Deaths that are clearly attributable to disease progression must not be reported as an AE'.*

The following sentence (13rd bullet)

Quality Defects and Falsified Medicinal Products

has been changed with

*'*Quality Defects, Falsified Medicinal Products and *Product Complaints'*

SECTION 8.1.3.4 (Reporting Requirements for Pregnancies/Breastfeeding):

The paragraph “Pregnanacies in Female Partners of Male Patients” has been removed because not applicable.

SECTION 8.3 (Reporting of Products Complaints Without Adverse Events):

This section has been added to define procedures for reporting of Roche product complaints without Adverse Events, to align the protocol to the protocol template Version 7.0 released on 16 Dec 2019:

8.3 REPORTING OF PRODUCT COMPLAINTS WITHOUT ADVERSE EVENTS

Report Roche product complaints without Adverse Events, where Product Complaint is any written or oral information received from a complainant that alleges deficiencies related to Identity, Quality, Safety, Strength, Purity, Reliability, Durability, Effectiveness, or Performance of a product after it has been released and distributed to the commercial market, to the sponsor. Report non-Roche-product complaints as per local regulation.

*APPENDIX 2 (*Data collection Overview) item h

The following words “AEs/SAEs/IRR/ADR” have been replaced with “*AEs/SAEs/AESI/SS*”.

APPENDIX 3.3.12 (OVERDOSES, MISUSES, ABUSES, OFF-LABEL USE, OCCUPATIONAL EXPOSURE, OR MEDICATION ERROR)

The following sentence:

‘Any overdose, misuse, abuse, off-label use, occupational exposure, medication error (including intercepted or potential), or any other incorrect administration of medicine under observation should be noted in the Drug Administration section of the CRF.’

has been replaced by:

‘Any overdose, misuse, abuse, off-label use, occupational exposure, medication error (including intercepted or potential), or any other incorrect administration of medicine under observation should be noted in the Drug Administration section of the CRF *as Special Situation (SS)*’.

NIS PROTOCOL (PRIMARY DATA COLLECTION)

TITLE:	**A NON-INTERVENTIONAL, RETROSPECTIVE AND PROSPECTIVE, MULTICENTER, SINGLE ARM STUDY EVALUATING THE EFFECTIVENESS AND SAFETY OF OBINUTUZUMAB IN PATIENTS WITH PREVIOUSLY UNTREATED ADVANCED FOLLICULAR LYMPHOMA** Short title: **U**ntreated Follicula**R** Lymphoma treated with O**B**inituzum**A**b in a **N**on-interventional study (URBAN)
PROTOCOL NUMBER:	ML41215
VERSION NUMBER:	2.0
STUDIED MEDICINAL PRODUCT	Obinutuzumab
AUTHOR:	SPARC Consulting Srl Via Archimede 94 - 20129 Milan, Italy Mail: [redacted] Phone number: ++ 39 02 43119667 / 87071294; Fax number: ++ 39 02 45476209
DATE FINAL:	See electronic date stamp
MARKETING AUTHORIZATION HOLDER:	Roche Registration GmbH Emil-Barell-Strasse 1 D-79639 Grenzach-Wyhlen - Germany
SPONSOR	Roche S.p.A. - Viale G.B. Stucchi 110 20900 Monza (MB) – Italy

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A NON-INTERVENTIONAL, RETROSPECTIVE AND PROSPECTIVE, MULTICENTER, SINGLE ARM STUDY EVALUATING THE EFFECTIVENESS AND SAFETY OF OBINUTUZUMAB IN PATIENTS WITH PREVIOUSLY UNTREATED ADVANCED FOLLICULAR LYMPHOMA** Short title: **U**ntreated Follicula**R** Lymphoma treated with O**B**inituzum**A**b in a **N**on-interventional study (URBAN)
PROTOCOL NUMBER:	ML41215
VERSION NUMBER:	2.0
STUDIED MEDICINAL PRODUCT	Obinutuzumab
SPONSOR	Roche S.p.A. Viale G.B. Stucchi 110 20900 Monza (MB) – Italy

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

_____
Treating Physician's Name (print)

_____ _____
Treating Physician's Signature Date

Please return a copy of this form to the CRA of this trial. Please retain the signed original for your study files.

1. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADCC	Antibody Dependent Cellular Cytotoxicity
ADCP	Antibody Dependent Cellular Phagocytosis
AE	Adverse Event
AESI	Adverse Event of Special Interest
AIFA	Agenzia Italiana del Farmaco
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutical Classification
BM	Bone Marrow
CDC	Complement Dependent Cytotoxicity
CHOP	Cyclophosphamide, Doxorubicin, Vincristine, Prednisone
CI	Confidence Interval
CLL	Chronic Lymphocytic Leukemia
CR	Complete Response
CR30	Complete Response at 30 months
CRO	Contract Research Organization
CRu	Complete Response unconfirmed
CTCAE	Common Terminology Criteria for Adverse Events
CVP	Cyclophosphamide, Vincristine, Prednisone
DoR	Duration of Response
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Oncology Cooperative Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EMA	European Medicine Agency
ePRO	Electronic Patient-reported Outcome
EQ-5D-5L	EuroQol 5-Dimension Questionnaire, 5-level version
EU	European Union
FACT-G	Functional Assessment of Cancer Therapy - General
FACT-Lym	Functional Assessment of Chronic illness Therapy-Lymphoma
FDG	18F-fluorodeoxyglucose
FL	Follicular Lymphoma
FLIPI	Follicular Lymphoma International Prognostic Index

Abbreviation	Definition
GPP	Good Pharmacoepidemiological Practices
HCP	Healthcare Professional
HIV	Human Immunodeficiency Virus
ICH	International Council for Harmonisation
IRB	Institutional Review Board
IRR	Infusion-related Reaction
ISPE	International Society of Pharmacoepidemiology
IWRS	Interactive Web Response System
LDH	Lactate Dehydrogenase
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NHL	Non-Hodgkin Lymphoma
NK	Natural Killer
ORR	Overall response Rate
OS	Overall Survival
PET	Positron Emission Tomography
PFS	Progression-free Survival
PR	Partial Response
POD24	Progression of disease at 2 years
PRO	Patient-reported Outcome
PS	Performance Status
PT	Preferred Term
QoL	Quality of Life
RBC	Red Blood Cells
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	The Statistical Analysis System software
SD	Stable Disease
SDV	Source Data Verification
SmPC	Summary of Product Characteristics
SOC	System Organ Class
STD	Standard Deviation
TEAE	Treatment-Emergent Adverse Event
TTLCB	Time from first dose to Loss of Clinical Benefit
TTNT	Time-To-Next Treatment

Abbreviation	Definition
ULN	Upper Limit of Normal
WBC	White Blood Cells
WHO-DRL	World Health Organization-Drug Reference List

2. SYNOPSIS

TITLE:	**A NON-INTERVENTIONAL, RETROSPECTIVE AND PROSPECTIVE, MULTICENTER, SINGLE ARM STUDY EVALUATING THE EFFECTIVENESS AND SAFETY OF OBINUTUZUMAB IN PATIENTS WITH PREVIOUSLY UNTREATED ADVANCED FOLLICULAR LYMPHOMA** Short title: **U**ntreated Follicula**R** Lymphoma treated with
PROTOCOL NUMBER:	ML41215
VERSION NUMBER:	1
DATE OF SYNOPSIS:	29 Oct 2020
STUDIED MEDICINAL PRODUCT	Obinutuzumab
MAIN AUTHOR:	SPARC Consulting Srl Via Archimede 94 20129 Milan, Italy
INDICATION:	Untreated advanced follicular lymphoma
SPONSOR	Roche S.p.A Viale G.B. Stucchi 110 20900 Monza (MB) – Italy

Research Question and Objectives

This study will evaluate the effectiveness and safety of Obinutuzumab in patients with previously untreated advanced follicular lymphoma (FL) treated with Obinutuzumab in routine clinical care as measured by the proportion of patients relapsed within 24 months from start of therapy (POD24).

Effectiveness Objectives

The primary effectiveness objective for this study is as follows:

- To evaluate the effectiveness of Obinutuzumab in combination with chemotherapy in previously untreated advanced follicular lymphoma (FL) patients, in the real world setting as measured by the proportion of patients relapsed within 24 months from start of therapy (POD24);

The secondary effectiveness objectives for this study are as follows:

- To evaluate the progression free survival (PFS) at 2 and 3 years;
- To evaluate the overall and complete response rates at mid and end of induction, and during and after maintenance therapy (including the complete response rate at 30 months [CR30]), as per clinical practice, with and without 18F-fluorodeoxyglucose−positron emission tomography (FDG-PET);
- To describe patient/disease characteristics and the second line regimens prescribed for patients who progressed after first line therapy during the overall study duration and within 24 months from start of therapy (POD24);

- To explore the effectiveness of Obinutuzumab in different patient subgroups, stratified by follicular lymphoma International Prognostic Index (FLIPI) – intermediate and high, ECOG performance status (PS), age at study entry, chemotherapy backbone choice, hepatitis infection (history of past/resolved infection or latent HBV after prophylaxis as per standard treatment guidelines), presence of autoimmune disease, history of renal failure and liver failure.

Safety Objective

The safety objective for this study is as follows:

- To evaluate the safety of Obinutuzumab in a real-world setting.

Other Objectives

- To describe the treatment pattern in first and second line of treatment;
- To evaluate methods applied to tumor and response evaluations according to used guidelines and clinical practice;
- To evaluate the FDG-PET response at end of induction and end of maintenance, as per clinical practice;
- To evaluate the Quality of life;
- To evaluate the presence of B symptoms;
- *To explore effectiveness of Obinutuzumab in real world setting*
- *To explore prescription profile*
- *To explore COVID-19 impact on therapy adherence*

Study Design

This is a retrospective and prospective primary data collection and secondary data use, non-interventional, multi-centre study designed to assess real-world effectiveness and safety of Obinutuzumab in previously untreated advanced FL patients, prescribed in first line with Obinutuzumab and chemotherapy, according to existing label.

The study will be conducted in approximately 50 Italian centres distributed all across the country and will collect data during treatment with Obinutuzumab and up to 3.5 years following the start of the treatment. Enrolment will be competitive across sites. Since the study is observational, the treating physician will make all treatment decisions according to his/her regular practice independent of this study. No treatment regimen is mandated by this protocol. Patients should be included after the start of treatment, including newly diagnosed FL patients. Patients included should have performed at least 2 cycles of induction treatment with Obinutuzumab and chemotherapy within 1 year from beginning of treatment.

During the treatment with Obinutuzumab, patient data will be collected at the clinical visits planned by the treating physician, including retrospective data of cycles performed before enrolment, baseline data and medical history. The collection of retrospective data will be those generated from the start of treatment with Obinutuzumab to study entry.

After cessation of Obinutuzumab treatment, patient data will be collected approximately every 3-6 months, as part of routine clinical practice visits, or remote contact, until lost to follow-up, withdrawal of consent or death, for up to 3.5 years following start of Obinutuzumab treatment. Follow-up data will include at least tumor assessments*, new anti-lymphoma therapy informations*, and safety data.

For each patient, the study will consist of a period of 42 months which can include: an induction treatment period (approximately 6 months) followed by a maintenance treatment period (approximately 24 months) and a follow-up period of one year, after the last Obinutuzumab administration. Patients will be followed for 3.5 years after the first treatment administration regardless of early discontinuation of treatment for any reason in any time point. Patients who discontinue treatment for reasons other than disease progression (e.g., toxicity, AE) will continue to have their data collected for tumor assessments performed as per clinical practice, until disease progression,

withdrawal of consent, study termination by the Sponsor, or death, whichever occurs first, regardless of whether patients start a new anti-cancer therapy.

Start Date of Study:
The study start date will be the date of the first data collection: the date from which information on the first study patient is recorded in the study database. The planned start date is July 2019.

End of Study
The end of the study will be the date from which the last information of the last patient *still in the study* is recorded in the study database. The planned end date is December 2024.

Length of Study
This study will last approximately 5 years.

Target Population
Patients must meet the following criteria for study entry:

1. Signed Informed consent according to local regulations, after performing at least 2 cycles of induction treatment with Obinutuzumab and chemotherapy, within 1 year from beginning of treatment;
2. Age ≥ 18 years.

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

1. Any contraindications to Obinutuzumab therapy according to local label for specific indication;
2. Concomitant participation in an interventional clinical study;
3. Patients not receiving treatment for untreated follicular lymphoma with Obinutuzumab according to standard of care and in line with the current summary of product characteristics (SmPC)/local labeling.

Studied Medicinal Product
The studied medicinal product is Obinutuzumab, an anti CD20, type II, monoclonal antibody that will be administered via intravenous (IV) infusion according to the SmPC (see Synopsis Table 1), in association with a chemotherapy regimen, during induction, and alone during maintenance treatment:

Synopsis Table 1. Follicular lymphoma: Obinutuzumab dose to be administered during induction and maintenance treatments (according to SmPc)

Cycle	Treatment day	Dose of Obinutuzumab
Cycle 1	Day 1	1000 mg
	Day 8	1000 mg
	Day 15	1000 mg
Cycles 2–6 or 2-8	Day 1	1000 mg
Maintenance	Every 2 months for 2 years or until disease progression (what occurs earlier)	1000 mg

Obinutuzumab will not be provided by the Marketing Authorization Holder (MAH)/sponsor for the study as this could influence the intended real-world use, and should instead follow local prescribing regulations and sourcing.

Variables

Only variables, obtained according to routine clinical practice and follow objectives can and should be documented in this study.

Primary Effectiveness Variable

- Progression of disease at 2 years (POD24), defined as the time from the date of treatment initiation with Obinutuzumab until the first documented progression of disease or death due to disease progression, whichever occurs first, within 24 months from the start of treatment with Obinutuzumab. Patients who have no disease progression and have not died due to disease progression or who are lost to follow-up at the time of analysis will be censored at the date of last tumor assessment where no progression was documented or the last date of follow-up for disease, whichever is last. Patients without post-baseline tumor assessments will be censored at the time of their baseline visit unless death due to disease progression occurs prior to their first scheduled tumor assessment. Patients who die for reasons not related to the disease progression within 24 months from the treatment start with Obinutuzumab will be excluded from the statistical analysis of the endpoint.

  Moreover, the POD24 will be also analyzed as binary variable. Number and percentage of patients with its 95% confidence interval for POD24 will be calculated.

Secondary Effectiveness Variables

- Progression free survival (PFS) at 2 and 3 years, defined as the time from the date of treatment initiation until the first documented progression of disease measured by routine clinical care or death from any cause, whichever occurs first. Patients who have no disease progression and have not died or who are lost to follow-up at the time of analysis will be censored at the date of last tumor assessment where no progression was documented or the last date of follow-up for disease, whichever is last. Patients without post-baseline tumor assessments will be censored at the time of their baseline visit unless death occurs prior to their first scheduled tumor assessment;
- Time to next treatment (TTNT), defined as the Time to initiation of subsequent systemic anti-cancer therapy following initiation of Obinutuzumab containing therapy. Patients not starting a subsequent systemic anti-cancer therapy will be censored at the date of the last study visit;
- Overall survival (OS), defined as the time from initiation of study treatment to death from any cause. Patients who still alive at the time of analysis and patients who are lost to follow-up will be censored at their last time known to be alive;
- Correlation between POD24 and OS;
- TTLCB, defined as the time from first dose to loss of clinical benefit as assessed by the treating physician (single or multiple reasons possible: e.g. disease progression, deterioration in ECOG PS, death, other). Patients who do not loss clinical benefit will be censored at the date of the last study visit. Patients without post-baseline tumor assessments will be censored at the time of their baseline visit unless death occurs prior to their first scheduled tumor assessment;
- Overall response rate (ORR);
- Complete response (CR);
- Complete response at 30 months (CR30);

- Duration of response (DoR) measured per clinical practice, defined as the time from first documentation of CR or partial response (PR) (whichever occurs first) until disease progression, as evaluated by the physician according to routine clinical practice or death. Patients who have no disease progression and have not died or who are lost to follow-up at the time of analysis will be censored at the date of last tumor assessment where no progression was documented or the last date of follow-up for disease, whichever is last;
- Time to response, defined as the time from first dose of Obinutuzumab to first documented response as assessed in clinical routine. Patients without response at the time of analysis and patients who are lost to follow-up will be censored at the date of their last tumour assessment. Patients without post-baseline tumor assessments will be censored at the time of their baseline visit unless death occurs prior to their first scheduled tumor assessment;
- Rate of patients with stable disease (SD);
- Effectiveness of Obinutuzumab in different patient subgroups, stratified by FLIPI (intermediate/high), ECOG-PS, age at study entry, hepatitis infection (history of past/resolved infection or latent HBV after prophylaxis as per standard treatment guidelines), chemotherapy backbone, presence of autoimmune disease, history of renal failure and liver failure;
- FDG-PET response at end of induction and end of maintenance, as per clinical practice. When PET is not performed, the alternative routine tumor assessment method will be collected.

Safety Variables

- Incidence, nature, seriousness, severity and relatedness of all adverse events (AEs) and serious adverse events (SAEs);
- Infusion related reactions (IRRs) management at each center as per clinical practice;
- Clinical laboratory abnormalities;
- Adverse events of special interest (AESI);
- Vital signs.

Other Variables of Interest

- Patient/disease characteristics: age, sex, ECOG PS, Ann Arbor staging, FLIPI (intermediate/high), medical history and history of FL, comorbidities, physical examination and vital signs;
- Treatment pattern:
  - Time from diagnosis to start of treatment with Obinutuzumab;
  - Duration of treatment with Obinutuzumab;
  - Dose modifications;
  - Treatment discontinuation;
  - Prophylaxis medications;
  - Type of chemotherapy chosen in association with Obinutuzumab;
  - Second line regimens prescribed for patients who progressed within two years after starting first line therapy;
  - Time to initiation of subsequent systemic anti-lymphoma therapy following initiation of Obinutuzumab containing therapy;
  - Adherence to treatments.
- Quality of life: EuroQol 5-Dimension Questionnaire, 5-level version (EQ-5D-5L); Functional Assessment of Chronic illness Therapy-Lymphoma (FACT-Lym);
- Presence of B symptoms;

- Concomitant medication prescribed or in current use from the start of therapy with Obinutuzumab until discontinuation of the treatment.
- *effectiveness of Obinutuzumab in real world setting;*
- *prescription profile*
- *COVID-19 impact on therapy adherence*

Data Sources

Patients' data will be recorded on eCRFs. The degree of detail and completeness of data collected is dependent on local clinical practice. Data from patient notes should be entered on the eCRF as soon as they become available. Data entered in the eCRF will not act as source documents.

Data will be collected from patient's records as kept by their attending physicians during daily clinical practice.

As when entering in the initial treatment/pre-treatment data are collected retrospectively, missing data might occur in the retrospective period as well the distribution of missing data might be different across the participating investigational sites.

Data Analysis

A detailed description of the statistical methods that will be used for the primary and secondary analyses will be provided in the Statistical Analysis Plan (SAP).

Effectiveness analysis population includes all patients who are enrolled and have received at least two cycles of Obinutuzumab. Safety analysis population includes all patients who are enrolled.

Data will be summarized using appropriate descriptive statistics. Categorical data will be presented as frequencies and percentages. For continuous data, arithmetic mean, standard deviation (STD), median, minimum, and maximum will be presented.

Time-to-event outcomes (POD24, PFS at 2 and 3 years, TTNT, OS, TTLCB, duration of response, and time to response) will be analyzed according to the survival analysis methods. The quartiles with their 95% confidence interval (CI) (estimated using Kaplan-Meier methods and Greenwood's formula) will be presented. Kaplan-Meier plots with a 95% CI will be prepared. Estimates for the survivor functions for all time to event endpoints will be obtained by the Kaplan-Meier approach.

POD24 will be also analyzed as binary variable. Therefore, number and percentage of patients with its 95% confidence interval for POD24 will be calculated.

Response rates (ORR, CR, CR30 and rate of patients with stable disease) will be presented with the number and proportions of responders and non-responders together with two-sided, 95% Clopper-Pearson CIs.

Adverse events are those with start date beyond or equal to the date of first administration of Obinutuzumab and until 185 days after the last Obinutuzumab dose intake or until starting a new anti-cancer therapy (whichever occurs first). After this period AEs that are believed to be related to prior study drug treatment will be collected.

The incidence of AEs and SAEs will be summarized according to the primary system-organ class (SOC) and within each SOC, by the Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term.

Summary statistical tables including frequency counts and percentages and the number of adverse events will be produced. The 95% confidence interval of the observed proportions (calculated using either the Clopper-Pearson methodology, or the Poisson distribution, for frequencies below 10%) will be provided.

An interim analysis will be performed approximately one year after the first patient is included in the study in order to evaluate safety data, demographic data, FLIPI and treatment choices.

A second interim analysis will be performed approximately two years after the first patient included in the study in order to evaluate safety and primary and secondary effectiveness data, and the impact of COVID-19 on the patient management.
The results of the first two interim analysis will be compared.
The final Analysis will be performed at the end of the study.

Study Size/Determination of Sample Size

Sample size of this clinical study is selected based on feasibility.

Sample size is justified for the primary effectiveness endpoint POD24 treated as binary variable.

A sample size of 300 evaluable patients will allow estimation of the two-sided 95% confidence interval with a width equal to 7.9% (precision 3.95%) of the POD24 when the expected percentage is equal to 13%.

The Clopper-Pearson's formula has been used for the computation.

Synopsys Table 2 provides the actual width and the precision of the 95% CI, and the 95% confidence limits for different percentages of POD24 when the sample size is equal to 300 evaluable patients.

Synopsis Table 2 - POD24 rate and corresponding 95% Confidence Intervals

POD24 (%)	Actual Width (%)	Precision (%)	95% Clopper-Pearson Exact CI (%)
11%	7.4	3.70	From 7.7 to 15.1
13%	7.9	3.95	From 9.4 to 17.3
15%	8.4	4.20	From 11.2 to 19.6
17%	8.8	4.40	From 12.9 to 21.7

Moreover, a sample size of 300 evaluable patients will allow estimation of the two-sided 95% confidence interval with a width equal to 9.4% (precision 4.70%) of the PFS rate at 3 years (treated as binary variable) when the expected percentage is equal to 80%.

Synopsis Table 3 provides the actual width and the precision of the 95% CI and the 95% confidence limits for different percentages of PFS at 3 years when the sample size is equal to 300 of evaluable patients.

Synopsis Table 3 - PFS rate at 3 yrs. and corresponding 95% Confidence Intervals

PFS (%)	Actual Width (%)	Precision (%)	95% Clopper-Pearson Exact CI (%)
70%	10.7	5.35	From 64.5 to 75.1
75%	10.1	5.05	From 69.7 to 79.8
80%	9.4	4.70	From 75.0 to 84.4
85%	8.4	4.20	From 80.4 to 88.8
90%	7.1	3.55	From 86.0 to 93.2

Notes:
From Gallium trial, PFS at 2 years has been estimated equal to 90% while PFS rate at 3 years to 80%.

3. PROTOCOL AMENDMENTS AND UPDATES

Any protocol amendments will be prepared by the Marketing Authorization Holder or designee.

Protocol amendments will be submitted to the Institutional Review Board (IRB)/Ethics Committee (EC) and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes that involve logistical or administrative aspects only (e.g., change in Site Operations Representative or contact information).

Substantial protocol amendments/updates so far: *Tracked in the section "Summary of changes" of the Protocol* ~~none.~~

4. RATIONALE AND BACKGROUND

Background on Follicular Lymphoma

Non-Hodgkin's lymphomas (NHL) are a heterogeneous group of lymphoproliferative tumours with varying behaviour and treatment-response patterns (*Armitage 1993*).

NHL is the most common hematologic malignancy in adults. In 2008, over 66,000 new cases were reported in the United States, with more than 19,000 deaths.

In Italy, it has been estimated that one in every 44 males and one in every 62 females will develop NHL, and that one in every 106 and one in every 152, respectively for the two sexes, will die of the disease (*AIRTUM Working Group. 2009*).

The majority of NHLs (also known as malignant lymphoma) are of B-cell origin and are characterized by the expression of a membrane antigen, CD20, which is important in cell cycle initiation and differentiation (*Anderson et al. 1984*). NHL can be divided into aggressive and indolent NHL. Indolent NHLs are a heterogeneous group of malignant lymphomas and account for about one-third of all NHLs.

Follicular lymphoma (FL) is the second most common lymphoma and is the most common subtype of indolent B-cell lymphomas diagnosed in the United States and Western Europe, accounting for approximately 35% of all NHLs, and 70% of indolent lymphomas (*Swerdlow et al. 2008*). The median age of diagnosis is at 65 years and the incidence is slightly increased among relatives of persons with FL (*Goldin et al. 2009*).

FL associated with follicle centre B cells that typically contain the *BCL2* chromosome trans location t(14:18), leading to overexpression of the intracellular anti-apoptotic protein Bcl-2.

Patients with FL are usually at diagnoses at an advances state of the disease. They generally present with asymptomatic lymphadenopathy, with waxing and waning present for years. Bone marrow involvement is present in 70% of patients, whereas involvement of other normal organs is uncommon. Less than 20% of patients present with B symptoms and also less than 20% of patients present with an increased serum lactate dehydrogenase (LDH) (*Freedman 2015*).

The clinical course of indolent NHL is characterized by remission and relapse (*Gallagher et al. 1986*). The disease initially responds to radiation and/or immunochemotherapy with conventional agents, but patients eventually suffer multiple relapses distinguished by increasing refractoriness and decreasing duration of response in subsequent lines of therapy. Patients with advance-stage disease are not usually cured with conventional treatment and ultimately die from recurrent disease or treatment-related toxicity.

Patients who are diagnosed without symptoms can be observed without treatment (so-called watchful waiting) for several years. However, treatment is required when the patient presents with symptoms at diagnosis or develops symptoms during observation (*Izutsu 2014*).

Treatment modalities for FL include chemotherapy, radiotherapy and immunotherapy against CD20, and stem cell transplantation, but a standard treatment approach for FL has not been established.

For FL patients requiring treatment, immunochemotherapy with rituximab, a monoclonal antibody directed against CD20, plus chemotherapy has demonstrated improvements in response rates, progression-free survival (PFS), and overall survival compared with chemotherapy alone (*Hiddemann et al. 2005*; *Herold et al. 2007*; *Marcus et al. 2008*; *Salles et al. 2008*). Rituximab in combination with chemotherapy (e.g., CHOP [cyclophosphamide, doxorubicin, vincristine, and prednisone], CVP [cyclophosphamide, vincristine, and prednisone], or purine analogue–based schemes such as those with fludarabine or bendamustine) for newly diagnosed patients with advanced Stage III and IV disease requiring treatment is strongly supported by International Guidelines (*Dreyling 2009*; *Zelenetz et al. 2010*).

In addition to immunochemotherapy induction, randomized clinical trials have also demonstrated the benefit of maintenance rituximab in responding patients in both previously untreated and relapsed FL (*van Oers et al. 2006*; *van Oers et al. 2010*; *Salles et al, 2011*).

Currently, the first-line treatment for FL is rituximab in combination with chemotherapy, followed by maintenance therapy with rituximab every two months for two years, as demonstrated by results of the PRIMA study (*Salles et al, 2011*). This regimen had determined a satisfactory result in most of treated patients, with a 10-year progression-free survival of 51%.

Despite these encouraging results, therapy for FL is not curative and presents with a chronic course (i.e. remitting-relapsing), with progressively shorter remissions and with increased risk of developing a transformation of the disease, i.e. the transition from an indolent malignant lymphoma to a more aggressive type of lymphoma. Patients who have an early disease progression (within 24 months) will have a more aggressive course and a shorter survival, and will be treated with more therapeutic lines, than those patients without an early progression. The majority of patients will ultimately die from progressive disease. Therefore, the introduction of new agents that may potentially alter the natural history of the disease is of great interest.

Background on Obinutuzumab

Obinutuzumab is a recombinant monoclonal humanised and glycoengineered Type II anti-CD20 antibody of the IgG1 isotype. It specifically targets the extracellular loop of the CD20 transmembrane antigen on the surface of non-malignant and malignant pre-B and mature B-lymphocytes, but not on haematopoietic stem cells, pro-B-cells, normal plasma cells or other normal tissue. Glycoengineering of the Fc part of Obinutuzumab results in higher affinity for FcγRIII receptors on immune effector cells such as natural killer (NK) cells, macrophages and monocytes as compared to non-glycoengineered antibodies.

In nonclinical studies, Obinutuzumab induces direct cell death and mediates antibody dependent cellular cytotoxicity (ADCC) and antibody dependent cellular phagocytosis (ADCP) through recruitment of FcγRIII positive immune effector cells. In addition, *in vivo*, Obinutuzumab mediates a low degree of complement dependent cytotoxicity (CDC). Compared to Type I antibodies, Obinutuzumab, a Type II antibody, is characterised by an enhanced direct cell death induction with a concomitant reduction in CDC at an equivalent dose. Obinutuzumab, as a glycoengineered antibody, is characterised by enhanced ADCC compared to non-glycoengineered antibodies at an equivalent dose. In animal models Obinutuzumab mediates potent B-cell depletion and antitumour efficacy. Furthermore, treatment with Obinutuzumab was able to control tumour growth when vehicle- and rituximab-treated tumours were not controlled (*Mössner et al. 2010*).

Obinutuzumab has been evaluated in a wide-ranging program of clinical trials in patients with B-cell malignancies. Efficacy as monotherapy has been reported in patients with relapsed/refractory indolent and aggressive NHL (*Salles et al. 2012*; *Salles et al. 2013*) and in chronic lymphocytic leukemia (CLL) of B-cell origin (*Cartron et al. 2014*). Improved outcomes have also been noted when Obinutuzumab has been added to chemotherapy in patients with B-cell NHL (*Radford et al. 2013*).

The Phase III GADOLIN trial tested the clinical efficacy of Obinutuzumab plus bendamustine followed by Obinutuzumab monotherapy in rituximab-refractory indolent NHL versus treatment with bendamustine alone. After a median follow-up time of 21.9 months in the Obinutuzumab plus bendamustine group and 20.3 months in the bendamustine monotherapy group, PFS was significantly longer with Obinutuzumab plus bendamustine (median not reached [95% CI 22.5 months-not estimable]) than with bendamustine monotherapy (14.9 months [12.8-16.6]; hazard ratio (HR) 0.55 [95% CI 0·40-0·74]; p=0·0001) (*Sehn et al. 2016*).

A phase III study (the GALLIUM trial) compared the efficacy and safety of induction with Obinutuzumab, as compared with rituximab, each combined with chemotherapy, followed by maintenance therapy with the same monoclonal antibody, in patients with previously untreated indolent NHL (follicular lymphoma or marginal-zone lymphoma) (*Marcus et al. 2017*). A total of 601 patients in each group were randomised. After a median follow-up of 34.5 months, Obinutuzumab-based chemotherapy resulted in a significantly lower risk of progression, relapse, or death than rituximab-based chemotherapy (estimated 3-year rate of PFS, 80.0% vs. 73.3%; HR for progression, relapse, or death, 0.66; 95% CI, 0.51 to 0.85; p = 0.001). Response rates were similar in the two groups (88.5% in the Obinutuzumab group and 86.9% in the rituximab group). At a median follow-up of 41 months (*Hiddeman et al. 2017*), PFS was superior for Obinutuzumab plus chemotherapy over rituximab-based chemotherapy (overall HR, 0.68; 95% CI, 0.54 to 0.87; p = 0.0016). At this follow-up, the median PFS has not yet been reached, and it is not expected to be reached based on statistical hypotheses. Therefore, it is expected that the GALLIUM study will improve the median PFS observed in the PRIMA study, in which patients received the same treatment scheme of that used in the control arm of the GALLIUM study (i.e. rituximab + chemotherapy followed by

maintenance therapy with rituximab). Furthermore, the evidence from the GALLIUM study has shown that patients with advanced FL (high or intermediate FLIPI score) treated with Obinutuzumab-based chemotherapy for 2 years have a reduction of 32% of risk of disease progression (*Marcus et al. 2017*). A further analysis (*Seymour et al, 2018*) of the progression of disease at 2 years (POD24) and its impact on overall survival (OS) has shown that treatment with Obinutuzumab plus chemotherapy was associated with a marked reduction of POD24 compared to rituximab-based chemotherapy and that POD24 was associated with poor prognosis, with mortality risk higher after earlier progression.

Overall, Obinutuzumab has an acceptable safety profile as emerged from clinical trials. The major safety events were infusion-related reactions (IRRs) and hematologic adverse events (AEs), primarily neutropenia and infections. IRRs were the most common AEs throughout all clinical trials (*Edelmann et al. 2016*). They comprised of various symptoms such as hypotension or hypertension, tachycardia, dyspnea, pyrexia, chills, nausea, vomiting, diarrhea, flushing and headache coinciding with drug infusion. However, IRRs mainly occurred during the first infusion and almost always resolved with slowing or interrupting the infusion and/or upon steroid administration. Incidences of IRRs in clinical trials range between 64 and 86%, the majority of reactions being described as grades 1 and 2. A relation between Obinutuzumab dose and intensity of the IRR was not observed. In the GALLIUM study (*Marcus et al. 2017*), adverse events of grade 3 to 5 were more frequent in the Obinutuzumab group than in the rituximab group (74.6% vs. 67.8%), as were serious adverse events (46.1% vs. 39.9%). The rates of adverse events resulting in death were similar in the two groups. The most common adverse events were infusion-related events that were considered by the investigators to be largely due to Obinutuzumab in 59.3% of patients and to rituximab in 48.9 % of patients.

Obinutuzumab (Gazyvaro®), in combination with chlorambucil, is indicated for the treatment of adult patients with previously untreated CLL and with comorbidities making them unsuitable for full-dose fludarabine based therapy. From October 2017, Obinutuzumab is also indicated, in combination with bendamustine followed by Obinutuzumab monotherapy, for the treatment of patients with FL who relapsed after, or are refractory to, a rituximab-containing regimen. Obinutuzumab has also received the approval from the European Medicines Agency (EMA) for use in combination with chemotherapy, followed by Obinutuzumab maintenance therapy in patients with previously untreated advanced follicular lymphoma.

4.1 STUDY RATIONALE

This observational study has been planned to evaluate the effectiveness of Obinutuzumab in combination with chemotherapy in previously untreated advanced FL patients, in the real world setting in Italy.

The study will allow to collect real-life data in a significant number of Italian patients when compared to participants in pivotal studies of Gazyvaro and thus will allow to verify

in routine practice (after physician hands-on) the effectiveness and safety management in 50 reference sites all over the country.

The stratification factors selected to this study are different from those presented in pivotal trials as the label allows to treat patients in a wider setting than the clinical trials eligibility criteria. This stratification will also allow to understand the profile of patients that are treated with Obinutuzumab in Italy.

As described above, Obinutuzumab has granted approval for use in combination with chemotherapy, followed by Obinutuzumab maintenance therapy in patients with previously untreated advanced FL. Thus, the study will include patients with untreated advanced FL for which the physician has decided to use Obinutuzumab according to the approved SmPC. These patients will be treated according to the approved scheme, i.e. Obinutuzumab will be administered according to the approved SmPC in association with a chemotherapy regimen during induction, and alone during maintenance treatment.

Patients enrolled in this study may benefit from treatment with Obinutuzumab. However, the assignment of the patients to any therapeutic strategy and thus also to treatment with Obinutuzumab is not decided in advance based the study protocol and is clearly separated from the possibility or decision to include the patients in the study. Therefore, the treating physician will make all treatment decisions according to his/her regular practice independent of this study. During the study, patient will undergo clinical visits as planned by the treating physician, according to standard clinical practice.

Although Obinutuzumab has resulted to be generally well tolerated, IRRs have been reported with the use of the product, however occurring predominantly during infusion of the first 1,000 mg. These events will be closely monitored during the study and appropriate measures for prevention of IRRs (adequate glucocorticoid, oral analgesic/anti-histamine, omission of antihypertensive medicine in the morning of the first infusion, and the Cycle 1 Day 1 dose administered over 2 days) will be used in the study to reduce the incidence of IRRs, as scheduled in the current SmPC of the product. All AEs will be duly monitored in the study and appropriate measures (including the discontinuation of treatment with Obinutuzumab) will be implemented for the protection of patients' healthcare.

Therefore, treatment with Obinotuzumab offers the potential for clinical benefit in patients with untreated advanced FL for which the treating physician has decided to start treatment with Obinotuzumab.

Patients will be fully informed of the potential risks in taking part in this study, and investigators will make a careful assessment of the potential benefits and risks of Obinutuzumab, by monitoring the clinical status of the patient and the potential occurrence of AEs events and toxicities.

Therefore, the current evidence on the efficacy and safety of Obinutuzumab administered according to the therapeutic indication for the drug in patients with

untreated advanced FL suggest that the benefits that can be achieved from the participation in this observational study will outweigh the potential risks.

This trial will be conducted in compliance with the Declaration of Helsinki (1964 and amendments) current with the Good Pharmacoepidemiology Practice (GPP) published by the International Society of Pharmacoepidemiology (ISPE) and all other applicable laws and regulations.

For information on the condition under observation and on the Obinutuzumab please refer ~~to the Investigator's Brochure and~~ to the most recent version of the Summary of Product Characteristics (SmPC) of Gazyvaro®, i.e. the brand name of Obinutuzumab, for further details on nonclinical and clinical studies.

5. RESEARCH QUESTION AND OBJECTIVES

5.1 RESEARCH QUESTION

This study will evaluate the effectiveness and safety of Obinutuzumab in patients with previously untreated advanced follicular lymphoma (FL) treated with Obinutuzumab in routine clinical care.

5.2 OBJECTIVES

5.2.1 Effectiveness Objectives

The primary effectiveness objective of this study is as follows:

- To evaluate the effectiveness of Obinutuzumab in combination with chemotherapy in previously untreated advanced follicular lymphoma (FL) patients, in the real world setting as measured by the proportion of patients relapsed within 24 months from start of therapy (POD24).

The secondary effectiveness objectives of this study are as follows:

- To evaluate the progression free survival (PFS) at 2 and 3 years;
- To evaluate the overall and complete response rates at mid and end of induction, and during and after maintenance therapy (including the complete response rate at 30 months [CR30]), as per clinical practice, with and without 18F-fluorodeoxyglucose−positron emission tomography (FDG-PET);
- To describe patient/disease characteristics and the second line regimens prescribed for patients who progressed after first line therapy during the overall study duration and within 24 months from start of therapy (POD24);
- To explore the effectiveness of Obinutuzumab in different patient subgroups, stratified by follicular lymphoma International Prognostic Index (FLIPI) – intermediate and high, ECOG performance status (PS), age at study entry, chemotherapy backbone choice, hepatitis infection (history of past/resolved infection or latent HBV after prophylaxis as per standard treatment guidelines), presence of autoimmune disease, history of renal failure and liver failure.

5.2.2 Safety Objectives

The safety objectives of this study are as follows:

- To evaluate the safety of Obinutuzumab in a real-world setting.

5.2.3 Other Objectives

- To describe the treatment pattern in first and second line of treatment;
- To evaluate methods applied to tumour and response evaluations according to used guidelines and clinical practice;
- To evaluate the FDG-PET response at end of induction and end of maintenance, as per clinical practice;
- To evaluate the Quality of life;
- To evaluate the presence of B symptoms;
- *To explore effectiveness of Obinutuzumab in real world setting;*
- *To explore prescription profile*
- *To explore COVID-19 impact on therapy adherence*

6. RESEARCH METHODS

6.1 STUDY DESIGN

This is a retrospective and prospective primary data collection and secondary data use, non-interventional, multi-center study designed to assess real-world effectiveness and safety of Obinutuzumab in previously untreated advanced FL patients, prescribed in first line with Obinutuzumab and chemotherapy, according to existing label.

The study will be conducted in approximately 50 Italian centers distributed all across the country and will collect data during treatment with Obinutuzumab and up to 3.5 years following the start of the treatment. Since the study is observational, the treating physician will make all treatment decisions according to his/her regular practice independent of this study. No treatment regimen is mandated by this protocol.

Patients should be included after the start of treatment, including newly diagnosed FL patients. Patients included should have performed at least 2 cycles of induction treatment with Obinutuzumab and chemotherapy within 1 year from beginning of treatment.

During the treatment with Obinutuzumab, patient data will be collected at the clinical visits planned by the treating physician, including retrospective data of cycles performed before enrolment, baseline data and medical history, as detailed in Section 6.4.2~~1~~. The collection of retrospective data will be those generated from the start of treatment with Obinotuzumab to study entry.

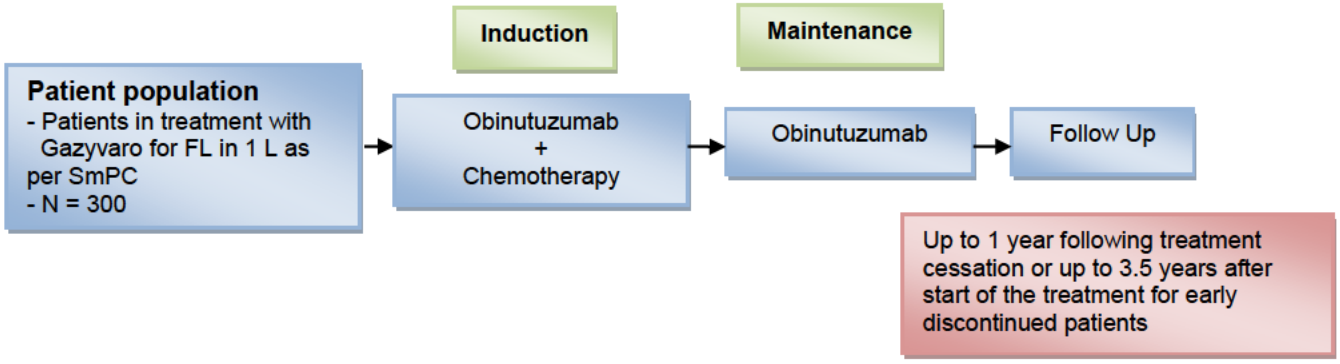
After cessation of Obinutuzumab treatment, patient data will be collected approximately every 3-6 months, as part of routine clinical practice visits, or remote contact, until loss to follow-up, withdrawal of consent or death, for up to 3.5 years following the start of Obinutuzumab treatment.

For each patient, the study will consist of a period of 42 months which can include: an induction treatment period (approximately 6 months) in which patients will receive Obinutuzumab and chemotherapy followed by a maintenance treatment period (approximately 24 months) in which patients will receive Obinutuzumab monotherapy and a follow-up period of one year, after the last Obinutuzumab administration. Patients will be followed for 3.5 years after the first treatment administration regardless of early discontinuation of treatment for any reason in any timepoint. Patients who discontinue treatment for reasons other than disease progression (e.g., toxicity, AE) will continue to have their data collected for tumor assessments performed as per clinical practice, until disease progression, withdrawal of consent, study termination by the Sponsor, or death, whichever occurs first, regardless of whether patients start a new anti-cancer therapy.

6.1.1 Overview of Study Design

A schedule of activities is provided in Appendix 2.

Figure 1 Study Scheme



Start Date of Study:

The study start date will be the date of the first data collection: the date from which information on the first study patient is recorded in the study database. The planned start date is July 2019.

End of Study:

The end of the study will be the date from which the last information of the last patient *still in the study* is recorded in the study database. The planned end date is December 2024.

The overall length of the study will be approximately 5 years.

This study will last 66 months. This period includes approximately 24 months of recruitment and 42 months after the last patient has started treatment with Obinutuzumab.

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

A data collection overview is provided in Appendix 2.

6.1.2 Rationale for Study Design

This will be an open-label, multicenter, national, non-interventional study. This was considered as the most appropriate design to evaluate the efficacy and safety of Obinutuzumab, administered during with chemotherapy during the induction phase and as monotherapy during the maintenance phase, according to the posology and method of administration approved in the current SmPc of Gazyvaro®, in patients with untreated advanced FL.

6.1.3 Number of Patients Observed in the Study

Approximately 300 patients will take part in this study.

6.1.4 Sites

This study will be conducted at approximately 50 sites in Italy.

Additional centers may be added or substituted if underperforming.

6.2 POPULATION

The patient population taking part in the study will comprise patients aged ≥ 18 years with untreated advanced FL.

Patients must meet the following criteria for study entry:

1. Signed Informed consent according to local regulations, after performing at least 2 cycles of induction treatment with Obinutuzumab and chemotherapy, within 1 year from beginning of treatment;
2. Age ≥ 18 years;

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

1. Any contraindications to Obinutuzumab therapy according to local label for specific indication;
2. Concomitant participation in an interventional clinical study;
3. Patients not receiving treatment for untreated follicular lymphoma with Obinutuzumab according to standard of care and in line with the current summary of product characteristics (SmPC)/local labeling

6.2.1 Rationale for Patient Population

The patient population taking part in the study will comprise patients aged ≥ 18 years in first treatment for advanced FL, in which Obinutuzumab are administered in combination with chemotherapy during the induction phase, followed by Obinutuzumab maintenance therapy. This indication and treatment scheme is that approved by the EMA as per EU countries agency and AIFA as per Italian local agency.

6.2.2 *Recruitment Procedure*

No specific procedures for recruitment (e.g. advertisements, published information or other) were used for the study.

The Principal Investigator or a co-investigator in each investigational site will verify the eligibility of each patient for the participation in the study based on adherence to inclusion/exclusion criteria. Eligible patients who signed the ICF were then included in the study.

6.2.3 Dosage, Administration, and Compliance

Dosing and treatment duration of any studied medicinal products collected as parts of this non-interventional study are at the discretion of the physician in accordance with local clinical practice and local labelling.

6.2.4 Concomitant Medication and Treatment

Concomitant medication prescribed for concomitant diseases and treatment for untreated advanced FL at the beginning of the observation period or introduced during the observation period will be documented in the eCRF from start of therapy with Obinutuzumab until discontinuation of the treatment, if applicable.

6.3 VARIABLES

Only variables, obtained according to routine clinical practice (with exception of quality of life questionnaires) and collected according to the study objectives can and should be documented in this study.

6.3.1 Primary Effectiveness Variable

Progression of disease at 2 years (POD24), defined as the time from the date of treatment initiation with Obinutuzumab until the first documented progression of disease or death due to disease progression, whichever occurs first, within 24 months from the start of treatment with Obinutuzumab. Patients who have no disease progression and have not died due to disease progression or who are lost to follow-up at the time of analysis will be censored at the date of last tumor assessment where no progression was documented or the last date of follow-up for disease, whichever is last. Patients without post-baseline tumor assessments will be censored at the time of their baseline visit unless death due to disease progression occurs prior to their first scheduled tumor assessment. Patients who die for reasons not related to the disease progression within 24 months from the treatment start with Obinutuzumab will be excluded from the statistical analysis of the endpoint.

Moreover, the POD24 will be also analyzed as binary variables. Number and percentage of patients with its 95% confidence interval for POD24 will be calculated.

6.3.2 Secondary Effectiveness Variable

- Progression free survival (PFS) at 2 and 3 years, defined as the time from the date of treatment initiation until the first documented progression of disease measured by routine clinical care or death from any cause, whichever occurs first. Patients who have no disease progression and have not died or who are lost to follow-up at the time of analysis will be censored at the date of last tumor assessment where no progression was documented or the last date of follow-up for disease, whichever is last. Patients without post-baseline tumor assessments will be censored at the time of their baseline visit unless death occurs prior to their first scheduled tumor assessment;
- Time to next treatment (TTNT), defined as the Time to initiation of subsequent systemic anti-cancer therapy following initiation of Obinutuzumab containing therapy. Patients not starting a subsequent systemic anti-cancer therapy will be censored at the date of the last study visit;
- Overall survival (OS), defined as the time from initiation of study treatment to death from any cause. Patients who still alive at the time of analysis and patients who are lost to follow-up will be censored at their last time known to be alive;
- Correlation between POD24 and OS;
- TTLCB, defined as the time from first dose to loss of clinical benefit as assessed by the treating physician (single or multiple reasons possible: e.g. disease progression, deterioration in ECOG PS, death, other). Patients who do not loss clinical benefit will be censored at the date of the last study visit. Patients without post-baseline tumor assessments will be censored at the time of their baseline visit unless death occurs prior to their first scheduled tumor assessment;
- Overall response rate (ORR);
- Complete response (CR);
- Complete response at 30 months (CR30);
- Duration of response (DoR) measured per clinical practice, defined as the time from first documentation of CR or partial response (PR) (whichever occurs first) until disease progression, as evaluated by the physician according to routine clinical practice or death. Patients who have no disease progression and have not died or who are lost to follow-up at the time of analysis will be censored at the date of last tumor assessment where no progression was documented or the last date of follow-up for disease, whichever is last;
- Time to response, defined as the time from first dose of Obinutuzumab to first documented response as assessed in clinical routine. Patients without response at the time of analysis and patients who are lost to follow-up will be censored at the date of their last tumour assessment. Patients without post-baseline tumor assessments will be censored at the time of their baseline visit unless death occurs prior to their first scheduled tumor assessment;

- Rate of patients with stable disease (SD);
- Effectiveness of Obinutuzumab in different patient subgroups, stratified by FLIPI (intermediate/high), ECOG-PS, age at study entry, hepatitis infection (history of past/resolved infection or latent HBV after prophylaxis as per standard treatment guidelines), chemotherapy backbone choice, presence of autoimmune disease, history of renal failure and liver failure;
- FDG-PET response at end of induction and end of maintenance, as per clinical practice. When PET is not performed, the alternative routine tumor assessment method will be collected.

6.3.3 Safety Variables

- Incidence, nature, seriousness, severity and relatedness of all adverse events (AEs) and serious adverse events (SAEs);
- Infusion related reactions (IRRs) management at each center as per clinical practice;
- Clinical laboratory abnormalities;
- Adverse events of special interest (AESI);
- Vital signs.

6.3.4 Other Variables of Interest

- Patient/disease characteristics: age, sex, ECOG PS, Ann Arbor staging, FLIPI (intermediate/high), medical history and history of FL, comorbidities, physical examination and vital signs;
- Treatment pattern:
  - Time from diagnosis to start of treatment with Obinutuzumab;
  - Duration of treatment with Obinutuzumab;
  - Dose modifications;
  - Treatment discontinuation;
  - Prophylaxis medications;
  - Type of chemotherapy chosen in association with Obinutuzumab;
  - Second line regimens prescribed for patients who progressed within two years after starting first line therapy;
  - Time to initiation of subsequent systemic anti-lymphoma therapy following initiation of Obinutuzumab containing therapy;
  - Adherence to treatments
- Quality of life: EuroQol 5-Dimension Questionnaire, 5-level version (EQ-5D-5L); Functional Assessment of Chronic illness Therapy-Lymphoma (FACT-Lym);

- Presence of B symptoms;
- Concomitant medication prescribed or in current use from the start of therapy with Obinutuzumab until discontinuation of the treatment.
- *effectiveness of Obinutuzumab in real word setting;*
- *prescription profile*
- *COVID-19 impact on therapy adherence*

6.4 DATA SOURCES

6.4.1 Collection of Data on the CRF

Patients' data will be recorded on eCRFs. The degree of detail and completeness of data collected is dependent on local clinical practice. Data from patient notes should be entered on the CRF as soon as they become available. Data entered in the eCRF will not act as source documents.

6.4.2 Data Collected during the Observation Period

During therapy with Obinutuzumab, laboratory assessments are routinely performed in accordance with current guidelines and local standard of care. When performed during the observational period, available results that represent an adverse event in according to CTCAE vs. 5, relevant symptom/signal of an event or abnormal laboratory finding that results in a change of the treatment in study will be documented in the eCRF. Most data will be documented during the treatment period when the respective assessments are usually performed according to standard of care. The proposed assessments and suggested timings for assessments in the protocol/observational plan are not mandatory. It is up to the treating physician to perform and document the assessments as performed in the real clinical setting.

In the routine care setting, patients are seen regularly by their treating physicians either for treatment or for regular assessment after treatment. Thus, no study-specific visits or evaluations are required by this protocol.

Tumor assessments collected in eCRF will comprise the following periods as available:

- Baseline tumor assessment
- During induction:
    - Mid induction: tumor assessment performed between cycle 2 and cycle 4 after the start of treatments
    - End induction: tumor assessment performed at the day of cycle 6 /8 (or when induction is early discontinued) until 2 month later
- After induction treatment:
    - 1 year after the start of treatment (from 10 to 14 months after the start of treatment)

- 2 years after the start of treatment (from 22 to 26 months after the start of treatment)
- 3 years after the start of treatment (from 34 to 40 months after the start of treatment)
- 1 year after end of maintenance as applicable

- Any tumor assessment, and the method used that shows disease progression, CR or CRu during induction or maintenance.

The lack of tumor assessments in those periods are not a protocol deviation as clinical practice should be followed.

Since the enrolment of patients into the study will occur after the treatment has already started (Patients included should have performed at least 2 cycles of induction treatment with Obinutuzumab but no later than the completion of 1 year of the treatment with Obinutuzumab), a retrospective data collection is expected.

Retrospective data applicable to the study includes but not limits to the following information available before ICF signature (enrolment):

- Information regarding previous cycles performed with Obinutuzumab and chemotherapy (at least 2 cycles and no longer than 1 year of treatment)
- Safety data
- Baseline condition (before start of the treatment)
- Medical history
- Relevant laboratory exams
- Concomitant medication and procedures
- Diagnostic information
- Tumor assessments and cancer history
- Imaging exams
- Demographic Data
- Physical exams, performance status and FLIPI classification

Data will be collected as availability in source document.

Safety data will be provided as aggregate data for retrospective visits. Minimal information such as the event term, seriousness classification and reason, relationship and duration of the event will be collected as available. For prospective data collection of safety, additional variables will be collected as available, such as grade, outcome, concomitant treatment, background causality, onset and end date.

Quality of life will be evaluated by means of the EuroQol 5-Dimension Questionnaire, 5-level version (EQ-5D-5L), and of the Functional Assessment of Chronic illness Therapy-Lymphoma (FACT-Lym).

The EuroQol 5-Dimension Questionnaire, 5-level version (EQ-5D-5L) (Appendix 4), is a validated self-report health status questionnaire that is used to calculate a health status utility score for use in health economic analyses (*EuroQol Group 1990*; *Brooks 1996*; *Herdman et al. 2011*).

The Functional Assessment of Chronic illness Therapy-Lymphoma (FACT-Lym) (*Webster et al, 2005*) (Appendix 5) is used to assess quality of life in patients with various forms of lymphoma. It contains 42 items (questions) covering quality of life, common lymphoma symptoms and treatment side-effects. The questionnaire begins with the Functional Assessment of Cancer Therapy - General (FACT-G), which contains 27 items covering four core quality of life subscales: Physical Wellbeing (7 items), Social/Family Wellbeing (7), Emotional Wellbeing (6), and Functional Wellbeing (7). The FACT-Lym also includes an Additional Concerns subscale (15 items), addressing issues typically experienced by lymphoma patients. Some of the issues covered include pain, itching, night sweats, trouble sleeping, fatigue and trouble concentrating. The FACT-Lym also asks patients about their concerns about lumps and swelling, fevers, infections, weight, appetite, emotional stability and treatment.

To ensure instrument validity and that data standards meet health authority requirements, questionnaires scheduled for administration during a clinic visit will be completed in their entirety by the patient prior to the performance of non-PRO assessments and the *treatment* administration ~~of study treatment~~ (where applicable).

Patients will use an electronic PRO (ePRO) device to capture PRO data on the same day of clinic visits. The ePRO device and/or instructions for completing the PRO questionnaires electronically will be provided by the investigator staff. The data will be transmitted via a pre-specified transmission method (e.g., web or wireless) automatically after entry to a centralized database at the ePRO vendor. The data can be accessed by the appropriate sponsor study personnel securely via the Internet.

In case patient is not able to complete the electronic questionnaires, e.g. due to technical issues, the PRO data will be completed by patient in paper records and later transferred into the electronic system by site staff. In case any survival follow-up contact is conducted by phone or in case of patient's compromised reading ability (e.g illiterate patients/ vision issues, etc) the PRO data for that visit will be collected in an interview performed by a trained site staff (via telephone or face-to-face, depending on how visit occurs), recorded in paper records (source document) and then transferred in electronic system.

PRO questionnaires (FACT-Lym, EQ-5D) should be administered *on Day 1 of alternate cycles during induction treatment period and at each cycle during manteinace treatment period. PRO Questionnaires should be administered on Day 1 of the cycle* prior to any treatment and assessments*, i.e. PRO questionnaires should be collected only when*

corresponding to a treatment cycle. PRO questionnaires should also be administered at first visit after reporting disease progression.

Please see Appendix 2 for the data collection overview (as per standard of care).

6.4.3 Data Collected at Study Completion

For patients who complete the observation period, the study completion visit should be documented.

~~Please see Appendix 2 for the data collection overview at the study completion visit.~~

6.4.4 Safety Data Collection

Clinical AEs, serious and non-serious, will be recorded in the eCRF during the total observation period, with physician's assessment of severity (mild, moderate, severe or in oncology studies using the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE]) and relationship to therapy (i.e., related or unrelated) as described in Appendix 3.

6.5 PATIENT, STUDY AND SITE DISCONTINUATION

6.5.1 Patient Discontinuation

Patients have the right at any time and for any reason to withdraw their consent that their data are collected and used for the study. Reasons for discontinuation of treatment with the medicinal product or withdrawal from the study may include, but are not limited to, the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues to receive study treatment;
- Investigator or Sponsor determines it is in the best interest of the patient;
- Pregnancy;
- Symptomatic deterioration attributed to disease progression;
- Intolerable toxicity related to Obinutuzumab, as determined by the investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event;
- Any medical condition that may jeopardize the patient's safety if he or she continues on study treatment;
- Confirmed disease progression per investigator assessment;
- Patient withdrawal of consent at any time;
- Patient is lost to follow-up.

6.5.2 Discontinuation from Treatment with Studied Medicinal Product

The decision for discontinuation from treatment lies with the treating physician in agreement with the patient's decision and is not regulated by this protocol.

The primary reason for early treatment discontinuation should be documented on the appropriate eCRF page. Every effort should be made to obtain information on patients who discontinue treatment.

Patients who discontinue treatment for reasons other than disease progression should continue to have its data collected for radiological assessment and minimal residual disease as collected by clinical practice until disease progression. Data of new anti-cancer therapy within 3.5 years after first line and survival status should also be collected as available.

6.5.3 Withdrawal from Study

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF page. Patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

6.5.4 Study and Site Discontinuation

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

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

The sponsor will notify the physician if the study is placed on hold, or if decided to discontinue the study.

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

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the Guidelines for Good Pharmacoepidemiological Practices (GPP) or any other pertinent local law or guideline

6.6 DATA MANAGEMENT

6.6.1 Data Quality Assurance

A contract research organization (CRO) will be responsible for the data management of this study, including quality checking of the data. Data entered manually will be collected via electronic data capture (EDC). Sites will be responsible for data entry into the EDC

system. In the event of discrepant data, site will be request data to clarify the discrepancy in the EDC system.

The contract research organization (CRO) Data Management will identify and implement the most effective data acquisition and management strategy for the clinical trial protocol and deliver datasets which support the protocol objectives. The CRO will produce eCRF specifications for the study based on their own templates including quality checking to be performed on the data.

Patient data will be entered into the eCRF and combined with data provided from other sources (e.g., ePRO data) in a validated data system. Clinical data management will be performed in accordance with applicable CRO standards and data cleaning procedures with the objective of removing errors and inconsistencies in the data which would otherwise impact on the analysis and reporting objectives, or the credibility of the Clinical Study Report. Adverse events and concomitant medications terms will be coded using validated dictionaries.

The eCRFs and correction documentation will be maintained in the EDC system audit trail. System backups for data stored at the CRO and records retention for the study data will be consistent with the CRO standard procedures.

The study data should be verified by the Clinical Research Associate (CRA), i.e. the study monitor, with the original data, thereafter all the records and clinical records of the subjects could be accessible. The investigator should allow the access to patient clinical records and the original data should be available for all the study duration. Also the subjects and parents/legal representatives should allow the access to their own clinical records; such condition is cleared and authorized when the subjects supply their authorization for the participation to the clinical study.

To ensure instrument validity and that data standards meet health authority requirements, questionnaires scheduled for administration during a clinic visit will be completed in their entirety by the patient prior to the performance of non-PRO assessments and the administration of study treatment (where applicable).

Patients will use an electronic PRO (ePRO) device to capture PRO data on the same day of clinic visits. ePRO data collection will be performed by the patients through a dedicated app installed on smartphone. The data will be transmitted via a pre-specified transmission method (e.g., web or wireless) automatically after entry to a centralized database at the ePRO vendor. In case application in smartphone cannot be used, ePRO data might be completed by patients directly in web-application at a computer available at site. The data can be accessed by the appropriate sponsor study personnel securely via the Internet.

In case patient is not able to complete the electronic questionnaires, e.g due to technical issues, the PRO data will be completed by patient in paper records and later transferred into the electronic system by site staff.

6.6.2 Electronic Case Report Forms

Clinical data will be captured using a study specific eCRF using a validated and Code of Federal Regulations (CFR) Part 11 compliant electronic data capture (EDC) system. Sites will receive training and have access to a manual for appropriate eCRF completion.

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

At the end of the study, the physician will receive the data related to patients from his or her site in an electronically readable format (e.g., on a compact disc). Data must be kept with the study records. Acknowledgement of receipt of the data is required.

6.6.3 Source Data Documentation

Site Operations Representative will perform ongoing SDV as defined in the Clinical Monitoring Plan to confirm that critical protocol data (i.e., source data) entered in the CRF by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, PROs, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in the clinical study.

Before study initiation, the types of source documents that contain study-relevant information will be clearly defined in the Clinical Monitoring Plan. The Clinical Monitoring Plan defines which kind of source data – if available from clinical routine - can be used for documentation into CRF. No additional source data creation beyond routine is allowed.

Source documents that are required to verify the validity and completeness of data entered in the CRF must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 6.8.4.

To facilitate SDV, the physicians and institutions must provide the marketing authorization holder direct access to applicable source documents and reports for

trial-related monitoring, marketing authorization holder audits, and IRB/EC review. The participating sites must also allow inspection by applicable health authorities.

6.7 STATISTICAL CONSIDERATIONS

A detailed description of the statistical methods that will be used for the primary and secondary analyses will be provided in the Statistical Analysis Plan (SAP).

The statistical analysis will be performed using the *R system*.~~SAS System version 9.4 or higher~~.

This is not a hypothesis testing study but an exploratory study with predefined precision of estimates for key efficacy and safety parameters; there are no formal statistical hypotheses tests to be tested, and there will be no adjustments for multiplicity of endpoints or within-subgroups comparisons.

As when entering in the initial patient's treatment/pre-treatment data are collected retrospectively, missing data might occur in the retrospective period as well the distribution of missing data might be different across the participating investigational sites.

Data will be summarized using appropriate descriptive statistics. Categorical data will be presented as frequencies and percentages. For continuous data, arithmetic mean, standard deviation (STD), median, minimum, and maximum will be presented. The 95% confidence interval of the observed proportions (calculated using either the Clopper-Pearson methodology, or the Poisson distribution, for frequencies below 10%) will be provided.

6.7.1 Effectiveness Analyses

Effectiveness analysis population includes all patients who are enrolled and have received at least two cycles of Obinutuzumab.

In general, the time to endpoint will be defined as an interval between the date of enrolment (date of first visit) and date of first occurrence of the event. For patients who are event free, the censoring time will be calculated as a time interval between date of enrolment and the patient`s final contact with available data concerning the event. The estimates and graphical presentation will be performed via Kaplan-Meier approach.

Logistic regression will be performed on the rate of endpoints in order to test the impact of covariates, i.e. age, sex, ECOG PS, Ann Arbor staging, FLIPI, hepatitis infection (history of past/ resolved infection or latent HBV after prophylaxis as per standard treatment guidelines), chemotherapy backbone choice, medical history and history of FL, comorbidities. The list of the covariates to be included in the multivariate models will be detailed and justified in the statistical analysis plan document.

Exploratory analysis between different medical treatments given or subgroup analysis will be performed using Cox regression model and including relevant covariates. The list of the covariates to be included in the multivariate models will be detailed and justified in the statistical analysis plan document.

Further analyses will be performed to investigate different types of bias that might be present in this type of study design, e.g. time-dependent confounding, informative censoring, informative treatment changes/discontinuations, heterogeneity of results, and how to handle missing data.

Corresponding 95% confidence intervals (CIs) will be provided for all statistical estimates.

Primary endpoint

The primary endpoint is progression of disease at 2 years (POD24).

POD24 will be analyzed according to the survival analysis methods. The quartiles with their 95% confidence interval (estimated using Kaplan-Meier methods and Greenwood's formula) will be presented. Kaplan-Meier plots with a 95% CI will be prepared. Estimates for the survivor function will be obtained by the Kaplan-Meier approach.

Moreover, the POD24 will be analyzed as binary variable. Number and percentage of patients with its 95% confidence interval for POD24 will be calculated.

Logistic regression analysis will be performed to assess which variables are predictive of POD24. To identify factors associated with POD24, logistic regression analysis will be performed with backwards selection (removing factors with $P > 0.05$). Univariable associations between factors and POD24 will be calculated by using the Chi-square test.

In the analysis of POD24 will be excluded patients who die within 24 months from the treatment start with Obinutuzumab for reasons not related to the disease progression.

Secondary endpoints

Time-to-event outcomes (PFS at 2 and 3 years, TTNT, OS, TTLCB, duration of response, and time to response) will be analyzed according to the survival analysis methods. The quartiles will their 95% confidence interval (estimated using Kaplan-Meier methods and Greenwood's formula) will be presented. Kaplan-Meier plots with a 95% CI will be prepared. Estimates for the survivor functions for all time to event endpoints will be obtained by the Kaplan-Meier approach.

Cox regression analysis will be used to assess which variables are predictive of OS as well as to evaluate the association between early POD and OS from a risk-defining

event, that is, survival from time of POD for early progressors or from 2 years after diagnosis.

Response rates (ORR, CR, CR30 and rate of patients with stable disease) will be presented with the number and proportions of responders and non-responders together with two-sided, 95% Clopper-Pearson CIs.

Exploratory endpoints

All exploratory endpoints will be analyzed using descriptive statistics only.

6.7.2 Safety Analyses

Safety analysis population includes all patients who are enrolled.

Adverse events are those with start date beyond or equal to the date of first administration of Obinutuzumab and until 185 days after the last Obinutuzumab dose intake or until starting a new anti-cancer therapy (whichever occurs first). After this period AEs that are believed to be related to prior study drug treatment will be collected.

All adverse events will be assigned to a Preferred Term (PT) and will be classified by primary System Organ Class (SOC) according to the MedDRA thesaurus version 22 or higher.

Adverse events will be reported on a per-patient basis within Preferred Term. This mean that even if a patient will report the same event repeatedly (i.e. events mapped to the preferred term) the event will be counted only once. In the latter case the event will be assigned the worst CTCAE severity and the strongest relationship to the study drug. The earliest date will regard as start date of the event and the latest date will regard as stop date of the event.

Data will be listed by study site, patient number, and study day. Events occurring on or after treatment on Day 1 (treatment-emergent adverse events - TEAEs) will be summarized by mapped term, appropriate thesaurus levels, and NCI CTCAE v5.0 grade. In addition, SAEs, including deaths, will be listed separately and summarized. AEs leading to treatment discontinuation will be listed.

Infusion related reactions (IRRs) and adverse events of special interest (AESI) will be summarized by descriptive statistics and will be listed.

Relevant laboratory and vital signs data will be displayed by time, with NCI CTCAE Grade 3 and 4 values identified, where appropriate. Additionally, all laboratory data will be summarized by grade with use of NCI CTCAE v5.0.

All medications reported will be coded using the WHO-DRL Dictionary version 2018 or higher and classified according to 3rd level ATC level subgroup and Preferred Term.

For clinical laboratory parameters, where appropriate, the reported values will be converted into SI units and if needed boundary values for reference ranges will be converted as well.

For each parameter the change from baseline to each post-baseline visit will be calculated. The ranges considered for such confront will be the local laboratory ranges values available at each individual site.

The following vital signs, when performed as per clinical practice, will be captured in the eCRF:

- Systolic and diastolic blood pressure (mmHg)
- Heart rate (bpm)
- Body temperature (°C)

For each variable the change from baseline to each post-baseline visit will be calculated.

6.7.3 Other Analyses

The following other analyses will be performed:

Use of Obinutuzumab in real world setting

Descriptive statistics for the use of Obinutuzumab in the real world setting will be performed.

At least the following conditions will be considered in the analysis:

- *Not performing obinutuzumab administration on Day 8 and Day 15 in Cycle 1 (without safety reasons)*
- *Maintenance period: administration of obinutizumab in an interval superior to 10 days from the expected date (every 2 months per label). NOTE: An analysis will be performed to assess if this condition will have impact on efficacy parameters (PFS/ POD24) and to explore the delay reason (COVID-19 or others)*
- *All the chemotherapy scheme used with Obinutuzumab in real world setting*

Prescription profile

Obinutuzumab prescription profile and chemotherapy backbone choice by Italian region, age range, patient's profile and site dimension (outlying sites/universities, etc.)

Impact of COVID-19

- *Safety (infections and COVID-19 related events)*
- *Maintenance delay or interruption due to pandemic status*
- *Therapy interruption due to patient's complications caused by COVID-19*

~~The results of biomarker analyses will be presented using descriptive statistics only.~~

6.7.4 Interim and Final Analyses and Timing of Analyses

An interim analysis will be performed approximately one year after the first patient is included in the study in order to evaluate safety data, demographic data, FLIPI and treatment choices.

A second interim analysis will be performed approximately two years after the first patient included in the study in order to evaluate safety and primary and secondary effectiveness data, and the impact of COVID-19 on the patient management.

The results of the first two interim analysis will be compared.

The final Analysis will be performed at the end of the study.

6.7.5 Determination of Sample size

Sample size of this clinical study is selected based on feasibility.

Sample size is justified for the primary effectiveness endpoint POD24 treated as binary variable.

A sample size of 300 evaluable patients will allow estimation of the two-sided 95% confidence interval with a width equal to 7.9% (precision 3.95%) of the POD24 when the expected percentage is equal to 13%.

The Clopper-Pearson's formula has been used for the computation.

Table 1 provides the actual width and the precision of the 95% CI and the 95% confidence limits for different percentages of POD24 when the sample size is equal to 300 evaluable patients.

Table 1 - POD24 rate and corresponding 95% Confidence Intervals

POD24 (%)	Actual Width (%)	Precision (%)	95% Clopper-Pearson Exact CI (%)
11%	7.4	3.70	From 7.7 to 15.1
13%	7.9	3.95	From 9.4 to 17.3
15%	8.4	4.20	From 11.2 to 19.6
17%	8.8	4.40	From 12.9 to 21.7

Moreover, a sample size of 300 evaluable patients will allow estimation of the two-sided 95% confidence interval with a width equal to 9.4% (precision 4.70%) of the PFS rate at 3 years (treated as binary variable) when the expected percentage is equal to 80%.

Table 2 provides the actual width and the precision of the 95% CI and the 95% confidence limits for different percentages of PFS at 3 years when the sample size is equal to 300 of evaluable patients.

Table 2 - PFS rate at 3 yrs and corresponding 95% Confidence Intervals

PFS (%)	Actual Width (%)	Precision (%)	95% Clopper-Pearson Exact CI (%)
70%	10.7	5.35	From 64.5 to 75.1
75%	10.1	5.05	From 69.7 to 79.8
80%	9.4	4.70	From 75.0 to 84.4
85%	8.4	4.20	From 80.4 to 88.8
90%	7.1	3.55	From 86.0 to 93.2

Notes: From Gallium trial, PFS at 2 years has been estimated equal to 90% while PFS rate at 3 years to 80%.

6.8 STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

6.8.1 Study Documentation

The physician must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the physician will receive the patient data, which include an audit trail containing a complete record of all changes to the data.

The sponsor shall ensure that the dataset and statistical programs used for generating the data included in the final study report are kept in electronic format and are available for auditing and inspection.

6.8.2 Site Audits and Inspections

The physician will permit the sponsor or representative to audit facilities and records relevant to this study.

The physician will also permit national and local health authorities to inspect facilities and records relevant to this study. In case the site will receive a notice for an inspection from regulatory authority, the investigator will promptly inform the sponsor.

6.8.3 Use of Site Computerized Systems

Patient's Report Outcome data will be completed by patients into a smartphone connected with a remote web-application or directly into the web-application in a computer, available at site.

When clinical observations are entered directly into a participating site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a

viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

6.8.4 Retention of Records

Archiving at the study site has to be for 15 years after final study report or first publication of study results, whichever comes later.

Records and documents pertaining to the conduct of this study must be retained by the *MAH*~~physician~~ for at least ~~*1*~~*2*5 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

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

All supporting functional parties will comply with the sponsor procedures regarding archiving and record management.

6.8.5 Administrative Structure

This trial will be sponsored and managed by Roche S.p.A. The Sponsor will provide clinical operations management, data management, and medical monitoring.

Approximately 50 sites in Italy will participate to enrol approximately 300 patients. Enrolment will be competitive across sites.

Enrolment will occur through an *eCRF* ~~interactive web response system (IWRS) or similar~~ system to capture electronically enrolled patients.

~~Accredited~~ Local laboratories will be used for routine monitoring; local laboratory ranges will be *included in eCRF* ~~collected~~ as applicable.

6.9 LIMITATIONS OF THE RESEARCH METHOD

This study will be conducted in approximately 50 sites in Italy and will reflect the standard of care in place in the selected investigational study sites. Therefore, caution should be used in the generalisation of data collected in this study.

Furthermore, the design of the trial may be associated with further limitations. As an example, the possible bias in patients' selection due to the uncontrolled design of the trial may have impact on results.

Finally, pooling of prospective and retrospective data collection will be done even though not equivalent and this needs to be taken into consideration when interpreting the results.

7. PROTECTION OF HUMAN SUBJECTS

7.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the Guidelines for GPP published by the International Society of Pharmacoepidemiology (ISPE) and the laws and regulations of the country in which the research is conducted.

7.2 INFORMED CONSENT

The sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Assent or Caregiver's Informed Consent Form, if applicable) *and the privacy form* will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The sponsor must review and approve any proposed deviations from the sponsor's sample Informed Consent Forms or any alternate Consent Forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final Consent Forms approved by the IRB/EC must be provided to the marketing authorization holder for archiving and for health authority submission purposes according to local requirements.

The Consent *and Privacy* Forms must be signed and dated by the patient or the patient's legally authorized representative before start of documentation of his or her data in the CRF. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to first documentation of this patient's data in the CRF.

By signing the form, the patient confirms that he/she has been informed about the study and agrees to pseudonymous data collection, pooling of data with similar scientific data (if applicable), and the possibility of monitoring activities. It is the accountability of the physician *for ascertaining that the subject has comprehended the information and* to obtain written informed consent from each patient participating in the study, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. The physician must also explain that the patient is completely free to refuse to enter the study or to withdraw from it at any time, for any reason and without losing the benefit of any medical care to which the patient is entitled or is presently receiving. A copy of each signed *and dated* Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by Site Operations Representative at any time.

7.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Site Operations Representative in consultation with the Scientific Responsible and reviewed

and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

In addition to the requirements for collecting and reporting all AEs, *adverse events of special interest (AESI)* and SAEs to the marketing authorization holder, physicians must comply with requirements for AE reporting to the local health authority and IRB/EC.

7.4 CONFIDENTIALITY

The sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in datasets that are transmitted to any marketing authorization holder location.

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

The sponsor, including affiliates, collaborators and licensees may use study data labeled with the patient ID numbers. Study data may also be shared with independent researchers or government agencies, but only after personal information that can identify the patient has been removed. Patients' study data may be combined with other patient's data and/or linked to other data collected from the patients. Patients' study data may be used to help better understand why people get diseases, how to best prevent, diagnose and treat diseases, and to develop and deliver access to new medicines, medical devices, and healthcare solutions to advance patient care.

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

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

8. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ ADVERSE REACTIONS

8.1 SAFETY REPORTING REQUIREMENTS FOR STUDIED MEDICINAL PRODUCTS

8.1.1 Safety Parameters and Definitions

The reporting requirements in this section apply to all studied medicinal products. Products are not considered "studied" anymore after the end of the wash out period

following its discontinuation. For safety reporting requirements for non-studied medicinal products, see Section 8.2.

Safety assessments will consist of monitoring and recording SAEs and non-serious AEs (including AEs of special interest), performing safety laboratory assessments, measuring vital signs, and conducting other tests that are deemed critical to the safety evaluation of the study as per standard medical practice.

8.1.1.1 Adverse Events

According to the International Conference of Harmonisation (ICH), an AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product, regardless of causal attribution. An AE can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Appendix 3
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., electrocardiogram [ECG], X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study medicine.

8.1.1.2 Assessment of Serious Adverse Events (Immediately Reportable to the Marketing Authorization Holder), Non-serious Adverse Events of Special Interest (AESI) and Other Non-serious Adverse Events

Serious Adverse Events

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

- Is fatal (i.e., the AE actually causes or leads to death)
- Is life-threatening (NOTE: The term “life-threatening” refers to an event in which the patient was at immediate risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires or prolongs inpatient hospitalization (see A)
- Results in persistent or significant disability/incapacity (i.e., the AE results in substantial disruption of the patient’s ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study medicine

- Is a significant medical event in the physician's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (e.g., rated as mild, moderate, or severe, or according to NCI CTCAE criteria; see Appendix 3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each AE recorded on the CRF (for detailed instructions, see Appendix 3).

Adverse Events of Special Interest AEs of special interest for this study include the following:

- *Tumor lysis syndrome (TLS), irrespective of causality*
- *Second malignancies*
- *Cases of potential medicine-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law (see Appendix 3).*
- *Suspected transmission of an infectious agent by the study medicine, as defined below:*
  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term only applies when a contamination of the study medicine is suspected

  ~~Serious IRRs;~~

  ~~Tumour lysis syndrome (irrespective of regulatory seriousness criteria);~~

  ~~Serious neutropenia~~

  ~~Serious infections;~~

  ~~Hepatitis B reactivation while receiving the appropriate anti-viral therapy.~~

Non-Serious Adverse Events other than Adverse Events of Special Interest
All non-serious AEs (in addition to AEs of special interest) must be collected according to the appropriate level of MedDRA classification.

The physicians are reminded of the possibility to report any adverse reactions (for which they suspect a causal role of a medicinal product) that come to their attention to the

marketing authorization holder of the suspected medicinal product, or to the concerned competent authorities via the national spontaneous reporting system.

The Marketing Authorization Holder is responsible to submit adverse reactions to the competent regulatory authority.

8.1.2 Methods and Timing for Capturing and Assessing Safety Parameters

The physician is accountable for ensuring that all AEs collected as per protocol (see Section 8.1.1.1 for definition) are recorded in the AE section of the CRF and reported to the marketing authorization holder in accordance with instructions provided in this section and in Section 8.1.3.

For each AE recorded in the AE section of the CRF, the physician will make an assessment of seriousness (see Section 8.1.1.2), severity (see Appendix 3), and causality (see Appendix 3).

8.1.2.1 Adverse Event Reporting Period

Qualified *healthcare professionals (HCPs)* will seek information on AEs at each patient contact. All AEs subject to the collecting and reporting requirements outlined in this protocol, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and in the AE section of the eCRF.

Once the patient is enrolled in the study, AEs will be collected during the treatment with Obinutuzumab and until 185 days after the last Obinutuzumab dose or until starting a new anti-cancer therapy (whichever occurs first). It includes available data of adverse events that occurred between start of treatment and enrolment in the study (retrospective data collection)..

After this period, AEs that are believed to be related to prior study drug treatment will be collected and should be notified to the competent authority in the Member State where the reactions occurred or to the marketing authorization holder of the suspected medicinal product, but not to both (to avoid duplicate reporting).

8.1.2.2 Procedures for Recording Adverse Events

HCPs should use correct medical terminology/concepts and MedDRA coding when recording AEs in the AE section of the CRF. Colloquialisms and abbreviations should be avoided.

Only one AE term should be recorded in the event field of the CRF.

See Appendix 3 for further specific instruction regarding:

- Infusion-Related Reactions
- Diagnosis versus signs and symptoms

- Adverse Events occurring secondary to other Adverse Events
- Persistent or recurrent Adverse Events
- Abnormal Laboratory Values
- Abnormal Vital Sign Values
- Abnormal Liver Function Tests
- Deaths
    - All events with an outcome or consequence of death should be classified as serious adverse events (SAEs) and reported to the marketing authorization holder immediately. In certain circumstances, however, suspected adverse reactions with fatal outcome may not be subject to expedited reporting. ~~(see Section 8.3).~~ All deaths that occur during the protocol-specified AE reporting period, regardless of relationship to study medicine, must be recorded in the AE section of the CRF and immediately reported to the marketing authorization holder. *Deaths that are clearly attributable to disease progression must not be reported as an AE*
- Pre-existing Medical Conditions
- Lack of Therapeutic Efficacy
- Hospitalization or Prolonged Hospitalization
- Overdoses, Misuses, Abuses, Off-Label Use, Occupational Exposure, or Medication Error *(SS: Special Situation)*
- Quality Defects, Falsified Medicinal Products *and Product Complaints*
- Drug Interactions

8.1.3 Reporting Requirements from Healthcare Professional to Marketing Authorization Holder

8.1.3.1 Immediate Reporting Requirements from Healthcare Professional to Marketing Authorization Holder

Certain events require immediate reporting to allow the Marketing Authorization Holder and the regulatory authorities to take appropriate measures to address potential new risks associated with the use of the medicine. The HCP must report such events to the marketing authorization holder immediately; under no circumstances should reporting take place more than 24 hours after the HCP learns of the event. The following is a list of events that the HCP must report to the marketing authorization holder within 24 hours after learning of the event, regardless of relationship to study medicine:

- SAEs
- Non-serious AESI
- Pregnancies

The HCP must report new significant follow-up information for these events to the marketing authorization holder immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

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

For reports of SAEs and non-serious AESI, including follow-up, HCPs should record all case details that can be gathered immediately (i.e., within 24 hours) in the AE page of the CRF and submit the report via the EDC system. A report will be generated and sent to Roche Drug Safety by the EDC system.

In the event that the EDC system is temporarily unavailable, please refer to Section 8.1.3.3.

HCPs must also comply with local requirements for reporting SAEs to the local health authority and IRB/EC.

8.1.3.2 Reporting Requirements for Non-Serious Adverse Events

For all non-serious AEs, including follow-up reports, HCPs must record all case details that can be gathered within 30 calendar days of learning of the event on the AE section of the CRF and submit the report via the EDC system. A report will be generated and sent to Roche Drug Safety to allow appropriate reporting to relevant competent authorities.

In the event that the EDC system is temporarily unavailable, please refer to Section 8.1.3.3.

8.1.3.3 If EDC System is Temporarily Unavailable

In the event that the EDC system is temporarily unavailable, a completed paper reporting form and fax coversheet should be faxed/scanned to Roche Drug Safety or its designee immediately (i.e., no more than 24 hours after learning of the event) or within 30 calendar days for non-serious AEs if not AESI, using the fax number or email address provided to physicians.

Once the system is available again, all information should additionally be entered and submitted via the EDC system.

8.1.3.4 Reporting Requirements for Pregnancies/Breastfeeding

Pregnancies/Breastfeeding in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the physician if they become pregnant during the study or within 5 months after the last dose of medicine. A Pregnancy Report should be completed by the physician immediately (i.e., no more than 24 hours after learning of the pregnancy) and sent to Roche Drug Safety. Pregnancy should not be recorded on the AE eCRF. The physician should discontinue Obinutuzumab and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any SAEs associated with the pregnancy (e.g., an event in the foetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the AE section of the eCRF.

Suspected adverse reactions that occur in infants following exposure to a medicinal product from breast milk should be reported to Roche Drug Safety.

~~Pregnancies in Female Partners of Male Patients~~ ~~Male patients will be instructed through the Informed Consent Form to immediately inform the physician if their partner becomes pregnant during the study or within 5 months after the last dose of study medicinal product. A Pregnancy Report should be completed by the physician immediately (i.e., no more than 24 hours after learning of the pregnancy) and sent to Roche Drug Safety. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study medicine. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the physician will update the Pregnancy Report with additional information on the course and outcome of the pregnancy. A physician who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.~~

Abortions

Any abortion should be classified as an SAE (as the marketing authorization holder considers abortions to be medically significant), recorded in the AE section of the eCRF, and reported to the marketing authorization holder immediately (i.e., no more than 24 hours after learning of the event; see Section 8.1.3.1).

Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female patient exposed to the medicine should be classified as an SAE, recorded in the AE section of the eCRF, and reported to the marketing authorization holder immediately (i.e., no more than 24 hours after learning of the event; see Section 8.1.3.1).

8.1.3.5 Reporting Requirements for Adverse Events originating from Patient Reported Outcomes

Although physicians are not expected to review the PRO data, if HCP/study personnel becomes aware of a potential adverse event during review of the PRO questionnaire data, he/she will determine whether the criteria for an adverse event have been met and, if so, these must be reported using the Adverse Event eCRF.

8.1.4 Follow-Up of Patients after Adverse Events

8.1.4.1 HCP Follow-Up

The HCP should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable by the HCP, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all SAEs considered to be related to studied medicinal product until a final outcome can be reported.

During the study period, resolution of AEs (with dates) should be documented in the AE section of the eCRF and in the patient's medical record to facilitate SDV.

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

8.1.4.2 Marketing Authorization Holder Follow-Up

For all AEs, the MAH or a designee may follow up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case. AE follow-up should be documented in the AE section of the eCRF.

8.2 SAFETY REPORTING REQUIREMENTS FOR NON-STUDIED PRODUCTS

Although adverse event information is not being actively solicited for non-studied products, the physician/consumers are reminded to report any adverse reactions (for which they suspect a causal role of a product) that come to their attention to the marketing authorization holder of the suspected product, or to the concerned competent authorities via the national spontaneous reporting system.

In addition, the following should also be reported if occurring during exposure to a marketed medicinal product, even in the absence of adverse events:

- Pregnancy
- Breastfeeding
- Abnormal laboratory findings
- Overdose, abuse, misuse, off-label use, medication error or occupational exposure
- Reports of lack of efficacy
- Product quality defects and falsified medicinal products

- Data related to a suspected transmission of an infectious agent via a medicinal product
- Drug interactions (including drug/drug, drug/food, drug/device and drug/alcohol)

When a patient is not exposed to a marketed medicinal product, but the HCP/consumer becomes aware of the potential for a medication error, or an intercepted medication error, this should also be reported.

8.3 *REPORTING OF PRODUCT COMPLAINTS WITHOUT ADVERSE EVENTS*

Report Roche product complaints without Adverse Events, where Product Complaint is any written or oral information received from a complainant that alleges deficiencies related to Identity, Quality, Safety, Strength, Purity, Reliability, Durability, Effectiveness, or Performance of a product after it has been released and distributed to the commercial market, to monza.complaint_office@roche.com. Reports can be done via mail, clearly stating the product, protocol number, description of the complaint. Report non-Roche-product complaints as per local regulation.

9. PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a study, the sponsor is dedicated to openly providing information on the study to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The sponsor will comply with all requirements for publication of study results.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the physician must agree to submit all manuscripts or abstracts to the sponsor prior to submission for publication or presentation. This allows the sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the physician.

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

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

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

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Appendix 1
List of Stand-Alone Documents Not Included in the Protocol

- List of contact details of responsible parties and all physicians are declared in Site Signature and Delegation of Responsibilities log of each site and will be archived in site's file and sponsor's file.

Appendix 2
Data Collection Overview (as per Standard of Care)

Data Collection (available data will be collected; no additional diagnostic or monitoring procedures will be applied to patients outside of routine clinical practice)	Enrolment visit [a]	Retrospective Data collection	Prospective Data Collected during Treatment Period (Induction and maintenance period)	Follow-up period [b]
Informed consent[c]	x			
Diagnosis confirmation (clinical stage, histology)		x		
Target Population	x	x		
Medical history and demographic data		x		
Concomitant treatments/medications[d]	x	X	x	
Treatment with Obinutuzumab	(x)[c]	(x)[c]	x	
Prophylaxis medication	x	x	x	
Laboratory assessments[e]	x	x	x	
Pregnancy test	x[f]	x[f]	x[f]	
Physical examination and Vital signs	x	x	x	
ECOG	x	x	x	x
B symptoms	x	x	x	x
QoL (Quality of life: EuroQol 5-Dimension Questionnaire, 5-level version (EQ-5D-5L); Functional Assessment of Chronic illness Therapy-Lymphoma (FACT-Lym) [g]	x		x	~~x~~
Chemotherapy regimen	x	x	x	
AEs/SAEs/*AESI*/*SS*~~IRR/ADR~~	x		x	x[k]
Retrospective Safety data collection		x[h]		
Tumor assessments	x	x	x	x
Ann Arbor	x	x		
FLIPI score assessment[i]	x	x		
BM evaluation	x	x	x	x
Response rate[j]	x	x	x	x
New anti-cancer therapy and survival status after end of treatment				x

[a] Items Concomitant treatments/medications, Treatment with obinutuzumab, Pregnancy test. Physical examination and Vital signs, Prophylaxis medication and Chemotherapy regimen apply only for patients still on treatment at the time of enrollment as part of their standard procedures for treatment. In case of patients

enrolled after treatment completion, these data will be collected as indicated in the Retrospective column and the prospective information will be collected as described in the Follow-up period.

[b] Approximately one-year follow-up after last dose of Obinutuzumab administration, as per clinical practice, or for patients that early discontinue the treatment up to 3.5 years after first treatment administration or until withdrawal of consent, study termination by the Sponsor, or death, whichever occurs first, regardless of whether patients start a new anti-cancer therapy. For patients that discontinue treatment before completing induction or maintenance, the follow up parameters can be collected in accordance with current patient's schedule visit and not every 2 months. Follow-up data will include at least tumor assessments, *new anti-lymphoma therapy informations*, and safety data.

[c] Patients included should have performed at least 2 cycles of induction treatment with Obinutuzumab and chemotherapy, within 1 year from beginning of treatment

[d] Including any medication used by the patient from 7 days prior to starting treatment with obinutuzumab.

[e] Laboratory tests will include: haematology (WBCs and differential count [at least neutrophils and monocyte %], RBCs, haemoglobin, haematocrit, platelet count) and blood chemistry (creatinine, beta-2 microglobulin, LDH, AST, ALT).

[f] Data collected if performed per clinical practice as clinically indicated.

[g] QoL will be completed prospectively period, every 2 cycles in induction treatment phase and every 2 months during maintenance treatment phase. For further instructions over QoL completion please refer to section 6.6.1. PRO questionnaires (FACT-Lym, EQ-5D) should be administered *on Day 1 of alternate cycles during induction treatment period and at each cycle during manteinace treatment period. PRO Questionnaires should be administered on Day 1 of the cycle* prior to any treatment and assessments, *i.e. PRO questionnaires should be collected only when corresponding to a treatment cycle*. PRO questionnaires should also be administered at first assessment after report of disease progression.

[h] AEs/SAEs/*AESI/SS*~~IRR/ADR~~ that occur prior ICF signature should be reported in eCRF as available; however only the event preferred term as per CTCAE vs 5.0 is required as Individual Case Safety Report are not applicable. Prospective safety that must be fully assessed and reported by study physician including assessment of seriousness (see Section 8.1.1.2), severity (see Appendix 3), and causality (see Appendix 3).

[i] FLIPI score (age, number of nodal sites, LDH level, haemoglobin, stage) or FLIPI2 (age, beta-2 microglobulin, bone marrow involvement, longest diameter of largest involved node, haemoglobin) collected at diagnosis.

[j] Response will be collected at mid of the induction (between 10 and 14 weeks after the start of treatments), end of the induction (at the day of cycle 6 until 1 month later) during maintenance (1 year after the start of treatment, i.e. from 10 to 14 months after the start of treatment; 2 years after the start of treatment, i.e. from 22 to 26 months after the start of treatment; 3 years after the start of treatment, i.e. from 34 to 38 months after the start of treatment), at the end of maintenance and at Follow-up as per clinical practice, as well as at any tumor assessment that shows disease progression, CR or CRu during induction or maintenance. The assessment of tumor response will be based on standard Cheson criteria and the Deauville 5-point scale (Appendix 6) (*Younes et al. 2017*).

[k] All adverse events data available in medical records after start of the treatment should be reported until 185 days after the last obinutuzumab dose or until starting a new anti-cancer therapy (whichever occurs first). After this period AEs that are believed to be related to prior study drug treatment will be collected.

Appendix 3
Methods for Assessing and Recording Adverse Events

3.1 Assessment of Severity of Adverse Events
3.2 Assessment of Causality of Adverse Events
3.3 Procedures for Recording Adverse Events

Appendix 3.1 Assessment of Severity of Adverse Events

The AE severity grading scale for the NCI CTCAE (v5.0) will be used for assessing AE severity. The table below will be used for assessing severity for AEs that are not specifically listed in the NCI CTCAE.

Adverse Event Severity Grading Scale

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

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

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

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

[c] If an event is assessed as a "significant medical event," it must be reported as an SAE *(see Section 8.1.3.1 for reporting Instructions),* per the definition of SAE in Section 8.1.1.2.

[d] Grade 4 and 5 events must be reported as SAEs *(see Section 8.1.3.1 for reporting instructions)*, per the definition of SAE in Section 8.1.1.2.

Appendix 3.2 Assessment of Causality of Adverse Events

For patients receiving combination therapy, causality will be assessed individually for each of the medicinal products.

Physicians should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to the study medicine, indicating “yes” or “no” accordingly. The following guidance should be taken into consideration:

Temporal relationship of event onset to the initiation of study medicine

Course of the event, considering especially the effects of dose reduction, discontinuation of study medicine, or reintroduction of study medicine (when applicable)

Known association of the event with the study medicine or with similar treatments

Known association of the event with the disease under study

Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event

Presence of non-treatment-related factors that are known to be associated with the occurrence of the event

Appendix 3.3 Procedures for recording Adverse Events

Appendix 3.3.1 Infusion-Related Reactions

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

Appendix 3.3.2 Diagnosis versus Signs and Symptoms

For AEs, other than infusion-related reactions (see Section 3.3.1) a diagnosis (if known) should be recorded in the AE section of the CRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded in the AE section of the CRF. If a diagnosis is subsequently established, all previously reported AEs based on signs and symptoms should be nullified and replaced by one AE report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis.

Appendix 3.3.3 Adverse Events Occurring Secondary to Other Events

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

If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the CRF.

If vomiting results in severe dehydration, both events should be reported separately on the CRF.

If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the CRF.

If dizziness leads to a fall and subsequent fracture, all three events should be reported separately on the CRF.

If neutropenia is accompanied by an infection, both events should be reported separately on the CRF.

All AEs should be recorded separately in the AE section of the CRF if it is unclear as to whether the events are associated.

Appendix 3.3.4 Persistent or Recurrent Adverse Events

A persistent AE is one that extends continuously, without resolution, between patient evaluation time points. Such events should only be recorded once in the AE section of the CRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent AE becomes more severe, the most extreme severity should also be recorded in the AE section of the CRF. If the event becomes serious, it should be reported to the marketing authorization holder immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 8.1.3.1 for reporting instructions). The AE section of the CRF should be updated by changing the event from "non-serious" to "serious," providing the date that the event became serious, and completing all data fields related to SAEs.

A recurrent AE is one that resolves between patient's evaluation timepoints and subsequently recurs. Each recurrence of an AE should be recorded separately in the AE section of the CRF.

Appendix 3.3.5 Abnormal Laboratory Values

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

Is accompanied by clinical symptoms

Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)

Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy

Is clinically significant in the physician's judgment

Note: For oncology studies, certain abnormal values may not qualify as AEs.

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

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 $\times$ the upper limit of normal [ULN] associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded in the AE section of the eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded in the AE section of the CRF, along with a descriptor indicating if the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be

characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as “hyperkalemia.”

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once in the AE section of the eCRF (see Appendix 3.3.4 for details on recording persistent AEs).

Appendix 3.3.6 Abnormal Vital Sign Values

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

Is accompanied by clinical symptoms

Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)

Results in a medical intervention or a change in concomitant therapy

Is clinically significant in the physician’s judgment

It is the physician’s responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an AE.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded in the AE section of the CRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once in the AE section of the CRF (see Appendix 3.3.4 for details on recording persistent AEs).

Appendix 3.3.7 Abnormal Liver Function Tests

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

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

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

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded in the AE section of the CRF (see Appendix 3.3.5) and reported to the marketing authorization holder immediately (i.e., no more than

24 hours after learning of the event) either as an SAE or a non-serious AE of special interest (see Section 8.1.3.1).

Appendix 3.3.8 Deaths

All deaths that occur during the protocol-specified AE reporting period (see Section 8.1.2.1), regardless of relationship to study medicine, must be recorded in the AE section of the eCRF and immediately reported to the marketing authorization holder (see Section 8.1.3.1).

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the AE section of the CRF. Generally, only one such event should be reported. The term **"sudden death"** should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without preexisting heart disease, within 1 hour after the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, **"unexplained death"** should be recorded on the AE section of the CRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

Appendix 3.3.9 Preexisting Medical Conditions

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

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

Appendix 3.3.10 Lack of Therapeutic Efficacy

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as AEs. These data will be captured as effectiveness assessment data only. In most cases, the expected pattern of progression will be based on standard criteria (i.e. Revised Response Criteria for Malignant Lymphoma [*Cheson et al. 2007*] and the Deauville 5-point scale [*Meignan et al. 2009*]). In rare cases, the determination of clinical progression will be based on symptomatic deterioration. However, every effort should be made to document progression through use of objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an AE. This exception from reporting includes events of disease progression with a fatal outcome which are clearly attributable to disease progression.

Appendix 3.3.11 Hospitalization or Prolonged Hospitalization

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE (per the definition of SAE in Section 8.1.1.2), except as outlined below.

The following hospitalization scenarios are not considered to be SAEs:

Hospitalization for respite care

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

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

Hospitalization solely due to progression of the underlying cancer

The following hospitalization scenarios are not considered to be SAEs but should be reported as AEs instead:

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

Appendix 3.3.12 Overdoses, Misuses, Abuses, Off-Label Use, Occupational Exposure, or Medication Error

Any overdose, misuse, abuse, off-label use, occupational exposure, medication error (including intercepted or potential), or any other incorrect administration of medicine under observation should be noted in the Drug Administration section of the CRF *as Special Situation (SS)*. Any overdose, abuse, misuse, inadvertent/erroneous administration, medication error (including intercepted or potential), or occupational exposure reports must be forwarded to the marketing authorization holder with or without an AE.

Reports with or without an AE should be forwarded to the marketing authorization holder as per non-serious timelines. If the associated AE fulfills the seriousness criteria, the event should be reported to the marketing authorization holder immediately (i.e., no more than 24 hours after learning of the event, see Section 8.1.3.1).

For the purpose of reporting cases of suspected adverse reactions, an occupational exposure to a medicine means an exposure to a medicine as a result of one's professional or non-professional occupation.

Appendix 3.3.13 Quality Defects, Falsified Products *and Products Complaints*

Reports of suspected or confirmed falsified product or quality defect of a product, with or without an associated AE, should be forwarded to the marketing authorization holder as

per non-serious timelines. If the associated AE fulfills the seriousness criteria, the event should be reported to the marketing authorization holder immediately (i.e., no more than 24 hours after learning of the event, see Section 8.1.3.1).

Appendix 3.3.14 Drug Interactions

Reports of suspected or confirmed drug interactions, including drug/drug, drug/food, drug/device and drug/alcohol, should be forwarded to the marketing authorization holder as per non-serious timelines. If the associated AE fulfills the seriousness criteria, the event should be reported to the marketing authorization holder immediately (i.e., no more than 24 hours after learning of the event, see Section 8.1.3.1).

Appendix 4
EuroQol 5-Dimension Questionnaire, 5-level version (EQ-5D-5L)

Sotto ciascun argomento, faccia una crocetta sulla casella (UNA SOLA) che descrive meglio la sua salute OGGI.

CAPACITÀ DI MOVIMENTO

Non ho difficoltà nel camminare ❑
Ho lievi difficoltà nel camminare ❑
Ho moderate difficoltà nel camminare ❑
Ho gravi difficoltà nel camminare ❑
Non sono in grado di camminare ❑

CURA DELLA PERSONA

Non ho difficoltà nel lavarmi o vestirmi ❑
Ho lievi difficoltà nel lavarmi o vestirmi ❑
Ho moderate difficoltà nel lavarmi o vestirmi ❑
Ho gravi difficoltà nel lavarmi o vestirmi ❑
Non sono in grado di lavarmi o vestirmi ❑

ATTIVITÀ ABITUALI (*per es. lavoro, studio, lavori domestici,attività familiari o di svago)*

Non ho difficoltà nello svolgimento delle attività abituali ❑
Ho lievi difficoltà nello svolgimento delle attività abituali ❑
Ho moderate difficoltà nello svolgimento delle attività abituali ❑
Ho gravi difficoltà nello svolgimento delle attività abituali ❑
Non sono in grado di svolgere le mie attività abituali ❑

DOLORE O FASTIDIO

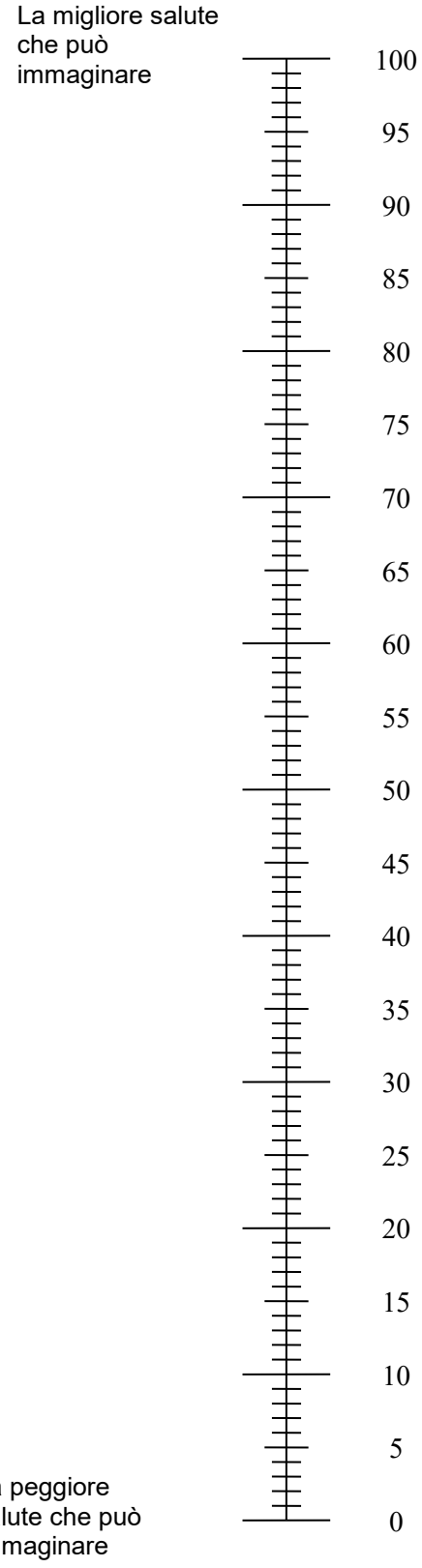
Non provo alcun dolore o fastidio ❑
Provo lieve dolore o fastidio ❑
Provo moderato dolore o fastidio ❑
Provo grave dolore o fastidio ❑
Provo estremo dolore o fastidio ❑

ANSIA O DEPRESSIONE

Non sono ansioso/a o depresso/a ❑
Sono lievemente ansioso/a o depresso/a ❑
Sono moderatamente ansioso/a o depresso/a ❑
Sono gravemente ansioso/a o depresso/a ❑
Sono estremamente ansioso/a o depresso/a ❑

- Vorremmo sapere quanto è buona o cattiva la sua salute OGGI.
- Questa è una scala numerata che va da 0 a 100.
- 100 rappresenta la migliore salute che può immaginare.
  0 rappresenta la peggiore salute che può immaginare.
- Segni una X sul punto della scala per indicare com'è la sua salute OGGI.
- Poi, scriva nella casella qui sotto il numero che ha segnato sulla scala numerata.

LA SUA SALUTE OGGI = ☐



Appendix 5
Functional Assessment of Chronic illness Therapy-Lymphoma (FACT-Lym), version 4

Sotto abbiamo elencato delle affermazioni ritenute importanti da persone con la sua stessa malattia.

La preghiamo di selezionare la sua risposta in riferimento agli <u>ultimi 7 giorni</u>.

	BENESSERE FISICO	**Per niente**	**Un po'**	**Abba-stanza**	**Molto**	**Moltis-simo**
GP1	**Mi manca l'energia**	0	1	2	3	4
GP2	Ho nausea	0	1	2	3	4
GP3	Ho difficoltà ad occuparmi delle necessità della mia famiglia a causa delle mie condizioni fisiche	0	1	2	3	4
GP4	Ho dolori	0	1	2	3	4
GP5	Mi danno fastidio gli effetti collaterali della cura	0	1	2	3	4
GP6	Mi sento male	0	1	2	3	4
GP7	Sono costretto/a a trascorrere del tempo a letto	0	1	2	3	4
	BENESSERE SOCIALE/FAMILIARE	**Per niente**	**Un po'**	**Abba-stanza**	**Molto**	**Moltis-simo**
GS1	Mi sento vicino/a ai miei amici	0	1	2	3	4
GS2	La mia famiglia mi sostiene moralmente	0	1	2	3	4
GS3	Ho appoggio morale dai miei amici	0	1	2	3	4
GS4	La mia famiglia ha accettato la mia malattia	0	1	2	3	4
GS5	Sono soddisfatto/a della comunicazione nella mia famiglia a proposito della mia malattia	0	1	2	3	4
GS6	Mi sento vicino/a al mio compagno/alla mia compagna (o alla persona che mi offre il maggiore appoggio)	0	1	2	3	4
Q1	*Indipendentemente dalla sua attività sessuale, la preghiamo di rispondere alla seguente domanda. Se preferisce non rispondere, barri questa casella* |__| *e passi alla prossima sezione.*					
GS7	Sono soddisfatto/a della mia attività sessuale	0	1	2	3	4

La preghiamo di selezionare la sua risposta in riferimento agli ultimi 7 giorni.

	BENESSERE FUNZIONALE	Per niente	Un po'	Abba-stanza	Molto	Moltis-simo
GF1	Sono in grado di lavorare (si intende anche il lavoro a casa)	0	1	2	3	4
GF2	Il mio lavoro (si intende anche il lavoro a casa) mi gratifica	0	1	2	3	4
GF3	Riesco a godermi la vita	0	1	2	3	4
GF4	Ho accettato la mia malattia	0	1	2	3	4
GF5	Dormo bene	0	1	2	3	4
GF6	Provo ancora piacere nel dedicarmi ad attività di tempo libero	0	1	2	3	4
GF7	Al momento, sono soddisfatto/a della qualità della mia vita	0	1	2	3	4

La preghiamo di selezionare la sua risposta in riferimento agli ultimi 7 giorni.

	ULTERIORI PROBLEMI	Per niente	Un po'	Abba-stanza	Molto	Moltis-simo
P2	In certe zone del corpo sento dolore	0	1	2	3	4
LEU1	Mi danno fastidio gli ingrossamenti e i gonfiori che ho in alcune parti del corpo (ad es. collo, ascelle, inguine)	0	1	2	3	4
BRM3	Mi dà fastidio la febbre	0	1	2	3	4
ES3	Ho sudori notturni	0	1	2	3	4
LYM1	Mi dà fastidio il prurito	0	1	2	3	4
LYM2	Ho difficoltà a dormire di notte	0	1	2	3	4
BMT6	Mi stanco facilmente	0	1	2	3	4
C2	Sto dimagrendo	0	1	2	3	4
Ga1	Mi manca l'appetito0	0	1	2	3	4
HI8	Ho difficoltà a concentrarmi	0	1	2	3	4

N3	Ho paura di prendere delle infezioni	0	1	2	3	4
LEU6	Mi preoccupo che possano manifestarsi nuovi sintomi della malattia	0	1	2	3	4
LEU7	Mi sento isolato/a dagli altri a causa della mia malattia o del trattamento	0	1	2	3	4
BRM 9	Ho alti e bassi di umore	0	1	2	3	4
LEU4	Ho difficoltà a fare programmi per il futuro a causa della mia malattia	0	1	2	3	4

Appendix 6
Criteria for Assessment of Tumor Response: standard Cheson criteria and the Deauville 5-point scale

	% Change in sum of diameters of target lesions from nadir				
	CR	PR	MR[a]	SD	PD
% change from baseline	• Complete disappearance of all target lesions and all nodes with long axis <10mm. • ⩾30% decrease in the sum of longest diameters of target lesions (PR) with normalization of FDG-PET	⩾30% decrease in the sum of longest diameters of target lesions but not a CR	⩾10% decrease in the sum of longest diameters of target lesions but not a PR (<30%)	<10% decrease or ⩽20% increase in the sum of longest diameters of target lesions	• >20% increase in the sum of longest diameters of target lesions • For small lymph nodes measuring <15 mm post therapy, a minimum absolute increase of 5mm and the long diameter should exceed 15mm • Appearance of a new lesion
FDG-PET	Normalization of FDG-PET (Deauvile score 1-3)	Positive (Deauville score 4-5)	Any	Any	Any
Bone marrow involvement	Not involved	Any	Any	Any	Any
New lesions	No	No	No	No	Yes or No

CR, complete response; CT, computerized tomography; FDG-PET, [18F]2-fluoro-2-deoxy-D-glucose; MR, minor response; PD, progression of disease; PR, partial response; SD, stable disease.
[a]A provisional category.