THE EU RISK MANAGEMENT PLAN FOR GAZYVARO®/OBINUTUZUMAB

RMP version to be assessed as part of this application:

RMP version number: 10.0

Data lock point for this RMP: 5 September 2024

Date of final sign off: See latest date in date stamps below

Date and Time (UTC)	Reason for Signing	Name
05-Sep-2024 14:01:04	Deputy QPPV	Tanrikulu, Yusuf (tanrikuy)
05-Sep-2024 19:08:23	Company Signatory (PV)	PPD

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OBINUTUZUMAB EU RMP V10.0.

Rationale for Submitting an Updated Risk Management Plan:

The European Union (EU) Risk Management Plan (RMP) version 10.0 is prepared to remove the guided questionnaires (GQs) for secondary malignancies, progressive multifocal leukoencephalopathy (PML) and hepatitis B reactivation. Information on these risks continues to be collected via routine individual case safety report (ICSR) follow-up. The European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) agreed to this update as part of procedure EMEA/H/C/PSUSA/00010279/202310, the review of the obinutuzumab PSUR with reporting period 1 November 2020 to 31 October 2023. In addition, the RMP has been updated based on EMA guidelines for pregnancy and breastfeeding women (GVP P.III).

In summary, the following updates are proposed in EU RMP v10.0.

Summary of Significant Changes in this RMP

Section in the RMP	Summary of changes
Part I: Product Overview	The ATC code was updated.
Part II: Module SI-Epidemiology of the Indication(s) and Target Populations	Updated information from recent international treatment guidelines (NHL and CLL)
Part II: Module SII-Nonclinical Part of the Safety Specification	Update to a subheading based on EMA guidelines for Pregnancy and Breastfeeding Women (GVP P. III).
Part II: Module SIV.3.-Populations Not Studied in Clinical Trials	Updates based on EMA guidelines for Pregnancy and Breastfeeding Women (GVP P. III) were added.
Part II: Module SV.1 -Post Authorization Experience	Updated to reflect exposure up to 31 October 2023.
Part III. Pharmacovigilance Plan	Updates to headings based on EMA guidelines for Pregnancy and Breastfeeding Women (GVP P. III). Removal of inclusion of GQs as part of routine pharmacovigilance activities.
Part V.3 Summary of Risk Minimization Measures	Removal of GQs from Table 28- Summary Table of Pharmacovigilance Activities and Risk-Minimization Activities by Safety Concern (second malignancies).
Annex 4	Removal of GQs for secondary malignancies, progressive multifocal leukoencephalopathy (PML) and hepatitis B reactivation.
Annex 7	Addition of summary tabulations of prospective and retrospective ICSRs on pregnancy have been appended. Cumulative Worldwide Market exposure added
Annex 8	Updated to reflect the changes to this EU RMP.

Details of Currently Approved RMP

Version number: 9.0

Approved with procedure: EMEA/H/C/002799/II/0047

Date of approval (opinion date): 21 July 2022

See page 1 for signature and date

Yusuf Tanrikulu (Deputy QPPV) Date

See page 1 for signature and date

PPD Date

PART I: PRODUCT OVERVIEW

Table 1 Product Overview

Active Substance (INN or common name)	Obinutuzumab
Pharmacotherapeutic group(s) (ATC Code)	L01FA03
Marketing Authorization Holder (or Applicant)	Roche Registration GmbH
Medicinal products to which this RMP refers	One
Invented name(s) in the European Economic Area (EEA)	Gazyvaro®
Marketing authorization procedure	Centrally authorized procedure
Brief description of the product including:	Chemical Class: Humanized, Type II anti-CD20 monoclonal antibody
	Summary of mode of action: Obinutuzumab mediates B-cell depletion and anti-tumoral activity. It specifically targets the extracellular loop of the CD20 antigen that is present on the surface of non-malignant and malignant pre B and mature B lymphocytes, but not on hemopoietic 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 and macrophages/monocytes. 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. Important information about its composition Obinutuzumab was derived by humanization and further engineering of the parental murine IgG1-κ antibody B-ly1. It is manufactured by fermentation of a recombinant Chinese hamster ovary K1 cell line with subsequent purification of the antibody.
Hyperlink to the Product Information	To be linked by RSG group
Indication(s) in the EEA	Current: Gazyvaro in combination with chlorambucil is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukemia (CLL) and with comorbidities making them unsuitable for full-dose fludarabine-based therapy.

	Gazyvaro in combination with bendamustine followed by Gazyvaro maintenance is indicated for the treatment of patients with follicular lymphoma (FL) who did not respond or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen. Gazyvaro in combination with chemotherapy, followed by Gazyvaro maintenance therapy in patients achieving a response, is indicated for the treatment of patients with previously untreated advanced follicular lymphoma.
	Proposed: Not applicable
Dosage in the EEA	Current: **CLL patients:** Obinutuzumab should be administered as an intravenous (IV) infusion diluted in sodium chloride 9 mg/mL (0.9%) solution for injection. Cycle 1 The recommended dose of obinutuzumab is 1,000 mg administered over Day 1 and Day 2, and on Day 8 and Day 15 of the first 28-day treatment cycle. Two infusion bags should be prepared for the infusion on Days 1 and 2 (100 mg for Day 1 and 900 mg for Day 2). Cycles 2 to 6 The recommended dose of obinutuzumab is 1,000 mg administered on Day 1. Obinutuzumab should be administered in combination with chlorambucil. Six treatment cycles should be administered, each of 28-day duration. **FL patients (relapsed/refractory):** The recommended dosage of obinutuzumab is 1,000 mg administered on Day 1, Day 8, and Day 15 of the first 28-day treatment cycle followed by 1,000 mg administered on Day 1 only for each subsequent 28-day treatment cycle (Cycles 2 to 6). Obinutuzumab should be administered in combination with bendamustine. *Maintenance* Patients who respond to induction treatment (i.e., the initial 6 treatment cycles) with obinutuzumab in combination with bendamustine or have stable disease should continue to receive obinutuzumab 1,000 mg as single-agent maintenance therapy once every 2 months for 2 years or until disease progression (whichever occurs first). **FL patients (previously untreated):**

	The recommended dosage of obinutuzumab is 1,000 mg administered on Day 1, Day 8, and Day 15 of the first cycle followed by 1,000 mg administered on Day 1 on only subsequent cycles. Obinutuzumab should be administered with chemotherapy as follows: Six 28-day cycles in combination with bendamustine[a], or Six 21-day cycles in combination with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone), followed by 2 additional cycles of obinutuzumab alone, or Eight 21-day cycles in combination with CVP (cyclophosphamide, vincristine, prednisolone). *Maintenance* Patients who achieve a complete or partial response to induction treatment with obinutuzumab in combination with chemotherapy (CHOP or CVP or bendamustine) should continue to receive obinutuzumab 1,000 mg as single-agent maintenance therapy once every 2 months for 2 years or until disease progression (whichever occurs first). Proposed label update: Gazyvaro should be administered at the standard infusion rate in Cycle 1. In patients who do not experience Grade ≥3 infusion related reactions (IRR) during Cycle 1, Gazyvaro may be administered as a short (approximately 90 minutes) duration infusion (SDI) from Cycle 2 onwards.
Pharmaceutical form(s) and strengths	Current: Obinutuzumab is supplied as a single 1,000 mg dose in a 50 mL glass vial containing 40 mL of liquid concentrate (25 mg/mL).
	Proposed: Not applicable
Is or will the product be subject to additional monitoring in the EU?	No

ADCC = antibody dependent cellular cytotoxicity; ADCP = antibody dependent cellular phagocytosis; CD = CHOP = cyclophosphamide, doxorubicin, vincristine and prednisone; CLL = chronic lymphocytic leukemia; CVP = cyclophosphamide, vincristine, prednisolone; EU = European Union; FL = Follicular lymphoma; IV = intravenous; NK = natural killer.

[a] See section 5.1 of the SmPC for information on bendamustine dose.

GLOSSARY OF ABBREVIATIONS

Abbreviation	Definition
ADCC	antibody-dependent cellular cytotoxicity
AEGT	adverse event group terms
AEPI	adverse event of particular interest
aNHL	aggressive Non-Hodgkin Lymphoma
anti-HBc	anti-hepatitis B core antibody
BMI	body mass index
CHOP	cyclophosphamide, doxorubicin, vincristine and prednisolone
CHMP	Committee for Medicinal Products for Human Us
Clb	chlorambucil
CLL	chronic lymphocytic leukemia
CrCl	creatinine clearance
CT	computerized tomography
CVP	cyclophosphamide, vincristine and prednisone
DLBCL	diffuse large B-cell lymphoma
DSMB	Data Safety Monitoring Board
EMA	European Medicines Agency
EORTC	the European Organisation for Research and Treatment of Cancer
EPAR	European Public Assessment Report
ESMO	European Society for Medical Oncology
EU	European Union
FC	fludarabine-cyclophosphamide
FCR	fludarabine, cyclophosphamide and rituximab
FDA	US Food and Drug Administration
FL	follicular lymphoma
G-benda	obinutuzumab and bendamustine
G-CHOP	obinutuzumab plus CHOP
GClb	obinutuzumab plus chlorambucil
GVP	good pharmacovigilance practices
HBcAb	hepatitis B core antibody
HBV	hepatitis B virus
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HLGT	high level group term (MedDRA)
HLT	high level term (MedDRA)

Abbreviation	Definition
IBD	International Birth Date
IL	Interleukin
iNHL	indolent Non-Hodgkin Lymphoma
IRR	infusion-related reaction
IV	intravenous
JCV DNA	John Cunningham viral DNA
MCL	mantle cell lymphoma
MedDRA PT	MedDRA preferred term
MI	myocardial infarction
MRI	magnetic resonance imaging
MZL	marginal zone lymphoma
NCI	National Cancer Institute
NCI CTC	National Cancer Institute common terminology criteria for adverse events
NHL	Non-Hodgkin Lymphoma
NK	natural killer
PFS	progression-free survival
PV	pharmacovigilance
PML	progressive multifocal leukoencephalopathy
PMN	polymorphonuclear neutrophil
RClb	rituximab plus chlorambucil
R/R	relapsed/refractory
SC	subcutaneous
SLE	systemic lupus erythematosus
SLL	small lymphocytic lymphoma
SmPC	summary of product characteristics
SMQ	standard MedDRA query
SOC	system organ class (MedDRA)
TLS	tumor lysis syndrome
TNF-α	tumor necrosis factor-α
TSE	transmissible spongiform encephalopathies

PART II: SAFETY SPECIFICATION

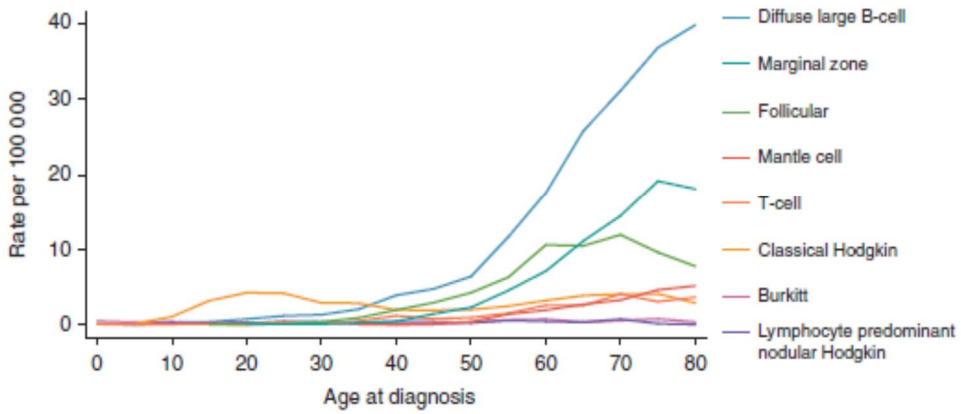
PART II: MODULE SI— EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1 NON HODGKIN LYMPHOMA (NHL)

INCIDENCE AND PREVALENCE

Non Hodgkin lymphoma (NHL) is a large heterogeneous group of hematological malignancies (as shown in Figure 1), which may be divided into aggressive (aNHL) and indolent (iNHL) forms. Information on the epidemiology of NHL subtypes is limited due to changes in the classification of NHLs in recent years and the fact that most cancer registries only record a diagnosis of NHL. As a result, the incidence and prevalence of particular subtypes in European countries is only available indirectly, derived from data on the overall population of patients with NHL. Therefore, NHL in general is discussed, and in addition the available information on relevant subtypes is summarized.

Figure 1 Age-specific Incidence per 100,000 Populations by NHL Subtype: Hematological Malignancy Research Network (HMRN) 2004–2012



Source: Original data source Smith et al. 2015.

The most common types of NHL are diffuse large B-cell lymphoma (DLBCL), which accounts for 38%–48% of NHL in Western countries, and follicular lymphoma (FL), which accounts for approximately 20% of NHL in Western countries as shown in Figure 1 (Novelli et al. 2013; Rodriguez-Abreu et al. 2007; Smith et al. 2015).

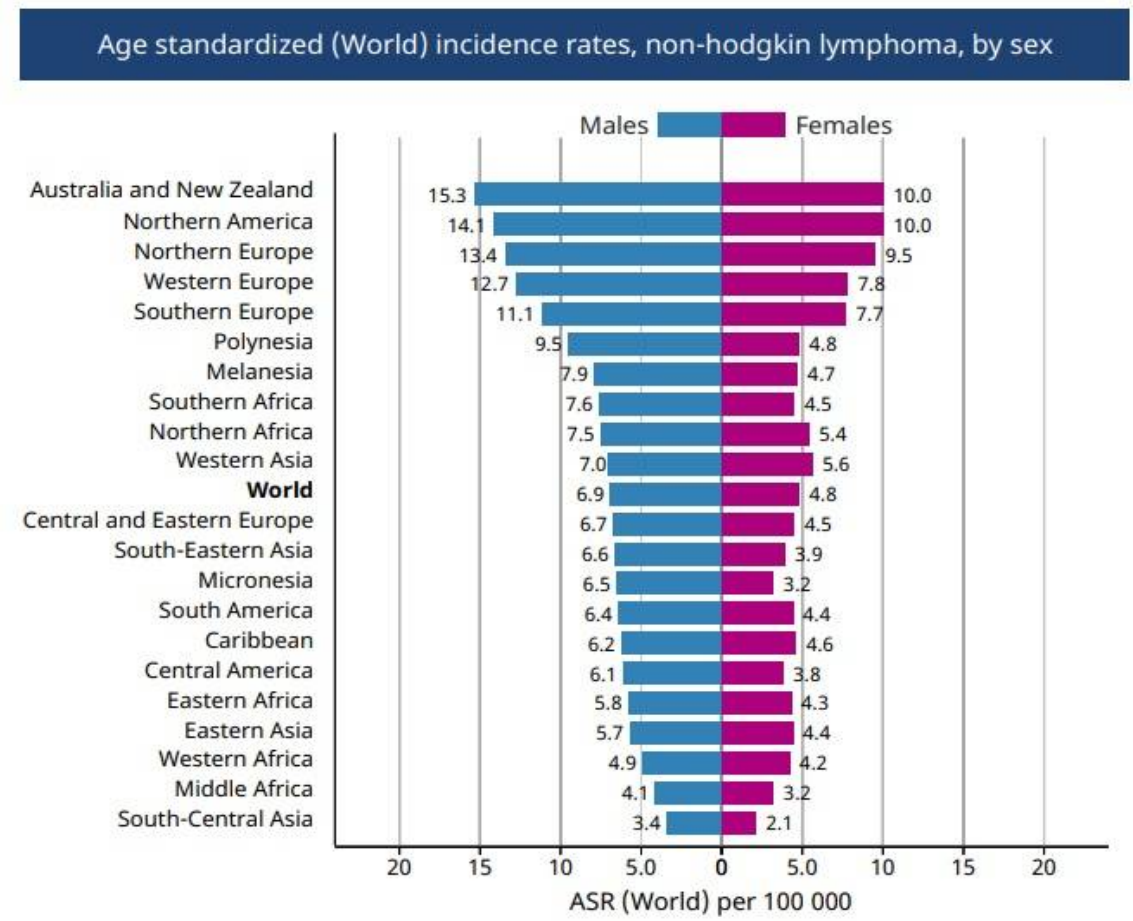
According to the latest World Health Organization (WHO) classification, the most common NHL in Western countries is DLBCL, accounting for around 31% of adult cases. Other common aggressive B-cell subtypes include mantle cell lymphoma (MCL) (6% of cases) and BL (2% of cases). Among indolent B-cell NHL, FL accounts for 22% of cases in the Western world, followed by marginal zone lymphoma (MZL) (8% of cases), chronic lymphocytic leukemia/small-cell lymphocytic lymphoma (CLL/SLL) (6% of cases) and lymphoplasmacytic lymphoma (LPL) (1% of cases) (De Leval et al. 2020).

According to the latest GLOBOCAN data, an estimated 509,600 new cases of NHL were diagnosed globally in 2018, comprising 2.8% of worldwide cancer diagnoses (Bray et al. 2018).

- Demographics

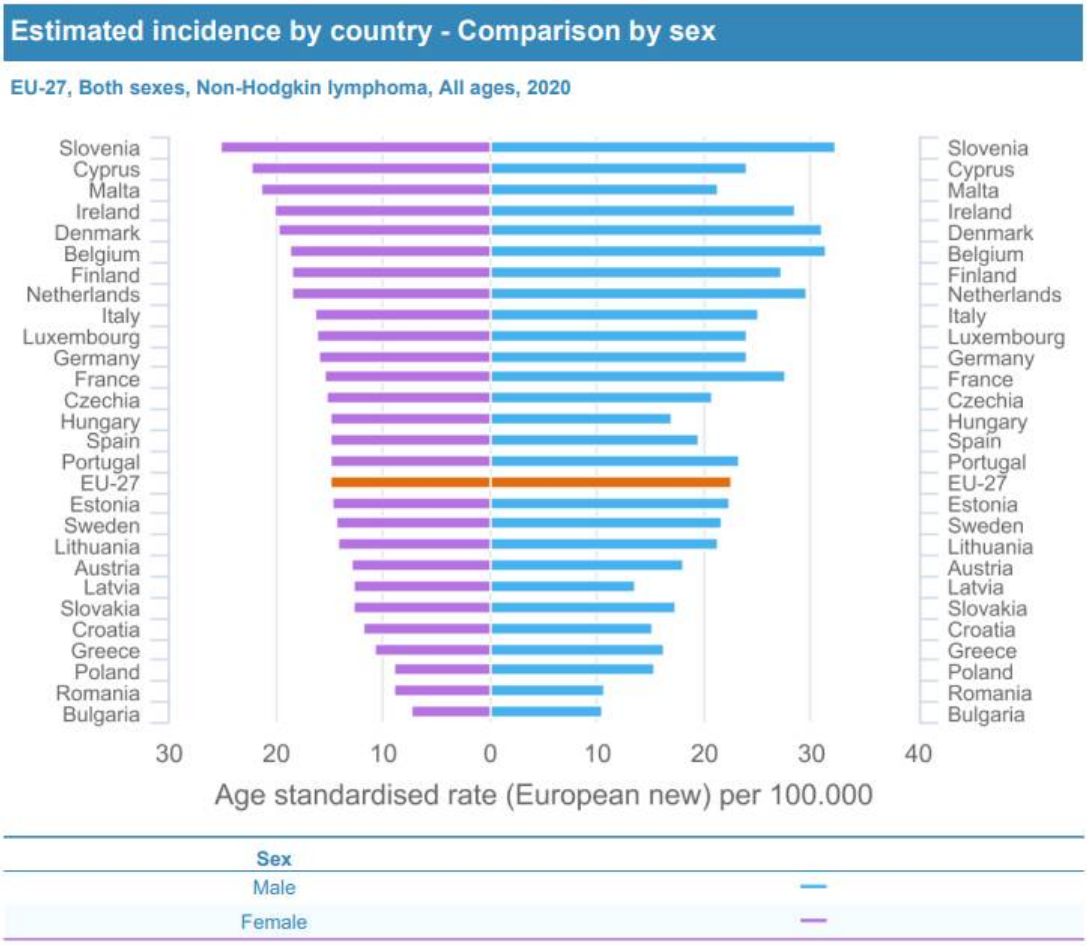
The incidence of NHL rises exponentially with age and the median age at diagnosis is 66 years (Howlader et al. 2014). The incidence is very low in individuals below 25 years of age (Howlader et al. 2014; Muller et al. 2005). NHL is more frequent in males than females in all age groups and is more common in developed countries (see Figure 2 and Figure 3 below).

Figure 2 Age-Standardized Incidence of NHL per 100,000 Populations Worldwide



Source: Bray et al. 2018.

Figure 3 European Age-Standardized Incidence of NHL per 100,000 by Gender in EU-27 Countries



Source: ECIS - European Cancer Information System

- Main treatment options

The European Society for Medical Oncology (ESMO) Clinical Practice Guidelines in FL (Dreyling et al. 2021) recommend to initiate therapy for patients with stage III/IV FL upon development of symptoms, including B symptoms, hematopoietic impairment, bulky disease, vital organ compression, ascites, pleural effusion or rapid lymphoma progression. Obinutuzumab in combination with chemotherapy is recommended as a first-line FL induction therapy. Recommended chemotherapy combination partners include CHOP, CVP, bendamustine (and lenalidomide in selected cases). Upon relapse or progression, the ESMO Guidelines recommend a non-cross-resistant regimen (e.g. bendamustine after CHOP or vice versa) as well as other options, including fludarabine-based, platinum-based or alkylating agents-based regimens.

Rituximab should be added if the previous antibody-containing scheme achieved more than 6 to 12 months duration of remission. In symptomatic cases with low tumor burden, rituximab monotherapy may be applied. In rituximab-refractory cases or remissions lasting <6 months, obinutuzumab with bendamustine (or other chemotherapy) plus obinutuzumab maintenance is a recommended regimen. National Comprehensive Cancer Network guidelines in B-cell lymphomas recommend 1L FL treatment with obinutuzumab (or rituximab) in combination with bendamustine, CHOP or CVP chemotherapy as preferred regimens (in addition to rituximab plus lenalidomide) (NCCN Guidance B-cell Lymphoma, v5 2023). Lenalidomide plus obinutuzumab is listed as "other recommended regimen". Obinutuzumab maintenance is also recommended amongst preferred 1L FL regimens.

For relapsed/refractory FL, NCCN guidelines list combinations of obinutuzumab (or rituximab) with bendamustine, CHOP, CVP as preferred regimens (in addition to lenalidomide plus rituximab). Obinutuzumab monotherapy and obinutuzumab with lenalidomide are listed as "other recommended regimens". Obinutuzumab maintenance is a preferred regimen in case of rituximab-refractory disease.

- Risk factors for the disease

Non-modifiable risk factors include age, gender, race/ethnicity, family history, autoimmune diseases, and immunosuppression. Modifiable risk factors included radiation, chemical exposure, obesity, tobacco smoking and alcohol, breast implants, and vitamin deficiency (Thandra et al. 2021).

- Natural history of the indicated condition in the untreated population

Mortality: There were an estimated 199,630 deaths worldwide, and 30,700 deaths in Europe (EU-28) from NHL in 2012 (Ferlay et al. 2013).

The long survival in conjunction with a high age at diagnosis results in a predominantly elderly patient population for this group of diseases, with a potentially high comorbidity burden.

Outcome of the (untreated) target disease: In Europe, the 5-year relative survival of NHL patients was 54.6% in the period 2000–2002 (Verdecchia et al. 2007). In the UK specifically, five-year overall survival is 75.6% in FL and 61.2% in marginal zone lymphoma (MZL). Despite progress in the treatment of FL in recent years, patients with advanced disease remain incurable with current immunochemotherapy regimes; relapse is inevitable for many patients, and many patients still die from progressive disease or immune dysfunction associated with the disease.

- Important co-morbidities

The main co-morbidities are cardiovascular diseases, hypertension, other malignancy, diabetes mellitus, chronic obstructive pulmonary disease and cerebrovascular diseases.

SI.2 CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

- Incidence and Prevalence

The World Health Organization (WHO) classification scheme considers B-cell chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) in an aggregate category (CLL/SLL) because of shared clinical-pathological features. The incidence rate of CLL is approximately three times that of SLL (Dores et al. 2007).

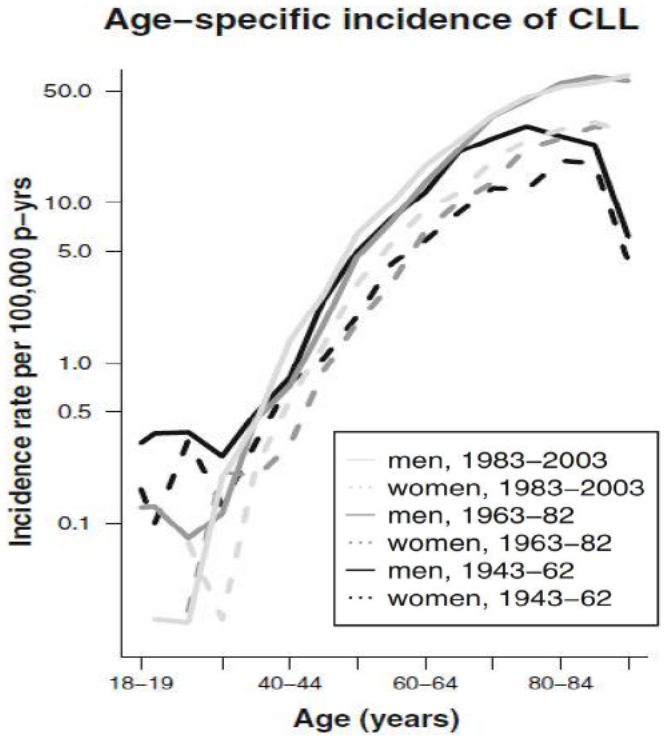
Of the hematological malignancies diagnosed between 2000 and 2002 in 44 European cancer registries as part of the HAEMACARE project, SLL/CLL was the most common subtype with 11,019 new cases and with a crude incidence of 4.92 per 100,000. Over the same period, the sex specific incidence rates were 5.87 and 4.01 per 100,000, for males and females respectively. The incidence rates showed a close similarity across European registries (Sant et al. 2010).

The 1-, 5- and 10-year prevalence estimates of CLL within the European Economic Area (EEA) in 2006 were 0.2 per 10,000, 0.9 per 10,000, and 2 per 10,000, respectively (Watson et al. 2008). The estimated prevalence of CLL in the EU in 2012 was 2.83 per 10,000 and in 2013 was 2.91 per 10,000. These estimates are based on applying a compound annual growth rate of 2.74% (i.e., the rate of increase observed from 2002 [2.16 per 10,000] to 2008 [2.54 per 10,000]) to the 2008 CLL prevalence estimate. The 2008 estimated CLL prevalence was calculated by applying the methods of (Watson et al. 2008) to the most recent leukemia International Agency for Research on Cancer (IARC) data (GLOBOCAN 2008) and data from the UK Office of National Statistics.

- Demographics

The incidence rate of CLL increases with age. Figure 4 shows the age and sex-specific observed incidence rate in Denmark based on data from the Danish Cancer Registry. The Danish Cancer Registry provides high-quality trend data that covers the entire Danish population, thus permitting an understanding of trends over time and giving epidemiological insight by population subgroups, for example incidence by age groups (Thygesen et al. 2009).

Figure 4 Age and Sex-Specific Incidence Rate of CLL in Denmark



Source: Reproduced from Thygesen et al. 2009.

- Main treatment options

The ESMO guidelines for diagnosis, treatment, and follow-up of patients with CLL and small lymphocytic lymphoma (SLL) list different treatment strategies for front-line therapy (Eichhorst et al. 2021). Continuous treatment with Bruton tyrosine kinase inhibitors such as ibrutinib until progression or time limited therapy with chemotherapy/anti-CD20 antibodies as well as the combination of venetoclax and obinutuzumab are recommended 1L therapies. The PI3K inhibitor idelalisib plus rituximab may be used in patients who are not eligible for any other therapies.

For treatment of relapsed and refractory disease, in case of symptomatic relapse within 3 years after fixed-duration therapy or non-response to therapy, the therapeutic regimen should be changed. One of the following treatment options should be chosen: venetoclax plus rituximab (for 24 months) or a BTKinhibitor (such as ibrutinib, acalabrutinib) as continuous therapy. Alternative options include the PI3K inhibitor idelalisib plus rituximab or chemoimmunotherapy unless a TP53 mutation or del(17p) is found; a response to prior bendamustine and rituximab (BR) should have lasted at least 3 years to justify re-administration, Fludarabine, cyclophosphamide and rituximab (FCR) is not recommended for repeated administration due to toxicity. In case of progression on B-Cell receptor inhibitors (BTKi or idelasisib) after prior chemoimmunotherapy, venetoclax-based therapy is the preferred treatment. In case of long-lasting remissions

(3 years or more) to prior time-limited therapy, patients may be re-exposed to the same treatment regimen. NCCN Guidelines on CLL recommend obinutuzumab as follows (in addition to other treatments, like e.g. bruton kinase inhibitors and combinations thereof) (NCCN Guidelines v3 2023):

- First line therapy, patients without del(17p)/TP53 mutation: in combination with venetoclax or acalabrutinib (part of "preferred regimens"), in combination with chlorambucil or ibrutinib and also as monotherapy and in combination with high-dose methylprednisone (part of "other recommended regimens")
- Relapsed/refractory CLL, patients without del(17p)/TP53 mutation: in combination with venetoclax (as part of "useful under certain circumstances), as monotherapy (part of "recommended regimens" after venetoclax or bruton kinase-based regimens)
- First line therapy, patients with del(17p)/TP53 mutation: in combination with venetoclax or acalabrutinib (part of "preferred regimens"), as monotherapy (part of "recommended regimens")

- Risk factors for the disease

Leukemias, myeloma, and other lymphoreticular neoplasms (Hernández et al. 1995).

Occupational solvent exposure and adult CLL: No risk in a population-based case-control study in four Nordic countries (Talibov et al. 2017).

- Natural history of the indicated condition in the untreated population

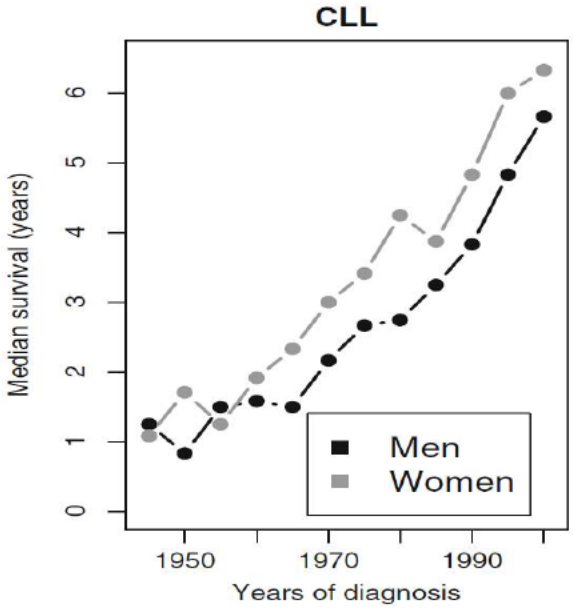
Mortality: There are no estimates in the literature of the total number of CLL deaths in Europe. There were approximately 54,000 deaths from leukemia of all kinds in 2008 (Ferlay et al. 2010). Figure 5 shows the trend of median survival times of CLL patients in Denmark from the year of diagnosis based on data from the Danish Cancer Registry (Thygesen et al. 2009).

In Europe, the 5-year relative survival of CLL and SLL patients in the period 2000–2002 was 69.1% (Marcos-Gragera et al. 2011).

- Important co-morbidities

In a study in unselected patients with CLL (Thurmes et al. 2008), nearly 89% had comorbid conditions at the time of diagnosis and over 46% had at least one major comorbidity (cardiopulmonary or vascular disease, diabetes, or a second cancer other than non-melanomatous skin cancer).

Figure 5 Median Survival Time of CLL Patients in Denmark Based on Data from the Danish Cancer Registry



Source: Reproduced from Thygesen et al. 2009.

PART II: MODULE SII— NONCLINICAL PART OF THE SAFETY SPECIFICATION

GENERAL SAFETY PHARMACOLOGY AND TOXICOLOGY

B-Cell depletion

The administration of weekly intravenous (IV) doses of obinutuzumab of up to 50 mg/kg for up to 26 weeks mediated marked B-cell depletion in the peripheral blood and lymphoid tissue of Cynomolgus monkeys. By the end of a 37-week recovery period, circulating B-cell recovery was variable (individual peak values ranged from 7% to 152% of baseline values), while lymphoid tissue B-cells fully reversed compared with controls.

Circulating natural killer (NK) cells were transiently decreased, probably due to NK cell apoptosis following antibody-dependent cellular cytotoxicity (ADCC).

Relevance to human usage: Yes

Discussion:

B-cell depletion and changes in effector cells are consistent with the desired pharmacology and mode of action of obinutuzumab. The observation is relevant to humans as B cell depletion may result in an increased risk of infection, including opportunistic infections and decrease in immunosurveillance of neoplasms.

Opportunistic infections

Three animals were sacrificed early in poor physical condition and with morphological evidence of inflammation that could indicate secondary opportunistic infections during the recovery phase of two of the shorter repeat-dose toxicity studies in Cynomolgus monkeys (one in the 4-week [subcutaneous] SC study and two in the 13-week IV study).

These opportunistic infections in individual animals were considered a possible secondary result of B-cell depletion.

Relevance to human usage: Yes

Discussion:

Infections have been reported in patients receiving obinutuzumab. Therefore, obinutuzumab should not be administered in the presence of active severe infections and particular attention should be given to patients who have had significant prior immunosuppressive treatment.

Cytokine release

The addition of obinutuzumab to human whole blood triggered statistically significant increases in levels of the pro-inflammatory cytokines, interleukin-6 (IL-6), IL-8, and tumor necrosis factor-α (TNF-α).

An in vitro study (Report No. 1062523) was conducted to explore the role of cytokine release in the higher rate and severity of infusion-related reactions (IRRs) observed in obinutuzumab-treated versus rituximab-treated patients. In alignment with clinical data, obinutuzumab induced stronger cytokine release, increased up-regulation of CD11b and caused greater B-cell depletion than rituximab and ofatumumab in this assay.

Relevance to human usage: Yes

Discussion:

In vitro tests explained the pathophysiology of the greater incidence and severity of IRRs seen in patients treated with obinutuzumab, compared with rituximab or ofatumumab (obinutuzumab triggers greater cytokine release than rituximab and ofatumumab).

Polymorphonuclear neutrophil (PMN) activation

Obinutuzumab bound CD16B (FcγRIIIB expressed by PMNs) with about 7-fold higher affinity, compared to non-glycoengineered wildtype parental antibodies, and activated PMNs (either purified neutrophils or neutrophils present in CLL whole blood), more efficiently than wildtype rituximab. Activation resulted in release of TNF-α, IL-6 and IL-8

and up to 47% phagocytosis of opsonized CLL targets by purified PMNs. Significant phagocytosis was observed in the presence of obinutuzumab in whole blood and was followed by up to 50% PMN death (Golay et al. 2013).

Relevance to human usage: Yes

Discussion: Early onset neutropenia observed in CLL patients with a high peripheral tumor load may be related to PMN activation and phagocytosis induced by obinutuzumab in vivo and reflects the specific mechanism of action of this glycoengineered antibody.

Reproductive and Developmental toxicity (neonates)

No adverse effects on male and female reproductive organs were observed in repeat-dose toxicity studies in Cynomolgus monkeys.

Administration of obinutuzumab to pregnant Cynomolgus monkeys from Day 20 post coitum until birth did not elicit embryo-fetal toxicity or teratogenicity, but resulted in a complete depletion of B-lymphocytes in infants. Concentrations of obinutuzumab in infant serum on Day 28 post-partum were in the range of concentrations in maternal serum, whereas concentrations in milk on the same day were very low, suggesting that exposure of infants occurred in utero. B-cell counts in infants returned to normal levels, and immunologic function was restored within six months post-partum.

Relevance to human usage: Yes

Discussion:

Since Immunoglobulin G (IgG) antibodies cross the placental barrier and B-cells are depleted in infants, it is recommended that women of child-bearing potential use effective contraceptive methods during and for up to 18 months after treatment with obinutuzumab.

Conclusion from the nonclinical safety evaluation:

The non-clinical safety development of obinutuzumab has contributed to identifying the following risks:

IRR, neutropenia, infections, and informing of the use of obinutuzumab in pregnant patients and their offspring.

PART II: MODULE SIII— CLINICAL TRIAL EXPOSURE

Within this module of the RMP, study data will generally be presented for obinutuzumab–exposed patients as follows:

Data from trials in CLL patients where the Sponsor has been unblinded to the treatment received:

1. Data from CLL patients in the pivotal Study BO21004 (CLL11), in which obinutuzumab was given with chlorambucil.
2. Data from CLL patients in the pooled monotherapy studies, BO20999 (GAUGUIN) and BO21003 (GAUSS).
3. Data from Phase I/II studies:
    - Study GAO4768g (GO25677, GAGE) in CLL patients in which obinutuzumab was given as monotherapy.
    - Study GAO4779g (GO01298, GALTON) in CLL patients, in which obinutuzumab was given with chemotherapy (fludarabine and cyclophosphamide [FC], bendamustine).

Data from trials in NHL patients where the Sponsor has been unblinded to the treatment received:

1. Data from Study GAO4753g (GO01297, GADOLIN), in patients with rituximab refractory iNHL, in which obinutuzumab is given in combination with bendamustine.
2. Data from NHL patients in the pooled monotherapy studies, BO20999 and BO21003.
3. Data from Study BO21223 (GALLIUM), in patients with iNHL, in which obinutuzumab is given in combination with chemotherapy (cyclophosphamide, doxorubicin, vincristine and prednisolone [CHOP], cyclophosphamide, vincristine and prednisone [CVP] or bendamustine).
4. Data from FL patients in Study BO21000 (GAUDI), in which obinutuzumab was given in combination with CHOP, FC or bendamustine chemotherapy.
5. Data from Study BO21005 (GOYA), in previously untreated DLBCL patients, in which obinutuzumab was given in combination with CHOP chemotherapy.

Note that data from studies in NHL are presented together in this section, and the tables for NHL include data from patients with both iNHL and aNHL.

It should be noted that figures for percentages presented in the tables and text in this section are taken directly from the original statistical outputs for each study. Thus the number of significant figures to which each percentage is expressed may vary from study to study as the methodology may vary between studies. The total number of patients exposed to obinutuzumab in these studies is shown in Table 2.

Table 2 Patients Exposed to Obinutuzumab in Clinical Studies (Oncology)

			Patients exposed to obinutuzumab	
Indication	**Study**	**Cut-Off Date**	**Total**	
CLL				
CLL all	BO21004	10 October 2017	372[a]	1500
	BO20999/ BO21003[b]	2 July 2012	38	
	GAO4768g	27 April 2013	78	
	GAO4779g	24 January 2013	41	
	MO28543	05 October 2018	971	
NHL				
NHL	BO20999/ BO21003[b]	2 July 2012	205	2118
iNHL	GAO4753g	30 November 2018	206	
	BO21000	4 November 2015	137[c]	
	BO21223	30 July 2021 (LPLV)	698[d]	
FL	MO40597	03 December 2020	113	
DLBCL	GAO4915g	2 July 2012	57	
	BO21005	31 January 2018	702	
Total	**-**	**-**	**-**	**3618**

CHOP=cyclophosphamide, doxorubicin, vincristine and prednisolone; CLL=chronic lymphocytic leukemia; DLBCL=diffuse large B-cell lymphoma; FL=follicular lymphoma; iNHL=indolent non-Hodgkin's lymphoma; LPLV=Last Patient Last Visit; NHL=non-Hodgkin's lymphoma.

[a] The figure for Study BO21004 includes 6 patients who participated in the safety run-in phase of the study and 30 patients who, at the data cut-off date, had crossed over from the chlorambucil arm to the obinutuzumab + chlorambucil arm of the study.

[b] Patients with CLL and NHL have been included in these studies.

[c] This figure represents the total patient population i.e. 56 patients with relapsed/refractory FL (28 patients [CHOP] + 28 patients [FC]) and 81 patients with previously-untreated FL (41 patients [benda] + 40 patients [CHOP]).

[d] A total of 1401 patients were randomized in the study (699 patients to the R-chemo arm and 702 patients to the G-chemo arm). Eleven patients withdrew from the study after randomization but prior to receiving study treatment. The overall safety population included 1390 patients in total, 692 patients in the R-chemo arm and 698 patients in the G-chemo arm.

Note: Exposure data has been updated for Study BO21004 (cut-off date: 10 October 2017), Study GAO4753g (cut-off date: 30 November 2018), Study MO28543 (cut-off date 05 October 2018), and Study MO40597 (cut-off date 03 December 2020).

- **Exposure to Obinutuzumab by Number of Infusions**

Obinutuzumab exposure is expressed in terms of the number of infusions received rather than the duration of exposure since the number of infusions is readily available for all studies and, considering that infusions have generally been administered in relatively consistent intervals, the number of infusions gives a good indication of the duration of treatment. Table 3 presents exposure by number of infusions in CLL patients. Table 4 presents exposure by number of infusions in NHL patients.

Table 3 Exposure to Obinutuzumab by Number of Infusions - CLL

	Number of infusions (at least)																		
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
BO21004[a]	372	339	332	329	320	312	308	294	0	0	0	0	0	0	0	0	0	0	0
BO20999/BO21003	38	34	34	34	30	29	26	26	26	14	2	2	2	2	2	2	2	2	2
GAO4768g	78	76	76	75	75	73	73	70	70	68	2	0	0	0	0	0	0	0	0
GAO4779g	41	40	40	38	37	37	33	26	0	0	0	0	0	0	0	0	0	0	0
MO28543	27	22	10	14	18	33	25	40	709	54	11	6	2	0	0	0	0	0	0
Total	**556**	**511**	**492**	**490**	**480**	**484**	**465**	**456**	**805**	**136**	**15**	**8**	**4**	**2**	**2**	**2**	**2**	**2**	**2**

CLL = chronic lymphocytic leukemia.

[a] The figures for study BO21004 include 6 patients who participated in the safety run–in phase of the study and 30 patients who, at the data cut-off date, had crossed over from the chlorambucil arm to the obinutuzumab+ chlorambucil arm.

Notes: Cut-off dates for data in this table are as follows: 10 October 2017 (BO21004), 2 July 2014 (BO20999, BO21003), 22 March 2016 (GAO4768g), 05 October 2018 (MO28543) and 24 January 2013 (GAO4779g).

The total number of patients who received obinutuzumab in each study is shown in the column Number of infusions (at least)=1.

Table 4 Exposure to Obinutuzumab by Number of Infusions – NHL

	Number of infusions (at least)																					
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**
iNHL																						
GAO4753g	206	200	196	193	185	177	172	168	155	139	127	119	105	99	97	90	82	81	77	70	0	0
BO20999/ BO21003[a]	205	200	190	186	155	140	128	121	117	63	57	55	46	43	39	34	10	9	0	0	0	0
BO21000	137	135	131	131	127	126	122	113	106	101	97	88	84	79	76	18	16	0	0	0	0	0
BO21223	698	684	684	679	675	669	659	653	633	619	602	588	567	559	552	540	525	514	501	482	211	205
MO40597	113	112	111	110	109	108	108	107	95	81	68	50	39	21	14	9	6	2	0	0	0	0
DLBCL																						
GAO4915g[b]	100	100	99	99	98	97	94	92	86	66	0	0	0	0	0	0	0	0	0	0	0	0
BO21005	702	687	675	667	661	644	628	615	594	519	0	0	0	0	0	0	0	0	0	0	0	0
Total	**2161**	**2118**	**2086**	**2065**	**2010**	**1961**	**1911**	**1869**	**1786**	**1588**	**951**	**900**	**841**	**801**	**778**	**691**	**639**	**606**	**578**	**552**	**211**	**205**

CCOD=clinical cutoff date; DLBCL=diffuse large B-cell lymphoma; EU RMP=European Union Risk Management Plan; iNHL=indolent non–Hodgkin's lymphoma; NHL=non-Hodgkin's lymphoma.

[a] The patient populations in Studies BO21003 and BO20999 were not restricted to patients with iNHL and also included patients with different histological subtypes of NHL.

[b] The figures for study GAO4915g exclude one patient who did not receive obinutuzumab but received chemotherapy only, hence the number of patients shown is lower than the number of patients in the safety population.

Note: Cut-off dates for data in this table are as follows: 30 November 2018 (GAO4753g), 02 July 2014 (BO20999 and BO21003), 4 November 2015 (BO21000), 30 July 2021 (BO21223), 23 December 2016 (GAO4915g), and 31 January 2018 (BO21005) and 03 December 2020 (MO40597).

Note: The total number of patients who received obinutuzumab in each study is shown in the column Number of infusions (at least)=1.

Note: There was no change to the exposure data since the CCOD used in EU RMP V8 for Study BO21223 (3 March 2017) because all patients had completed treatment then.

- **Exposure to Obinutuzumab by Dose**

The figures discussed in this section reflect the planned maximum dose per infusion and do not take into account instances where the complete dose was not administered, e.g., due to infusion-related reactions.

Table 5 presents exposure by dose in CLL patients. Table 6 presents exposure by dose in NHL patient. It should be noted that where a patient has received more than one dose level, this table shows only the highest dose that the patient received.

Patients have been treated with maximum doses ranging from 100 mg to 2000 mg. The majority of patients in obinutuzumab studies included in this RMP have received the 1000 mg dose (approximately 3441/3661; 94% of patients).

Table 5 Exposure by Dose - CLL

CLL		Number of patients				
Maximum dose of exposure	**BO21004[a] obinutuzumab + chlorambucil**	**BO20999/BO21003 obinutuzumab monotherapy**	**GAO4768g obinutuzumab monotherapy**	**GAO4779g obinutuzumab + chemotherapy**	**MO28543 obinutuzumab + chemotherapy**	**Total**
800 mg	-	3	-	-	**-**	**3**
1000 mg	372	26	40	41	**971**	**1450**
1200 mg	-	4	-	-	**-**	**4**
2000 mg	-	5	38	-	**-**	**43**
Total	**372**	**38**	**78**	**41**	**971**	**1500**

CLL=chronic lymphocytic leukemia.

[a] The figures for Study BO21004 include 6 patients who participated in the safety run-in phase of the study and 30 patients who, at the data cut-off date, had crossed over from the chlorambucil arm to the obinutuzumab+ chlorambucil arm.

Note: Cut-off dates for data in this table are as follows: 10 October 2017 (BO21004), 2 July 2014 (BO20999, BO21003), 22 March 2016 (GAO4768g), 05 October 2018 (MO28543) and 24 January 2013 (GAO4779g). Dosing for all studies shown was complete at the time of the cut-off dates used and hence figures for these studies remain unchanged.

The figures in this table reflect the planned maximum dose per infusion and do not take account of instances where the complete dose was not administered.

Table 6 Exposure by Dose - NHL

NHL	Number of patients							
Maximum dose of exposure	**GAO4753g obinutuzumab + bendamustine**	**BO20999[a]/ BO21003 obinutuzumab monotherapy**	**GAO4915g[d] obinutuzumab + chemotherapy**	**BO21000 obinutuzumab + CHOP, FC or bendamustine**	**BO21223 obinutuzumab + CHOP, CVP or bendamustine**	**BO21005 obinutuzumab + CHOP**	**MO40597 obinutuzumab + chemotherapy**	**Total**
100 mg	-	2	-	-	-			2
200 mg	-	6	-	-	-			6
400 mg	-	41	-	28	-			69
800 mg[b]	-	11	-	-	-			11
1000 mg	206	91	100	81	698	702	113	1991
1200 mg	-	5	-	-	-			5
1600 mg[c]	-	44	-	28	-			72
2000 mg	-	5	-	-	-			5
Total	206	205	100	137	698	702	113	2161

Table 6 Exposure by Dose – NHL (cont.)

CCOD=clinical cutoff date; CHOP=cyclophosphamide, doxorubicin, vincristine and prednisolone; CVP=cyclophosphamide, vincristine and prednisone/prednisolone; EU RMP=European Union Risk Management Plan; FC=fludarabine and cyclophosphamide; NHL=non-Hodgkin's lymphoma.

[a] The lowest dose of obinutuzumab tested in Study BO20999 was 50 mg. Patients treated with this dose received higher doses in subsequent infusions.

[b] Five patients who received a maximum dose of 800 mg in Study BO20999 received this dose during retreatment and had previously received lower doses of obinutuzumab.

[c] Patients treated with 1600 mg in studies BO20999 and BO21000 received this dose as a loading dose and received 800 mg in subsequent infusions (6 patients in Study BO20999 who initially received this regimen received the same regimen on retreatment).

[d] The figure for study GAO4915g excludes one patient who did not receive obinutuzumab but received chemotherapy only, hence the number of patients shown is lower than the number of patients in the safety population.

Note: Cut-off dates for data in this table are as follows: 30 November 2018 (GAO4753g), 02 July 2014 (BO20999 and BO21003), 4 November 2015 (BO21000), 23 December 2016 (GAO4915g), and 31 January 2018 (BO21005), 03 December 2020 (MO40597), and 30 July 2021 (BO21223).

Note: The figures in this table reflect the planned maximum dose per infusion and do not take account of instances where the complete dose was not administered.

Note: There was no change to the exposure data since the CCOD used in EU RMP V8 for Study BO21223 (3 March 2017) because all patients had completed treatment then.

In addition to the NHL patients listed in Table 6, 12 patients were enrolled in the Japanese Study JO21900. These patients received maximum obinutuzumab doses of 400, 800, 1200, and 2000 mg (n = 3 at each dose level).

- **Observation Time**

Observation time is generally defined as the time between the first administration of obinutuzumab (or the date of randomization) and either the date of the last available assessment or the date of death. Data on observation time in CLL and NHL patients are presented in Table 7 and Table 8, respectively.

Table 7 Observation Time – CLL

CLL	Number of patients				
Observation time	**BO21004[a] obinutuzumab + chlorambucil**	**BO20999/BO21003 obinutuzumab monotherapy**	**GAO4768g obinutuzumab monotherapy**	**GAO4779g obinutuzumab + chemotherapy**	**MO28543 obinutuzumab + chemotherapy**
>0 months	333 (100%)	38 (100%)	78 (100.0%)	41 (100%)	972 (100%)
≥3 months	316 (95%)	37 (97.4%)	78 (100.0%)	41 (100%)	934 (96.1%)
≥6 months	310 (93%)	36 (94.7%)	78 (100.0%)	40 (97.6%)	913 (93.9%)
≥9 months	305 (92%)	32 (84.2%)	77 (98.7%)	36 (87.8%)	895 (92.1%)
≥12 months	299 (90%)	31 (81.6%)	75 (96.2%)	20 (48.8%)	883 (90.8%)
≥1.5 years	290 (87%)	26 (68.4%)	75(92.3%)	2 (4.9%)	846 (87.0%)
≥2 years	279 (84%)	24 (63.2%)	72 (48.7%)	0 (0%)	799 (82.2%)
≥2.5 years	270 (81%)	15 (39.5%)	70 89.7%)	0 (0%)	749 (77.1%)
≥3 years	250 (75%)	9 (23.7%)	67 (85.9%)	0 (0%)	602 (61.6%)
≥3.5 years	239 (72%)	4(10.5%)	53 (67.9%)	0 (0%)	529 (54.4%)
≥4 years	0 (0%)	2 (5.3%)	0 (0%)	0 (0%)	353 (36.3%)
≥4.5 years	0 (0%)	2 (5.3)	0 (0%)	0 (0%)	107 (11.0%)

CLL=chronic lymphocytic leukemia.

[a] The data for Study BO21004 is based on the Intent-to-Treat population, so the number of exposed patients differs from the safety population. In addition, the figures do not include 6 patients who participated in the safety run-in phase of the study and 30 patients who, at the data cut-off date, had crossed over from the chlorambucil arm to the obinutuzumab+chlorambucil arm.

Note: Cut-off dates for data in this table are as follows: 10 October 2017 (BO21004), 2 July 2014 (BO20999, BO21003), 22 March 2016 (GAO4768g), 24 January 2013 (GAO4779g), 5 October 2018 (MO28543).

Table 8 Observation Time – NHL

NHL	Number of patients						
Observation time	**GAO4753g[a] obinutuzumab + bendamustine**	**BO20999/ BO21003 obinutuzumab monotherapy**	**GAO4915g obinutuzumab + chemotherapy**	**BO21000 obinutuzumab + CHOP, FC or bendamustine**	**BO21223[a] obinutuzumab + CHOP, CVP or bendamustine**	**BO21005[a] Obinutuzumab + CHOP**	**MO40597 obinutuzumab + chemotherapy**
> 0 months	204 (100%)	205 (100%)	100 (100.0%)	137 (100%)	702 (100%)	704 (100%)	113 (100%)
≥ 3 months	198 (97.1%)	189 (92.2%)	100 (100.0%)	133 (97%)	688 (98%)	679 (96.4%)	109 (96.5%)
≥ 6 months	186 (91.2%)	180 (87.8%)	97 (97.0%)	132 (96%)	681 (97%)	655 (93.0%)	103 (91.2%)
≥ 9 months	183 (89.7%)	172 (83.9%)	92 (92.0%)	131 (96%)	671 (95.6%)	637 (90.5%)	64 (56.6%)
≥ 12 months	175 (85.8%)	164 (80.0%)	90 (90.0%)	129 (94%)	665 (94.7%)	614 (87.2%)	35 (31.0%)
≥ 1.5 years	166 (81.4%)	153 (74.6%)	84 (84.0%)	126 (92%)	654 (93.2%)	582 (82.7%)	7 (6.2%)
≥ 2 years	152 (74.5%)	145 (70.7%)	81 (81.0%)	125 (91%)	637 (90.7%)	564 (80.1%)	0
≥ 2.5 years	145 (71.1%)	121 (59.0%)	79 (79.0%)	123 (90%)	624 (88.9%)	546 (77.6%)	0
≥ 3 years	135 (66.2%)	50 (24.4%)	78 (78.0%)	121 (88%)	611 (87.0%)	529 (75.1%)	0
≥ 3.5 years	127 (62.3%)	19 (9.3%)	74 (74.0%)	118 (86%)	599 (85.3%)	499 (70.9%)	0
≥ 4 years	118 (57.8%)	8 (3.9%)	58 (58.0%)	112 (82%)	590 (84.0%)	354 (50.3%)	0
≥ 4.5 years	110 (53.9%)	6 (2.9%)	27 (27.0%)	67 (49%)	575 (81.9%)	217 (30.8%)	0
≥ 5 years	96 (47.1%)	2 (1.0%)	12 (12.0%)	39 (28%)	563 (80.2%)	141 (20.0%)	0
≥ 5.5 years	80 (39.2%)	1 (0.5%)	0	24 (18%)	557 (79.3%)	81 (11.5%)	0
≥ 6 years	66 (32.4%)	1 (0.5%)	0	6 (4%)	547 (77.9%)	26 (3.7%)	0
≥ 6.5 years	48 (23.5%)	0	0	1 (1%)	537 (76.5%)	0	0

Table 8 Observation Time – NHL (cont.)

NHL	Number of patients						
Observation time	**GAO4753g[a] obinutuzumab + bendamustine**	**BO20999/ BO21003 obinutuzumab monotherapy**	**GAO4915g obinutuzumab + chemotherapy**	**BO21000 obinutuzumab + CHOP, FC or bendamustine**	**BO21223[a] obinutuzumab + CHOP, CVP or bendamustine**	**BO21005[a] Obinutuzumab + CHOP**	**MO40597 obinutuzumab + chemotherapy**
≥ 7 years	0	0	0	0	506 (72.1%)	0	0
≥ 7.5 years	0	0	0	0	424 (60.4%)	0	0
≥ 8 years	0	0	0	0	297 (42.3%)	0	0
≥ 8.5 years	0	0	0	0	174 (24.8%)	0	0
≥ 9 years	0	0	0	0	78 (11.1%)	0	0
≥ 9.5 years	0	0	0	0	16 (2.3%)	0	0
≥ 10 years	0	0	0	0	0	0	0

CHOP = cyclophosphamide, doxorubicin, vincristine and prednisolone; FC = fludarabine-cyclophosphamide; NHL = non-Hodgkin lymphoma.

[a] The data for these studies are based on the intent-to-treat population, so the number of reported patients differs from the safety population.

Note: Cut-off dates for data in this table are as follows: 30 November 2018 (GAO4753g), 2 July 2014 (BO20999, BO21003), 4 November 2015 (BO21000), 23 December 2016 (GAO4915g), 31 January 2018 (BO21005), 3 December 2020 (MO40597), and 30 July 2021 (BO21223).

- **Exposure to Obinutuzumab by Age Group and Gender**

Exposure by age group and gender in CLL and NHL patients is shown in Table 9 and Table 10, respectively.

Table 9 Exposure by Age Group and Gender - CLL

CLL	Number of patients												
	BO21004[a] obinutuzumab + chlorambucil		BO20999/BO21003 obinutuzumab monotherapy		GAO4768g obinutuzumab monotherapy		GAO4779g obinutuzumab + chemotherapy		MO28543 obinutuzumab + chemotherapy		Total		
Age group (years)	M	F	M	F	M	F	M	F	M	F	M	F	Total
< 45	1	2	0	2	3	2	3	1	26	8	33	15	48
≥ 45 to < 60	20	15	7	3	12	2	13	3	174	83	226	106	332
≥ 60 to < 65	15	17	6	2	8	4	4	3	89	53	122	79	201
≥ 65 to < 75	88	44	5	4	19	12	12	1	196	115	320	176	496
≥ 75	102	68	5	4	8	8	0	1	131	96	246	177	423
Total	226	146	23	15	50	28	32	9	616	355	947	553	1500

CLL=chronic lymphocytic leukemia.

[a] The figures for Study BO21004 include 6 patients who participated in the safety run-in phase of the study and 30 patients who, at the data cut-off date, had crossed over from the chlorambucil arm to the obinutuzumab+chlorambucil arm.

Note: Cut-off dates for data in this table are as follows: 10 October 2017 (BO21004), 2 July 2014 (BO20999, BO21003), 22 March 2016 (GAO4768g), 24 January 2013 (GAO4779g) and 5 October 2018 (MO28543). Demographic information for all studies shown was complete at the time of the cut-off dates used and hence figures for these studies remain unchanged.

Table 10 Exposure by Age Group and Gender - NHL

NHL	Number of patients																
	GAO4753g obinutuzumab + bendamustine		BO20999/ BO21003 obinutuzumab monotherapy		BO21000 obinutuzumab + CHOP, FC or bendamustine		GAO4915g[a] obinutuzumab + chemotherapy		BO21223 obinutuzumab + CHOP, CVP or bendamustine		BO21005 obinutuzumab + CHOP		MO40597 obinutuzumab + chemotherapy		Total		
Age group (years)	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	Total
< 45	16	3	8	3	10	9	17	5	40	51	67	33	11	7	169	111	280
≥ 45 to < 60	37	28	37	30	29	25	14	10	114	126	99	100	20	15	350	334	684
≥ 60 to < 65	17	15	23	14	8	16	4	12	69	65	61	57	7	9	189	188	377
≥ 65 to < 75	31	30	36	27	16	19	18	12	87	94	109	108	14	21	311	311	622
≥ 75	16	13	14	13	1	4	4	4	26	26	30	38	5	4	96	102	198
Total	117	89	118	87	64	73	**57**	**43**	336	362	366	336	**57**	**56**	**1115**	**1046**	**2161**

CCOD=clinical cutoff date; CHOP=cyclophosphamide, doxorubicin, vincristine and prednisolone; CVP=cyclophosphamide, vincristine and prednisone/prednisolone; EU RMP=European Union Risk Management Plan; FC=fludarabine and cyclophosphamide; NHL=non-Hodgkin's lymphoma.

[a] The figures for study GAO4915g exclude one patient who did not receive obinutuzumab but received chemotherapy only, hence the number of patients shown is lower than the number of patients in the safety population.

Note: Cut-off dates for data in this table are as follows: 30 November 2018 (GAO4753g), 02 July 2014 (BO20999 and BO21003), 04 November 2015 (BO21000), 23 December 2016 (GAO4915g), 31 January 2018 (BO21005), 3 December 2020 (MO40597), and 30 July 2021 (BO21223).

Note: There was no change to the exposure data since the CCOD used in EU RMP V8 for Study BO21223 (3 March 2017) because all patients had completed treatment then.

- **Exposure to Obinutuzumab by Race**

Exposure by ethnic or racial origin in CLL and NHL patients is shown in Table 11 and Table 12, respectively.

Table 11 Exposure by Ethnic or Racial Origin – CLL

CLL	Number of patients					
Ethnic/racial origin	**BO21004[a] obinutuzumab + chlorambucil**	**BO20999/BO21003 obinutuzumab monotherapy**	**GAO4768g obinutuzumab monotherapy**	**GAO4779g obinutuzumab + chemotherapy**	**MO28543 obinutuzumab + chemotherapy**	**Total**
White	354	37	73	41	775	1280
Asian	8	1	0	0	29	38
Other	10	0	5	0	25	40
NA	0	0	0	0	143	143
Total	**372**	**38**	**78**	**41**	**972**	**1501**

CLL=chronic lymphocytic leukemia.

[a] The figures for Study BO21004 include 6 patients who participated in the safety run-in phase of the study and 30 patients who, at the data cut-off date, had crossed over from the chlorambucil arm to the obinutuzumab + chlorambucil arm.

Note: Cut-off dates for data in this table are as follows: 10 October 2017 (BO21004), 2 July 2014 (BO20999, BO21003), 22 March 2016 (GAO4768g), 24 January 2013 (GAO4779g) and 5 October 2018 (MO28543). Information on the race of patients in all studies was complete at the time of the cut-off dates used and hence figures for these studies remain unchanged.

Table 12 Exposure by Ethnic or Racial Origin – NHL

NHL	Number of patients							
Ethnic/racial origin	**GAO4753g obinutuzumab + bendamustine**	**BO20999/ BO21003 obinutuzumab monotherapy**	**BO21000 obinutuzumab + CHOP, FC or bendamustine**	**GAO4915g[a] obinutuzumab + chemotherapy**	**BO21223 obinutuzumab + CHOP, CVP or bendamustine**	**BO21005 obinutuzumab + CHOP**	**MO40597 obinutuzumab + chemotherapy**	**Total**
White	182	203	133	81	579	426	82	1686
American Indian or Alaska Native	1	0	0	0	0	0	0	1
Black or African American	5	0	0	9	3	0	0	17
Asian	6	0	1	4	104	260	27	402
Other/Unknown	12	2	3	6	12	16	4	55
Total	**206**	**205**	**137**	**100**	**698**	**702**	**113**	**2161**

CCOD=clinical cutoff date; CHOP=cyclophosphamide, doxorubicin, vincristine and prednisolone; CVP= cyclophosphamide, vincristine and prednisone/prednisolone; EU RMP=European Union Risk Management Plan; FC=fludarabine and cyclophosphamide; NHL=non-Hodgkin's lymphoma.

[a] The figures for study GAO4915g exclude one patient who did not receive obinutuzumab but received chemotherapy only, hence the number of patients shown is lower than the number of patients in the safety population.

Note: Cut-off dates for data in this table are as follows: 30 November 2018 (GAO4753g), 02 July 2014 (BO20999 and BO21003), 4 November 2015 (BO21000), 23 December 2016 (GAO4915g), 31 January 2018 (BO21005), 03 December 2020 (MO40597), and 30 July 2021 (BO21223).

Note: There was no change to the exposure data since the CCOD used in EU RMP V8 for Study BO21223 (3 March 2017) because all patients had completed treatment then.

PART II: MODULE SIV— POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAM

Table 13 Important Exclusion Criteria in Pivotal Studies in the Development Program

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies. Known sensitivity or allergy to murine products	Patients with known hypersensitivity to Obinutuzumab or to any of its excipients were excluded from clinical trials to avoid risk of anaphylactic shock/reaction.	No	Hypersensitivity to the active substance or to any of the excipients has been contraindicated as per EU SmPC.
Transformation of CLL to aggressive NHL	Transformed CLL (Richter's syndrome) is a well-characterized progression of disease which requires aggressive treatment.	No	There is currently insufficient safety and efficacy data for obinutuzumab to be given to patients with transformed NHL.
Central nervous system lymphoma, prior DLBCL, or histological evidence of transformation to a high-grade or diffuse large B-cell lymphoma.	Transformed iNHL, DLBCL and CNS lymphomas are distinct medical entities which require specific treatment	No	The approved indication is for patients with follicular lymphoma who have not responded to or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen. There is currently insufficient safety and efficacy data for obinutuzumab to be given to patients with transformed NHL, DLBCL or CNS lymphoma.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
iNHL Ann Arbor Stage I and non-bulky stage II disease	Stage I and non-bulky stage II disease are not generally treated with systemic therapy as standard.	No	The available safety data don't suggest that iNHL patients with earlier stage disease are at a higher risk of AEs compared to later stage disease.
Individual organ/system impairment ("One or more individual organ/ system impairment score of 4 as assessed by the CIRS definition, excluding the Eyes, ears, nose, throat and larynx organ system").	These are mainly life-limiting or immediately life-threatening conditions. Patients with these conditions would require careful assessment and may not be suitable for active treatment of FL or CLL	No	Section 4.1 (Therapeutic indications), Section 4.4 Warnings & Precautions" and Section 5.2 of the EU SmPC adequately describes the populations studied.
Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results, including significant cardiovascular disease (such as New York Heart Association Class III or IV cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina) or pulmonary disease (including obstructive pulmonary disease and history of bronchospasm).	These are mainly significant, uncontrolled or life-threatening conditions. Patients with these conditions would require careful assessment and may not be suitable for treatment.	No	Section 4.1 (Therapeutic indications) and warning & precautions of the EU SmPC adequately describes the populations studied.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Inadequate renal function (creatinine clearance <30 mL/min).	These patients have severe renal impairment and could be at risk of complications from tumor lysis syndrome (TLS) and IRRs.	No	Section 4.2 (Posology and method of administration) of the EU SmPC indicates that the safety and efficacy of Gazyvaro has not been established in patients with severe renal impairment (creatinine clearance < 30 mL/min).
Inadequate liver function (NCI CTC Grade 3 liver function tests) unless due to underlying disease	These patients were excluded from CLL trials at the specific request of the FDA because of reports of safety issues in hepatically impaired patients dosed with chlorambucil.	No	There is no reason to expect that patients with liver impairment will be at increased risk of adverse events with obinutuzumab. In addition Section 4.2 (Posology and method of administration) of the EU SmPC states that the safety and efficacy of Gazyvaro in patients with impaired hepatic function has not been established, and that no specific dose recommendations can be made.
History of other malignancy which could affect compliance with the protocol or interpretation of results.	Patients with a history of other relevant malignancies were excluded in order to facilitate interpretation of efficacy data.	No	This was a protocol requirement for efficacy reasons – a contraindication would not be appropriate for routine practice. Clinicians should be able to use clinical judgment.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Patients with active bacterial, viral, or fungal infection requiring systemic treatment. Patients with known infection with HIV or HTLV-1. Patients with positive hepatitis C serology unless HCV (RNA) is confirmed negative.	A careful benefit-risk evaluation is needed. Immunosuppressive treatments should not be given to patients with active infections as the patient cannot fight the infection and is at risk of complications.	No	Infections are included in Section 4.4 (Special warnings and precautions for use) of the EU SmPC, where it is stipulated that Gazyvaro should not be administered in the presence of an active infection and caution should be exercised when considering the use of Gazyvaro in patients with a history of recurring or chronic infections.
Patients with positive serology for hepatitis B defined as positivity for HBsAg or anti-hepatitis B core antibody (anti-HBc) antibody. Patients positive for anti-HBc may be treated with obinutuzumab if HBV viral DNA is not detectable.	These patients are at risk of reactivation of the hepatitis B virus.	No	Hepatitis B reactivation is included in Section 4.4 (Special warnings and precautions for use) of the EU SmPC. which states that HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with anti-CD20 antibodies including Gazyvaro (see Section 4.8).
Vaccination with a live vaccine within 28 days prior to randomization.	Following immunotherapy patients have limited ability to mount an immune response to a live vaccination and are at increased risk of infection from the vaccination.	No	Immunization is included in Section 4.4 of the EU SmPC (Special warnings and precautions for use), which states that vaccination with live virus vaccines is not recommended during treatment and until B-cell recovery.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Patients with a history of confirmed progressive multifocal leukoencephalopathy (PML)	Immunosuppressive treatments are known to allow reactivation of PML with serious and often fatal consequences.	No	PML is included in Section 4.4 (Special warnings and precautions for use) of the EU SmPC, where it is stipulated that a diagnosis of PML should be considered in any patient presenting with new-onset or changes to pre-existing neurologic manifestations.
Pregnancy and lactation	Pregnancy and lactation are standard contraindications in clinical studies, especially in patients with advanced malignancy and when cytotoxic drugs are given.	No	In Section 4.6 (Fertility, pregnancy and lactation) of the EU SmPC, it is stated that women of childbearing potential must use effective contraception during and for 18 months after treatment with Gazyvaro. Section 4.6 of the EU SmPC also indicates that women should be advised to discontinue breast-feeding during Gazyvaro therapy and for 18 months after the last dose of Gazyvaro.
Fertile men or women of childbearing potential unless surgically sterile or using an adequate measure of contraception	Effective contraception is required throughout the study for at least 18 months after the last dose of obinutuzumab, because of the long half-life of humanized monoclonal antibodies and the potential for prolonged lymphopenia.	No	Section 4.6 of the EU SmPC (Fertility, pregnancy and lactation), states that women of childbearing potential must use effective contraception during and for 18 months after treatment with Gazyvaro and Section 5.3 of the EU SmPC (Preclinical safety data) states that no specific studies in animals have been performed to evaluate the effect of obinutuzumab on fertility.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Corticosteroid use > 30 mg/day of prednisone or equivalent, for purposes other than lymphoma symptom control.	This was a protocol requirement to facilitate interpretation of safety and efficacy data in the studies (since corticosteroids have potent effects on normal and malignant lymphocytes).	No	Corticosteroids are a component of treatment regimens used for patients with FL (e.g., CHOP) –. Clinicians should be able to use clinical judgment
Life expectancy < 12 months	This was a protocol requirement to help ensure a reasonably homogenous patient population with a sufficiently long life expectancy to potentially benefit from treatment.	No	This exclusion criterion was not related to the safety of the patient.
Participation in another clinical trial with drug intervention within 28 days prior to start of Cycle 1 and during the study	This was a protocol requirement to facilitate interpretation of safety and efficacy data.	No	This exclusion criterion was not related to the safety of the patient.
Recent major surgery (within 4 weeks prior to the start of Cycle 1), other than for diagnosis	This was a protocol requirement to help ensure a reasonably homogenous population of patients fit enough to receive immunochemotherapy.	No	This exclusion criterion was not related to the safety of the patient.
Patients with non-follicular lymphoma: prior treatment with chemotherapy or immunotherapy	These were protocol requirements to help ensure a reasonably homogenous population and facilitate interpretation of safety and efficacy data.	No	This exclusion criterion was not related to the safety of the patient.

Criterion	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
Prior treatment with cytotoxic drugs or rituximab for another condition or prior use of an anti-CD20 antibody	These were protocol requirements to help ensure a reasonably homogenous population and facilitate interpretation of efficacy data.	No	This exclusion criterion was not related to the safety of the patient.
Prior use of any monoclonal antibody within 3 months of the start of the Cycle 1.	This was a protocol requirement to facilitate interpretation of safety and efficacy data.	No	This exclusion criterion was not related to the safety of the patient.
History of sensitivity to mannitol	Hypersensitivity to mannitol was an exclusion criterion in trials in which bendamustine was given because bendamustine is formulated in mannitol (an excipient).	No	Hypersensitivity to mannitol is not relevant to obinutuzumab labelling and is not included in bendamustine SmPC as a contraindication.

AE=adverse event; anti-HBc=anti-hepatitis B core antibody; CHOP=cyclophosphamide, doxorubicin, vincristine and prednisolone; CLL=chronic lymphocytic leukemia; DLBCL=diffuse large B-cell lymphoma; EU=European Union; FDA=U.S. Food and drug administration; FL=follicular lymphoma; HBsAg=hepatitis B surface antigen; HBV=Hepatitis B virus; HCV=Hepatitis C virus; HIV=Human immunodeficiency virus; HTLV=human T-lymphotropic; iNHL=indolent non-Hodgkin's lymphoma; IRRs=Infusion related reactions; NCI CTCAE=National Cancer Institute Common Terminology criteria for adverse events; NHL=non–Hodgkin's lymphoma; PML=progressive multifocal leukoencephalopathy; SmPC=Summary of Product Characteristics; RNA=ribonucleic acid.

[a] In Study BO21223, patients with creatinine clearance $<$40 mL/min were excluded.

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMS

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

These points are addressed in the following manner: for the detection of rare events, the total of 4,454 exposed patients, there is a 97% probability of detecting at least one event whose underlying probability is 0.1% in the population. Any rare event that occurs in 99.9% of already has been observed. Cumulative and/or prolonged exposure effects are mostly relevant in the NHL indication: patients have been observed at median total doses of 8,000 mg during induction and 10,000 mg during maintenance in Study GAO4753g, and median doses of 22,000 mg in Study BO21223. Patients have appropriate risk assessment follow ups to characterize long latency effects (labelling regarding risk of infections, monitoring of patients with HBV reactivation).

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

No specific post-authorization usage data in special populations has been reported for obinutuzumab as of 31 October 2023 DLP of the PBRER 1126136. Details on exposure in special populations are provided in Table 14

Table 14 Exposure of Special Populations Included or Not in Clinical Trial Development Program

Type of special population	Exposure
Pregnant women	5 patients [a]
Breastfeeding women	Not included in the clinical development program
Patients with relevant comorbidities	
Patients with hepatic impairment	Not included in the clinical development program
Patients with renal impairment	372 patients
Subpopulations carrying relevant genetic polymorphisms	787 patients
Patients with a disease severity different from inclusion criteria in clinical trials	68 patients
Population with relevant different ethnic origin	Refer to Table 11, Table 12
Other	
Children (0-18 years):	Not included in the clinical development program.
Elderly aged ⩾75 years:	Refer to Table 9, Table 10

[a] Three were NHL patients receiving obinutuzumab and 2 were partners of NHL patients receiving obinutuzumab.

PART II: MODULE SV— POST-AUTHORIZATION EXPERIENCE

SV.1 POST-AUTHORIZATION EXPOSURE

SV.1.1 Method used to calculate exposure

Obinutuzumab patient exposure was estimated uniformly across the world.

In the US, EEA, and RoW, the MAH assumed that commercially exposed patients received the standard obinutuzumab dose of 1000 mg per administration and therefore that each obinutuzumab 1000 mg vial sold is assumed to equal one obinutuzumab administration.

The number of patient exposure is estimated by dividing the number of obinutuzumab 1000 mg vials sold by the estimated number of vials consumed per course of treatment.

In the US, it was assumed that each patient received an average of seven obinutuzumab administrations in CLL and six in NHL. In the EEA and RoW, based on market research in EU5 (France, Germany, Italy, Spain, UK), it was assumed that each patient received an average of seven obinutuzumab administrations.

Obinutuzumab is only available for IV administration.

Claims and primary market research tracking data for the US (for the US) and primary market research tracking data in the EU5 (for EEA and RoW) were used to estimate the breakdown of commercially-exposed patients receiving obinutuzumab per label (first line [1L] CLL, relapsed/refractory and 1L follicular lymphoma (FL) or as a result of off-label use (relapsed/refractory CLL, iNHL and aggressive NHL). Obinutuzumab was approved for first line treatment of FL in the EU in September 2017. The breakdown shows use of obinutuzumab in first line FL after approval as on-label use (“1L FL”) and use before approval as off-label use (“Other iNHL (1L & Relapsed/Refractory [R/R] iNHL including FL if off-label)”). Breakdown includes segmentation by age (≤ 65 vs. > 65) and by gender.

The exposure number was obtained by using sale’s database which has the actual number of patients used in the all facilities. After the launch in Japan (29 August 2018), the actual number in all facilities is 5,700 patients, and this is the exposure for the reporting period of the last PBRER with DLP 31 October 2023.

Japan patient exposure data cannot be split into further information such as sex and age since sale’s database do not have the information.

For Japan, the license-holder did not collect data on the distribution of exposures by disease type, gender or age. Therefore, MAH make the following assumptions:

All exposed patients are FL patients: Gazyva is approved in Japan for 1L and R/R FL (but not 1L CLL)

- The allocation of exposed FL patients by line of therapy (1L vs R/R), age, and gender is the same as in US, EEA and RoW.
- Till the period 31 October 2023 Japan numbers were segregated into Age, Sex buckets using Ex US split. But, due to the alignment with Chugai it has been agreed that in case of Japanese patient exposure should not apply general split instead it should be put in the unknown bucket from this interval.

SV.1.2 Exposure

Since the International Birth Date (IBD; 1 November 2013) and 31 October 2023 (data lock point [DLP] for the last PBRER), an estimated cumulative total of 185,051 patients have received obinutuzumab (see Annex 7) from marketing experience.

Approximately 62% (n=113,984) of the exposed patients were elderly (>65 years), and 37% (n=68,487) were ≤ 65 years. Cumulatively, 64,489 patients were exposed to obinutuzumab in the United States, compared to 66,169 patients in the EU and 44,728 patients in the RoW in the post-marketing setting.

PART II: MODULE SVI— ADDITIONAL E.U. REQUIREMENTS FOR THE SAFETY SPECIFICATION

POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

Obinutuzumab is a therapeutic monoclonal antibody developed for use in oncology and as such has minimal potential to be misused for illegal purposes.

PART II: MODULE SVII— IDENTIFIED AND POTENTIAL RISKS

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

No new safety concerns have been identified since this module of the RMP was last submitted.

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMAITON

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Information on Important Identified Risks

1. Infusion-Related Reactions

MedDRA Terms:

For assessment of the risk of IRR based on the data collected in clinical studies, IRRs are defined in this analysis as adverse events (AEs) that are deemed related to any study treatment (not specific to obinutuzumab) by the investigator, which occurred during infusion or within 24 hours from the end of infusion. In this analysis, multiple symptoms of one IRR that were experienced by the same patient (e.g., hypotension, chills, nausea, pyrexia) were each classified as individual AEs.

In addition, for Studies BO21004 and MO40597, this risk was also assessed based on reports of IRR obtained from a dedicated case report form page provided to investigators.

For MedDRA terms that are used for post-marketing surveillance of IRRs, see Annex 7.

Potential mechanisms:

The mechanism by which IRRs are triggered is not clearly understood, however, evidence suggests that IRRs may be linked to the release of cytokines and/or other chemical mediators from immune effector cells such as NK cells, macrophages/monocytes and/or neutrophils; potentially also from B-cells targeted by obinutuzumab. This is a class effect of monoclonal antibodies in general and those targeting CD20 in particular. Anaphylactic or hypersensitivity reactions to the intravenous administration of protein may also play a part in some patients.

Cytokine release can occur as a consequence of the antibody-antigen interaction between obinutuzumab and the CD20 antigen on B lymphocytes, resulting in Fc receptor crosslinking of FcγRIII on immune effector cells such as natural killer cells and macrophages/monocytes and subsequent cytokine release from these cells. Compared to conventional IgG1 antibodies, the FcγRIII affinity of obinutuzumab is enhanced due to glycoengineering, resulting in a higher potential for cytokine release. This could explain the higher incidence of cytokine related infusion reactions with obinutuzumab. In addition, increased numbers of circulating B cells in CLL compared to NHL patients may

amplify the magnitude of FcγRIII engagement and thus downstream cytokine induction (Winkler et al. 1999).

Obinutuzumab-mediated cytokine secretion was assessed in human whole blood. Obinutuzumab induced stronger cytokine release, increased up-regulation of CD11b and stronger B-cell depletion than rituximab and ofatumumab in this assay (Report No. 1062523).

In the clinical setting, TNF-α, interferon (IFN)-γ, IL-6, IL-8 and IL-10 cytokine levels were monitored prior to, during and post-infusion at Cycle 1 and some subsequent cycles in studies BO20999, BO21003 and BO21000.

In Study BO21003, interferon-γ, TNF-α, IL-6, IL-8 and IL-10 cytokine levels were monitored pre-infusion, mid-infusion, at the end of infusion and 2- 5 hours post-infusion. For the first infusion, the levels of all the measured cytokines increased after the start of treatment, peaking mid-infusion and dropping thereafter to pre-infusion levels by the next infusion (Cycle 2 Day 1). The pattern of cytokine release during subsequent infusions for IL-6, IL-8 and IL-10 followed a similar trend as with the first infusion. However, the magnitude of the increase pre- to mid-infusion was less pronounced when compared with the first infusion. Interferon-γ and TNF-α levels remained relatively unchanged during subsequent infusions.

Overall, in studies BO21000, BO21003 and BO20999, increases in IL-6, IL-8, IL-10 and TNF-α occurred mainly during the first infusion of the first cycle of obinutuzumab; subsequent infusions did not notably increase the levels of these cytokines. On average, the cytokine levels returned to baseline values, suggesting the transient and non-persistent nature of cytokine increases following exposure to obinutuzumab.

In summary, cytokine release is believed to be related to Fc receptor crosslinking of FcγRIII on immune effector cells upon interaction between obinutuzumab and the CD20 antigen on B lymphocytes. Glycoengineering of obinutuzumab results in enhanced FcγRIII affinity on immune effector cells such as NK cells, macrophages/monocytes and neutrophils. Severe symptoms such as acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock may occur in patients with high numbers of circulating lymphocytes such as patients with CLL. Further, the medical literature suggests that the IRRs of anti-CD20 antibodies are the consequence of cytokine release (Wing et al. 1996; Winkler et al. 1999; Dillman and Hendrix 2003; Wing 2008).

As assessed in studies BO21000, BO20999 and BO21003, IRRs follow a similar course to cytokine release. Indeed, high incidences of IRRs and notable increases of cytokine levels at Cycle 1 Day 1 were observed; likewise, there was a decrease in the incidence of IRRs as well as a return to baseline values (or lower) of cytokine levels at subsequent infusions.

Overall, given the similar time course and the biological plausibility, the evidence supports a causal association between the increase in cytokine levels (IL-6, IL-8, IL-10, and TNF-α) and the occurrence of IRRs.

Evidence source(s) and strength of evidence:

Clinical trial data are from studies BO20999, BO21000, BO21003, BO21004, BO21005, BO21223, GAO4753g, GAO4768g, GAO4779g, GAO4915g, MO28543 and MO40597.

Characterization of the risk:

Background incidence/prevalence

The results of a systematic review by Roche of published observational data for infusion related reactions in CLL and NHL patients are shown in Table 15.

Table 15 Incidence of Infusion Related Reactions in NHL and CLL Patients, as Reported in Epidemiological Studies

Treatment	Adverse event[a]	Cancer	Median age of patients	Incidence proportion, new events /total population. Range across studies with median if more than one study, otherwise study estimate with 95% CI
Rituximab containing	All grades	NHL	62	23.7% [95% CI: 17.3-30.1%]
	All grades	DLBCL	62	20.7% [95% CI: 14.2-27.2%]
	All grades	CLL	67	58.3% [95% CI: 48.3-67.7%]
	Grade 1 or 2	NHL	62	21.3% [95% CI: 15.1-27.5 %]
	Grade 1 or 2	DLBCL	62	18.7% [95% CI: 12.4-24.9 %]
	Grade 1 or 2	CLL	67	55.2% [95% CI: 45.3-64.8 %]
	Grade 3 or 4	NHL	62	2.4% [95% CI: 0.1-4.7%]
	Grade 3 or 4	DLBCL	62	2.0% [95% CI: 0-4.2%]
	Grade 3 or 4	CLL	67	5.2% [95% CI: 2.3-11.6%]
	Grade 3 hypotension	DLBCL	53	1.3% [95% CI: 0-3.7%]
	Grade 3 anaphylaxis	DLBCL	53	1.3% [95% CI: 0-3.7%]
	Grade 3 bronchospasm	DLBCL	53	1.3% [95% CI: 0-3.7%]

Treatment	Adverse event[a]	Cancer	Median age of patients	Incidence proportion, new events /total population. Range across studies with median if more than one study, otherwise study estimate with 95% CI
Other	Grade 1 or 2	NHL	50	5.1% [95% CI: 0-10.7%]

CLL=chronic lymphocytic leukemia; NHL = Non-Hodgkin Lymphoma; DLBCL = diffuse large B-cell lymphoma.

[a] Adverse event definitions used in studies: U.S. National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events, version 4.0.

Source: Kaminski et al. 2000; Rueda et al. 2008; Hong et al. 2012; Norin et al. 2015.

Frequency with 95% CI

The reported frequency of IRRs across different studies is variable; in the CLL population ranging from 66% (BO21004, first line population, obinutuzumab + chlorambucil) to 100% (R/R population in pooled monotherapy studies BO21003 and BO20999); and in the NHL population extending from 66.7% (GAO4753g, rituximab-refractory population receiving concomitant bendamustine) to 82% (R/R population in pooled monotherapy studies BO21003 and BO20999) in studies in which the sponsor is unblinded to the treatment received.

FL (BO21223)

IRRs were less frequent in the R-chemo arm (349/597 patients [58.5%]) compared to the G-chemo arm (406/595 patients [68.2%]).

MZL (BO21223)

A total of 55 patients (59.1%) in the R-chemo arm and 80 patients (79.2%) in the G-chemo arm had experienced an IRR.

BO21000 – First-Line Patient Population

In the iNHL population of Study BO21000, the reported frequency of IRRs ranged from 70% to 78% in the first line setting.

DLBCL (BO21005)

IRRs were more frequent in the G-CHOP arm (324 of 702 patients [46.2%]) compared with the R-CHOP arm (226 of 701 patients [32.2%]).

DLBCL (GAO4915g)

Overall, 69% (69/100) of patients had at least one IRR adverse event.

CLL (MO28543)

IRRs were reported in 635/971 (65.4%) patients overall. The proportion of patients who experienced IRRs was similar across all chemotherapy combinations (G-monotherapy, G-Clb, G-B and G-FC), but was somewhat greater among patients with relapsed/refractory disease compared to those with untreated disease (236/341 [69.2%] versus 399/630 [63.3%], respectively). IRRs were most common at the first infusion of (cycle 1 Day 1 and Day 2 combined), occurring in 602/971 (62.0%) of patients. Fewer than 4% of patients experienced IRRs at any subsequent infusion following the first infusion of Cycle 1.

Short-duration infusion - FL (MO40597)

A total of 71 patients (62.8%) experienced at least one IRR event, mostly in Cycle 1. The incidence of Grade 3 IRRs was 6.2% overall (of which the majority occurred in Cycle 1), and there were no Grade 4 or 5/fatal IRRs reported. No patients in the SDI population reported Grade 3 IRRs in Cycle 2. No patients discontinued the study due to IRRs during Cycle 2 or following SDI at subsequent cycles.

One patient experienced a Grade 3 IRR event of hypertension following SDI at Cycle 5 several minutes after completing the infusion. The patient had a history of chronic kidney disease and hypertension, and was receiving multiple antihypertensive agents. The event resolved on the same day.

Overall, the incidence and nature of IRR events after SDI was comparable with those observed after standard duration infusion.

Seriousness / Outcomes

CLL (BO21004-Stage 1a)

In Stage 1a of Study BO21004 (by the data cut-off date of 10 October 2017), 11% of patients (27/241) in the obinutuzumab arm experienced serious IRRs. In the cross-over population (30 patients in Study BO21004 crossed over from the Clb arm to the chlorambucil+obinutuzumab arm) of the same study (by the data cut-off date of 9 May 2013), 7% of patients had serious IRRs (see Table 16).

In Stage 1a of Study BO21004, of the 167 patients treated with obinutuzumab who experienced IRRs, 19 patients (11%) discontinued treatment, 87 patients (52%) had dose modifications and 147 patients (88%) had treatment for their IRRs. Of the 16 patients who experienced IRRs in the cross-over population, 2 (13%) discontinued treatment, 12 (75%) had dose modifications and 81% received treatment for the events.

CLL (BO21004- Stage 2)

By the data cut-off date (10 October 2017) for the Stage 2 analysis of Study BO21004 (GClb vs. RClb), a total of 10% of patients (34/336) experienced serious IRRs and 11% of patients (25/336) had discontinued treatment due to IRRs in the GClb arm (see Table 16). The number of patients who discontinued study treatment due to IRRs was higher in the GClb arm than in the RClb arm (11% vs. 2%). In almost all patients who experienced IRRs from both arms, the events resolved (100% in the GClb arm vs. 99% in the RClb arm), but more patients in the GClb arm experienced IRRs that necessitated treatment (86% in the GClb arm vs. 69% in the RClb arm).

CLL (GAO4779g)

The incidence of serious IRR in first line CLL patients who received concomitant fludarabine and cyclophosphamide or bendamustine in Study GAO4779g was 12.2%.

CLL (MO28543)

A total of 12.2% patients experienced serious IRRs, with similar incidences between patients with relapsed/refractory and untreated disease (19.6% (67/341) versus 19.4% (122/630), respectively). Of the patients with at least one IRR (65.4%, 635/971), 6.0% (38/635) discontinued study treatments and 62.2% (395/635) had dose interruptions, dose reduction or infusion rate modification. Majority of patients experiencing IRRs received treatment (80.5%, 511/635) and the events were resolved (98.3%, 624/635).

CLL and NHL (BO20999 and BO21003; pooled studies)

In pooled monotherapy trials (BO20999 and BO21003), serious IRRs were reported in 26% of the CLL and 5% of the NHL population.

iNHL (GAO4753g)

In Study GAO4753g, the overall incidence of IRRs was lower in the benda arm (62.6%) compared with the obinutuzumab and bendamustine (G-benda arm) (66.7%); as was the incidence of Grade 3 and 4 IRRs (5.4% in the benda arm versus 11.3% in the G-benda arm) and serious IRRs (1.5% in the benda arm versus 4.4% in the G-benda arm). Of the patients with at least one IRR, there were 0/127 patients in the benda arm versus 5/136 patients (3.7%) in the G-benda arm with IRRs leading to withdrawal from treatment, 2/127 (1.6%) in the benda arm versus 7/136 patients (5.1%) in the G-benda arm with IRRs leading to dose reductions, and 13/127 patients (10.4%) in the benda arm versus 52/136 patients (38.2%) in the G-benda arm with IRRs leading to dose interruptions. In both treatment arms, most of the patients experiencing IRRs received treatment for this AE and most IRRs resolved.

FL (BO21223)

The majority of IRRs were Grade 1 or 2 in both arms and no fatal (Grade 5) IRRs occurred in this study. In both treatment arms, most of the patients experiencing IRRs received treatment for this AE. The majority of IRRs resolved either spontaneously, with dose interruptions or with treatment.

MZL (BO21223)

Nine patients experienced a serious IRR in the R-chemo arm (9.7%) and 10 patients in G-chemo arm (9.9%). Three patients each in the R-chemo and G-chemo arm had AEs that required discontinuation. For all patients but one in the G-chemo and all but three patients in the R-chemo arm the AEs had resolved.

FL (BO21000) - First-Line Patient Population

Overall Treatment Period

In the G+CHOP group, two patients (5%) had a total of 6 serious IRRs. One patient had AEs that required discontinuation, and 19 patients (68%) had AEs requiring dose modification/infusion rate adjustments. For all but one patient the AEs had resolved. In the G+benda group, five patients (12%) had a total of 22 serious adverse events (SAEs). No AEs led to treatment discontinuation, and all resolved. For 17 patients (53%), a dose modification (including infusion rate adjustment and interruption) was required

DLBCL (BO21005)

The overall incidence of the following IRRs were higher in the G-CHOP arm compared with the R-CHOP arm (expressed as R-CHOP vs. G-CHOP): all-grade IRRs (32.2% vs. 46.2%), Grade 1-2 IRRs (28.9% vs. 36.5%), (Grade 3–5 IRRs (3.3% vs. 9.7%) and serious IRRs (0.9% vs. 2.8%).

For the majority of patients, (93.4% in the R-CHOP arm and 94.4% in the G-CHOP arm) IRRs resolved either spontaneously, with dose interruptions, or with treatment.

For 4 patients in each treatment arm, chemotherapy was withdrawn because of an IRR (including 1 patient with a fatal myocardial infarction), see details below.

A single case of fatal IRR was reported. This case report concerned a previously untreated PPD-year-old male DLBCL patient enrolled in the Phase III Study BO21005, who experienced fatal myocardial infarction (MI) within 24 hours of the first infusion of obinutuzumab (1000 mg). This patient had a medical history of acute MI 12 years previously, and his concurrent conditions included dilated cardiomyopathy and hypertension.

Short-duration infusion - FL (MO40597)

No serious adverse events of IRR were reported.

Other Studies (All indications)

In other obinutuzumab studies, the incidence of serious IRRs was <6.5% (see Table 16).

Outcome of IRRs across all studies

IRRs were reported as resolved in at least 70% of the population that experienced IRRs in each study. In the remainder of the patients, the event outcome was reported as ongoing at the time of reporting or not recovered/not resolved (see Table 16).

Table 16 Frequency of Related IRRs in Obinutuzumab Studies

Study	Total No. of patients N	Patients with at least 1 event N (%)	Patients with severe (Grade 3 or 4) events N (%)	Patients with fatal (Grade 5) events N (%)	Patients with serious events N (%)	Patients who discontinued antibody treatment due to AE[a] N (%)	Patients with all AEs reported as resolved[a,c] N (%)
BO21004 Chemotherapy CLL							
Obinutuzumab arm (Stage 1a)	241	167 (69.3)	50 (20.7)	0	27 (11.2)	19 (11.4)	167 (100.0)
Cross-over GClb arm[b]	30	16 (53.3)	6 (20.0)	0	2 (6.7)	2 (12.5)	16 (100.0)
Run-in phase	6	5 (83.3)	0	0	1 (16.7)	0	4 (80.0)
Obinutuzumab arm (Stage 2)	336	222 (66.1)	66 (19.6)	0	34 (10.1)	25 (11.3)	221 (99.5)
Rituximab arm (Stage 2)	321	121 (37.7)	13 (4.0)	0	5 (1.6)	3 (2.5)	120 (99.2)
Pooled monotherapy studies BO20999 + BO21003							
CLL	38	38 (100.0)	17 (44.7)	0	10 (26.3)	3 (7.9)	37 (97.4)
NHL	205	169 (82.4)	24 (11.7)	0	11 (5.4)	3 (1.8)	161 (95.3)
GAO4768g Monotherapy CLL 1000/2000 mg	78	72 (92.3)	13 (16.6)	0	5 (6.4)	2 (2.8)	72[c] (100.0)
GAO4779g Chemotherapy CLL (FC/benda)	41	38 (92.7)	9 (21.9)	0	5 (12.2)	1 (2.6)	29[c] (76.3)
MO28543 CLL							
Previously untreated	630	399 (63.3)	122 (19.4)	0	75 (11.9)	22 (5.5)	390 (97.7)
Relapsed/refractory	341	236 (69.2)	67 (19.6)	0	43 (12.6)	13 (5.5)	234 (99.2)

Study	Total No. of patients N	Patients with at least 1 event N (%)	Patients with severe (Grade 3 or 4) events N (%)	Patients with fatal (Grade 5) events N (%)	Patients with serious events N (%)	Patients who discontinued antibody treatment due to AE[a] N (%)	Patients with all AEs reported as resolved[a,c] N (%)
BO21003 Phase II monotherapy NHL							
Obinutuzumab arm	87	70 (80.5)	9 (10.3)	0	2 (2.2)	3 (4.3)	67 (95.7)
Rituximab arm	86	44 (51.1)	5 (5.8)	0	1 (1.2)	1 (2.3)	42 (95.5)
BO21000 FL CHOP/Benda							
First-line Patient Population (Overall Treatment Period)							
G-benda group	41	32 (78.0)	4 (9.8)	0	5 (12.2)	0	32 (100.0)
G-CHOP group	40	28 (70.0)	7 (17.5)	0	2 (5.0)	1 (3.6)	27 (96.4)
BO21223 FL patient population[d]							
R-chemo arm	597	349 (58.5)	40 (6.7%)	0	14 (2.3)	0	327 (93.7)
G-chemo arm	595	406 (68.2)	74 (12.4)	0	34 (5.7)	4 (1.0)	374 (92.1)
BO21223 MZL patient population							
R-chemo arm	93	55 (59.1)	15 (16.1)	0	9 (9.7)	2 (3.6)	52 (94.5)
G-chemo arm	101	80 (79.2)	13 (12.9)	0	10 (9.9)	3 (3.8)	79 (98.8)

Study	Total No. of patients N	Patients with at least 1 event N (%)	Patients with severe (Grade 3 or 4) events N (%)	Patients with fatal (Grade 5) events N (%)	Patients with serious events N (%)	Patients who discontinued antibody treatment due to AE[a] N (%)	Patients with all AEs reported as resolved[a,c] N (%)
BO21005 Chemotherapy DLBCL (CHOP) all population							
G-CHOP	702	324 (46.2)	67 (9.5)	1 (0.1)	20 (2.8)	5 (1.5)	306 (94.4)
R-CHOP	701	226 (32.2)	23 (3.3)	0	6 (0.9)	3 (1.3)	211 (93.4)
GAO4915g Chemotherapy aNHL CHOP all population data	100	69 (69.0)	5 (5.0)	0	2 (2.0)	0	66[c] (95.7)
GAO4753g iNHL							
G-benda arm	204	136 (66.7)	23 (11.3)	0	9 (4. 4)	5 (3.7)	184 (90.19)
benda arm	203	127 (62.6)	11 (5. 4)	0	3 (1.5)	0	107 (84.25)
Short-duration infusion - FL (MO40597)	113	71 (62.8)	7 (6.2)	0	0	2 (2.8)	70 (98.6)

Table 16 Frequency of Related IRRs in Obinutuzumab Studies (cont.)

AE = adverse event; aNHL = aggressive NHL; Benda = bendamustine; Clb = chlorambucil; CLL = chronic lymphocytic leukemia; CHOP = cyclophosphamide, doxorubicin, vincristine and prednisone; FC = fludarabine and cyclophosphamide; FL = follicular lymphoma; G = obinutuzumab; GClb = obinutuzumab and chlorambucil; iNHL = indolent NHL; IRR = infusion-related reactions; NHL = non-Hodgkin lymphoma; R = rituximab.

[a] The percentages shown in the columns “Patients who discontinued antibody treatment due to AE” and “Patients with all AEs resolved” are based on the number of patients with at least one event.

[b] The data cut-off date for the cross-over arm in Study BO21004 is 9 May 2013

[c] The numbers of patients with all AEs resolved in studies BO21005, BO21223, GAO4768g, GAO4779g and GAO4915g have been calculated by subtracting the number of patients with ongoing or unresolved AEs from the total number of patients with AEs. Patients with unknown outcomes were included were included in ‘the unresolved or ongoing’ category.

Note: Cut-off dates for data in this table are as follows: 10 October 2017 (BO21004), 02 July 2014 (BO20999 and BO21003), 22 March 2016 (GAO4768g), 24 January 2013 (GAO4779g), 04 November 2015 (BO21000), 31 January 2018 (BO21005), 23 December 2016 (GAO4915g) 30 November 2018 (GAO4753g), 05 March 2019 (MO28543), 3 December 2020 (MO40597); and 30 July 2021 (BO21223).

Note: Figures in table are to 1.D.P

Note: All AEs related to any study treatment (as assessed by the investigator) that started during the infusion or within 24 hours of completion of the infusion were included and multiple symptoms of a single IRR (e.g., hypotension, chills, nausea, or pyrexia) are captured as individual adverse events.

Severity and Nature of Risk

Severity of IRRs

CLL (BO21004- Stage 1a)

In Stage 1a of Study BO21004 (GClb vs. Clb) (by the data cut-off date of 10 October 2013), overall 167/241 patients (69%) experienced 253 IRRs, although the majority of these events were Grade 1 or 2 (196/253 events [77%]). Fifty out of 241 patients (21%) in the GClb arm experienced Grade 3 or 4 IRRs (see Table 16).

CLL (BO21004- Stage 2)

By the data cut-off date (10 October 2017) for the Stage 2 analysis of Study BO21004 (GClb vs. RClb), overall 222/336 patients (66%) had experienced 324 IRRs in the GClb arm, with the majority being Grade 1 or 2 (251/324 events [77%]). Sixty-six patients out of 336 (20%) experienced Grade 3 or 4 IRRs. No Grade 5 IRRs were reported (see Table 16).

CLL and NHL (BO20999 and BO21003; pooled studies)

In the pooled monotherapy studies (BO21003 and BO20999), 45% of the CLL population reported severe (Grade 3 or 4) IRRs, while 12% of the NHL population reported Grade 3 or 4 events (see Table 16).

CLL (GAO4779g)

In Study GAO4779g, 21.9% patients receiving obinutuzumab with concomitant chemotherapy experienced severe events (see Table 16).

iNHL (GAO4753g)

In Study GAO4753g, in which patients with rituximab-refractory iNHL received treatment with bendamustine, with or without obinutuzumab, the majority of IRRs were Grade 1 or 2 and there were no fatal (Grade 5) IRRs.

FL (BO21223)

The majority of IRRs were Grade 1 or 2 in both arms and no fatal (Grade 5) IRRs occurred in this study.

MZL (BO21223)

In both arms, the majority of IRRs were Grade 1 or 2. No IRRs were Grade 5.

FL (BO21000) - First-Line Patient Population

The majority of IRRs were Grade 1 or 2: Eight out of 146 AEs (5%) in the G-benda group and 18 out of 157 AEs (11%) in the obinutuzumab plus CHOP (G-CHOP) group were Grade 3 AEs. There were no grade 4 or 5 AEs.

DLBCL (BO21005)

The overall incidence of the following IRRs were higher in the G-CHOP arm compared with the R-CHOP arm (expressed as R-CHOP vs. G-CHOP): all-grade IRRs (32.2% vs. 46.2%), Grade 3–5 IRRs (3.3% vs. 9.7%), and serious IRRs (0.9% vs. 2.8%). IRRs led to interruption of chemotherapy in 4 of 226 patients (1.8%) in the R-CHOP arm and 10 of 324 patients (3.1%) in the G-CHOP arm.

CLL (MO28543)

Grade ≥3 IRR AEs were reported for 193 (19.9%) patients overall; 125 (19.8%) patients in the previously untreated group (17.7% of fit patients and 22.3% of non-fit patients) and for 68 (19.9%) patients in the relapsed/refractory group. There were no patients with Grade 5 IRR AEs.

Short-duration infusion - FL (MO40597)

The majority of patients (62.8%) experienced at least one IRR AE during induction including IRRs after standard duration infusion at Cycle 1). Seven IRR events (6.2%) were Grade 3. No patients experienced Grade 4 or 5 IRR AEs. Of the 110 patients from the safety evaluable population who received SDIs at any point in the study, 15 (13.6%) experienced Grade 1 IRRs, 7 (6.4%) experienced Grade 2 IRRs, and 1 (0.9%) experienced Grade 3 IRRs after SDI. There were no Grade ⩾3 IRRs after SDI at Cycle 2. One patient experienced Grade 3 IRR event of hypertension after SDI at Cycle 5 (See Frequency with 95% CI above).

Other studies (All indications)

In other studies, the frequency of severe events (Grade 3 or 4) was less than 20%.

Nature of IRRs

In all studies to date, IRRs predominantly occurred with the first infusion and their incidence and severity typically decreased with subsequent infusions. Cases of cytokine release syndrome have been reported with obinutuzumab (see also Potential Mechanisms, above for further information on IRRs and cytokine release).

CLL (BO21004- Stage 1a)

In Stage 1a of Study BO21004, 177 out of 241 patients who received GClb (73%) developed a related IRR event (AEs that occurred within 24 hours of infusion) on Day 1 of Cycle 1 and this was reduced to 1% by Cycle 6; Grade 3 or 4 related IRRs were reported only during Cycle 1 and Cycle 2, but the incidence of these decreased substantially after Day 1 (from 110 reactions on Cycle 1 Day 1 to 5 reactions on Cycle 1 Day 8). Very few related serious IRRs were reported beyond the first infusion (three at Cycle 1 Day 8 and one at Cycle 2 Day 1).

CLL (BO21004- Stage 2)

Data from the Stage 2 analysis of Study BO21004 showed that 234 out of 336 patients in the GClb arm (70%) developed related IRRs (all AEs occurring within 24 hours of infusion) on Day 1 of Cycle 1; only 1 patient had an IRR at Cycle 6. IRRs also occurred mainly on first infusion in the RClb arm (29% of patients at Cycle 1, compared with Cycle 6, when only 1% of patients developed IRRs). The decrease in the incidence of IRRs with subsequent cycles was less pronounced in the RClb arm than in the GClb arm, with a higher incidence of related IRRs observed at Cycle 2 in the RClb arm than the GClb arm (a decrease from 29% in Cycle 1 to 14% in Cycle 2 was seen in the RClb arm compared with a decrease from 70% to 3% in the GClb arm). More serious related IRRs were reported in the RClb arm at Cycle 2 (11) compared with the first infusion (4). This trend was not observed in the GClb arm (where a decrease was seen from 146 serious IRRs at first infusion to 1 serious IRR at Cycle 2). The number of Grade 3-5 events decreased considerably with subsequent infusions in both arms. No Grade 5 events were reported.

The first four protocol amendments for Study BO21004 were implemented in order to reduce the risk and severity of IRRs and the latest amendment made it mandatory to split the first infusion of obinutuzumab over two days (100 mg on Day 1 and 900 mg on Day 2) as well as reducing the rate of infusion. The Stage 2 analysis of Study BO21004 showed that with each amendment the incidence of IRRs at first infusion decreased (from 88.7% before the first amendment to 52.9% after the fourth amendment). However, the rates of Grade 3-4 IRRs (which were based on a relatively small number of patients), were similar before and after mitigation measures were implemented.

Analysis of the Stage 2 data from Study BO21004, showed that frequently reported AEs in patients enrolled before the amendment were IRRs (preferred term) (71%), nausea (25%), pyrexia (24%), chills (22%), hypotension (21%), vomiting (18%), dyspnea (13%), flushing (14%), hypertension (8%), headache (6%), tachycardia (6%), diarrhea (6%) and bronchospasm (5%). In patients enrolled after the amendment, the common AEs were IRRs (preferred term) (61%), chills (23%), nausea (20%), pyrexia (19%), hypotension (17%), vomiting (15%), dyspnea (14%), flushing (11%), dizziness (6%), bronchospasm (6%), tachycardia (5%) and hypertension (4%).

CLL (GAO4768g and GAO4779g)

In Study GAO4768g, 91% of patients (71/78) experienced IRRs with the first infusion. Eight events (11.2%) were serious. During or after the second infusion, only 9% of patients had an IRR, with more IRRs seen in patients in the obinutuzumab 1000 mg arm (16%) compared with the obinutuzumab 2000mg arm (3%). None of the events occurring after the second or subsequent infusions were serious or severe.

In Study GAO4779g 88% of patients experienced IRRs at the first infusion (10 events were serious and all of them occurred in the G-benda arm). Only 14% of patients experienced an IRR during or after the second infusion. A similar percentage of patients experienced IRRs on Day 1 of Cycle 2 and Day 1 of Cycle 3. At Cycle 3, an imbalance was observed between the treatment arms, with more patients experiencing IRRs in the bendamustine arm than the FC arm (16% versus 6%). No severe or serious events occurred after the second or subsequent infusions.

iNHL (GAO4753g)

In Study GAO4753g in patients with rituximab-refractory iNHL, the higher incidence of IRR in the G-benda arm was mostly driven by a higher incidence of hypotension (0.5% vs. 9.8%), fatigue (9.4% vs. 18.1%), pyrexia (5.4% vs. 11.8%), and “infusion-related reactions” (preferred term) (57.6% vs. 62.7%).

A total 42.4% of patients in the benda arm and 53.4% of patients in the G benda arm had an IRR in Cycle 1. Within the first cycle, in patients exposed to G-benda, the incidence of IRR was highest on Day 1 (37.3%) and gradually decreased on Days 2, 8 and 15 (24.1%, 6.3% and 4.2%, respectively).

FL (BO21223)-First-Line Patient Population

The most frequent symptoms of IRRs ($\geq$ 5% occurrence in the G-chemo arm) were as follows (percentages expressed as R-chemo vs. G-chemo): nausea (19.3% vs. 24.2%), chills (6.9% vs. 15.0%), pyrexia (5.5% vs. 13.6%), vomiting (7.5% vs 10.4%), fatigue (6.9% vs. 6.7%), dyspnea (4.7% vs. 7.6%), headache (4.2% vs. 8.4%), flushing (3.7% vs. 5.4%), and constipation (3.2% vs. 5.2%). Within the first Cycle, the incidence of IRRs was 43.6% in R-chemo and 59.8% in G-chemo. The incidence of IRRs decreased with subsequent cycles (percentages expressed as R-chemo vs. G-chemo): Cycle 2: 18.4% vs 11.8%; Cycle 3: 13% vs 7.7%, etc).

FL (BO21000) - First-Line Patient Population

The most commonly reported events in either group were pyrexia, chills, nausea and vomiting. Two patients in the G-CHOP group had related AEs, nausea (in both patients) and agitation. One patient in the G-benda group had a related AE of nausea.

DLBCL (BO21005)

The percentage of patients with IRRs was higher in the G-CHOP arm (42.9%) compared with the R-CHOP arm (26.2%) during Cycle 1, but was similar between treatment arms in subsequent cycles. The incidence of Grade 3–5 IRRs, serious IRRs, and IRRs leading to antibody withdrawal was also higher in the G-CHOP arm compared with the R-CHOP arm in Cycle 1 but similar between the treatment arms in subsequent cycles.

The incidence of IRRs decreased considerably between Cycle 1 and Cycle 2 in both the G-CHOP arm (42.9% to 4.5%) and R-CHOP arm (26.2% to 4.1%), and continued to decrease in subsequent cycles. By Cycle 8, no patient in either treatment arm experienced a Grade 3–5 IRR, serious IRR, or IRR leading to withdrawal of any component of therapy.

Short-duration infusion - FL (MO40597)

The nature of IRR events occurring at Cycle 1 (standard infusion) and at Cycle 2 and subsequent infusions (short duration infusion) were similar to IRR events observed in other studies involving standard infusion. The most frequently reported IRR symptoms and signs occurring after SDI at Cycle 2 were nausea and vomiting. The majority were Grade 1.

Impact on quality of life

The impact of IRRs will vary depending on the symptoms experienced by individual patients. Since the majority of patients experience transient IRRs, there appears to be no substantial impact on quality of life for the patients. The administration of the first infusion as a split dose requires an additional hospital visit.

Risk factors and risk groups

The following specific patient characteristics were suggested to be potential risk factors for CLL patients who experienced IRRs related to obinutuzumab in Study BO21004 by the study Data Safety Monitoring Board (DSMB) in September 2011:

- High tumor burden (circulating lymphocyte count >100 $x10^9$/L)
- Binet Stage C CLL at screening (Rai III/IV)
- Low body mass index (BMI <20)
- Hypertension necessitating anti-hypertensive treatment.

A risk factor analysis of the Stage 2 data from Study BO21004 did not allow clear identification of the patients at a higher risk of IRRs.

Increased tumor burden is considered a risk factor for IRR. However, no clear effect of tumor burden (as assesses by circulating lymphocyte count ≥$100x10^9$ cells/L) was seen

on the incidence of IRRs. In the GClb arm of BO21004 (Stage 2 analysis), there was no difference in IRR incidence based on tumor burden. The incidence of all grade IRRs in patients with high tumor burden was 67% and in patients with a low tumor burden, it was 66%. Similarly, the incidence of Grade 3-4 IRRs was also comparable in patients with high and low tumor burden (22% vs. 19%).

The incidence of IRRs as per Binet staging at baseline was analyzed. The incidence of all grade IRRs was comparable in patients with Binet stage A and C and lower in patients with Binet stage B at baseline (A, B, C: 67%, 57%, 75%). A similar trend was seen with Grade 3-4 (23%, 13%, 26%) and serious IRRs (11%, 8%, 12%).

The incidence of all grade and Grade 3-4 IRRs in the GClb arm was comparable in patients with BMI $<$ 20 and $\geq$ 20 (all grades 60% vs. 66% and Grade 3-4, 20% vs. 20%). The incidence of IRRs remained the same irrespective of whether patients received anti-hypertensive treatment or not (all grade IRR, 66% vs 66%, and Grade 3-4, 20% vs. 19%).

In addition to the analysis of risk factors proposed by the DSMB, an extensive risk factor analysis was also performed in patients who developed an IRR compared to patients who did not experience any IRR event based on the characteristics of patients at baseline. These included age, gender, BMI (median BMI and BMI$>$30), estimated creatinine clearance (median CrCl and CrCl$<$ or $\geq$70ml/min), radiologically assessed sum of product of diameters for target lesions, circulating lymphocyte count (median lymphocyte count, count $>25x10^9$ cells/L and count$>100x10^9$ cells/L) and medical history of diabetes, coronary artery disease, hypertension and hypercholesterolemia. Assessment of all the above-mentioned potential risk factors revealed no conclusive differences in baseline characteristics of patients with or without IRRs.

Preventability

Infusions should be administered in an environment where full resuscitation facilities are immediately available, and under the close supervision of a physician.

The incidence and severity of IRRs may be reduced by premedication with antipyretics, antihistamines and steroids and appropriate patient monitoring and treatment.

Patients with high circulating lymphocyte counts or high tumor burden should receive adequate hydration and premedication with uricostatics (e.g., allopurinol).

Patients should discontinue therapy if they experience anaphylaxis, acute respiratory distress, life-threatening infusion reactions, second occurrence of a Grade 3 IRR or prolonged or recurrent infusion reactions.

Patients with pre-existing cardiac or pulmonary conditions and patients with high tumor burden (i.e. high peripheral lymphocyte count ($>25 \times 10^9$/L) should be closely monitored.

Detailed recommendations for reducing the incidence and severity of IRRs associated with the administration of obinutuzumab are presented in risk Minimization Measures.

Impact on the benefit-risk balance of the product

The impact of IRR on the benefit-risk balance of obinutuzumab is considered low. In the majority of patients IRRs were mild to moderate and were manageable with the proposed risk mitigation measures.

No new aspects of the important identified risk of IRR became available to the MAH to date in Study BO21004. The benefit-risk profile of obinutuzumab in the approved indications remains unchanged and favorable.

Public health impact

No public health impact is envisaged in view of the population treated and the limitations placed upon administration of obinutuzumab by virtue of the warnings and precautions and dosage instructions in the product label. Use outside of controlled environments by non-healthcare professionals is not anticipated.

2. Infections

MedDRA Terms:

All preferred terms (PTs) from the MedDRA system organ class “Infections and infestations” and Roche Standard MedDRA Query “Opportunistic infection.”

Potential mechanisms:

Given its anticipated mode of action resulting in profound B-cell depletion, obinutuzumab is likely to be associated with an increased risk of infections. Additional chemotherapy and underlying malignancy are important contributing factors.

Evidence source(s) and strength of evidence:

Clinical trial data are from studies BO20999, BO21000, BO21003, BO21004, BO21005, BO21223, GAO4753g, GAO4768g, GAO4779g, and GAO4915g.

Characterization of the risk:

Background incidence/prevalence

A systematic review by Roche of published observational data on infections in CLL and NHL patients has been conducted and a summary of identified incidence and prevalence estimates for infections is provided below. Incidence and prevalence estimates are

summarized by risk of overall infection, infections where IV antibiotics were required and serious viral infections.

Overall infection

Lanini and co-authors (Lanini et al. 2011) carried out a systematic review and a meta-analysis to compare the relative risk of overall severe infections (Grade 3 or 4) in malignant lymphoma patients treated with standard chemotherapy or with the addition of rituximab to standard chemotherapy. Their meta-analysis included 17 randomized clinical trials in a total of 5,259 patients. The patients included both untreated and refractory and both aggressive and indolent lymphoma patients. The pooled meta-analysis suggested the same risk of overall severe infections for patients treated with standard chemotherapy and rituximab plus standard chemotherapy, the relative risk = 1.00 (95% CI: 0.87, 1.14).

Two meta-analyses of rituximab maintenance therapy suggest an increased risk of overall infection from rituximab maintenance therapy (Aksoy et al. 2009; Vidal et al. 2009). Vidal and co-authors (Vidal et al. 2009) carried out a systematic review and a meta-analysis of randomized clinical trials to evaluate efficacy of rituximab maintenance therapy versus observation, but also looked at AEs reported in identified trials. Three trials included rates of infection-related AEs. The FL patients that underwent rituximab maintenance therapy had more infection-related AEs than patients in observation arm (relative risk = 1.99; 95% CI: 1.21, 3.27), and particularly a greater risk of Grade 3 or 4 infection-related AEs (relative risk = 2.90; 95% CI: 1.24, 6.76) comparing rituximab maintenance therapy to observation. Vidal and co-authors acknowledge that there are limitations of their study, particularly that studies included in the meta-analysis differed in their induction therapy, and some patients didn't receive rituximab as part of their induction therapy. In a meta-analysis of five randomized clinical trials (Aksoy et al. 2009), rituximab maintenance therapy significantly increased the risk of infection (all grade) in patients with lymphoma compared to observation (relative risk = 2.82; 95% CI: 1.28, 6.23). The analysis also suggested that patients who were heavily pre-treated and predominantly with fludarabine containing regimens were more prone to infectious complications during rituximab maintenance therapy. Some of the trials in the meta-analysis by Aksoy and co-authors (Aksoy et al. 2009) included previously untreated patients whereas other trials included patients previously treated with one or more lines of systemic treatment. The trials included in the AE meta-analysis by Vidal and co-authors (Vidal et al. 2009) are also included in the meta-analysis by Aksoy and co-authors (Aksoy et al. 2009) with two additional trials. Whereas the Vidal et al. study was focused on FL patients, the study by Aksoy et al. included both FL and mantle cell lymphoma (MCL) patients. Generally when studying the risk of infection, the risk is difficult to quantify because of confounding factors, primarily concomitant use of immunosuppressive or chemotherapeutic agents and patients' underlying conditions, as well as under-reporting.

Infections where IV antibiotics required

Among CLL patients treated with rituximab-free regimens, the range of reported incidence rates for infections where IV antibiotics was required was 0.00–0.03 per person-year and the range of reported incidence proportion was 0%-9.8%. The reported infections were: enterococci, enteric rods, pseudeomonas spp, pleomorphic, pseudomonas, nocardia asteroids, *Campylobacter jejuni*, *Salmonella enterica*, *Escherichia coli*, and *Klebsiella* pneumonia (Robak et al. 2002a; Shvidel et al. 2003; Francis et al. 2006; Delgado et al. 2008).

Serious viral infections

Among CLL patients treated with rituximab-free regimens, the range of reported incidence rates serious viral infections was 0.00–0.03 per person-year and the range of reported incidence proportion was 0%–9.8%. The reported infections were: respiratory virus (required hospitalization), influenza, parainfluenza, metapneumovirus, and respiratory syncytial virus. The prevalence of hepatitis B virus (HBV) (treatment not reported) in CLL patients was in the range 5%-21.8%. The prevalence of hepatitis C virus (HCV) (treatment not reported) was in the range 0%-33.3% in CLL patients. In chemotherapy treated CLL patients, the prevalence of serious viral infection (Grade 3 or 4, as defined by WHO classification) was in the range 0%-9.5% (Gharagozioo et al. 2001; Hausfater et al. 2001; Robak et al. 2002a; Francis et al. 2006; Takeshita et al. 2006; Chen et al. 2008; Delgado et al. 2008; Okan et al. 2008; Rossi et al. 2009; Chuang et al. 2010; Kang et al. 2011; Pinato et al. 2012).

Frequency with 95% CI

CLL (BO21004- Stage 1a)

In the safety run-in phase of Study BO21004 in previously untreated CLL patients with comorbidities, 5 out of 6 patients developed infections. In the Stage 1a analysis (GClb vs. Clb) (by the data cut-off date of 10 October 2017), 101/241 patients (42%) in the GClb arm and 46/116 patients (40%) in the Clb arm developed infections.

CLL (BO21004- Stage 2)

By the data cut-off date (10 October 2017) for the Stage 2 analysis of Study BO21004, 130/336 patients (39%) in the GClb arm had developed infections compared with 122/321 patients (38%) in the RClb arm. In the crossover group of the same study (30 patients crossed over from Clb treatment to the arm receiving obinutuzumab + chlorambucil), 10 out of 30 patients (33%) developed infections. Thus, despite the higher incidence of neutropenia in patients receiving obinutuzumab compared with Clb or rituximab + Clb in Study BO21004, no corresponding increase in the incidence of infection has been seen in the obinutuzumab arm.

No correlation has been found between prolonged B-cell depletion and the severity of events of infection in obinutuzumab-treated patients in study BO21004.

CLL and NHL (BO20999 and BO21003; pooled studies)

When treated with obinutuzumab monotherapy, patients with CLL appear to be at more risk of infections as compared to NHL patients. In the pooled monotherapy trials BO20999 and BO21003, 21 out of 38 CLL patients (55%) and 98 out of 205 NHL patients (48%) experienced infection.

There was no notable difference in the incidence of infection between the rituximab and obinutuzumab arms in the randomized part of Study BO21003: 42 patients out of a total of 86 (49%) experienced infection in the rituximab group and 41 out of a total of 87 patients in the obinutuzumab arm (47%) experienced an event of infection.

CLL (GAO4779g)

In previously untreated CLL patients receiving obinutuzumab with concomitant chemotherapy (Study GAO4779g), infections occurred in 20 out of 41 patients (48.8%).

iNHL (GAO4753g)

In Study GAO4753g (entire study), the incidence of all-grade infections was higher in the G-benda arm than in the benda arm with 59.1% of benda-treated patients and 68.1% of G-benda treated-patients experiencing at least one infection at some time during the study.

FL (BO21223)

The incidence of infection AEs was lower in the R-chemo arm (445/597 patients [74.5%]) than the G-chemo arm (487/595 patients [81.8%]).

MZL (BO21223)

The majority of patients experienced a Grade 2 or 3 AE, with Grade 3-5 AEs occurring in 20 patients (21.5%) in the R-chemo and 35 patients (34.7%) in the G-chemo arm.
Of these, 2 patients in the R-chemo and 7 patients in the G-chemo arm experienced a Grade 5 (fatal) infection.

FL (BO21000) First Line population

G-Benda group: A total of 34 patients (83%) had at least one infection AE of any grade.

G-CHOP group: A total of 30 patients (75%) had at least one infection AE of any grade (see Table 17 for further details).

DLBCL (BO21005)

The incidence of infection AEs was higher in the G-CHOP arm (386 of 702 patients [55.0%]) compared with the R-CHOP arm (317 of 701 patients [45.2%]).

DLBCL (GAO4915g)

A total of 58 patients (58%) had at least one infection AE of any grade. Fatal infection was reported in 1 patient.

Short-duration infusion - FL (MO40597)

A total of 53 patients (46.9%) had at least one infection AE of any grade. Fourteen patients (12.4%) had an infection of Grade 3 or 4. There were no cases of infection with a fatal outcome.

Seriousness / Outcomes

CLL (BO21004- Stage 1a)

In the Stage 1a analysis of Study BO21004 (by the data cut-off date of 10 October 2017), a comparable incidence of serious infections was reported in patients treated with Clb and patients treated with obinutuzumab and Clb (15% vs. 12%). Fatal infections were reported in 7 patients (6%) receiving Clb and 1 patient receiving GClb.

CLL (BO21004- Stage 2)

By the cut-off date (10 October 2017) for the Stage 2 analysis (GClb vs. RClb), serious infections had been reported in 43/336 patients (13%) in the GClb arm and 47/321 patients (15%) in the RClb arm. Two cases of infection with a fatal outcome (in 1% of patients) had been reported in each arm in this study at the time of the Stage 2 analysis of study BO21004.

CLL and NHL (BO20999 and BO21003; pooled studies)

In pooled monotherapy studies in the R/R population, serious infections were reported in 4 out of 38 patients (11%) with CLL and 12 out of 205 patients (6%) with NHL. One further NHL patient experienced an infection, the seriousness of which was not reported. There was no notable difference in the frequency of serious infections in the obinutuzumab and rituximab arms in a Phase II monotherapy study BO21003 in NHL patients (6% vs. 5%). Two fatal cases were reported in the pooled monotherapy studies; one in the CLL (3%) and one in the NHL (<1%) cohort.

iNHL (GAO4753g)

In Study GAO4753g (entire study), the incidence of all-grade infections was higher in the G-benda arm than in the benda arm, with 120/203 benda-treated patients (59.1%) and 139/204 G-benda treated-patients (68.1%) experiencing at least one infection. A similar proportion in each arm experienced Grade 3-5 infections (39 [19.2%] vs. 46 [22.5%]) and fatal infections (7 patients in the benda arm, 6 patients in G-benda). The difference between arms was mainly driven by the infections in the G-benda arm occurring during obinutuzumab maintenance (52.5% of patients in G-benda arm).

FL (BO21223)

Serious infections were more frequently reported in the G-chemo arm (117/595 patients [19.7%]) than in the R-chemo arm (100/597 patients [16.8%]). Of the patients who experienced an infection, a similar proportion of patients in each treatment arm discontinued treatment, (5.2% and 5.7% in the R-chemo and G-chemo arms) or had dose reductions as a result of the event (1.6% and 1.0% in the R-chemo and G-chemo arms). Most patients received treatment for the infection (86.5% and 89.3% of patients with infections in the R-chemo and G-chemo treatment arms, respectively).

MZL (BO21223)

A higher proportion of patients experienced serious infections in the G-chemo arm compared to the R-chemo arm (38/101; 37.6% and 21/93; 22.6%, respectively). Treatment was withdrawn in 4 patients in the R-chemo arm and 8 patients in the G-chemo arm. The majority of patients received treatment for an infection AE in both treatment arms (92.8% in the R-chemo arm and 94.2% in the G-chemo arm). The AE was still unresolved in 8 patients in the R-chemo and 10 patients in the G-chemo arm (11.6% each) at the time of data cut-off.

FL (BO21000) First Line population

G-Benda arm: Six patients (15%) had an SAE of infection. Of the patients with infection AEs, three patients required treatment discontinuation due to the AE. AEs leading to dose modification were reported in seven patients (21%). All patients received treatment for their AEs. The infections resolved in 32 patients (94%).

G-CHOP arm: A total of 14 patients (35%) had an SAE. Of the patients with infection AEs, three patients required treatment discontinuation due to the AE. AEs leading to dose modification were reported in eight patients (27%). All patients received treatment for their AEs and the infections resolved in 29 patients (97%) (see Table 17 for further details).

DLBCL (BO21005)

The frequency of serious infections was 13.8% in the R-CHOP arm and 17.4% in the G-CHOP arm.

The majority of infectious AEs in both treatment arms were Grade 1 or 2 in severity. The frequency of Grade 3–5 infections was 15.8% in the R-CHOP arm and 19.5% in the G-CHOP arm, with 11 patients (1.6%) in the R-CHOP arm and 16 patients (2.3%) in the G-CHOP arm experiencing Grade 5 (fatal) infections.

Among patients who experienced an infection, a similar percentage of patients in each treatment arm discontinued any treatment, (6.0% in the R-CHOP arm vs. 6.5% in the G-CHOP arm) or had dose reductions as a result of the event (2.8% in the R-CHOP arm vs. 3.1% in the G-CHOP arm). Most patients (91.5% in the R-CHOP arm and 89.9% in the G-CHOP arm) received treatment for the infection.

Short-duration infusion - FL (MO40597)

Overall, 11 patients (9.7%) experienced serious infections. There were no fatal infections reported.

All studies: Discontinuation of treatment and event outcome

Across all studies, the proportion of patients who discontinued treatment due to infections was 10% or less. The infection events were reported to have resolved in the majority of patients in all studies, with the percentage of patients reported to have recovered ranging from 80-100% (see Table 17 for further details).

Table 17 Frequency of Infections in Obinutuzumab Studies

Study	Total no. of patients N	Patients with at least 1 event N (%)	Patients with severe (Grade 3 or 4) events N (%)	Patients with fatal (Grade 5) events N (%)	Patients with serious events N (%)	Patients who discontinued antibody treatment due to AE N (%)[a]	Patients with all AEs resolved N (%)[a, e, f]
BO21004 Chemotherapy CLL							
Obinutuzumab chlorambucil arm (Stage 1a)	241	101 (41.9)	27 (11.2)	1 (0.4)	29 (12.0)	1 (1.0)	92 (91.1)
Chlorambucil arm (Stage 1a)	116	46 (39.7)	9 (7.8)	7 (6.0)	17 (14.7)	4 (8.7)	38 (82.6)
Cross-over GClb arm[b]	30	10 (33.3)	4 (13.3)	0	3 (10.0)	1 (10.0)	9 (90.0)
Run-in phase	6	5 (83.3)	0	0	2 (33.3)	0	5 (100.0)
Obinutuzumab chlorambucil arm (Stage 2)	336	130 (38.7)	39 (11.6)	2 (0.6)	43 (12.8)	3 (2.3)	117 (90.0)
Rituximab chlorambucil arm (Stage 2)	321	122 (38.0)	44 (13.7)	2 (0.6)	47 (14.6)	6 (4.9)	111 (91.0)
Pooled monotherapy studies BO20999 + BO21003							
CLL	38	21 (55.3)	5 (13.2)	1 (2.6)	4 (10.5)	0	19 (90.5)
NHL	205	98 (47.8)	12 (5.9)	2 (1.0)	14 (6.8)[c]	1 (1.0)	85 (86.7)
GAO4768g Monotherapy CLL 1000/2000 mg	78	33 (42.3)	3 (3.8)	0	4 (5.1)	0	31 (94.0)

Study	Total no. of patients N	Patients with at least 1 event N (%)	Patients with severe (Grade 3 or 4) events N (%)	Patients with fatal (Grade 5) events N (%)	Patients with serious events N (%)	Patients who discontinued antibody treatment due to AE N (%)[a]	Patients with all AEs resolved N (%)[a, e, f]
GAO4779g Chemotherapy CLL (FC/Benda)	41	20 (48.8)	5 (12.2)	0	4 (9.8)	1 (5.0)	16 (80.0)
BO21003 Phase II monotherapy NHL							
Obinutuzumab arm	87	41 (47.1)	4 (4.6)	2 (2.3)	7 (8.0)	1 (1.1)	34 (82.9)
Rituximab arm	86	42 (48.8)	3(3.5)	1 (1.2)	4 (4.7)	3 (7.1)	36 (85.7)
BO21000 Chemotherapy FL CHOP/Benda First-line patient population							
G+Benda arm	41	34 (82.9)	10 (24.4)	0	6 (14.6)	3 (8.8)	32 (94.1)
G+Benda arm	40	30 (75.0)	14 (35.0)	0	14 (35.0)	3 (10.0)	29 (97.7)
BO21223 Chemotherapy FL population data							
R-Chemo	597	445 (74.5)	106 (23.8)	4 (0.7)	100 (16.8)	23 (5.2)	416 (93.5)
G-Chemo	595	487 (81.8)	124 (25.5)	9 (1.5)	117 (19.7)	26 (5.3)	430 (88.3)
BO21223 Chemotherapy MZL population							
R-Chemo	93	69 (74.2)	18 (19.4)	2 (2.2)	21 (22.6)	3 (4.3)	61 (88.4)
G-Chemo	101	86 (85.1)	28 (27.7)	7 (6.9)	38 (37.6)	8 (9.3)	76 (88.4)

Study	Total no. of patients N	Patients with at least 1 event N (%)	Patients with severe (Grade 3 or 4) events N (%)	Patients with fatal (Grade 5) events N (%)	Patients with serious events N (%)	Patients who discontinued antibody treatment due to AE N (%)[a]	Patients with all AEs resolved N (%)[a, e, f]
BO21005 Chemotherapy DLBCL (CHOP) all population data							
G-CHOP	702	386 (55)	121 (17.2)	16 (2.3)	122 (17.4)	23 (o6.0)	345 (89.4)
R-CHOP	701	317 (45.2)	100 (14.3)	11 (1.6)	97 (13.8)	19 (6.0)	293 (92.4)
GAO4915g Chemotherapy NHL CHOP all population data[d]	100	58 (19.0)	17 (17.0)	1 (1.0)	19 (19.0)	2 (10.5)[e]	54 (93.1)
GAO4753g (iNHL) Overall Infections							
G-benda arm	204	139 (68.1)	46 (22.5)	6 (2.9)	38 (18.6)	6 (4.3)	128 (92.08)
Benda arm	203	120 (59.1)	39 (19.2)	7 (3.4)	36 (17.7)	0	109 (90.83)

Study	Total no. of patients N	Patients with at least 1 event N (%)	Patients with severe (Grade 3 or 4) events N (%)	Patients with fatal (Grade 5) events N (%)	Patients with serious events N (%)	Patients who discontinued antibody treatment due to AE N (%)[a]	Patients with all AEs resolved N (%)[a, e, f]
Short-duration infusion - FL (MO40597)	113	53 (46.9)	14 (12.4)	0	11 (9.7)	1 (0.9)	45 (84.91)

AE = adverse event; aNHL = aggressive NHL; Benda = bendamustine; Clb = chlorambucil; CLL = chronic lymphocytic leukemia, CHOP = cyclophosphamide, doxorubicin, vincristine and prednisone; FC = fludarabine and cyclophosphamide, GClb = obinutuzumab and chlorambucil; iNHL = indolent NHL, NHL = non-Hodgkin's Lymphoma.

[a] The percentages shown in the columns "Patients who discontinued antibody treatment due to AE" and "Patients with all AEs resolved" are based on the number of patients with at least one event.

[b] The data cut-off date for the cross-over arm in Study BO21004 is 9 May 2013.

[c] One NHL patient each in the pooled monotherapy studies (BO20999 and BO21003 experienced infections where the seriousness was not reported. These patients are excluded from the figures for serious events in this table.

[d] The figures shown from ongoing studies where the sponsor remains blinded to the treatment received include patients from all treatment arms.

[e] The numbers of patients with all AEs resolved have been calculated by subtracting the number of patients with ongoing or unresolved AEs from the total number of patients with AEs.

[f] 'Unknown resolution' was not counted as resolved.

Note: Cut-off dates for data in this table are as follows: 10 October 2017 (BO21004), 02 July 2014 (BO20999 and BO21003), 22 March 2016 (GAO4768g), 24 January 2013 (GAO4779g), 04 November 2015 (BO21000, 31 January 2018 (BO21005), 23 December 2016(GAO4915g), 30 November 2018 (GAO4753g), 3 December 2020 (MO40597), and 30 July 2021 (BO21223).

Note: Figures in table are to 1.D.P

Severity and Nature of Risk

B-cell depletion and/or neutropenia may affect the incidence and severity of infections in patients receiving obinutuzumab. With rituximab, the rate of infections has been shown to be increased with maintenance treatment suggesting that the duration of B-cell depletion may be of relevance to the risk of infection. Obinutuzumab is more potent in terms of B-cell depletion and it was assumed that it may further increase the risk of infections compared to rituximab.

CLL (BO21004- Stage 1a)

In the Stage 1a analysis of Study BO21004 (GClb vs. Clb) (by the data cut-off date of 10 October 2017), severe infections were reported in both the GClb treated population and the Clb treated population (GClb 11% vs. Clb 8%).

CLL (BO21004- Stage 2)

By the data cut-off date (10 October 2017) for the Stage 2 analysis of Study BO21004 (GClb vs. RClb), the incidence of severe infections was comparable between the two arms (GClb 12% vs. RClb 14%).

CLL and NHL (BO20999 and BO21003; pooled studies)

In pooled monotherapy studies (BO20999 and BO21003), 13% of patients in the CLL cohort and 6% of patients in the NHL cohort developed severe infections. The available data from the Phase II study BO21003 (R/R NHL population, obinutuzumab monotherapy) is suggestive of a comparable incidence of severe infections in the rituximab and obinutuzumab arms (3% vs. 5%).

CLL (GAO4779g)

In previously untreated CLL patients receiving concomitant chemotherapy (GAO4779g), 5 out of 41 patients (12.2%) developed severe infections.

iNHL (GAO4753g)

In Study GAO4753g (entire study), a similar proportion of patients in each arm experienced Grade 3-5 infections (G-benda:46 [22.5%] vs. benda:39 [19.2%]) and fatal infections (7 patients in the benda arm, 6 patients in G-benda).

FL (BO21223)

The majority of infection AEs were Grade 1 or 2 in both treatment arms (1250/1409 AEs [88.7%] in the R-chemo arm and 1443/1635 AEs [88.3%] in the G-chemo arm). The number of patients with Grade 3-5 infections was higher in the G-chemo arm

(133/595 patients [22.4%]) than in the R-chemo arm (110/597 patients [18.4%]), with 4 patients in the R-chemo arm (0.7%; PTs: pneumonia, sepsis, abdominal sepsis, and septic shock) and 9 patients (1.5%; PTs: pneumonia [5], and 1 each of sepsis, lower respiratory tract infection, respiratory tract infection, and staphylococcal bacteraemia) in the G-chemo arm experiencing fatal infections.

Opportunistic infections were reported in 4 patients in the R-chemo arm and 8 patients in the G-chemo arm. No Grade 4 or 5 opportunistic infection AEs were reported. Grade 3 AEs were reported for 5 patients in the G-chemo arm and no patients in the R-chemo arm.

Due to higher incidence of infections in this study, additional analysis about the nature of infection was performed to understand whether the patients were experiencing more opportunistic infections. Roche standard adverse event group terms (AEGT) "Opportunistic infections" was used to identify AEs.

Fungal opportunistic infections were reported in the R-chemo arm (single cases of oropharyngeal candidiasis, pneumocystis jirovecii infection, and upper respiratory fungal infection) and in the G-chemo arm (two cases of pneumocystis jirovecii pneumonia and individual cases of aspergillus infection, esophageal candidiasis, pneumonia fungal, and sinusitis fungal).

The incidence of Herpes Zoster infection was reported as follows (percentages expressed as R-chemo vs. G-chemo; preferred terms): herpes zoster (6.7% vs. 10.9%); genital herpes zoster (0.2% vs. 0), herpes zoster infection neurological (0.2% vs. 0), herpes zoster oticus (0 vs. 0.2%), ophthalmic herpes zoster (0 vs. 0.2%), and varicella zoster virus infection (0 vs. 0.2%). Other significant infections reported infrequently were Cytomegalovirus infections (0 in the R-chemo arm vs. three patients (0.5%) in the G-chemo arm.

Granulocyte colony stimulating factors [prophylaxis was administered to 174 patients in the R-chemo arm and 180 patients in the G chemo arm. Of those patients who received prophylaxis, 16.7% of patients in the R-chemo arm and 16.1% of patients in the G-chemo arm developed Grade 3-5 infections. In patients who did not receive G-CSF prophylaxis, 19.1% of patients in the R-chemo arm and 25.1% of patients in the G-chemo arm developed Grade 3-5 infections.

MZL (BO21223)

The majority of patients experienced a Grade 2 or 3 AE, with Grade 3-5 AEs occurring in 20 patients (21.5%) in the R-chemo and 35 patients (34.7%) in the G-chemo arm. Of these, 2 patients in the R-chemo and 7 patients in the G-chemo arm experienced a Grade 5 (fatal) infection.

FL (BO21000) First Line population

G-Benda arm: Grade ≥ 3 events were reported in 10 patients (25%). Six patients (15%) had an SAE.

G-CHOP arm: Grade ≥ 3 events were reported in 14 patients (36%). Fourteen patients (35%) had an SAE.

The most common infections reported were respiratory tract infections (including both upper and lower respiratory tract infection) and urinary tract infections.

DLBCL (BO21005)

Grade 5 AEs by PT occurring in more than 1 patient were pneumonia (5 patients) and sepsis (3 patients) in the R-CHOP arm and septic shock (6 patients) and pneumonia (5 patients) in the G-CHOP arm.

When infections were analyzed by cycle the incidence of infection AEs was generally similar (≤5% difference) between treatment arms at each cycle.

A total of 48 patients (6.8%) in the R-CHOP arm and 76 patients (10.8%) in the G-CHOP arm experienced infections during follow-up.

Short-duration infusion - FL (MO40597)

In total, 14 patients (12.4%) experienced Grade ≥3 infections. The most common Grade ≥3 infections were pneumonia (2.7%) and staphylococcal infection (1.8%).

Impact on quality of life

Infection can affect the quality of life of the individual patient and may be fatal. The degree of impact is dependent on many factors including the severity of infection, the site involved, the age of the patient and the presence of comorbidities.

Risk factors and risk groups

Patients with CLL and NHL are predisposed to common as well as opportunistic infections as a result of a number of disease-related factors including B cell dysfunction, immunoglobulin deficiency, abnormal T-cell function, and neutropenia resulting from infiltration of the bone marrow.

Preventability

Physicians should exercise caution when treating patients with a history of recurrent or chronic infections or with underlying conditions that may predispose patients to infections.

Particular attention should be given to patients who have had significant prior immunosuppressive treatment such as high dose chemotherapy and stem cell transplant.

Advice should be given to patients to minimize the risks of acquiring infections from endogenous sources e.g., oral hygiene, avoidance of constipation etc. Dental assessment may be warranted prior to starting treatment in some cases.

Signs or symptoms of infection should result in prompt evaluation and collection of appropriate samples for bacteriological investigation prior to starting antibiotic or other treatment by the treating physician.

Empiric therapy with broad-spectrum antibiotics should be initiated promptly in all patients with suspected infections (including those receiving antimicrobial prophylaxis) to reduce the risk of serious morbidity and mortality.

Antibiotic prophylaxis may be considered in high risk patients as it is associated with significantly reduced occurrence of fever, fewer clinically-documented and microbiologically-documented infections, fewer infections due to both gram-positive and gram-negative bacteria, fewer cases of bacteremia, and a lower risk of infection-related death.

Impact on the benefit-risk balance of the product

The impact on the benefit-risk balance of infections on obinutuzumab is considered low given the implemented risk minimization measures. The infection events were in general manageable and reported to have resolved in the majority of patients (62%–90%) across all pivotal studies. Adequate risk minimization activities which inform the patients and HCPs are implemented.

Public health impact

No public health impact is foreseen for this risk in view of the population treated and the limitations placed upon administration of obinutuzumab by virtue of the warnings and precautions in the product information.

3. Thrombocytopenia

MedDRA terms

SMQ (narrow): Haematopoietic Thrombocytopenia.

Potential mechanisms

Thrombocytopenia may be mediated through complement and cytokine cascades and may occur secondary to toxic effects of chemotherapy on bone marrow function or due

to some autoimmune phenomenon, but data on the mechanism of thrombocytopenia are sparse. An increased reporting rate of acute thrombocytopenia in the time window of infusion reactions has been described in patients treated with rituximab, suggesting that acute thrombocytopenia may be a possible infusion-related reaction (Report No. 1032924), but the cause is uncertain.

Evidence source(s) and strength of evidence

Clinical trial data are from studies BO20999, BO21000, BO21003, BO21004, BO21005, BO21223, GAO4753g, GAO4768g, GAO4779g, and GAO4915g.

Characterization of the risk

Background incidence/prevalence

The results of a systematic review by Roche of the published observational data for thrombocytopenia in CLL and NHL patients are shown in Table 18. This table summarizes identified incidence estimates. The epidemiological studies identified primarily used the WHO toxicity criteria or National Cancer Institute common terminology criteria for AEs (NCI CTC) to define thrombocytopenia. No articles were identified relating specifically to the background incidence of acute thrombocytopenia in CLL or NHL patients.

Table 18 Incidence Proportions and Incidence Rates of Thrombocytopenia AEs in CLL and NHL Patients, as Reported in Epidemiological Studies

Treatment	Adverse event	Cancer	Patient age	Incidence proportion, new events/ total population. Range across studies, (median if more than one study), [95% confidence interval]	Incidence rate, new events/100 person-years. Range across studies with median if more than one study, otherwise study estimate with 95% confidence interval
Untreated	All grades	CLL	Median: 63.3	10% [95% CI: 0-23.1%]	6.0 [95% CI: 0-14.4]
Rituximab-containing regimen	All grades	CLL	Median: 77	28.6% [95% CI: 25.1-32.2%]	8.6 [95% CI: 7.3-9.8]
	All grades	DLBCL	>60	8.2% [95% CI: 2.4-14.1%]	3.3 [95% CI: 0.9-5.7]
	Grade 1 or 2	NHL	Range of medians: 48-62	5%-14% (median: 9.5%)	1.9-4.0 (median: 3)
	Grade 3 or 4	CLL	Median: 73	13.9% [95% CI: 7.6-20.2%]	11.1 [95% CI: 5.7-16.6]
	Grade 3 or 4	NHL	Range of medians: 26-71	2%-100% (median: 45%)	11.4-20.4 (median: 19.4)
	Grade 3 or 4	DLBCL	Range of medians: 53-74	5.1%-55.0% (median: 10%)	2.4-14.2 (median: 3.1)
Other	All grades	CLL	Range of medians: 61-77	19.5%-32.9% (median: 21.9%)	1.8-19.9 (median: 9.9)
	All grades	NHL	N/A	64.6% [95% CI: 55.0-74.2%]	15.0 [95% CI: 11.3-18.8]
	All grades	MCL	Median: 64	63.3% [95% CI: 46.1-80.6%]	47.2 [95% CI: 26.0-68.4]
	Grade 1 or 2	NHL	Median: 74	9.6% [95% CI : 1.6-17.6%]	Not available
	Grade 3 or 4	CLL	Median: 61	4.9% [95% CI : 0.2-9.5%]	5.0 [95% CI : 0.1-9.8]

Treatment	Adverse event	Cancer	Patient age	Incidence proportion, new events/ total population. Range across studies, (median if more than one study), [95% confidence interval]	Incidence rate, new events/100 person-years. Range across studies with median if more than one study, otherwise study estimate with 95% confidence interval
	Grade 3 or 4	NHL	Range of medians: 59-74	7.7%-75% (median: 25%)	11.7-48.6 (median: 30.2)
	Grade 3 or 4	NHL	Median: 7.1	62.5% [95% CI : 52.8-72.2%]	21.4 [95% CI: 16.0-26.9]
	Grade 3 or 4	MCL	Range of medians: 58-64	20%-36.7% (median: 28.3)	8.2 [95% CI: 4.0-36]

CI= Confidence interval; CLL = chronic lymphocytic leukemia; DLBCL = diffuse large B-cell lymphoma; MCL = mantle cell lymphoma; NHL= Non-Hodgkin Lymphoma.

References: CLL: Schiavone et al. 2003; Fiegl et al. 2010; Danese et al. 2011; Smolej et al. 2012;

NHL: Cohen et al. 2001; Nuckel et al. 2003; Santoro et al. 2003; Acquatella et al. 2004; Aviles et al. 2004; Matutes et al. 2004; Olivieri et al. 2005; Woehrer et al. 2005; Cattaneo et al. 2006; Garcia-Suarez et al. 2007; Liauw et al. 2006; Neumann et al. 2006; Aydin et al. 2007; Jacene et al. 2007; Robak et al. 2007; Rueda et al. 2008; Aguiar et al. 2009; Lignon et al. 2010; Ahn et al. 2011; Mohamedbhai et al. 2011; Hou et al. 2012; Meguro et al. 2012; Shin et al. 2012; Warsch et al. 2012; Weide et al. 2012; Zinzani et al. 2012.

Frequency with 95% CI:

CLL (BO21004 – Stage 1a)

In the run-in phase of Study BO21004 (first line CLL patients), none of the 6 patients developed thrombocytopenia. In the Stage 1a analysis of this study (GClb vs. Clb) (by the data cut-off date of 10 October 2017), 41/241 patients (17%) in the obinutuzumab arm developed thrombocytopenia as an adverse event; 12 of these events (5%) were reported within 24 hours of obinutuzumab infusion (acute thrombocytopenia). In the Clb arm, 11/116 patients (9%) developed thrombocytopenia and none of these events were reported within 24 hours of infusion. Among the 30 cross-over patients (GClb arm) (by the data cut-off date of 9 May 2013), 7 (23%) developed thrombocytopenia. One case of acute thrombocytopenia (3%) was reported in the crossover population.

CLL (BO21004 – Stage 2)

By the data cut-off date (10 October 2017) for the Stage 2 analysis of Study BO21004 (GClb vs. RClb), 54/336 patients (16%) had developed thrombocytopenia in the GClb arm and 22/321 patients (7%) in the RClb arm. Acute thrombocytopenia (occurring during the first 24 hours after infusion) was observed in 4% of patients in the GClb arm and in 1% of patients in the RClb arm.

CLL (GAO4768g)

In another ongoing obinutuzumab monotherapy study in CLL patients (GAO4768g), 17 out of 78 patients (21.8%) developed thrombocytopenia; 5 cases (6.4%) occurred within 24 hours of infusion.

CLL and NHL (BO20999 and BO21003; pooled studies)

A higher incidence of thrombocytopenia was noted in CLL patients compared to NHL patients in the pooled monotherapy trials in the R/R population (studies BO20999 and BO21003). In the CLL population, 7 out of 38 patients (18%) developed thrombocytopenia; 4 (11%) experienced acute thrombocytopenia. In the NHL population, 11 out of 205 patients (5%) developed thrombocytopenia; 5 (2%) of these were acute in onset.

In the Phase II study BO21003 (NHL, monotherapy, obinutuzumab vs. rituximab), 1 out of 87 patients (1%) in the obinutuzumab arm developed thrombocytopenia while no cases were reported in the rituximab arm.

iNHL (GAO4753g)

In Study GAO4753g, the incidence of thrombocytopenia was higher in the benda arm than in the G-benda arm (24.6% vs. 14.7%). The higher rate of thrombocytopenia in the benda arm was probably due to the higher dose of bendamustine (120mg/m^2/dose) in the benda alone arm compared with the G-benda arm (90mg/m^2/dose).

FL (BO21223)

The incidence of thrombocytopenia AEs was lower in the R-chemo arm (49/597 patients [8.2%]) compared to the G-chemo arm (75/595 patients [12.6%]). Seven patients (1.2%) in the G-chemo arm and no patients in the R-chemo arm had acute thrombocytopenia.

MZL (BO21223)

A greater proportion of patients experienced thrombocytopenia in the G-chemo arm (19/101; 18.8%) compared to the R-chemo arm (7/93; 7.5%). One patient each (1.1% in R-chemo arm and 1.0% in G-chemo arm) had acute thrombocytopenia.

FL (BO21000) First Line population

A total of seven patients (six [15%] in the G-benda group, one [3%] in the G-CHOP group) had at least one thrombocytopenia AE.

Two patients receiving G-benda had a total of four acute thrombocytopenia AEs and one patient who received G-CHOP had one acute thrombocytopenia AE.

DLBCL (BO21005)

The incidence of thrombocytopenia AEs was higher in the G-CHOP arm (70 of 702 patients [10.0%]) compared with the R-CHOP arm (18 of 701 patients [2.6%]).

One patient (0.1%) in the R-CHOP arm and 6 patients (0.9%) in the G-CHOP arm had acute thrombocytopenia

Short-duration infusion - FL (MO40597)

A total of 21 patients (18.6%) experienced at least one thrombocytopenia AE.

Other studies (All indications)

In the remaining studies of obinutuzumab with concomitant chemotherapy (irrespective of indication), thrombocytopenia was reported in between 6% and 20.5% of patients (see Table 19 for further details).

Table 19 Frequency of Thrombocytopenia in Obinutuzumab Studies

Study	Total no. of patients N	Patients with at least 1 event N (%)	Patients with severe (Grade 3 or 4) events N (%)	Patients with fatal (Grade 5) events N (%)	Patients with serious events N (%)	Patients who discontinued antibody treatment due to AE N (%)[a]	Patients with all AEs resolved N (%)[a, d, f]
BO21004 Chemotherapy CLL Obinutuzumab arm (Stage 1a)	241	41 (17.0)	30 (12.4)	0	2 (0.8)	1(2.4)	33 (80.5)
Chlorambucil arm (Stage 1a)	116	11 (9.5)	6 (5.2)	0	1 (0.9)	0	3 (27.3)
Cross-over GClb arm[b]	30	7 (23.3)	3 (10.0)	0	0	0	5 (71.4)
Run-in phase	6	0	0	0	0	0	0
Obinutuzumab arm (Stage 2)	336	54 (16.1)	39 (11.6)	0	4 (1.2)	4 (7.4)	45 (83.3)
Rituximab arm (Stage 2)	321	22 (6.9)	11 (3.4)	0	1 (0.3)	3 (13.6)	17 (77.3)
Pooled monotherapy studies BO20999 + BO21003 CLL	38	7 (18.4)	5 (13.1)	0	1 (2.6)	0	7 (100.0)
NHL	205	11 (5.4)	6 (2.9)	0	1 (0.5)	0	10(90.9)
GAO4768g Monotherapy CLL 1000/2000 mg	78	17 (21.8)	11 (14.1)	0	1 (1.3)	3 (17.6)	16 (94.1)
GAO4779g Chemotherapy CLL (FC/Benda)	41	8 (19.5)	6 (14.6)	0	0	2 (25)	7 (87.5)

Study	Total no. of patients N	Patients with at least 1 event N (%)	Patients with severe (Grade 3 or 4) events N (%)	Patients with fatal (Grade 5) events N (%)	Patients with serious events N (%)	Patients who discontinued antibody treatment due to AE N (%)[a]	Patients with all AEs resolved N (%)[a, d, f]
BO21003 Phase II monotherapy NHL Obinutuzumab arm	87	1 (1.1)	0	0	0	0	1 (100.0)
Rituximab arm	86	0	0	0	0	0	0
BO21000 Chemotherapy FL CHOP/Benda **First-line Patient Population** **G+ Benda Arm**	41	6 (14.6)	4 (9.8)	0	0	0	4 (66.7)
G+CHOP Arm	40	1 (2.5)	1 (2.5)	0	0	0	1 (100.0)
BO21223 Chemotherapy FL patient population data **R-Chemo**	597	49 (8.2)	18 (3.0)	0	1 (0.2)	1 (2.0)	38 (77.5)
G-Chemo	595	75 (12.6)	37 (6.2)	0	4 (0.7)	1 (1.3)	65(86.7)
BO21223 Chemotherapy MZL patient population **R-Chemo**	93	7 (7.5)	4 (4.3)	0	2 (2.2)	0	4 (57.1)

Study	Total no. of patients N	Patients with at least 1 event N (%)	Patients with severe (Grade 3 or 4) events N (%)	Patients with fatal (Grade 5) events N (%)	Patients with serious events N (%)	Patients who discontinued antibody treatment due to AE N (%)[a]	Patients with all AEs resolved N (%)[a, d, f]
G-Chemo	101	19 (18.8)	12 (11.9)	0	1 (1.0)	0	18 (94.7)
BO21005 Chemotherapy aNHL (CHOP) all population data[c]							
G-CHOP	702	70 (10)	40(5.7)	0	12 (1.7)	6 (8.6)	61 (87.1)
R-CHOP	701	18 (2.6)	12 (1.7)	0	2 (0.3)	1 (5.6)	16 (88.9)
GAO4915g Chemotherapy NHL CHOP all population data	100	6 (6.0)	5 (5.0)	0	0	0	0
GAO4753g Overall Thrombocytopenia AEs							
G-benda arm[e]	204	30 (14.7)	22 (10.8)	0	5 (2.5)	4 (13.3)	25 (83.3)
Benda arm	203	50 (24.6)	32 (15.7)	0	0	0	41 (82)

Study	Total no. of patients N	Patients with at least 1 event N (%)	Patients with severe (Grade 3 or 4) events N (%)	Patients with fatal (Grade 5) events N (%)	Patients with serious events N (%)	Patients who discontinued antibody treatment due to AE N (%)[a]	Patients with all AEs resolved N (%)[a, d, f]
Short-duration infusion - FL (MO40597)	113	21 (18.6%)	8 (7.1)	0	1(0.9)	1 (4.76)	16 (76.2%)

AE = adverse event; aNHL = aggressive NHL; Benda = bendamustine; Clb = chlorambucil; CLL = chronic lymphocytic leukemia; CHOP = cyclophosphamide, doxorubicin, vincristine and prednisone; FC = fludarabine and cyclophosphamide; G = obinutuzumab; GClb = obinutuzumab and chlorambucil; iNHL = indolent NHL; MZL = marginal zone lymphoma; NHL = Non-Hodgkin Lymphoma; R = rituximab;

[a] The percentages shown in the columns "Patients who discontinued antibody treatment due to AE" and "Patients with all AEs resolved" are based on the number of patients with at least one event.

[b] The data cut-off date for the cross-over arm in Study BO21004 is 9 May 2013.

[c] The figures shown from ongoing studies where the sponsor remains blinded to the treatment received include patients from all treatment arms.

[d] The numbers of patients with all AEs resolved in Study GAO4915g has been calculated by subtracting the number of patients with ongoing or unresolved AEs from the total number of patients with AEs.

[e] Note that the dose of bendamustine in the G-benda arm was 90 mg/m^2 vs 120 mg/m^2 in the benda arm in Study GAO4753g

[f] 'Unknown resolution' was not counted as resolved.

Note: Cut-off dates for data in this table are: 10 October 2017 (BO21004), 02 July 2014 (BO20999 and BO21003), 22 March 2016 (GAO4768g), 24 January 2013 (GAO4779g), 4 November 2015 (BO21000), 31 January 2018 (BO21005), 23 December 2016 (GAO4915g), 30 November 2018 (GAO4753g), 3 December 2020 (MO40597), and 30 July 2021 (BO21223).

Note: Figures in table are to 1.D.P

Seriousness / Outcomes

Thrombocytopenia is asymptomatic and resolves spontaneously in the majority of patients. Acute thrombocytopenia is defined as thrombocytopenia occurring during infusion or within 24 hours post infusion.

All Studies (all indications)

A small number of patients, ≤3%) experienced serious thrombocytopenia across all obinutuzumab trials irrespective of the population and indication (see Table 19). The incidence of serious acute thrombocytopenia (i.e., thrombocytopenia occurring within 24 hours of obinutuzumab infusion) was ⩽1% in all studies (see Table 19). The number of patients who discontinued treatment due to thrombocytopenia was also very low (see Table 19 and Table 20 for details).

In the majority of patients, the outcome of thrombocytopenia was reported as resolved/recovered.

CLL (BO21004-Stage 1a)

In the Stage 1a analysis (GClb vs. Clb) of Study BO21004 (by the data cut-off date of 10 October 2017), 2 patients (1%) in the GClb arm and 1 patient (1%) in the Clb arm experienced serious events of thrombocytopenia. One event of serious acute thrombocytopenia was reported in the GClb arm.

CLL (BO21004-Stage 2)

By the data cut-off date (10 October 2017) for the Stage 2 analysis of Study BO21004 (GClb vs. RClb), 4/336 patients (1%) in the GClb arm and 1 patient (<1%) in the RClb arm experienced serious events of thrombocytopenia. One serious acute thrombocytopenia event was reported in the GClb arm.

iNHL (GAO4753g)

In study GAO4753g, 47/198 patients (23.7%) in the benda arm versus 29/194 (14.9%) in the G-benda arm experienced at least one thrombocytopenia event. Five patients (2.5%) in the G-benda arm experienced serious thrombocytopenia compared with none in the benda arm. Fourteen patients withdrew from study treatment in the benda arm (14/50; 28.0%) compared with 7 patients in the G-benda arm (7/30; 23.3%). Thrombocytopenia resolved in the majority of patients in both arms (24/29 [82.7%] in the G-benda arm and 39/47 [83%] in the benda arm).

FL (BO21223)

Thrombocytopenia was reported as serious in one patient (0.2%) in the R-chemo arm and in four patients (0.7%) in the G-chemo arm. Of the patients who had a thrombocytopenia event, one patient (1/49 patients; [2.0%]) in the R-chemo arm and two patients (2/75 patients [2.7%]) in the G-chemo arm discontinued study treatment due to thrombocytopenia. A higher proportion of patients with a thrombocytopenia event in the G-chemo arm received treatment for this AE (21/75 patients; [28.0%]) than in the R-chemo arm (8/49 patients [16.3%]).

The majority of acute thrombocytopenia events (8/10 AEs) were Grade 3-4, with two of the seven patients experiencing serious acute thrombocytopenia. No patients discontinued study treatment due to acute thrombocytopenia. Four of the seven patients with acute thrombocytopenia received treatment.

MZL (BO21223)

Thrombocytopenia was reported as serious in 2 patients (2.2%) in the R-chemo arm and 1 patient (1%) in the G-chemo arm). Two patients in the R-chemo arm (2/7; 28.6%) and 6 patients in the G-chemo arm (6/19; 31.6%) received treatment for the AE. No patients had AEs that required discontinuation. One patient in the G-chemo arm and 3 patients in the R-chemo arm had AEs that were unresolved at the time of data cut-off.

One patient each in the R-chemo arm and G-chemo arm (1.1% vs 1.0%) experienced acute thrombocytopenia. Acute thrombocytopenia was reported as serious in R-chemo arm (1/93; 1.1%). No patients had AEs that required discontinuation. The patients received treatment for the event.

FL (BO21000) First Line population

No SAEs of thrombocytopenia were reported in this study and nor led to discontinuation. One patient in each group had an AE leading to dose modification. Two patients receiving G-benda had thrombocytopenia AEs that were unresolved.

DLBCL (BO21005)

Grade 3–5 thrombocytopenia events were more frequently reported in the G-CHOP arm (40 of 702 patients [5.7%]) compared with the R-CHOP arm (12 of 701 patients [1.7%]). No patient experienced a Grade 5 (fatal) event of thrombocytopenia during the study.

SAEs of thrombocytopenia were reported for 2 patients (0.3%) in the R-CHOP arm and 12 patients (1.7%) in the G-CHOP arm.

Among patients with a thrombocytopenia event, one patient in the R-CHOP arm and 6 patients in the G-CHOP arm discontinued study treatment because of thrombocytopenia.

The percentage of patients receiving treatment for thrombocytopenia was higher in the R-CHOP arm (15 of 18 patients [83.3%]) compared with G-CHOP arm (45 of 70 patients [64.3%]). Thrombocytopenia AEs were considered ongoing or unresolved at the end of study in 2 and 9 patients in the R-CHOP and G-CHOP treatment arms, respectively.

The majority of the acute thrombocytopenia events (6 of 7 AEs) were Grade 3–4, and 5 events (all in the G-CHOP arm) were SAEs. No patient experienced a Grade 5 (fatal) event of acute thrombocytopenia. Six patients received treatment for acute thrombocytopenia, 1 in the R-CHOP arm and 5 in the G-CHOP arm. One patient (16.7%) in the G-CHOP arm discontinued study treatment because of acute thrombocytopenia.

DLBCL (GAO4915g)

There were no SAEs. No patients experienced acute thrombocytopenia, all thrombytopenic events resolved.

Short-duration infusion - FL (MO40597)

One patient had thrombocytopenia reported as an SAE. The patient’s platelet count reached low level of 22 × 10^9/L. The event was considered by the investigator to be caused by a flare of systemic lupus erythematosus. The patient did not experience bleeding events.

Table 20 Frequency of Acute Thrombocytopenia in Obinutuzumab Studies

Study	Total no. of patients N	Patients with at least 1 event N (%)	Patients with severe (Grade 3 or 4) events N (%)	Patients with fatal (Grade 5) events N (%)	Patients with serious events N (%)	Patients who discontinued antibody treatment due to AE[a] N (%)	Patients with all AEs resolved N (%)[a, d]
BO21004 Chemotherapy CLL							
Obinutuzumab arm (Stage 1a)	241	12 (5.0)	12 (5.0)	0	1 (0.4)	0	12 (100.0)
Chlorambucil arm (Stage 1a)	116	0	0	0	0	0	0
Cross-over GClb arm[b]	30	1 (3.3)	1 (3.3)	0	0	0	1 (100.0)
Run-in phase	6	0	0	0	0	0	0
Obinutuzumab arm (Stage 2)	336	14 (4.2)	13 (3.9)	0	1 (0.4)	0	14 (100.0)
Rituximab arm (Stage 2)	321	3 (0.9)	2 (0.6)	0	0	0	3 (100.0)
Pooled monotherapy studies BO20999 + BO21003							
CLL	38	4 (10.5)	4 (10.5)	0	0	0	4 (100.0)
NHL	205	5 (2.4)	4 (2.0)	0	1 (0.5)	0	5 (100.0)
GAO4768g Monotherapy CLL 1000/2000 mg	78	5 (6.4)	3 (3.8)	0	0	0	5 (100.0)
GAO4779g Chemotherapy CLL (FC/Benda)	41	0	0	0	0	0	0

Study	Total no. of patients N	Patients with at least 1 event N (%)	Patients with severe (Grade 3 or 4) events N (%)	Patients with fatal (Grade 5) events N (%)	Patients with serious events N (%)	Patients who discontinued antibody treatment due to AE[a] N (%)	Patients with all AEs resolved N (%)[a, d]
BO21003 Phase II monotherapy NHL							
Obinutuzumab arm	87	0	0	0	0	0	0
Rituximab arm	86	0	0	0	0	0	0
BO21223 Chemotherapy FL Patient population data							
R-Chemo	597	0	0	0	0	0	0
G-Chemo	595	7 (1.2)	5 (0.8)	0	2 (0.3)	0	7 (100.0)
BO21223 Chemotherapy MZL patient population							
R-Chemo	93	1 (1.1)	1 (1.1)	0	1 (1.1)	0	1 (100.0)
G-Chemo	101	1 (1.0)	1 (1.0)	0	0	0	1 (100.0)
BO21005 Chemotherapy aNHL (CHOP) all population data[c]							
G-CHOP	702	6 (0.9)	5 (0.7)	0	5 (0.7)	1 (16.7)	5 (83.3)
R-CHOP	701	1 (0.1)	1 (0.1)	0	0	0	1 (100)
BO21000							
First-line Patient Population							

Study	Total no. of patients N	Patients with at least 1 event N (%)	Patients with severe (Grade 3 or 4) events N (%)	Patients with fatal (Grade 5) events N (%)	Patients with serious events N (%)	Patients who discontinued antibody treatment due to AE[a] N (%)	Patients with all AEs resolved N (%)[a, d]
G+ Benda Arm	41	2 (4.9)	1 (2.4)	0	0	0	2 (100.0)
G+CHOP Arm	40	1 (2.5)	1 (2.5)	0	0	0	1 (100.0)
GAO4915g Chemotherapy NHL CHOP all population data	100	0	0	0	0	0	0
GAO4753g Overall Acute Thrombocytopenia AEs							
G-benda arm[e]	204	1 (0.5)	1 (0.5)	0	1 (0.5)	0	1 (100.0)
Benda arm	203	0	0	0	0	0	0
Short-duration infusion - FL (MO40597)	113	1 (0.9)	1 (0.9)	0	1 (0.9)	0	1 (100.0)

Table 20 Frequency of Acute Thrombocytopenia in Obinutuzumab Studies (cont.)

AE = adverse event; aNHL = aggressive NHL; Benda = bendamustine; Clb = chlorambucil; CLL = chronic lymphocytic leukemia; CHOP = cyclophosphamide, doxorubicin, vincristine and prednisone; FC = fludarabine and cyclophosphamide; FL=follicular lymphoma; GClb = obinutuzumab and chlorambucil; iNHL = indolent NHL; NHL = non-Hodgkin's lymphoma

[a] The percentages shown in the columns "Patients who discontinued antibody treatment due to AE" and "Patients with all AEs resolved" are based on the number of patients with at least one event.

[b] The data cut-off date for the cross-over arm in Study BO21004 is 9 May 2013.

[c]

[c] The figures shown from ongoing studies where the sponsor remains blinded to the treatment received include patients from all treatment arms.

[d] The numbers of patients with all AEs resolved have been calculated by subtracting the number of patients with ongoing or unresolved AEs from the total number of patients with AEs.

[e] The dose of bendamustine in the G-benda arm was 90 mg/m^2 vs 120 mg/m^2 in the benda arm in Study GAO4753g.

Note: Cut-off dates for data in this table are as follows: 10 October 2017 (BO21004), 02 July 2014 (BO20999 and BO21003), 22 March 2016 (GAO4768g), 24 January 2013 (GAO4779g), 04 November 2015 (BO21000), 31 January 2018 (BO21005), 20 December 2013 (GAO4915g), 30 November 2018 (GAO4753g), 03 December 2020 (MO40597), and 30 July 2021 (BO21223).

Note: Figures in table are to 1.D.P

Severity and Nature of Risk

CLL (BO21004- Stage 1a)

In the Stage 1a analysis of Study BO21004 (GClb vs. Clb) (by the data cut-off date of 10 October 2017), a higher number of patients experienced Grade 3 or 4 thrombocytopenia in the obinutuzumab arm compared to the Clb arm; 41/241 (17%) versus 11/116 (9%). In the obinutuzumab arm, 12/241 patients (5%) experienced thrombocytopenia that occurred within 24 hours of infusion. All acute events were severe (Grade 3 or 4). Despite the severity, all events resolved, and none of the events led to discontinuation of obinutuzumab. Five patients received treatment for the event and in five patients, the obinutuzumab dosage was modified. In the Clb arm, no acute events were reported.

CLL (BO21004 – Stage 2)

In the Stage 2 analysis of Study BO21004 (GClb vs. RClb) (by the data cut-off date of 10 October 2017), more patients developed Grade 3 and 4 thrombocytopenia in the GClb arm than in the RClb arm (11% vs. 3%). This was driven by the events occurring during the first cycle (8% vs. 2%). In the GClb arm, the majority of patients recovered (83%), with fewer discontinuations of study treatment than in the RClb arm, but with more dose modifications. The proportion of patients who received treatment for the event was comparable between the two arms (GClb 24% vs. RClb 23%). Only 14/336 patients (4%) experienced acute thrombocytopenia in the GClb arm. The majority of acute thrombocytopenia events (13/14) were severe (Grade 3 or 4). Fewer patients had acute thrombocytopenia in the RClb arm (1 patient with Grade 2 and 2 patients with Grade 3). The outcome was reported as resolved in all patients, in both of the treatment arms.

CLL (GAO4799g and GAO4768g)

In non-comparative studies in first-line CLL patients, severe thrombocytopenia was experienced by 6 out of 41 patients (14.6%) receiving concomitant treatment with FC/bendamustine in Study GAO4779g, and 11 out of 78 patients (14.1%) receiving obinutuzumab monotherapy in Study GAO4768g. No acute events were reported in Study GAO4779g, whereas 45.5% of the patients who experienced thrombocytopenia in Study GAO4768g (5/11) had events that occurred during the first 24 hours. In one patient the event remained unresolved at the clinical cut-off date.

CLL and NHL (BO20999 and BO21003; pooled studies)

In the pooled monotherapy studies BO20999 and BO21003 in the relapsed/refractory population, the incidence of severe events of thrombocytopenia was higher in the CLL population than in the NHL cohort. In the CLL population, 5 out of 38 patients (13%) developed severe thrombocytopenia; 4 of these events (11%) occurred within 24 hours of infusion. In the NHL population, of the 6 out of 205 patients (3%) who developed severe thrombocytopenia, 4 (2%) had an acute episode.

iNHL (GAO4753g)

In Study GAO4753g, the incidence of Grade 3/5 thrombocytopenia was higher in the benda arm than in the G-benda arm (32/203 [15.8%] vs 22/204 [10.8%]). There were no Grade 5 events of thrombocytopenia in either of the arms. One patient (0.5%) experienced Grade 3 acute thrombocytopenia in the G-benda arm compared with none in the benda arm. In this patient, acute thrombocytopenia was reported as an SAE and required study treatment interruption. The SAE resolved following treatment.

FL (BO21223)

Grade 3-4 events were more frequently reported in the G-chemo arm (36/595 patients [6.1%]) than in the R-chemo arm (16/597 patients [2.7%]). Seven patients (1.2%) in the G-chemo arm and no patients in the R-chemo arm had acute thrombocytopenia. The majority of acute thrombocytopenia events (5/7 AEs) were Grade 3-4, with two of the seven patients experiencing serious acute thrombocytopenia.

MZL (BO21223)

No Grade 1/2/3 or 5 AEs were reported. In the R-chemo arm, AE severity was evenly distributed across Grades 1-4 and no Grade 5 AE was recorded. In the G-chemo arm, the same proportion of patients experienced Grade 1-2 AEs as Grade 3-4 AEs (7/19; 7.0% and 12/19; 11.9%) respectively.

Grade 4 AE of acute thrombocytopenia was reported in 1 patient each in the R-chemo and G-chemo arm. No Grade 5 AEs were observed.

FL (BO21000)

G-Benda: A total of six patients (15%) had at least one thrombocytopenia**.** Two patients had a Grade 3 AE and two patients had Grade 4 AEs.

G-CHOP: One patient (3%) had thrombocytopenia**.** The patient had three Grade 4 AEs and two Grade 3 AEs.

G-Benda: Two patients had a total of four acute thrombocytopenia AEs (3 Grade 2, and 1 Grade 3).

G-CHOP: One patient who received G+CHOP had one Grade 3 acute thrombocytopenia AE.

DLBCL (BO21005)

Grade 3–5 thrombocytopenia events were more frequently reported in the G-CHOP arm (40 of 702 patients [5.7%]) compared with the R-CHOP arm (12 of 701 patients [1.7%]).

The majority of the acute thrombocytopenia events (6 of 7 AEs) were Grade 3–4, and 5 events (all in the G-CHOP arm) were SAEs. No patient experienced a Grade 5 (fatal) event of acute thrombocytopenia.

The percentage of patients with AEs of thrombocytopenia was highest in Cycle 1 (1.0% in the R-CHOP arm and 6.4% in the G-CHOP arm) compared with subsequent cycles. The frequency of thrombocytopenia AEs was higher in the G-CHOP arm compared with the R-CHOP arm in Cycle 1 but the frequency of the thrombocytopenia AEs was similar between treatment arms in subsequent cycles. The numbers of Grade 3–5 AEs, SAEs, and AEs leading to antibody withdrawal followed a similar trend as for all thrombocytopenia AEs.

Short-duration infusion - FL (MO40597)

Eight patients experienced a Grade 3 or 4 AEs of thrombocytopenia. There were no severe or serious events of bleeding reported among these patients. There were no Grade 5 events of thrombocytopenia.

Other Studies

In other studies, the incidence of severe thrombocytopenia was <15% (see Table 19 and Table 20 for details).

Hemorrhagic Events

Severe thrombocytopenia may be associated with spontaneous hemorrhage.

CLL (BO21004 – Stage 2)

Information is presented below based on all hemorrhagic events reported in Stage 2 of Study BO21004 (by the data cut-off date of 10 October 2017), irrespective of whether a patient had experienced an AE of thrombocytopenia. Hemorrhagic events were defined by any preferred term from the following SMQs (all narrow): Hemorrhagic

cerebrovascular conditions, Haemorrhage laboratory terms and hemorrhage excluding laboratory terms

The overall incidence of hemorrhagic events was comparable between the treatment arms (8% RClb vs. 8% GClb) with the majority of events being Grade 1 or 2 in severity. The number of Grade 5 hemorrhagic events was balanced between the treatment arms (4 RClb vs 4 GClb). Of note, the use of concomitant medications such as anticoagulants and platelet aggregation inhibitors, which are possible confounding factors for the risk of bleeding, was balanced between the arms.

Hemorrhagic AEs were reported as serious in a similar proportion of patients in both study arms (2% in each arm). The majority of hemorrhagic AEs resolved (76% RClb and 70% GClb) and few patients discontinued study treatment for this reason (1 RClb vs 3 GClb). Amongst patients with hemorrhagic AEs, 36% and 44% in the RClb and GClb arms, respectively, received treatment for these events.

An evaluation of hemorrhagic events by cycle showed that the incidence of all-grade hemorrhagic events was similar between the study arms in Cycle 1 (2% each) and beyond Cycle 1. However, all fatal (Grade 5) hemorrhagic events (4 cases) in the GClb arm occurred in Cycle 1 in contrast to such events in the RClb arm (4 cases) which occurred later (beyond 1 year after first administration of study drug). Of the eight events, one case (hemorrhagic stroke in the GClb arm) was considered by the investigator as treatment-related.

The clinical course of the four fatal hemorrhagic events in the GClb arm is described below:

Patient PPD: A PPD-year-old man with CLL, received obinutuzumab 1000 mg on Study Days 1, 8, and 15 as well as Clb 32 mg on Study Days 1, and 15. Platelet counts on Study Days 1, 9 and 15 were 147 x 10^9/L, 74 x 10^9/L and 142 x 10^9/L, respectively, prior to each infusion of obinutuzumab. On Study Day 18, the patient was hospitalized for a cerebrovascular accident, which resulted in death. The investigator assessed the cerebrovascular accident as unrelated to obinutuzumab and Clb. A possible confounding factor was concomitant exposure to acenocoumarol prior to, during the course of treatment and until the fatal event.

Patient PPD: A PPD-year-old man with lung involvement with CLL as well as thrombocytopenia related to CLL (treated with numerous transfusions; platelet count on Study Day 1 was 11x10^9/L) received the first dose of obinutuzumab 100 mg (as planned per protocol) and Clb (38 mg) on Study Day 1. He was hospitalized with IRR, fever and chills on the same day of infusion. On Study Day 2, the patient was diagnosed with pulmonary alveolar hemorrhage and obinutuzumab and Clb were permanently discontinued. The patient had a low platelet count and received platelet transfusions on Study Days 2 and 3. Platelet counts did not increase substantially (17×10^9/L on Study

Day 3 and 23×10^9/L on Study Day 4). The patient had progressive shortness of breath, was afebrile and was coughing blood. On Study Day 5, the patient's condition worsened and he developed massive hemoptysis. The investigator assessed the fatal pulmonary alveolar hemorrhage as unrelated to obinutuzumab and chlorambucil. The patient was not exposed to any concomitant medication which could explain the hemorrhagic event during the course of treatment and prior to the hemorrhagic event.

Patient PPD: A PPD-year-old woman with CLL, received obinutuzumab 1000 mg and Clb 22 mg on Study Day 1. On Study Day 16, the patient hit her head and had a traumatic cental nervous system (CNS) injury. She was subsequently hospitalized on Study Day 19 having suffered an epileptic attack with focal seizures without recovery of consciousness. A cranial computed tomography (CT) scan revealed a subdural hematoma in the right temporal region which later resulted in death on Study Day 26. The platelet counts on Study Days 1 and 19 were 185 x 10^9/L and 121 x 10^9/L, respectively. The investigator assessed the subdural hematoma as unrelated to obinutuzumab and chlorambucil. A possible confounding factor was concomitant exposure to aspirin prior to, during the course of treatment and until the fatal event.

Patient PPD: An PPD-year-old man with CLL, received obinutuzumab 1000 mg on Study Days 1 and 8, as well as Clb 32 mg on Study Day 1. On Study Day 1, the platelet count was 93 x10^9/L. On Study Day 8, prior to the second infusion, the platelet count was 73 x10^9/L. On Study Day 10, the patient was hospitalized with hemorrhagic stroke. A cerebral CT scan revealed right temporal CNS hemorrhage with advanced penetration of the ventriculus lateralis. The patient died on Study Day 17 due to hemorrhagic stroke which the Investigator assessed as related to obinutuzumab and chlorambucil. A possible confounding factor was concomitant exposure to certoparin sodium during the course of treatment and until the fatal event.

Due to the small number of patients with fatal hemorrhages, the incomplete laboratory data (platelet count) specifically on the day of the hemorrhagic event and confounding factors (disease itself: low platelets due to CLL prior to treatment start, coexisting medical conditions and concomitant treatments: use of platelet inhibitors, anticoagulants), no clear relationship was found between thrombocytopenia and haemorrhages in the Stage 2 analysis of Study BO21004. Only one patient (PPD) in the GClb arm who had a fatal pulmonary alveolar hemorrhage also had concurrent Grade 4 low platelet counts which was present at baseline, however, there were other plausible explanations for the cause of death.

CLL (GAO4799g and GAO4768g)

No clear relationship between the incidence of hemorrhagic AEs and thrombocytopenia events could be established in CLL patients in studies GAO4768g and GAO4779g. No hemorrhagic AEs were reported in the 16 patients for whom thrombocytopenia was

reported as an AE in Study GAO4768g. Of the 8 patients with AEs of thrombocytopenia in Study GAO4779g, only one patient developed a hemorrhagic AE (Grade 1 petechiae).

iNHL (GAO4753g)

In Study GAO4753g, the overall incidence of hemorrhagic events was similar between the treatment arms (23/203 [11.3%] in the benda arm vs. 24/204 [11.8%] in the G-benda arm), with the majority of events being of Grade 1 or 2 severity in both arms. However, more patients experienced serious AEs in the G-benda arm (6/204; 2.9%) compared with the benda arm (3/203; 1.5%). Grade 3/4 thrombocytopenia was not associated with significant hemorrhagic events in this study.

FL (BO21223)

The incidence of hemorrhagic events was similar in the two treatment arms: 71/597 patients (11.9%) in the R-chemo arm and 72/595 patients (12.1%) in the G-chemo arm. The majority of hemorrhagic events were Grade 1-2, and the incidence of Grade 3-5 AEs was comparable (1.2% in the R-chemo arm vs. 1.0% in the G-chemo arm). Grade 5 hemorrhagic events were reported in four patients - (cerebral hematoma and cerebrovascular accident in the R-chemo arm and gastric hemorrhage and upper gastrointestinal haemorrhage in the G-chemo arm). Serious AEs were reported for 6/597 patients (1.0%) in the R-chemo arm and 7/595 patients (1.2%) in the G-chemo arm.

The most frequently reported (> 0.5% of patients in either treatment arm) hemorrhagic events were (percentages expressed as R-chemo vs. G-chemo): epistaxis (2.3% vs. 1.8%), contusion (2.3% vs. 2.9%), conjunctival hemorrhage (1.5% vs 0.0%), hematuria (1.0% vs. 1.2%), rectal hemorrhage (1.0% vs. 0.7%), hematoma (0.5% vs. 0.5%), heavy menstrual bleeding (0.5% vs. 0.3%), hemorrhoidal haemorrhage (0.2% vs 0.7%), vaginal haemorrhage (0.2% vs. 0.5%), hemetochezia (0% vs 0.5%), and petechiae (0% vs. 0.5%) . The type of hemorrhagic events were comparable (< 1% difference between the two treatment arms), except for conjunctival hemorrhage which was more frequently observed in the R-chemo arm (1.5%) compared with G-chemo arm (no events).

Three patients in the G-chemo arm and 1 patient in the R-chemo arm had treatment interrupted due to hemorrhagic AEs. One patient in the R-chemo arm and no patient in the G-chemo arm was withdrawn from treatment due to a hemorrhagic AE.

MZL (BO21223)

The incidence of hemorrhagic events was similar in the two treatment arms: 13/93 patients (14.0%) in the R-chemo arm and 14/101 patients (13.9%) in the G-chemo arm.

The majority of hemorrhagic events were Grade 1-2. One patient (1.1%) in the R-chemo arm and no patients in the G-chemo arm reported Grade 5 hemorrhagic event.

Serious AEs were reported in 4 (4.3%) and 2 (2.0%) patients in R-chemo and G-chemo arms, respectively.

No patients had treatment withdrawn due to a hemorrhagic AE. Four patients in the R–chemo arm and 4 patients in the G-chemo arm received treatment for the AE (4/13; 30.8% and 4/14; 28.6% in the R-chemo and G-chemo arms respectively). For all but 2 patients in the R-chemo arm and 1 patient in the G-chemo arm, the AE resolved.

FL (BO21000) First Line Population

G-Benda: Four patients (10%) had hemorrhagic events (rectal hemorrhage, vitreous hemorrhage, menorrhagia and hematoma). All but one event were Grade 1 or 2 in severity: one patient had one Grade 3 AE.

G-CHOP: Seven patients (18%) had hemorrhagic events (gingival bleeding [two patients], hematuria [two patients], mouth hemorrhage, disseminated intravascular coagulation and post-procedural hemorrhage). All events were Grade 1 or 2 in severity. Two patients had hemorrhagic SAEs.

G-Benda and G-CHOP: No patients required treatment discontinuation or modification as a result of a hemorrhagic event, and all but one event resolved.

DLBCL (BO21005)

The incidence of hemorrhagic events was higher in the G-CHOP arm (65 of 702 patients [9.3%]) compared with the R-CHOP arm (41 of 701 patients [5.8%]). The majority of hemorrhagic events were Grade 1–2; the incidence of Grade 3–5 hemorrhagic AEs was 1.4% in the R-CHOP arm and 3.3% in the G-CHOP arm. Grade 5 hemorrhagic events were reported for 9 patients (4 in the R-CHOP arm and 5 in the G-CHOP arm).

Serious hemorrhagic events were reported for 11 of 701 patients (1.6%) in the R-CHOP arm and 24 of 702 patients (3.4%) in the G-CHOP arm.

Eight patients had treatment interrupted due to hemorrhagic AEs, 1 in the R-CHOP arm and 7 in the G-CHOP arm, and 9 patients had treatment withdrawn because of hemorrhagic AEs, 5 in the R-CHOP arm and 4 in the G-CHOP arm. The percentage of patients who received treatment for the hemorrhagic event was comparable between treatment arms (39.0% in the R-CHOP arm and 49.2% in the G-CHOP arm).

DLBCL (GAO4915g)

A total of 17 patients (17%) experienced 20 hemorrhagic events, 17 were Grade 1- 2 events and 3 were Grade 3-4 events. There were no fatal events. Five patients had 5 SAEs. Three patients had treatment received due to adverse events. There was one Grade 3-4 hemorrhagic event during Cycle 1 of intra-abdominal hemorrhage with no corresponding thrombocytopenia reported, and two Grade 3-4 hemorrhagic events after

Cycle 1 (occurring in Cycle 4 and Cycle 5). Hemorrhagic events occurred most commonly in Cycle 1 (8 adverse events).

Short-duration infusion - FL (MO40597)

One patient experienced an SAE of lower gastrointestinal haemorrhage during induction. The event was attributed by the investigator to rivaroxoban (an anticoagulant). The event resolved.

All studies (All indications)

Across all studies, the majority of patients with thrombocytopenia who experienced haemorrhagic events had other risk factors for hemorrhages, such as concomitant medication with e.g., anticoagulants or platelet aggregation inhibitors or relevant medical history e.g., hypertension, hemorrhoids etc. In many patients thrombocytopenia did not coincide with the hemorrhagic events.

Based on the available data and given the confounding factors available in the majority of patients, a clear correlation between the incidence of thrombocytopenia and hemorrhagic adverse events in patients treated with obinutuzumab could not be established.

Impact on quality of life

Additional monitoring and hospitalization in symptomatic cases can potentially affect the patient’s quality of life. In case of a hemorrhagic event, the impact may be very important, including the risk of fatal bleeding.

Risk factors and risk groups

No specific risk factors have been identified by Roche for non-acute thrombocytopenia (i.e. thrombocytopenia occurring more than 24 hours after obinutuzumab infusion). However, possible risk factors for acute thrombocytopenia (based on the published rituximab literature), may be high tumor burden, bone marrow involvement, splenomegaly and histological subtypes of MCL and hairy cell leukemia. In general, patients with CLL appear to be more at risk of thrombocytopenia than NHL patients (see Frequency, above).

Preventability

Thrombocytopenia cannot be prevented. Patients who experience thrombocytopenia should be closely monitored with regular laboratory tests until resolution in order to prevent complications.

Transfusion of blood products according to institutional practice is at the discretion of the treating physician.

Impact on the benefit-risk balance of the product

Thrombocytopenia was asymptomatic and resolved spontaneously in the majority of obinutuzumab-treated patients. The impact of thrombocytopenia on the benefit-risk balance of obinutuzumab is considered low. Adequate risk minimization measures are implemented.

Public health impact

The public health impact of this risk is likely to be limited in view of the population treated and the limitations placed upon administration of obinutuzumab by virtue of the warnings and precautions in the product label.

4. Worsening of Pre-existing Cardiac Conditions

MedDRA terms:

All preferred terms in the MedDRA system organ class “Cardiac disorders”.

Potential mechanisms:

No direct cardiac toxicity is expected as the expression of CD20 receptors has not been identified in cardiac tissue. In nonclinical studies, no cardiac toxicity was observed in monkeys. However, fluid overload or infection may trigger cardiac complications such as ischemic events or decompensation of chronic heart failure. IRRs may contribute to the high incidence of cardiac events.

Evidence source(s) and strength of evidence:

Clinical trial data are from studies BO20999, BO21000, BO21003, BO21004, BO21005, BO21223, GAO4753g, GAO4768g, GAO4779g, and GAO4915g.

Characterization of the risk:

Background incidence/ prevalence:

The results of a systematic review by Roche of published observational data for cardiac events in CLL and NHL patients are shown in Table 21. Only studies with relevant estimates in NHL patients were identified. The table below summarizes identified incidence estimates.

Table 21 Summary of Incidence of Cardiac Events in NHL Patients, as Reported in Identified Epidemiological Studies

Treatment	Adverse event	Cancer	Median Patient age	Incidence proportion, new events / total population. Range across studies, (median if more than one study), [95% confidence interval]	Incidence rate, new events/100 person-years. Range across studies with median if more than one study, otherwise study estimate with 95% confidence interval
Rituximab-containing regimen	Heart failure	DLBCL	70	4.8% [95% CI: 0-13.9%]	4.4 [95% CI: 0-13.0]
Other	Heart failure	NHL	70	3.7%-13.4% (median: 7.9%)	1.60 [95% CI: 1.21-2.00]
	Heart failure	DLBCL	54.5	0% (one study with 100 patients)	0 (person-years of exposure was 269.2)
	Stroke	NHL	49	2.3% [95% CI: 1.0-3.7%]	0.28 [95% CI: 0.11-0.44]

CI = Confidence interval ; DLBCL = diffuse large B-cell lymphoma; NHL = Non-Hodgkin Lymphoma.

References: Cartron et al. 2001; Aviles et al. 2004; Kuittinen et al. 2006; Moser et al. 2006b; Rigacci et al. 2007; Hershman et al. 2008; Armenian et al. 2011; Meguro et al. 2012.

Frequency with 95% CI:

CLL (BO21004- Stage 1a)

In Stage 1a of Study BO21004 (by the data cut-off date of 10 October 2017), the incidence of cardiac events was higher in the GClb arm (38/241 patients [16%]) than in the Clb arm (7/116 patients [6%]).

CLL (BO21004- Stage 2)

By the data cut-off date (10 October 2017) of the Stage 2 analysis of Study BO21004 (GClb vs. RClb), the incidence of cardiac events was higher in the GClb arm (50/336 patients [15%]) than in the RClb arm (32/321 patients [10%]).

FL (BO21223)

The incidence of cardiac AEs was slightly lower in the R-chemo arm (63/597 patients [10.6%] compared with the G-chemo arm (86/595 patients [14.5%]). When IRRs cardiac events (AEs occurring during infusion or during first 24 hours from end if infusion) were excluded, the incidence in R-chemo was 9.0% and in G-chemo was 10.9%.

MZL (BO21223)

A lower incidence of cardiac AEs was reported in the R-chemo arm (11/93; 11.8%) compared with the G-chemo arm (25/101; 24.8%).

FL (BO21000) First Line population

The cardiac adverse event of particular interest (AEPI) analysis includes not only AEs reported in the cardiac disorders system organ class (SOC), but also potential cardiac events reported only under the signs and symptoms of an IRR. There were 3 patients (7%) receiving G+benda and eight patients (20%) receiving G+CHOP who had such cardiac events. The incidence of cardiac AEs reported from studies with obinutuzumab ranges between 0% and 20 %. Further details are shown in Table 22.

DLBCL (BO21005)

The incidence of cardiac AEs was higher in the G-CHOP arm (77 of 702 patients [11.0%]) compared with the R-CHOP arm (56 of 701 patients [8.0%]).

DLBCL (GAO4915g)

A total of 16 patients (16%) experienced 22 cardiac events; one patient had a fatal event (cardiovascular disorder unknown diagnosis) and 4 patients had serious adverse events.

Short-duration infusion - FL (MO40597)

Cardiac events were reported in 6/113 patients (5.3%), of whom 5 patients had pre-existing cardiac conditions. The cardiac events reported were angina pectoris, arrhythmia, atrial fibrillation, cardiac arrest, cardiac failure, and cardiorenal syndrome. Four patients (3.5%) experienced Grade ≥3 cardiac events. Three patients (2.7%) experienced serious cardiac events.

Table 22 Frequency of Cardiac Adverse Events in Obinutuzumab Studies

Study		Total No. of patients	Patients with at least 1 event N (%)	Patients with serious events
BO21004 Chemotherapy CLL	Obinutuzumab arm (Stage 1a)	241	38 (15.8)	18 (7.5)
	Chlorambucil arm (Stage 1a)	116	7 (6.0)	4 (3.4)
	Cross-over GClb arm[a]	30	0	0
	Run-in Phase	6	0	0
	Obinutuzumab arm (Stage 2)	336	50 (14.9)	20 (6.0)
	Rituximab arm (Stage 2)	321	32 (10.0)	14 (4.4)
Pooled monotherapy studies BO20999 + BO21003	CLL	38	6 (15.8)	1 (2.6)
	NHL	205	37 (18.0)	11 (5.4)
GAO4768g Monotherapy CLL 1000/2000 mg		78	8 (10.3)	3 (3.8)
GAO4779g Chemotherapy CLL (FC/Benda)		41	2 (4.9)	1 (2.4)
BO21003 Phase II monotherapy NHL	Obinutuzumab arm	87	9 (10.3)	2 (2.3)
	Rituximab arm	86	1 (1.2)	1 (1.1)
BO21000 Chemotherapy FL CHOP/Benda First-line patient population **G+Benda Arm**		41	3 (7.3)	0
G+CHOP Arm		40	8 (20.0)	1 (2.5)
BO21223 Chemotherapy FL patient population **R-Chemo**		597	63 (10.6)	12 (2.0)
G-Chemo		595	86 (14.5)	27 (4.5)
BO21223 Chemotherapy MZL patient population **R-Chemo**		93	11 (11.8)	2 (2.2)
G-Chemo		101	25 (24.8)	14 (13.9)

Study	Total No. of patients	Patients with at least 1 event N (%)	Patients with serious events
BO21005 Chemotherapy aNHL (CHOP) all population data [b]			
G-CHOP	702	77 (11.0)	31 (4.4)
R-CHOP	701	56 (8.0)	23 (3.3)
GAO4915g Chemotherapy NHL CHOP all population data	100	16 (16.0)	4 (4.0)
GAO4753g Overall cardiac events			
G-benda arm	204	25 (12.3)	7 (3.4)
Benda arm	203	13 (6.4)	3 (1.5)
Short-duration infusion - FL (MO40597)	113	6 (5.3)	3 (2.7)

aNHL=aggressive NHL; Benda=bendamustine; CHOP=cyclophosphamide, doxorubicin, vincristine and prednisone; CLL=chronic lymphocytic leukemia; FC=fludarabine and cyclophosphamide, GClb=obinutuzumab and chlorambucil; iNHL=indolent NHL, MZL=marginal zone lymphoma, NHL=non-Hodgkin's lymphoma; G=obinutuzumab; R=rituximab.

[a] The data cut-off date for the cross-over arm in Study BO21004 is 9 May 2013.

[b] The figures shown from ongoing studies where the sponsor remains blinded to the treatment received include patients from all treatment arms.

Note: Cut-off dates for data in this table are as follows: 10 October 2017 (BO21004), 02 July 2014 (BO20999 and BO21003), 22 March 2016 (GAO4768g), 24 January 2013 (GAO4779g), 04 November 2015 (BO21000), 31 January 2018 (BO21005), 23 December 2016 (GAO4915g), 30 November 2018 (GAO4753g) 3 December 2020 (MO40597), and 30 July 2021 (BO21223).

Note: Figures in table are to 1.D.P

Seriousness / Outcomes

CLL (BO21004 - Stage 1a)

In Stage 1a of Study BO21004 (by the data cut-off date of 10 October 2017), a higher incidence of serious cardiac events was found in patients treated with obinutuzumab and Clb (18/241 patients; 7%) compared with those treated with Clb alone (4/116 patients; 3%). This difference in incidence was partly driven by symptoms of IRRs. One of the 18 patients who experienced a serious cardiac event in the GClb arm was actually randomized to Clb treatment and inadvertently received one dose of obinutuzumab (which was a PPD-year old male patient experienced atrial thrombosis 1 year after study start. He received anti-vitamin K for the event. The outcome was unresolved). The events reported in the other 17 patients in the GClb arm included tachycardia (6), cardiac failure and cardiac failure congestive (5), MI (3), atrial fibrillation (2), acute coronary syndrome (1), atrial thrombosis (1), cyanosis (1), and nodal rhythm (1).

Two of the events of MI had a fatal outcome. A PPD-year-old male patient was found dead in his bed more than 4 months after receiving the last dose of obinutuzumab; an autopsy concluded that the patient had had an MI. This was reported as unrelated to obinutuzumab use. The second fatal MI occurred in a PPD-year-old male patient, 995 days after initiating study treatment. He had arterial hypertension and was concomitantly treated with amlodipine, metoprolol succinate, allopurinol, and hydrochlorothiazide. Of the remaining 16 serious events in obinutuzumab-treated patients, only two were not resolved (one cardiac failure event and one atrial thrombosis event), both experienced by same patient (a PPD-year-old male, with a relevant cardiovascular medical history of cardiac failure, carotid artery stenosis, hypertension, and atrial fibrillation). These events occurred at day 351 (atrial thrombosis) and at day 519 (cardiac failure) and were not considered related to the study treatment.

Seven of the events in the obinutuzumab-treated patients occurred on Day 1; these events were considered related to study treatment, which was subsequently discontinued. Among these events, a clinical pattern was observed: 6 out of 7 events were tachycardia events. The remaining nine events occurred in patients over 70 years old with underlying cardiac conditions that predisposed them to such cardiac events (ischemic conditions, atrial fibrillation, and cardiac failure). No pattern of latency was observed (the event onset ranged from Day 140 to Day 516).

In the Clb arm of Study BO21004, 7 patients experienced eight events: cardiac failure (2), MI (2), angina pectoris (1), cardiac failure chronic (1), coronary artery disease (1), and tachyarrhythmia (1).

CLL (BO21004- Stage 2)

In the Stage 2 data analysis (GClb vs. RClb) (by the data cut-off date of 10 October 2017), a comparable incidence of serious cardiac events was observed in the GClb arm (6%) and the RClb arm (4%). However, there were more deaths from cardiac events in the RClb arm (6 patients [2%]) than in the GClb arm (2 patients [1%]).

CLL (GAO4768g and GAO4779g)

In Study GAO4768g, 3.8% of patients developed serious cardiac AEs. They were MI (in the 1000 mg arm), and acute coronary syndrome and sinus bradycardia (in the 2000 mg arm). One of the three events (MI) had a fatal outcome. This event, which occurred in a PPD-year-old male patient, with a medical history of coronary artery disease, myocardial infarction, hypertension, hyperlipidemia and obstructive sleep apnea, developed 88 days after initiating the study therapy. The remaining two events resolved. Acute coronary syndrome occurred on Day 1, during the infusion (the patient's concurrent conditions were coronary artery disease, hypertension, and hyperlipemia). The event of sinus bradycardia occurred during the first 24 hours after the first infusion and resolved with appropriate treatment.

In Study GAO4779g, one patient (2.4%) developed a serious cardiac AE of tachycardia. The event, which was reported in bendamustine arm, occurred on Day 1 and was considered an IRR. It resolved with appropriate treatment.

iNHL (GAO4753g)

In Study GAO4753g, the incidence of all grade cardiac AEs during the study (including the induction, maintenance, and follow-up phases) was higher in the G-benda arm (all grade: 25/204 [12.3%]; Grade 3-5: 10/204 [4.9%]) compared to the benda arm (all grade: 13/203 [6.4%]; Grade 3-5: 4/203 [2.0%]). The higher incidence of cardiac events in the G-benda arm was due to a higher incidence of different cardiac events in the G-benda arm: cardiac failure (0% vs. 2.0%), sinus bradycardia (0% vs. 1.5%), atrial fibrillation (1.5% vs. 2.5%) and tachycardia (1.0% vs. 2.0%). The majority of cardiac events were Grade 1 or 2 in severity (benda arm: 11 events vs. G-benda arm: 19 events). One fatal event of myocardial infarction occurred in an PPD-year-old male in the G-benda arm during the follow-up (post monotherapy). Some of the patients had cardiac events that were associated with IRRs. Cardiac events occurred during or within 24 hours of the infusion and therefore considered an IRR were: tachycardia (1 patient in the benda arm and 2 patients in the G-benda arm), palpitations (2 patients in the G-benda arm), sinus bradycardia (2 patients in the G-benda arm) and atrial fibrillation (1 patient in the benda arm).

FL (BO21223)

Serious cardiac AEs were more frequently reported in the G-chemo arm (27/595 patients [4.5%] versus 12/597 patients [2.0%] in the R-chemo arm. Serious cardiac AEs more frequently reported in the G-chemo arm were: atrial fibrillation (0.2% in the R-chemo arm vs 0.7% in the G-chemo arm), sinus bradycardia (0.0% in the R-chemo arm vs 0.8% in the G-chemo arm), and acute myocardial infarction (0.0% vs 0.7%; three of the four patients had previous or concurrent coronary disease, and were > 65 years of age).

Of the patients who experienced all grade cardiac events, one patient (1.6%) in the R–chemo arm and two patients (2.3%) in the G-chemo arm had any treatment withdrawn. The patient in the R-chemo arm had treatment withdrawn due to cardiac failure and cardiogenic shock. In the G-chemo arm, one patient had treatment withdrawn due to tachycardia and one patient had treatment withdrawn due to ventricular dysfunction.

For most patients with cardiac events (50/63 patients [79.4%] in the R-chemo arm and 71/86 patients [82.6%] in the G-chemo arm), the event had resolved by the data cut-off date.

MZL (BO21223)

A greater proportion of patients in the G-chemo arm experienced serious cardiac AEs than in the R-chemo arm (14/101; 13.9% and 2/93; 2.2% respectively). No patients in either treatment group had treatment withdrawn due to a cardiac AE. Most patients received treatment for the AE (81.8% and 64.0% in the R-chemo and G-chemo arms respectively). Of the 25 patients in the G-chemo arm, 6 patients had an unresolved AE and of the 11 patients in the R-chemo arm, 2 patients had an unresolved AE.

FL (BO21000) First Line population

G-Benda arm: No patient had a cardiac SAE. Of the 3 patients who had cardiac AEs, none discontinued treatment as a result of the AE. One had cardiac AEs that led to dose modification. All 3 AEs resolved.

G-CHOP arm: One patient had two cardiac SAEs. Of the 8 patients who had cardiac AEs, none discontinued treatment as a result of the AE. Four patients had AEs that led to dose modification. A total of seven AEs resolved.

NHL (BO20999)

One patient experienced fatal AE (cardio-respiratory arrest).

DLBCL (BO21005)

Serious cardiac AEs were reported at a similar frequency in the G-CHOP arm (31 of 702 patients [4.4%]) and R-CHOP arm (23 of 701 patients [3.3%]).

The majority of serious cardiac AE preferred terms were observed with comparable frequency between treatment arms. Serious cardiac AEs occurring in >1 patient in either treatment arm and that were more frequently reported in the G-CHOP arm were: atrial fibrillation (0.6% in the R-CHOP arm vs. 1.3% in the G-CHOP arm), cardiac failure (0.4% vs. 1.0%), myocardial infarction (0.3% vs. 0.4%), and cardiac failure congestive (0.1% vs. 0.4%).

Short-duration infusion - FL (MO40597)

Three patients experienced cardiac SAEs. The events were arrhythmia, atrial fibrillation, cardiac arrest, and cardiorenal syndrome. The outcome for the events of atrial fibrillation was reported as recovered, the event of arrhythmia was reported as not recovered, and the event of cardiorenal syndrome as resolved. One patient had a fatal AE of cardiac arrest during the safety follow-up phase. The AE was considered by the investigator to be not related to study treatment.

Severity and Nature of Risk

CLL (BO21004- Stage 1a)

In Stage 1a of Study BO21004 (GClb vs. Clb) (by the data cut-off date of 10 October 2017), 11 patients (5%) in the GClb arm and 5 patients (4%) in the Clb arm developed severe (Grade 3 or 4) cardiac events.

CLL (BO21004- Stage 2)

By the data cut-off date (10 October 2017) of the Stage 2 analysis of Study BO21004 (GClb vs. RClb), the majority of cardiac events were of Grade 1 or 2. A total of 13 patients (3%) in the GClb arm and 8 patients (2%) in the Clb arm were reported with Grade 3 or 4 cardiac events.

FL (BO21223)

The majority of cardiac events (including IRRs) overall were Grade 1 or 2, with a higher incidence in the G-chemo arm [(61/83 events [73.5%] in the R-chemo arm versus 108/135 events [80.0%] in the G-chemo arm]. The number of patients with Grade 3–5 AEs was slightly higher in the G-chemo arm (17/597 patients [2.8%] in the R-chemo arm vs. 25/595 patients [4.2%] in the G-chemo arm), due to mainly Grade 3 cardiac AEs (11 patients in the R-chemo arm vs. 18 patients in the G-chemo arm). Incidence of Grade 3–5 cardiac events (R-chemo 1.9% and 1.8% in G-chemo) and cardiac SAEs (R-chemo 1.1% and 2.6% in G-chemo) was low and balanced between arms in patients without pre-existing cardiac conditions.

There were four fatal cardiac AEs in total, two in each arm (cardiac arrest and myocardial infarction in the R-chemo arm, and two cases of cardiogenic shock in the G-chemo arm). In the R-chemo arm, the patient who died from cardiac arrest) was an elderly patient (PPD years old) who was hypertensive; the patient who died from myocardial infarction had hypertension, thrombosis right leg and valvular aortic stenosis at baseline. The fatal cardiac AEs in the G-chemo arm occurred in elderly patients (≥65 years old) with pre-existing cardiac conditions. One patient was PPD years old and had ongoing atrial fibrillation and hypertension at baseline. The second patient was PPD years old and had coronary artery disease, high cholesterol, hypertension and a history of myocardial infarction and triple bypass surgery.

The eight most frequently occurring cardiac events were as follows (R-chemo vs G-chemo): palpitations (18/597 patients [3.0%] vs. 16/595 patients [2.7%]); tachycardia 8/597 patients [1.3%] vs.19/595 patients [3.2%]); atrial fibrillation (9/597 patients [1.5%] vs. 11/595 patients [1.8%]); sinus tachycardia (3/597 patients [0.5%] vs.7/595 patients [1.2%]); angina pectoris (4/597 patients [0.7%] vs. 4/595 patients [0.7%]); coronary

artery disease (4/597 [0.7%] vs. 3/595 [0.5%]); Sinus bradycardia [0/597 [0%] vs. 7/595 [1.2%]; and cardiac failure (4/597 [0.7%] vs. 2/595 [0.3%]).

MZL (BO21223)

The majority of cardiac AEs were Grade 2 in the R-chemo arm and Grade 3 in the G-chemo arm; only one Grade 5 AE cardiac event (cardiac failure) was reported and this was in the G-chemo arm.

FL (BO21000) First Line population

All cardiac AEs were Grade 1 or 2 in both treatment groups, with the exception of one Grade 4 AE of cardiomyopathy which occurred in the G-CHOP arm.

DLBCL (BO21005)

Two patients (0.3%) in the R-CHOP arm and 14 patients (2.0%) in the G-CHOP arm had cardiac events that occurred during or within 24 hours of the end of an infusion and were therefore considered to be infusion-related events. One patient in the G-CHOP arm experienced a Grade 5 cardiac infusion-related event (myocardial infarction).

A total of 15 patients (2.1%) in the R-CHOP arm and 19 patients (2.7%) in the G-CHOP arm experienced cardiac events during follow-up.

Short-duration infusion - FL (MO40597)

Three patients experienced cardiac SAEs. The events consisted of arrhythmia, atrial fibrillation, cardiac arrest, and cardiorenal syndrome.

Other Studies (All indications)

Cardiac AEs that were experienced by patients exposed to obinutuzumab ranged from palpitations to myocardial infarction and cardiac failure with fatal outcome.

No specific effect of the drug on the heart has been identified.

Impact on quality of life

The degree to which the quality of life of individual patients will be affected will depend on the nature and the severity of the cardiac event. Some events might be life-threatening or even fatal. In most cases, patients will be hospitalized.

Risk factors and risk groups

The incidence of CLL and NHL rises markedly with age. Similarly, cardiac events such as heart failure are primarily diseases of aging, with 75% of existing and new cases

occurring in individuals over 65 years of age. Concomitant chemotherapy (for example bendamustine and cyclophosphamide) and radiation are also associated with cardiac effects.

Preventability

Patients with a history of cardiac disease and with comorbidities should be monitored closely. In particular, the amount and rate of administration of fluid administered to prevent TLS must take into consideration any potential underlying cardiac condition such as cardiac failure.

Impact on the benefit-risk balance of the product

The impact of worsening of pre-existing cardiac condition on the benefit-risk balance of obinutuzumab is considered low with the proposed risk mitigation measure.

No new aspects of the important identified risk of worsening of pre-existing cardiac condition became available to the MAH in any indications to date. The benefit-risk profile of obinutuzumab in the approved indications remains unchanged and favorable.

Public health impact

None expected.

Information on Important Potential Risks

1. Second Malignancies

MedDRA terms: All preferred terms in the MedDRA system organ class “Neoplasms, benign, malignant and unspecified (including cysts and polyps)”.

Potential mechanisms:

Cancer patients undergoing radiotherapy and/or cytotoxic treatment with potentially mutagenic or immunosuppressive substances are at increased risk of developing second malignancies. Obinutuzumab, by depleting antigen-presenting B cells, may weaken the capacity of the immune system to mount an anti-tumor immune response.

The increased incidence of second malignancies in patients with CLL and NHL may be attributable to multiple factors, including immune dysfunction associated with the underlying disease (especially in patients with CLL,) carcinogenic side effects of the various chemotherapeutic agents and radiotherapy, and the increased and close medical surveillance that patients with CLL and NHL receive from trained oncologists (Faguet 1979; Hisada et al. 2001).

Evidence source(s) and strength of evidence:

Clinical trial data are from studies BO20999, BO21000, BO21003, BO21004, BO21005, BO21223, GAO4753g, GAO4768g, GAO4779g, and GAO4915g.

Characterization of the risk:

Background incidence/ prevalence:

Epidemiology data suggest that patients with CLL are at a higher risk of experiencing a second malignancy compared with the general population and this appears to be independent of exposure to treatment. The incidence rate of second malignancies in untreated FL patients is similar to that in the general population (Beiggi et al. 2013).

Patients with NHL are known to be at risk of developing second malignancies (Donin et al. 2016), including therapy-related second malignancies, such as myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) (Stone et al. 1994; Howe et al. 2003). Non-melanoma skin cancers (basal cell carcinoma and squamous cell carcinoma) were the most frequently reported second malignancies in the BO21223 study (11 patients in the R-chemo arm and 16 patients in the G-chemo arm). The most frequent non-cutaneous second malignancies observed in the BO21223 study (breast, prostate, colorectal and lung cancers) is consistent with the most frequent second primary malignancies reported in the general population of NHL patients in the US (Donin et al. 2016). The same population-based study found that the risk of developing a second primary malignancy was particularly high in NHL patients compared to patients with other tumor types (around three times higher in NHL survivors than survivors of breast or prostate cancer).

The results of a systematic review by Roche of published observational data for second malignancies in CLL and NHL patients are summarized in Table 23. This table summarizes identified incidence estimates. The majority of identified epidemiological studies are cancer registry studies, and many of these studies do not have individual patient level treatment information and the incidence proportion and incidence rate are reported for all CLL or NHL patients independent of treatment. The definitions of second malignancy vary across these studies, which makes comparison of studies difficult. The definitions used in identified epidemiological studies are most often for a second malignancy diagnosed within a given period after NHL diagnosis – typically this period is one month, three months or twelve months. A few studies define second malignancy from time of first CLL or NHL treatment to time of diagnosis of second malignancy.

Table 23 Incidence Proportion and Incidence Rate of Second Malignancies in CLL and NHL Patients, as Reported in Epidemiological Studies

	Incidence rate per person year, range across studies	Incidence proportion, range across studies	Prevalence, range across studies
CLL patients			
Untreated	Not available	12.2% (95CI: 7.6%-16.8%)	Not available
Other treatment	0.02-0.05	8.6%-18.1%	2.8%-6.0%
NHL patients			
Untreated	Not available	Not available	Not available
Other treatment	0.0-0.03	0.7%-18.1%	2.8%-6.9%

CLL = chronic lymphocytic leukemia; NHL= Non-Hodgkin Lymphoma.

References: CLL: Kyasa et al. 2004; Robak et al. 2007; Callea et al. 2006; Schollkopf et al. 2007; Fiegl et al. 2010; Morton et al. 2010; Royle et al. 2011a.

NHL: Brennan et al. 2000; Aviles et al. 2001; Dong et al 2001; Leung et al. 2001; Barista et al. 2002; Brennan et al. 2005; Brown et al. 2005; Nachbaur et al. 2005; Okines et al. 2005; Guadagnolo et al. 2006; Liauw et al. 2006; Mudie et al. 2006; Moser et al. 2006a; Tward et al. 2006; Maule et al. 2007; Bluhm et al. 2008; Hemminiki et al. 2008; Oehler-Janne et al. 2008; Sacchi et al. 2008a; Sacchi et al. 2008b; Cabras et al. 2009; Seshadri et al. 2009; Toda et al. 2009; Morton et al. 2010; Royle et al. 2011b; Meguro et al 2012.

Second malignancies occurring 6 months after the start of therapy will be considered for monitoring this risk in the post-marketing setting; however, it will not always be possible to identify this 6-month time window, and therefore the data will be analyzed on an individual patient level. In the clinical trial setting, second malignancies should be considered an adverse event of special interest (AESI) in all currently ongoing and future oncology clinical studies and should be collected during the whole duration of clinical trials; including upon studies completion, when the event is to be reported via spontaneous reporting systems.

Frequency with 95% CI:

The incidence of adverse events per study is provided in Table 24 and ranges between 0% and 15%.

Table 24 Frequency of Second Malignancies in Obinutuzumab Studies

Study		Total No. of patients	Patients with at least 1 event N (%)
BO21004 Chemotherapy CLL	Obinutuzumab arm (Stage 1a)	241	33 (13.7)
	Chlorambucil arm (Stage 1a)	116	8 (6.9)
	Cross-over GClb arm[a]	30	3 (10.0)
	Run-in Phase	6	0
	Obinutuzumab arm (Stage 2)	336	37 (11.0)
	Rituximab arm (Stage 2)	321	33 (10.3)
Pooled monotherapy studies BO20999 + BO21003	CLL	38	2 (5.3)
	NHL	205	11 (5.4)
GAO4768g Monotherapy CLL 1000/2000 mg		78	0
GAO4779g Chemotherapy CLL (FC/Benda)		41	0
BO21003 Phase II Monotherapy NHL	Obinutuzumab arm	87	7 (6.9)
	Rituximab arm	86	2 (2.3)
BO21000 Chemotherapy FL CHOP/Benda First-line population data G+Benda arm		41	6 (14.6)
G+CHOP arm		40	1 (2.5)
BO21223 Chemotherapy FL patient population R chemo[b] G Chemo[b]		597 595	75 (12.6) 104 (17.5)
R chemo[c]		597	59 (9.9)

Study	Total No. of patients	Patients with at least 1 event N (%)
G Chemo[c]	595	78 (13.1)
BO21223 Chemotherapy MZL patient population **R chemo[b]** **G Chemo[b]**	 93 101	 17 (18.3) 19 (18.8)
R chemo[c] **G Chemo[c]**	93 101	15 (16.1) 17 (16.8)
BO21005 Chemotherapy aNHL (CHOP) all population data [d] **G-CHOP**	 702	 22 (3.1)
R-CHOP	701	26 (3.7)
GAO4915g Chemotherapy NHL CHOP all population data	100	1 (1.0)
GAO4753g Overall Second Malignancies **G-Benda**	 204	 28 (13.7)
Benda	203	15 (7.4)

Study	Total No. of patients	Patients with at least 1 event N (%)
Short-duration infusion - FL (MO40597)	113	3 (2.7)

aNHL =aggressive NHL; Benda = bendamustine; CHOP =cyclophosphamide, doxorubicin, vincristine and prednisone; CLL =chronic lymphocytic leukemia; FC =fludarabine and cyclophosphamide, GClb =obinutuzumab and chlorambucil; iNHL =indolent NHL; G =obinutuzumab; NHL =non–Hodgkin's Lymphoma; R =rituximab; SMQ = Standardized MedDRA Query; SOC = System Organ Class.

[a] The data cut-off date for the cross-over arm in Study BO21004 is 9 May 2013.

[b] SOC defined second malignancies.

[c] SMQ-defined second malignancies.

[d] The figures shown from ongoing studies where the sponsor remains blinded to the treatment received include patients from all treatment arms

Note: Figures in table are to 1.D.P

Note: Second malignancies starting 6 months after first drug intake

Note: Cut-off dates for data in this table are as follows: 10 October 2017 (BO21004), 02 July 2014 (BO20999 and BO21003), 22 March 2016 (GAO4768g), 24 January 2013 (GAO4779g), 04 November 2015 (BO21000), 31 January 2018 (BO21005), 23 December 2016 (GAO4915g), 30 November 2018 (GAO4753g), 03 December 2020 (MO40597), and 30 July 2021 (BO21223).

Seriousness / Outcomes

CLL (BO21004 – Stage 1a)

In Stage 1a of Study BO21004 (by the data cut-off date of 10 October 2017), 33 patients (14%) receiving GClb have been reported with malignancies (39 events) diagnosed more than 6 months after starting study therapy, while 8 patients (7%) on Clb monotherapy have been reported with 8 such events (see Table 24). The most frequently reported secondary malignancies by SMQ were basal cell carcinoma (1 patient Clb and 5 patients GClb) and squamous cell carcinoma of skin (0 patients Clb and 6 patients GClb).

The rates of secondary malignancies per 100 PY were higher in the GClb arm. The rates for secondary malignancy by SOC were 1.77 (95% CI: 0.77, 3.50) in the Clb arm and 4.28 (95% CI: 3.14, 5.69) in the GClb arm. The rates for secondary malignancy by SMQ were 1.77 (95% CI: 0.77, 3.50) in the Clb arm and 4.10 (95% CI: 2.99, 5.48) in the GClb arm.

CLL (BO21004 – Stage 2)

By the data cut-off date (10 October 2017) for the Stage 2 analysis of Study BO21004 (GClb vs. RClb), the proportion of patients who experienced second malignancies 6 months after starting treatment or later was comparable in the GClb and RClb arms (11% vs. 10%). The most frequently reported malignancies by SMQ were squamous cell carcinoma of skin (2% RClb vs. 2% GClb), basal cell carcinoma (1% RClb vs. 2% GClb), and squamous cell carcinoma (2% RClb vs. 1% GClb).

The rates of secondary malignancies per 100 PY were consistent in both treatment arms. The rates for secondary malignancy by SOC were 3.69 (95% CI: 2.73, 4.88) in the RClb arm and 3.53 (95% CI: 2.64, 4.63) in the GClb arm. The rates for secondary malignancy by SMQ were 3.17 (95% CI: 2.28, 4.28) in the RClb arm and 3.33 (95% CI: 2.46, 4.40) in the GClb arm.

CLL and NHL (BO20999 and BO21003; pooled studies)

In the pooled data from CLL patients in studies BO20999 and BO21003, two serious events were reported from Study BO20999. Lung cancer was diagnosed in an PPD-year-old male patient 8 months after he started treatment with the study drug. The patient died 6 months later. The investigator considered the event to be unrelated to obinutuzumab use. Renal cancer was diagnosed in a PPD-year-old male patient 5 months after study start. However, nephrectomy was performed 6 weeks later i.e. more than 6 months after study start (which qualified this report for inclusion as per the definition, see MedDRA terms, above). The event was reported as resolved and related to study medication by the investigator.

In pooled data from NHL patients in studies BO20999 and BO21003, 11 patients reported 14 malignancies. Eight of these adverse events were reported in 7 patients from Study BO21003; these are described below. The remaining five adverse events were reported from Study BO20999 and included chronic myeloid leukemia, renal cell carcinoma, squamous cell carcinoma (all three of which were considered to be serious) and squamous cell carcinoma of the skin (two events in same patient, reported as non-serious). Chronic myeloid leukemia was reported in a PPD-year-old female patient 3 years after study start and it was persisting at the time of the last report. Renal cell carcinoma was reported in a PPD-year-old male patient who had a 13 mm lesion on his left kidney on a CT scan 2 years before study enrollment. A CT scan and biopsy during the study showed renal cell carcinoma. The event was reported to have lasted 67 days (presumably after the biopsy) and to have resolved (however, no surgery has been explicitly reported). Both skin lesions were reported to have resolved.

NHL (BO21003)

In Study BO21003, 7 patients developed malignancies starting more than 6 months after the first study drug intake. Only two of the reported events (myelodysplastic syndrome and neoplasm malignant) was considered serious by the investigator. These events occurred 22 and 36 months after the start of the study drug. The outcome for myelodysplastic syndrome was not reported, neoplasm malignant had fatal outcome. The remaining 5 patients experienced non-serious events of skin lesions (two events), benign laryngeal neoplasm, which was reported as resolved (one event), salivary gland adenoma, which was reported as resolved (one event), and uterine leiomyoma and lipoma (both in the same patient). The latter events were reported to be ongoing as no further assessment or treatment were deemed necessary. In the comparator arm (rituximab), 2 patients experienced non-serious events (skin cancer and basal cell carcinoma).

iNHL (GAO4753g)

In Study GAO4753g, the proportion of patients who experienced second malignancies 6 months after starting treatment or later was higher in the G-benda arm (all grade: 28/204 [13.7%]; Grade 3-5: 16/204 [7.8%]) compared to the benda arm (all grade: 15/203 [7.4%]; Grade 3-5: 12/203 [5.9%]) Second malignancies SOC AEs reported in at least 2 patients in either treatment arm (expressed as benda vs. G-benda) were: basal cell carcinoma (0.5% vs. 2.9%), myelodysplastic syndrome (0.5% vs. 2%), squamous cell carcinoma (1% vs. 1.5%), acute myeloid leukaemia (1% vs. 0.5), malignant melanoma (0.5% vs. 1%), bladder cancer (0 vs. 1.0%), leukaemia (1% vs. 0%) and meningioma (0% vs. 1%)

FL (BO21223)

Using the SOC “Neoplasms, benign, malignant and unspecified (including cysts and polyps)” definition of second malignancies (Note that this definition for second malignancies includes benign conditions such as cysts, skin papillomas, seborrheic keratosis, and anogenital warts) starting at least 6 months after the first study drug intake) (defined by any PT under the SOC “Neoplasms benign, malignant and unspecified [incl cysts and polyps]”), 75/597 patients (12.6%) in the R-chemo arm and 104/595 patients (17.5%) in the G-chemo arm experienced second malignancies.

Second malignancies were also analysed using the SMQ ”Tumors Malignant and Unspecified” (which excludes benign disorders such as cysts, skin papillomas, seborrheic keratosis, and anogenital warts), 59/597 patient (9.9%) in the R-chemo arm and 78/595 patients (13.1%) in the G-chemo arm experienced second malignancies starting at least 6 months after the first study drug intake. Non-melanomatous skin cancers (basal cell carcinoma [BCC] or squamous cell carcinoma [SCC]) were the most frequently reported tumors (17 patients in the R-chemo arm and 23 patients in the G-chemo arm). Hematological malignancies were reported in both the R-chemo and G-chemo arm, but there was no clear pattern in the timing of onset, and no clear association with any particular chemotherapy regimen. Of the 9 malignancies reported (two in the R-chemo arm and seven in the G-chemo arm), one was non-Hodgkin’s lymphoma, one was cutaneous T-cell lymphoma, three were Hodgkin’s lymphoma, three were acute myeloid leukemia (AML), and one was acute lymphocytic leukemia.

Four patients in the G-chemo arm were diagnosed as having myelodysplastic syndrome (categorized by the investigator as NCI CTCAE Grade 4 in severity). These AEs were not captured by the SMQ “tumors malignant and unspecified,” but they are shown per the SOC definition of second malignancies.

The remaining malignancies were solid tumors and occurred with a similar incidence in the two treatment arms (3.6% in the R-chemo vs. 4.0% in the G-chemo arm). No clear pattern was observed in the type of tumor, timing of onset of the AE, chemotherapy regimen in either treatment arm.

Sixteen Grade 5 (fatal) second malignancies were reported, 9 patients (1.5%) in the R-chemo arm and 7 patients (1.2%) in the G-chemo arm. In the R-chemo arm, these AEs were neuroendocrine carcinoma of the skin, gastric cancer, colon cancer, malignant melanoma, non–small cell lung cancer, non-Hodgkin’s lymphoma, acute myeloid leukemia, lung neoplasm malignant, and lung adenocarcinoma. In the G-chemo arm, these AEs were non-small cell lung cancer (in 2 patients), acute lymphocytic leukemia (in 2 patients), hepatic cancer, acute myeloid leukemia, and gastric cancer.

Second malignancies (by SMQ) have also been analyzed after adjustment for differences in observation time. For Grade 1-2 AEs the incidence rate (i.e., rate per 100

patient-years) was 1.4 (95% CI: 0.80, 2.27) in the R-chemo arm vs. 1.5 (95% CI: 0.89, 2.37) in the G-chemo arm; for Grade 3-5 AEs the rate was 1.62 (95% CI: 1.01, 2.45) in the R-chemo arm vs. 1.4 (95% CI: 0.86, 2.17) in the G-chemo arm; for unrelated SAEs the rate was 1.26 (95% CI: 0.77, 1.94) in the R-chemo arm vs. 1.55 (95% CI: 1.01, 2.27) in the G-chemo arm; and for related SAEs the rate was 0.17 (95% CI: 0.06, 0.38) in the R-chemo arm vs. 0.39(95% CI: 0.22, 0.65) in the G-chemo arm.

MZL (BO21223)

Using the SOC Neoplasms, benign, malignant and unspecified (including cysts and polyps), 17/93 patients (18.3%) in the R-chemo arm and 19/101 patients (18.8%) in the G-chemo arm reported second malignancies.

Using the SMQ “Malignant or unspecified tumours”, 15/93 patient (16.1%) in the R–chemo arm and 17/101 patients (16.8%) in the G-chemo arm reported second malignancies.

FL (BO21000) First Line population

Seven patients in total experienced a second malignancy at least 6 months after first study drug intake. Of the six patients in the G-benda group, one had a Grade 3 AE (squamous cell carcinoma of skin), and one had a Grade 4 AE (myelodysplastic syndrome) which was also an SAE. One patient in the G-CHOP group had a Grade 3 AE (squamous cell carcinoma of skin). None of the AEs led to treatment discontinuation or modification. No malignancy occurred in more than one patient in each group.

DLBCL (BO21005)

Using the SOC definition of second malignancies (“Neoplasms benign, malignant and unspecified (incl cysts and polyps)” starting at least 6 months after the first dose of study drug (which includes both benign and malignant tumors), 26 of 701 patients (3.7%) in R-CHOP treatment arm and 22 of 702 patients (3.1%) in G-CHOP treatment arm reported second malignancies.

The majority of second malignancies were Grade 3 in severity (16 of 26 in the R-CHOP arm and 8 of 22 in the G-CHOP arm); 4 patients in the G-CHOP arm and 1 patient in the R-CHOP arm experienced Grade 4 second malignancies. Ten patients (5 in each arm) died from second malignancies.

DLBCL (GAO4915g)

One patient in the trial experienced a second malignancy (hepatocellular carcinoma).

Short-duration infusion - FL (MO40597)

Three patients (2.7%) experienced a second malignancy.

- One patient experienced Bowen's disease during maintenance on Study Day 391. This was a maximum Grade 2 SAE, considered by the investigator to be unrelated to study treatment, and did not require changing the dose of obinutuzumab. The event was reported as resolved.
- One patient experienced squamous cell carcinoma of the skin during induction on Study Day 184. This was a maximum Grade 2 non-serious AE, considered by the investigator to be unrelated to study treatment, and did not require changing the dose of obinutuzumab. The event was reported as resolved.
- One patient experienced malignant melanoma during induction on Study Day 185. This was a maximum Grade 2 non-serious AE, considered by the investigator to be unrelated to study treatment, and did not require changing the dose of obinutuzumab. The event was reported as resolved.

Severity and Nature of Risk

It appears that a significant number of the reported events refer to skin lesions, of which some were pre-existing at study start. The latter events have been included in this discussion based on the time that surgical removal of the lesions was performed. All skin lesions reported to date have been non-melanomatous skin cancers or similar lesions (e.g., keratoacanthoma). These lesions are generally easily curable with surgery, radiotherapy and/or topical treatments. Myelodysplasia and acute myeloid leukemia are also reported relatively frequently. These events may be linked to the patient's underlying condition and/or prior treatment. No patterns can be identified among the remaining events, which mainly comprise solid tumors that commonly occur in elderly patients (lung cancer, prostate cancer, rectal cancer etc).

Impact on quality of life

The impact on the quality of life of the individual patient will depend on the nature and severity of the event. The impact of an advanced second malignancy on an individual patient would be significant because of the likely poor prognosis of such a disease, the aggressive treatment required and the potentially fatal outcome.

Risk factors and risk groups

CLL and FL may transform into an aggressive large-cell lymphoma (called Richter's transformation in CLL) or prolymphocytic leukemia. In addition, patients treated for CLL and NHL can develop therapy-related myelodysplastic syndrome or acute myeloid leukemia. Patients with CLL and NHL may also have a higher risk of developing secondary solid tumors. Exposure to genotoxic agents such as alkylating agents,

topoisomerase inhibitors and radiation are particularly relevant for patients with NHL or CLL.

Preventability

The treating physician should be aware of the risk of second malignancies in CLL and NHL patients. Screening for second malignancies should be carried out in suspected cases.

Impact on the benefit-risk balance of the product

Given the severity and nature of second malignancies, despite that limited number of cases which are confounded by risk factors, second malignancies are considered an important potential risk. The marketing authorization holder continues to assess the nature and severity of second malignancies observed in obinutuzumab-exposed patients and its impact on benefit-risk profile.

Public health impact

No public health impact.

SVII.3.2. Presentation of the Missing Information

Information on Missing Information

None

PART II: MODULE SVIII— SUMMARY OF THE SAFETY CONCERNS

Table 25 Summary of safety concerns

Summary of safety concerns	
Important identified risks	Infusion related reactions Infections Thrombocytopenia Worsening of pre-existing cardiac conditions
Important potential risks	Second malignancies
Missing information	None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

ROUTINE PHARMACOVIGILANCE ACTIVITIES BEYOND ADVERSE REACTIONS REPORTING AND SIGNAL DETECTION

None

Other forms of routine pharmacovigilance activities for pregnancy and/or breastfeeding

The Roche standard pregnancy follow-up process was implemented for all products to request additional information on the medication history of the exposed parent, relevant medical history for the mother and father, previous obstetric history, the current pregnancy, fetal and infant conditions, and results of tests and investigations for any pregnancy complication or congenital abnormality during pregnancy or within the first year of the infant's life.

Cumulative data will be presented in Periodic Safety Update Reports (PSURs)/PBRERs.

Other forms of routine pharmacovigilance activities

None

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities are considered by the MAH to be sufficient to obtain and analyse relevant post-marketing safety data for all safety concerns with the aim to fully assess the safety of the product.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table 26 On-going and Planned Additional Pharmacovigilance Activities

Study title/ Status	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
None	None	None	None	
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
None	None	None	None	None
Category 3 - Required additional pharmacovigilance activities				
None	None	None	None	None

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PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

IV.1 PLANNED AND ONGOING POST-AUTHORIZATION IMPOSED EFFICACY STUDIES THAT ARE CONDITIONS OF THE MARKETING AUTHORISATION OR THAT ARE SPECIFIC OBLIGATIONS

There are no ongoing or planned post authorization efficacy studies for obinutuzumab.

PART V: RISK-MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK-MINIMIZATION ACTIVITIES)

RISK-MINIMIZATION PLAN

V.1 ROUTINE RISK-MINIMIZATION MEASURES

Table 27 Description of Routine Risk Minimization Measures by Safety Concern

Safety concern	Routine risk minimization activities
Infusion related reactions	**Routine risk communication:** Section 4.2 of the EU SmPC: Posology and method of administration Section 4.4 of the EU SmPC: Special warnings and precautions for use Section 4.8 of the EU SmPC: Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Corticosteroid premedication is recommended for patients with follicular lymphoma (FL) and mandatory for chronic lymphocytic leukemia (CLL) patients in the first cycle to reduce the risk of infusion related reactions. Refer to section 4.4 of the SmPC for detailed information. **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Gazyvaro is a prescription only medicine
Infections	**Routine risk communication:** Section 4.4 of the EU SmPC: Special warnings and precautions for use Section 4.8 of the EU SmPC: Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Gazyvaro should not be administered in the presence of an active infection and caution should be exercised when considering the use of Gazyvaro in patients with a history of recurring or chronic infections. Refer to section 4.4 and 4.8 of the SmPC for detailed information. **Other risk minimization measures beyond the Product Information:**

Safety concern	Routine risk minimization activities
	Medicine's legal status: Gazyvarro is a prescription only medicine
Thrombocytopenia	**Routine risk communication:** Section 4.4 of the EU SmPC: Special warnings and precautions for use Section 4.8 of the EU SmPC: Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Patients should be closely monitored for thrombocytopenia, especially during the first cycle; regular laboratory tests should be performed until the event resolves, and dose delays should be considered in case of severe or life-threatening thrombocytopenia. Refer to section 4.4 and 4.8 of the SmPC for detailed information. **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Gazyvaro is a prescription only medicine
Worsening of pre-existing cardiac conditions	**Routine risk communication:** Section 4.4 of the SmPC- Special warnings and precautions for use Section 4.8 of the SmPC- Undesirable Effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Patients with a history of cardiac disease should be monitored closely. In addition, these patients should be hydrated with caution in order to prevent a potential fluid overload. Refer to Section 4.4 and 4.8 of the SmPC for detailed information **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Gazyvaro is a prescription only medicine
Second malignancies	**Routine risk communication:** Section 4.8 of the EU SmPC: Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Gazyvaro is a prescription only medicine

CLL=chronic lymphocytic leukemia, EU=European union;FL=follicular leukemia, SmPC= Summary of product characteristics.

V.2. ADDITIONAL RISK-MINIMIZATION MEASURES

None.

V.3 SUMMARY OF RISK-MINIMIZATION MEASURES

Table 28 Summary Table of Pharmacovigilance Activities and Risk-Minimization Activities by Safety Concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Infusion related reactions	**Routine risk communication:** Section 4.2 of the EU SmPC: Posology and method of administration Section 4.4 of the EU SmPC: Special warnings and precautions for use Section 4.8 of the EU SmPC: Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Corticosteroid premedication is recommended for patients with FL and mandatory for CLL patients in the first cycle. Premedication to reduce the risk of infusion related reactions. Hypotension, as a symptom of IRRs, may occur during Gazyvaro intravenous infusions. Therefore, withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each Gazyvaro infusion and for the first hour after administration. Patients who have pre-existing cardiac or pulmonary conditions should be monitored carefully throughout the infusion and the post-infusion period.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Refer to section 4.4 of the SmPC for detailed information. **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Gazyvaro is a prescription only medicine **Additional risk minimization measures:** None	
Infections	**Routine risk communication:** Section 4.4 of the EU SmPC: Special warnings and precautions for use Section 4.8 of the EU SmPC: Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Gazyvaro should not be administered in the presence of an active infection and caution should be exercised when considering the use of Gazyvaro in patients with a history of recurring or chronic infections. Refer to section 4.4 and 4.8 of the SmPC for detailed information. **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Gazyvaro is a prescription only medicine **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Thrombocytopenia	**Routine risk communication:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and**

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Section 4.4 of the EU SmPC: Special warnings and precautions for use Section 4.8 of the EU SmPC: Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Patients should be closely monitored for thrombocytopenia, especially during the first cycle; regular laboratory tests should be performed until the event resolves, and dose delays should be considered in case of severe or life-threatening thrombocytopenia. Refer to section 4.4 and 4.8 of the SmPC for detailed information. **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Gazyvaro is a prescription only medicine **Additional risk minimization measures:** None	**signal detection:** None **Additional pharmacovigilance activities:** None
Worsening of pre-existing cardiac conditions	**Routine risk communication:** Section 4.4 of the SmPC- Special warnings and precautions for use Section 4.8 of the SmPC- Undesirable Effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Patients with a history of cardiac disease should be monitored closely. In addition, these patients should be hydrated with	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Safety concern	Risk minimization measures	Pharmacovigilance activities
	caution in order to prevent a potential fluid overload. Refer to Section 4.4 and 4.8 of the SmPC for detailed information **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Gazyvaro is a prescription only medicine	
Second malignancies	**Routine risk communication:** Section 4.8 of the EU SmPC: Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Gazyvaro is a prescription only medicine **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

CLL = chronic lymphocytic leukemia, EU = European union; FL = follicular leukemia, IRR = infusion related reaction, SmPC = Summary of product characteristics.

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PART VI: SUMMARY OF THE RISK-MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR GAZYVARO (OBINUTUZUMAB)

This is a summary of the risk management plan (RMP) for Gazyvaro. The RMP details important risks of Gazyvaro, and how more information will be obtained about Gazyvaro risks and uncertainties (missing information).

Gazyvaro summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Gazyvaro should be used.

This summary of the RMP for Gazyvaro should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Gazyvaro's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Gazyvaro is authorized for chronic lymphocytic leukemia and non-Hodgkin lymphoma (See SmPC for full indication). It contains obinutuzumab as the active substance and it is given by intravenous route.

Further information about the evaluation of Gazyvaro's benefits can be found in Gazyvaro EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERIZE THE RISKS

Important risks of Gazyvaro, together with measures to minimize such risks and the proposed studies for learning more about Gazyvaro risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In addition to these measures, information about adverse events is collected continuously and regularly analyzed including periodic safety update report assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of Important Risks and Missing Information

Important risks of Gazyvaro are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Gazyvaro. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	Infusion related reactions Infections Thrombocytopenia Worsening of pre-existing cardiac conditions
Important potential risks	Second malignancies
Missing information	None

II.B Summary of Important Risks

Important identified risk - Infusion related reactions	
Evidence for linking the risk to the medicine	Clinical trial data from studies BO20999, BO21000, BO21003, BO21004, BO21005, BO21223, GAO4753g, GAO4768g, GAO4779g, GAO4915g, and MO40597.
Risk factors and risk groups	The following specific patient characteristics were suggested to be potential risk factors for CLL patients who experienced IRRs related to obinutuzumab in Study BO21004 by the study Data Safety Monitoring Board (DSMB) in September 2011. High tumor burden (circulating lymphocyte count $>100 \times 10^9$/L) Binet stage C CLL at screening (Rai III/IV) Low body mass index (BMI <20) Hypertension necessitating anti-hypertensive treatment. A risk factor analysis of the Stage 2 data from Study BO21004 did not allow clear identification of the patients at a higher risk of IRRs.

Important identified risk - Infusion related reactions	
	Increased tumor burden is considered a risk factor for IRR. However, no clear effect of tumor burden (as assesses by circulating lymphocyte count $\geq 100 \times 10^9$ cells/L) was seen on the incidence of IRRs. In the GClb arm of BO21004 (Stage 2 analysis), there was no difference in IRR incidence based on tumor burden. The incidence of all grade IRRs in patients with high tumor burden was 67% and in patients with a low tumor burden, it was 66%. Similarly, the incidence of grade 3-4 IRRs was also comparable in patients with high and low tumor burden (22% vs. 19%). The incidence of IRRs as per Binet staging at baseline was analyzed. The incidence of all grade IRRs was comparable in patients with Binet stage A and C and lower in patients with Binet stage B at baseline (A, B, C: 67%, 57%, 75%). A similar trend was seen with grade 3-4 (23%, 13%, 26%) and serious IRRs (11%, 8%, 12%). The incidence of all grade and Grade 3-4 IRRs in the GClb arm was comparable in patients with body mass index (BMI) < 20 and ≥ 20 (all grades 60% vs. 66% and Grade 3-4, 20% vs. 20%). The incidence of IRRs remained the same irrespective of whether patients received anti-hypertensive treatment or not (all grade IRR, 66% vs 66%, and Grade 3-4, 20% vs. 19%). In addition to the analysis of risk factors proposed by the DSMB, an extensive risk factor analysis was also performed in patients who developed an IRR compared to patients who did not experience any IRR event based on the characteristics of patients at baseline. These included age, gender, BMI (median BMI and BMI>30), estimated creatinine clearance (median CrCl and CrCl< or $\geqslant$70ml/min), radiologically assessed sum of product of diameters for target lesions, circulating lymphocyte count (median lymphocyte count, count >25x10^9 cells/L and count>100x10^9 cells/L) and medical history of diabetes, coronary artery disease, hypertension and hypercholesterolemia. Assessment of all the above-mentioned potential risk factors revealed no conclusive differences in baseline characteristics of patients with or without IRRs. In Study MO40597, the incidence of nature of IRRs after short-duration infusion at Cycle 2 and subsequent cycles in patients with FL was similar to that observed in patients receiving standard-duration infusion.

Important identified risk - Infusion related reactions	
Risk minimization measures	**Routine risk communication:** Section 4.2 of the EU SmPC: Posology and method of administration Section 4.4 of the EU SmPC: Special warnings and precautions for use Section 4.8 of the EU SmPC: Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Corticosteroid premedication is recommended for patients with FL and mandatory for CLL patients in the first cycle. Premedication to reduce the risk of infusion related reactions. Hypotension, as a symptom of IRRs, may occur during Gazyvaro intravenous infusions. Therefore, withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each Gazyvaro infusion and for the first hour after administration. Patients who have pre-existing cardiac or pulmonary conditions should be monitored carefully throughout the infusion and the post-infusion period. Refer to section 4.4 of the SmPC for detailed information. **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Gazyvaro is a prescription only medicine **Additional risk minimization measures** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important identified risk- Infections	
Evidence for linking the risk to the medicine	Clinical trial data from studies BO20999, BO21000, BO21003, BO21004, BO21005, BO21223, GAO4753g, GAO4768g, GAO4779g, GAO4915g, and MO40597.
Risk factors and risk groups	Patients with CLL and NHL are predisposed to common as well as opportunistic infections as a result of a number of disease-related factors including B cell dysfunction, immunoglobulin deficiency, abnormal T-cell function, and neutropenia resulting from infiltration of the bone marrow.
Risk minimization measures	**Routine risk communication:** Section 4.4 of the EU SmPC: Special warnings and precautions for use Section 4.8 of the EU SmPC: Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Gazyvaro should not be administered in the presence of an active infection and caution should be exercised when considering the use of Gazyvaro in patients with a history of recurring or chronic infections. Refer to section 4.4 and 4.8 of the SmPC for detailed information. **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Gazyvaro is a prescription only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important identified risk- Thrombocytopenia	
Evidence for linking the risk to the medicine	Clinical trial data from studies BO20999, BO21000, BO21003, BO21004, BO21005, BO21223, GAO4753g, GAO4768g, GAO4779g, GAO4915g, and MO40597.
Risk factors and risk groups	No specific risk factors have been identified by Roche for non-acute thrombocytopenia (i.e. thrombocytopenia occurring more than 24 hours after obinutuzumab infusion). However, possible risk factors for acute thrombocytopenia (based on the published rituximab literature), may be high tumor burden, bone marrow involvement, splenomegaly and histological subtypes of mantle cell lymphoma and hairy cell leukemia. In general, patients with CLL appear to be more at risk of thrombocytopenia than NHL patients.
Risk minimization measures	**Routine risk communication:** Section 4.4 of the EU SmPC: Special warnings and precautions for use Section 4.8 of the EU SmPC: Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Patients should be closely monitored for thrombocytopenia, especially during the first cycle; regular laboratory tests should be performed until the event resolves, and dose delays should be considered in case of severe or life-threatening thrombocytopenia. Refer to section 4.4 and 4.8 of the SmPC for detailed information. **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Gazyvaro is a prescription only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important identified risk- Worsening of pre-existing cardiac conditions	
Evidence for linking the risk to the medicine	Clinical trial data from studies BO20999, BO21000, BO21003, BO21004, BO21005, BO21223, GAO4753g, GAO4768g, GAO4779g, GAO4915g, and MO40597.
Risk factors and risk groups	The incidence of CLL and NHL rises markedly with age. Similarly, cardiac events such as heart failure are primarily diseases of aging, with 75% of existing and new cases occurring in individuals over 65 years of age. Concomitant chemotherapy (for example bendamustine and cyclophosphamide) and radiation are also associated with cardiac effects.
Risk minimization measures	**Routine risk communication:** Section 4.4 of the SmPC- Special warnings and precautions for use Section 4.8 of the SmPC- Undesirable Effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** Patients with a history of cardiac disease should be monitored closely. In addition, these patients should be hydrated with caution in order to prevent a potential fluid overload. Refer to Section 4.4 and 4.8 of the SmPC for detailed information **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Gazyvaro is a prescription only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

Important potential risk- Second malignancies	
Evidence for linking the risk to the medicine	Clinical trial data from studies BO20999, BO21000, BO21003, BO21004, BO21005, BO21223, GAO4753g, GAO4768g, GAO4779g, GAO4915g, and MO40597.
Risk factors and risk groups	CLL and FL may transform into an aggressive large-cell lymphoma (called Richter's transformation in CLL) or prolymphocytic leukemia. In addition, patients treated for CLL and NHL can develop therapy-related myelodysplastic syndrome or acute myeloid leukemia. Patients with CLL and NHL may also have a higher risk of developing secondary solid tumors. Exposure to genotoxic agents such as alkylating agents, topoisomerase inhibitors and radiation are particularly relevant for patients with NHL or CLL.
Risk minimization measures	**Routine risk communication:** Section 4.8 of the EU SmPC: Undesirable effects **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other risk minimization measures beyond the Product Information:** **Medicine's legal status:** Gazyvaro is a prescription only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None

II.C Post-Authorization Development Plan

II.C.1 Studies that are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Gazyvaro.

II.C.2 Other Studies in Post-Authorization Development Plan

There are no studies which are conditions of the post-authorization development plan of Gazyvaro.

ANNEX 4:

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

NOT APPLICABLE

ANNEX 6: DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES (if applicable)

ANNEX 6: DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES

Not applicable