22 May 2014
EMA/CHMP/231450/2014
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Gazyvaro

International non-proprietary name: OBINUTUZUMAB

Procedure No.: EMEA/H/C/002799/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Product information

Name of the medicinal product:	Gazyvaro
Applicant:	Roche Registration Ltd 6 Falcon Way Shire Park Welwyn Garden City AL7 1TW UNITED KINGDOM
Active substance:	OBINUTUZUMAB
International Nonproprietary Name/Common Name:	OBINUTUZUMAB
Pharmaco-therapeutic group (ATC Code):	(L01)
Therapeutic indication:	Gazyvaro in combination with chlorambucil is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) and with comorbidities making them unsuitable for full-dose fludarabine based therapy (see section 5.1).
Pharmaceutical form:	Concentrate for solution for infusion
Strength:	1000 mg
Route of administration:	Intravenous use
Packaging:	vial (glass)
Package size:	1 vial

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List of abbreviations

ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody-dependent cellular phagocytosis
ASO RQ-PCR	allelic-specific oligonucleotide real-time quantitative polymerase chain reaction
AUC	area under the plasma concentration-time curve
BMI	Body Mass Index
CDC	complement-dependent cytotoxicity
CHMP	Committee for Medicinal Products for Human Use
CHOP	cyclophosphamide, doxorubicin, vincristine, and prednisone
CI	confidence interval
CIRS	Cumulative Illness Rating Scale
Clb	chlorambucil
CLL	chronic lymphocytic leukemia
C_{max}	maximum plasma concentration
CR	complete response
CrCl	creatinine clearance
CRi	complete response with incomplete marrow recovery
CSR	clinical study report
CT	computed tomography
CYP	cytochrome P450
DDI	drug-drug interaction
DFS	disease-free survival
DLBCL	diffuse large B cell lymphoma
DLT	dose limiting toxicity
DS	drug substance
DSMB	Data Safety Monitoring Board
EFS	event-free survival
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EORTC QLQ	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
ESMO	European Society for Medical Oncology
FC	fludarabine, cyclophosphamide

FCR	fludarabine, cyclophosphamide and rituximab
FDA	Food and Drug Administration
GA101	obinutuzumab (RO5072759)
GClb	obinutuzumab plus chlorambucil
GCLLSG	German CLL Study Group
GCP	Good Clinical Practice
G-CSF	granulocyte-colony stimulating factor
HAHA	human anti-human antibody
HIV	human immunodeficiency virus
HR	hazard ratio
HRQoL	health-related quality of life
iDCC	independent Data Coordinating Center
IgG	immunoglobulin G
IgHV	immunoglobulin heavy chain variable region
iNHL	indolent non-Hodgkin's lymphoma
IRC	Independent Review Committee
IRR	infusion related reaction
ITT	intent-to-treat
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
MAA	Marketing Authorization Application
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
NCI	National Cancer Institute
NHL	non-Hodgkin's lymphoma
nPR	nodular partial response
ORR	overall response rate
OS	overall survival
PCR	pentostatin, cyclophosphamide, rituximab
PD	progressive disease
PFS	progression free survival
PK	pharmacokinetic
popPK	population pharmacokinetics

PR	partial response
QoL	quality of life
RClb	rituximab plus chlorambucil
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SOC	system organ class
TLS	tumor lysis syndrome
ZAP70	zeta-chain-associated protein kinase 70

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Roche Registration Ltd submitted on 25 April 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Gazyvaro, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 20 September 2012.

Gazyvaro was designated as an orphan medicinal product EU/3/12/1054 on 10 October 2012. Gazyvaro was designated as an orphan medicinal product in the following indication: Treatment of chronic lymphocytic leukaemia.

The applicant applied for the following indication Treatment of patients with previously untreated chronic lymphocytic leukaemia (CLL).

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Gazyvaro as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website: ema.europa.eu/Find medicine/Rare disease designations.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that obinutuzumab was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

The application contained a critical report pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, addressing the possible similarity with authorised orphan medicinal products.

New active Substance status

The applicant requested the active substance obinutuzumab contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union

Scientific Advice

The applicant received Scientific Advice from the CHMP on 29 May 2009 and 21 October 2010. The Scientific Advices pertained to quality, non-clinical and clinical aspects of the dossier. The applicant did not seek Protocol Assistance at the CHMP.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer of the active substance

Roche Diagnostics GmbH

Nonnenwald 2

82377 Penzberg

GERMANY

Manufacturer responsible for batch release

Roche Pharma AG

Emil-Barell-Strasse 1

79639 Grenzach-Wyhlen

GERMANY

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Jens Ersbøll Co-Rapporteur: Pierre Demolis

- The application was received by the EMA on 25 April 2013.
- The procedure started on 22 May 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 26 August 2013. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 9 August 2013.
- CHMP AR on similarity dated 19 July 2013.
- PRAC RMP Advice and Overview on 5 September 2013.
- During the meeting on 19 September 2013, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 20 September 2013.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 February 2014.

- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 31 March 2014.
- PRAC RMP Advice and Overview on 10 April 2014.
- During the CHMP meeting on 25 April 2014, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 29 April 2014.
- PRAC RMP Advice and Overview on 8 May 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 13 May 2014.
- During the meeting on 22 May 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Gazyvaro.

2. Scientific discussion

2.1. Introduction

Problem statement

Chronic lymphocytic leukemia (CLL) is a malignant lymphoproliferative disorder that accounts for approximately 30% of adult leukemias and 25% of non-Hodgkin's lymphomas (NHL). The incidence of CLL decreases from West to East; in Caucasian males the incidence is 4.3/100,000, whereas in Asian males it is 0.7/100,000. There are about 8,500 new cases annually in the Unites States of America and numbers are similar in the European Union (EU).

The World Health Organization classification scheme considers B-cell CLL and small lymphocytic lymphoma (SLL) in an aggregate category (CLL/SLL) because of shared clinical-pathological features. 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 rate 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. The estimated prevalence of CLL in the EU in 2012 was 2.83 per 10,000 and in 2013 is 2.91 per 10,000.

The incidence rate of CLL increases with age. Over the period 2005 to 2009, the median age at diagnosis of CLL in the US was 72 years of age. Approximately 0.0% were diagnosed under the age of 20; 0.2% between 20 and 34; 1.6% between 35 and 44; 9.0% between 45 and 54; 20.9% between 55 and 64; 26.5% between 65 and 74; 27.8% between 75 and 84; and 14.0% were aged 85 years or more. 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.

Approximately 95% of CLL has a B-cell origin with a characteristic immunophenotype (CD5+, CD23+, weak surface expression of CD19, CD20, CD79b and IgM or IgD) and blood smear morphology (mature-looking lymphocytes, Gumprecht's shadows). CLL is an indolent disease with a variable patient survival time, from less than 2 years to 20 years or more. Many CLL patients initially present with lymphocytosis only and no other symptoms. Advanced disease stages are characterized by the appearance of lymphadenopathy, either hepatomegaly or splenomegaly, and bone marrow failure.

B−symptoms (i.e., fever, night sweats, and weight loss), general fatigue and recurrent infections are common in patients with late stage CLL, but may also be found earlier in the course of the disease.

Asymptomatic patients with early-stage CLL (Rai Stage I/II or Binet Stage A or B) are usually monitored until they meet the criteria for treatment, since there is no survival benefit associated with early intervention.

Available treatments generally induce remission, although nearly all patients relapse, and CLL remains an incurable disease, with the possible exception of the rare option of allogeneic stem cell transplantation, which due to its toxicity and intensity and the need for a donor is available only to a very small fraction of younger patients. None of the available treatment options is adequate for all CLL patients.

Age is one of the most important prognostic factors in CLL. Another important prognostic factor in the elderly is the burden of comorbidity (such as cardiopulmonary or vascular disease, diabetes or a second cancer other than nonmelanomatous skin cancer). Survival is significantly impaired in CLL patients with multiple comorbidities (≥2) or with severe comorbidity. Both age and the incidence and burden of comorbidity should influence the choice of treatment strategy for individual patients. Adequate supportive treatment is necessary for the prevention of toxicities as well as for the improvement of health-related quality of life in elderly CLL patients. Treatment decisions in elderly CLL patients needs to be made carefully in each patient taking into consideration not only the stage and risk factors of the disease but also the patients' physical condition and social environment.

Currently, immunochemotherapy with fludarabine, cyclophosphamide, and rituximab (FCR) is the standard of care for previously untreated patients with CLL who require treatment and are able to tolerate intense chemotherapy (European Society of Medical Oncology Guidelines 2011; National Comprehensive Cancer Network Guidelines, 2013). As demonstrated in a large randomized Phase III trial (CLL8), a complete remission rate of 44%, a median progression-free survival (PFS) of 52 months, and a 3-year overall survival of 87% can be expected with FCR treatment in previously untreated patients with CLL (Hallek et al. 2010). However immunochemotherapy with FCR is often withheld from medically unfit patients because comorbid conditions and age-related changes of organ function may increase the occurrence of sustained cytopenia, T-cell depletion, and opportunistic infections.

If considered ineligible for fludarabine-based immunochemotherapy because of comorbidity or other age-related problems, CLL patients are frequently treated with the alkylating drug chlorambucil (Clb) or bendamustine. The European Society for Medical Oncology (ESMO) treatment guidelines for this patient population refer to Clb as the treatment standard. Although Clb is generally well tolerated, complete responses are rare, and the duration of remissions is usually shorter than 1.5 years

About the product

Obinutuzumab is a recombinant monoclonal humanised and glycoengineered Type II anti-CD20 antibody of the IgG1 isotype. It specifically targets the extracellular loop of the CD20 transmembrane antigen on the surface of non-malignant and malignant pre-B and mature B-lymphocytes, but not on haematopoietic stem cells, pro-B-cells, normal plasma cells or other normal tissue. Glycoengineering of the Fc part of obinutuzumab results in higher affinity for FcγRIII receptors on immune effector cells such as natural killer (NK) cells, macrophages and monocytes as compared to non-glycoengineered antibodies (SmPC, section 5.1; see Non-clinical aspects).

Obinutuzumab is being developed for the treatment of various hematological malignancies. This application was seeking approval for obinutuzumab in combination with chlorambucil for previously untreated patients with CLL.

The sponsor applied for the following indication: Gazyvaro in combination with chlorambucil is indicated for the treatment of patients with previously untreated CLL. The recommended indication for approval is: Gazyvaro in combination with chlorambucil is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) and with comorbidities making them unsuitable for full-dose fludarabine based therapy (see SmPC, section 5.1).

Gazyvaro should be administered under the close supervision of an experienced physician and in an environment where full resuscitation facilities are immediately available (see SmPC, section 4.2).

Gazyvaro is for intravenous use. It should be given as an intravenous infusion through a dedicated line after dilution (see SmPC, section 6.6). Gazyvaro infusions should not be administered as an intravenous push or bolus.

The duration of treatment is six treatment cycles, each of 28 day duration. The recommended dose of Gazyvaro is shown in Table 1.

Table 1: Dose of Gazyvaro to be administered during 6 treatment cycles each of 28 days duration

Cycle	Day of Treatment	Dose of Gazyvaro
Cycle 1	Day 1	100 mg
	Day 2 (or Day 1 continued)	900 mg
	Day 8	1000 mg
	Day 15	1000 mg
Cycles 2 – 6	Day 1	1000 mg

Instructions on the rate of infusion are shown in Table 2 (SmPC, section 4.2).

Table 2: Standard infusion rate in the absence of infusion reactions/hypersensitivity

Cycle	Day of treatment	Rate of infusion
Cycle 1	Day 1 (100 mg)	Administer at 25 mg/hr over 4 hours. Do not increase the infusion rate.
	Day 2 (or Day 1 continued) (900 mg)	Administer at 50 mg/hr. The rate of the infusion can be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr.
	Day 8	Infusions can be started at a rate of 100 mg/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr.
	Day 15	
Cycles 2-6	Day 1	

Management of IRRs may require temporary interruption, reduction in the rate of infusion, or treatment discontinuations of Gazyvaro as outlined below (SmPC, section 4.2; see also section 4.4).

- Grade 4 (life threatening): Infusion must be stopped and therapy must be permanently discontinued.
- Grade 3 (severe): Infusion must be temporarily stopped and symptoms treated. Upon resolution of symptoms, the infusion can be restarted at no more than half the previous rate (the rate being used at the time that the IRR occurred) and, if the patient does not experience any IRR symptoms, the infusion rate escalation can resume at the increments and intervals as appropriate for the treatment dose (see Table 2). The Day 1 (Cycle 1) infusion rate may be increased back up to 25 mg/hr after 1 hour, but not increased further. The infusion must be stopped and therapy permanently discontinued if the patient experiences a second occurrence of a Grade 3 IRR.

- Grade 1 2 (mild to moderate): The infusion rate must be reduced and symptoms treated. Infusion can be continued upon resolution of symptoms and, if the patient does not experience any IRR symptoms, the infusion rate escalation can resume at the increments and intervals as appropriate for the treatment dose (see Table 2). The Day 1 (Cycle 1) infusion rate may be increased back up to 25 mg/hr after 1 hour, but not increased further.

Type of Application and aspects on development

Legal basis

The application for marketing authorisation through the centralised procedure for Gazyvaro (obinutuzumab) concentrate for solution for infusion, was submitted according to Article 8.3 of Directive 2001/83/EC. The application is a complete and independent application, for a new active substance.

Prior to initiating the Phase III program in CLL, Scientific Advice on the proposed design of study BO21004/CLL11 and the development plans to support registration of obinutuzumab was sought in 2009 and follow-up in 2010 from CHMP. Overall consensus was reached on:

– Design of Pivotal BO21004/CLL11 study.

– Overall design as a three-arm study with three primary pairwise comparisons

– Chlorambucil as an active control

– The use of investigator-assessed PFS as the primary endpoint in the BO21004/CLL11 protocol but Independent review Committee (IRC)-assessed PFS as the primary endpoint for registration purposes in the US

– Statistical Analysis Plan (SAP) for the BO21004/CLL three arm analysis and filing plan.

The applicant requested the approval for the following indications:

Gazyvaro in combination with chlorambucil is indicated for the treatment of patients with previously untreated chronic lymphocytic leukaemia (CLL) (see section 5.1).

The final indication following CHMP review of this application is:

Gazyvaro in combination with chlorambucil is indicated for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) and with comorbidities making them unsuitable for full-dose fludarabine based therapy (see section 5.1).

2.2. Quality aspects

2.2.1. Introduction

Obinutuzumab is a humanised monoclonal antibody based on a human IgG1 (κ) framework directed against CD20 found on most malignant and benign B cells.

The mechanism of action of anti-CD20 monoclonal antibodies involves a combination of (1) antibody-dependent cell-mediated cytotoxicity and phagocytosis (ADCC and ADCP) (2) caspase-independent apoptosis or direct cell death induction and (3) complement-dependent cytotoxicity (CDC) to different degrees.

Therapeutic CD20 antibodies can be divided in two subclasses (Type I and Type II) based on the different mechanisms of depleting B-cells. Both subtypes recruit immune effector cells and mediate ADCC. Type I antibodies mediate potent CDC. In contrast, Type II antibodies such as obinutuzumab induce enhanced direct cell death while CDC activity is strongly reduced.

The recombinant antibody is produced in Chinese Hamster Ovary (CHO) cells and consists of two heavy chains and two light chains with inter- and intra-chain disulfide bonds that are typical of IgG1 antibodies. The calculated molecular mass of intact obinutuzumab is 146 kDa (peptide chains only, with heavy chain C-terminal lysine residue, with heavy chain N-terminal glutamines).

The CH2 domain of each heavy chain also has a single conserved glycosylation site predominantly with biantennary complex- and hybrid-type N-glycans with reduced levels of core-fucosylation. The production cell line for obinutuzumab is glycoengineered in order to obtain this modified glycosylation pattern with reduced levels of core-fucosylation.

Obinutuzumab was derived by humanisation of the parental B-Ly1 mouse antibody and subsequent glycoengineering leading to a significantly increased FcγRIIIa binding mediated by a modified glycosylation pattern, which is related to enhanced ADCC.

2.2.2. Active Substance

Manufacture

The active substance is manufactured at Roche Diagnostics GmbH, Nonnenwald 2, D-82377, Penzberg, Germany.

Cell culture process

Obinutuzumab is produced in a fed-batch process using a WCB as starting material. The antibody is secreted into the cell culture medium.

For production of obinutuzumab, a vial of the WCB is thawed. The cells are then cultivated in shake flasks and bioreactors of increasing volumes.

The production culture is harvested and filtered prior to purification of obinutuzumab.

Cell culture conditions and in-process controls (IPCs) have been sufficiently described and are considered appropriate.

Purification process

The obinutuzumab purification process consists of a series of chromatography, viral inactivation, filtration and ultrafiltration/diafiltration steps.

Raw materials

Development genetics

The monoclonal IgG1 antibody obinutuzumab was derived and humanised from the original murine version B-Ly1. The antibody is expressed in CHO cells. The antibody genes were co-transfected together with genes encoding glycosylation modifying enzymes in order to engineer the oligosaccharide structure attached to the antibody.

Cell banking system

A two-tiered cell banking system of Master Cell Bank (MCB) and Working Cell Bank (WCB) was developed and maintained in accordance to current Good Manufacturing Practices (cGMP) and ICH guidelines.

Procedures followed for the preparation of the MCB and WCB were described. An extensive range of tests was performed for their characterisation, in accordance to ICH guidelines, including identity, viability, stability, presence of adventitious agents.

Raw materials used in manufacture

Raw materials used throughout the manufacture of obinutuzumab are carefully addressed.

Process validation

Development, evaluation, and verification of the obinutuzumab process were built upon a comprehensive science- and risk-based approach. This incorporates process and product understanding developed from obinutuzumab-specific studies as well as platform knowledge gained from similar molecules and processes.

Manufacturing process development

During pharmaceutical development, three different active substance manufacturing processes were established for obinutuzumab.

Characterisation

Physicochemical characterisation:

Electrospray ionization mass spectrometric (ESI-MS) analysis confirmed that the molecular mass is in accordance with the predicted mass from the amino acid sequence of obinutuzumab. The mass for deglycosylated non-reduced obinutuzumab is approximately 146 kDa.

Tryptic peptide mapping confirmed the primary structure.

The N-termini of the light chain and heavy chain were confirmed by peptide map analysis.

All disulfide linked peptides were identified by liquid chromatography – mass spectrometry (LC-MS) analysis of non-reduced obinutuzumab.

Free sulfhydryl groups were measured using a reduced LC-MS peptide map from tryptic digests after derivatisation of free sulfhydryl groups in native obinutuzumab.

The extent of glycation was assessed using ESI-MS.

Oxidation was assessed using a tryptic peptide map.

Deamidation products were assessed using a tryptic peptide map with MS detection.

Obinutuzumab was analysed by size-exclusion high-performance liquid chromatography (SE-HPLC) to determine the amount of high-molecular weight species (HMWS) and low-molecular weight species (LMWS).

Sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS PAGE) was performed for both reduced and non-reduced samples.

Ion-exchange high-performance liquid chromatography (IE-HPLC) was performed to investigate charge variants.

The higher order structure of obinutuzumab was confirmed by Fourier transform infrared (FTIR) spectroscopy.

Biological characterisation:

Biological characterisation of obinutuzumab included:

• Potency by bioassay (ADCC)

• FcRn Binding

• Direct Cell Death Assay

Variants and impurities

The impurities of obinutuzumab active substance are controlled either by the process or by release testing and relevant IPCs. The process- and product-related impurities of obinutuzumab active substance are:

- Product variants: size-related variants, charge-related variants, acidic variants, glycosylation variants;

- Adventitious agents: endotoxins, bacteria and fungi, mycoplasma, adventitious viruses, mouse minute virus (MMV);

• Process related impurities such as Protein A, CHO host cell proteins (CHOP), host cell DNA and various raw materials.

It was found that for all obinutuzumab active substance batches tested, the level of these impurities was within the acceptable limits.

Specification

The release specifications for obinutuzumab active substance have been suitably justified and are supported by consistent data from multiple lots. The specifications contain test for pharmacopoeial methods as well as specific methods to ensure sufficient safety and quality with respect to identity, purity, quantity and potency.

Stability

The design of the stability program, including the testing intervals and temperature storage conditions, are in accordance to current guidelines. The tests chosen are a subset of tests from the release specifications selected for stability-indicating properties.

On the basis of the stability data provided, a shelf life of 36 months is claimed and is found acceptable.

2.2.3. Finished Medicinal Product

Pharmaceutical development

The finished product is a liquid, clear to opalescent, colourless to slightly brownish aqueous solution composed of 25 mg/mL obinutuzumab, with the following excipients:

- L-histidine/L-histidine hydrochloride buffer;

- Trehalose dihydrate;

- Poloxamer 188.

Gazyvaro does not contain antimicrobial preservatives.

Each 50 mL vial contains 1000 mg obinutuzumab. The concentrate is diluted in 0.9% (w/v) sodium chloride solution prior to administration.

Manufacture of the product

The manufacturing process of the finished product includes the following steps:

- Thawing the active substance;

- The thawed bulk is transferred through a sterilised 0.22 µm membrane filter into a steam-sterilised stainless steel storage vessel.

- From the storage vessel, the filtered finished product solution is sterile filtered (0.22 µm) in-line within a closed system directly into the filler.

- The finished product solution is filled into the sterilised, depyrogenated vials by means of sterilised filling equipment under laminar flow in a Grade A environment. The filled vials are conveyed to the stoppering unit where they are stoppered with sterilised stoppers.

- Filled and stoppered vials are crimped with aluminium seals fitted with plastic flip-off cap.

Capped vials are stored at 2°C - 8°C.

- Filled and capped vials are 100% visually inspected by means of manual or automatic inspection. After the inspection process, the vials are quarantined and stored at 2°C - 8°C.

Product specification

Appropriate specifications for obinutuzumab finished product have been developed. The specifications contain tests for pharmacopoeial methods as well as specific methods.

Stability of the product

Real-time and accelerated stability studies were initiated in accordance to ICH guidelines and per protocol to monitor the time-temperature stability of cGMP lots of finished product. On the basis of the data provided, the claimed shelf life for the finished product is 36 months at 2-8°C.

Adventitious agents

Safety in relation to non-viral and viral adventitious agents has been sufficiently demonstrated.

Acceptable virus removal and inactivation capacity of the obinutuzumab active substance manufacturing process have been demonstrated.

Post-Approval Lifecycle Management Plan

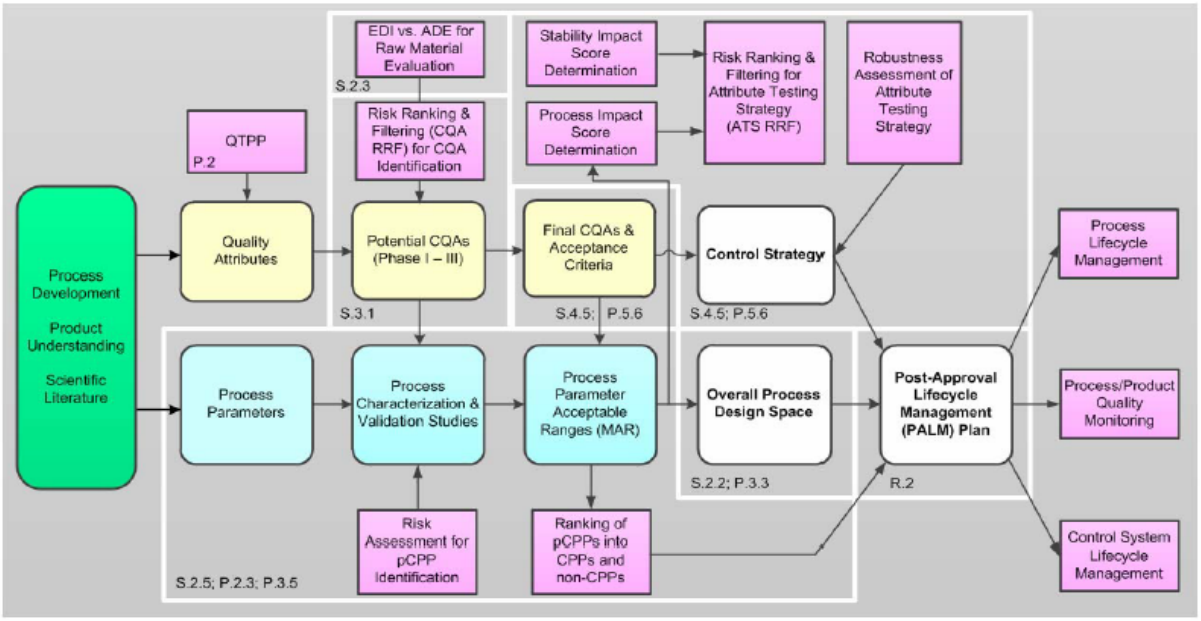
The post-approval lifecycle management (PALM) plan described in the dossier specifies how the Applicant will:

- Monitor the obinutuzumab process and product quality attributes to ensure that both remain within a controlled state post-approval;
- Update the obinutuzumab control system as necessary based on further process and product knowledge;
- Manage changes to process parameter targets within the design space.

2.2.4. Overview of the Quality by Design approach

The standard elements in Modules 2 and 3 supporting a recombinant antibody filing are present in the obinutuzumab dossier. In addition, the use of risk assessments and decision tools is described, providing transparency into the definition of Critical Quality Attributes (CQAs), Critical Process Parameters (CPPs), acceptable process parameter ranges, the active substance and finished product control systems and process monitoring. These tools have been developed as part of an integrated risk management system building on concepts expressed in ICH Q8, Q9 and Q10, and key decision criteria were calibrated using information from the Applicant's approved products. This systematic approach to risk assessment is based on an understanding of the connections between the product quality and the manufacturing process and rests strongly on platform knowledge for recombinant antibody products manufactured by the Applicant.

The decision-making framework for identification of obinutuzumab CQAs and CPPs, as well as the development of an overall control strategy, are depicted in Figure 1.



ADE=acceptable daily exposure; ATS=attribute testing strategy; CPP=critical process parameter; CQA=critical quality attribute; EDI=estimated daily intake; MAR=multivariate acceptable range; PALM=post-approval lifecycle management; PC = process characterization; pCPP=potential critical process parameter; PV = process validation; QbD=quality by design; QTPP = quality target product profile; RRF=risk ranking and filtering.

Figure 1: Approach to Implementing Quality by Design for obinutuzumab

Quality Target Product Profile

Obinutuzumab is an IgG1 antibody made in a manner typical of the Applicant's platform monoclonal antibody process, using IgG1 frameworks, cell culture production host cells, process conditions, operational strategies, and the number and sequence of downstream unit operations similar to those used for several of the Applicant's licensed antibodies. Knowledge derived from this process and product platform experience, along with other relevant process development knowledge, obinutuzumab product understanding (product characterisation based on prior knowledge), and relevant scientific literature, informed the Risk Ranking and Filtering (RRF) assessments that guided the identification of a Quality Target Product Profile (QTTP) and CQAs and the design of process characterisation studies.

Quality Attributes

Quality attributes are divided into the following assessment categories: product variants, process-related impurities, raw materials, leachables, adventitious agents, composition and strength and other attributes specific to the finished product (table 3).

Table 3: Categories of Obinutuzumab Quality Attributes

Category of Attribute	Assessment	Rationale for Approach
Product variants Size-related variants Charge-related variants Oxidation-related variants Glycosylation Structural variants	CQA RRF	Impact to patient safety and product efficacy is specific to the variant in question, the product's mechanism of action and route of administration, clinical experience, etc.
Process-related Impurities Host cell proteins Host cell DNA Leached protein A	CQA RRF	With appropriate justification, data from similar products can be used to assess safety in addition to product-specific clinical experience.
Raw Materials Cell culture and purification components (nutrients, trace elements, salts, buffers, etc.)	Comparison of EDI_0 and ADE CQAs if $EDI_0 > ADE$	Raw materials for which the estimated daily intake before downstream clearance (EDI_0) is higher than the acceptable daily exposure (ADE) are potential risks to the patient.
Leachables Compounds leaching into the Drug Substance or Drug Product originating from process equipment (e.g. filters) and/or primary packaging materials (e.g. stoppers)	CQA if detected above trace level	Leachables have a potential impact to patient safety only if they are present above trace level.
Adventitious Agents Viral purity Microbiological purity Endotoxins	None required, obligatory CQA	Potentially high impact to patient safety.
Drug Substance and Drug Product Composition and Strength Protein content Osmolality pH Appearance (color, opalescence, clarity) L-Histidine content Trehalose content Poloxamer 188 content	None required, obligatory CQA	Potentially high impact to patient safety and product efficacy.
Drug Product Specific Subvisible particles Visible particles Extractable volume Sterility	None required, obligatory CQA	Potentially high impact to patient safety and product efficacy.

ADE = acceptable daily exposure; CQA = critical quality attribute; EDI = estimated daily intake; RRF = risk ranking and filtering.

Product Variants and Process-Related Impurities

Criticality of product variants and process-related impurities was assessed using an RRF approach and acceptance criteria were established for CQAs as applicable. The CQA RRF approach involved assigning both impact and uncertainty scores to each quality attribute.

Impact Scores were assigned based on the magnitude or severity of the effect on four components: biological activity, pharmacokinetics (PK), immunogenicity and safety.

Uncertainty scores were based on the level of knowledge of the particular quality attribute. Product variants were assessed on a product-specific basis to account for the unique modifications, mechanism of action, route of administration, non-clinical and clinical experience, *in vitro* studies and other factors that influence potential risk to patients. Prior knowledge was applied as applicable; in part to assess risk for process-related impurities in products manufactured using this same platform process.

The relative risk score for each attribute is obtained by multiplying the impact and uncertainty scores

Raw materials and leachables

For raw materials, a comparison of each estimated daily intake before downstream clearance (EDI_0) with its corresponding acceptable daily exposure (ADE) was used to identify obinutuzumab raw material that pose a potential toxicity risk. ADE are based on toxicology data and EDIs are based on the assumption that no clearance occurs downstream of where the raw material is introduced.

Raw materials with EDI_0 > ADE are considered as CQAs. They required further assessment which demonstrated downstream clearance in the obinutuzumab manufacturing process.

Leachables are related to compounds that leach into the active substance or finished product from elastomeric or plastic components of process equipment or the container and closure system. The approach for identification of specific leachables as CQAs was dependent on whether a specific compound can be detected. No leachables were detected for obinutuzumab. Based on these results, leachables were not classified as CQAs for obinutuzumab.

Other CQAs

The attributes adventitious agents (viral purity, microbiological purity, and endotoxins) and active substance and finished product composition and strength (protein content, osmolality, pH, appearance (colour, opalescence, clarity), L-histidine content, trehalose content, and poloxamer 188 content as well as the finished product specific attributes (subvisible particles, visible particles, extractable volume and sterility) were classified as CQAs without further assessment.

CQA acceptance criteria

Acceptance criteria are established for attributes which have been identified as “critical”, have been observed at quantifiable levels, and exhibit values outside the range of the reference material. The acceptance criteria for CQAs that have an impact on safety or immunogenicity were based on the information available from the obinutuzumab clinical studies or information on other clinical or marketed products considering indication, treatment regime and patient population. General information on safety and immunogenicity from literature was also considered when setting acceptance criteria for obinutuzumab variants that potentially can impact safety/immunogenicity.

Site- and Scale-Independent Process Validation

Overview

Site- and scale-independent process evaluation and verification studies were performed for the active substance in a stepwise approach. Process understanding developed during process and product development, platform knowledge, and scientific and engineering principles were initially brought together using a risk assessment tool.

For each unit operation, process parameters potentially impacting CQAs (potential CPPs [pCPPs]) or KPIs were investigated in univariate and/or multivariate studies.

Subsequently, linkage studies were performed to understand the behaviour of the overall process under worst-case conditions in order to assess the cumulative, process-wide impact on the CQAs.

The objective of this progression of studies was to formally identify CPPs and non-CPPs, further refine process parameter acceptable ranges, referred to as multivariate acceptable ranges (MARs) and define a process-wide design space.

Statistical modelling

Generally, process data was described using means, sample standard deviations and coefficients of variation. Means and standard deviations were interpreted in relation to the CQA target ranges or practically significant difference (PSD) limits. Furthermore, the impact of different process parameters on each CQA was analysed.

Qualification of scale-down models

Qualified scale-down models of the cell culture and purification unit operations were used for process evaluation studies in order to predict performance at manufacturing scale.

Linkage studies

Linkage studies were performed for CQAs that are affected by more than one unit operation. From the multivariate regression models, worst-case conditions were calculated to identify the parameter settings leading to the worst-case CQA value. These worst-case conditions of the unit operations were used for the linkage studies.

Identification of critical process parameters

A parameter is identified as a CPP when its variation has a relevant impact on at least one CQA. The Applicant expressed criticality as a quantitative metric, the impact ratio.

Based on the impact ratio, the process parameters are classified as follows:

• Non-CPP:

Process parameters with a low impact ratio are considered to be non-CPPs.

• Low-impact CPP:

Process parameters with a medium impact ratio were categorised as low-impact CPP.

• High-impact CPP:

Process parameters with a high impact ratio were categorised as high-impact CPPs.

Design Space

Based on the outcomes of the process evaluation studies and the linkage studies the process-wide design space for the active substance was defined. It includes all the unit operations, the process parameters describing operation of each of the unit operations, and the raw materials used. The design space is limited by the multivariate acceptable ranges (MAR) for all process parameters (CPPs and non-CPPs).

Changes to the target/set point for all process parameters within their MARs are considered to be movement within the design space. Changes to the MARs of CPPs or non-CPPs would be considered to be movement outside the design space.

Control Strategy

Overview

The approach to defining the control strategy for the active substance and finished product is based on the enhanced process knowledge and product understanding enabled by the QbD approach. For identified quality attributes, several risk assessments were performed to enable development of a suitable control system, including:

• Determination of acceptance criteria for CQAs, if applicable (see above);

• Evaluation of the ratio of the estimated daily intake (EDI_0) to the acceptable daily exposure (ADE) for raw materials (see above);

• Evaluation of the appropriate attribute testing strategy (ATS), taking into account process impact and stability impact (see below);

• Robustness assessment of the proposed testing strategy (see below).

These risk assessments were performed for all quality attributes, including those determined to be non-critical and those that require testing to meet compendial requirements.

The integral part of the overall control system is the ATS, which comprises the elements of batch release, release-relevant in-process control, stability testing, and the monitoring program.

Process impact score

The process impact score is used, in combination with the CQA impact score to generate an ATS score for the active substance and finished product manufacturing processes, which is used to define the overall attribute testing strategy for each CQA (see below).

The process impact score represents an estimation of the residual risk that a CQA could exceed its acceptable production range defined as CQA-TR when the process is operated within its acceptable ranges.

A procedure was developed for determining the process impact score reflecting increasing criticality.

Stability impact score

The stability impact score is used in combination with the CQA impact score to generate an ATS score for active substance and finished product that assesses whether or not testing of an attribute should be performed as part of the stability program. The overall process flow for determining the stability impact score is summarised in the form of a decision tree.

The stability impact score is determined for each quality attribute.

Attribute testing strategy risk assessment

The ATS RRF tool multiplies, for all quality attributes, the CQA impact score with either the process impact score or the stability impact score. The highest impact score is used for each CQA.

The scoring results in a recommendation of the following testing strategies:

- For high ATS scores: Control system testing for the attribute is required.

- For medium ATS scores: Monitoring testing (periodic or continual) is required for these attributes. For low ATS scores: No testing is required.

The ATS RRF assessment is performed four times: for active substance manufacture, active substance storage, finished product manufacture, and finished product storage.

Robustness assessment of the attribute testing strategy

Once the attribute testing strategy has been proposed for each attribute, and the appropriate test methods and limits have been defined, a robustness assessment is performed on this testing strategy.

This assessment is performed for all quality attributes in order to evaluate the proper control of the attribute in the defined ATS. The assessment ensures evaluation of the application of the ATS to molecule and process-specific attributes, and adds evaluation of the capability and suitability of the available analytical methods.

Post-Approval Lifecycle Management Plan

The post-approval lifecycle management (PALM) plan described in the dossier specifies how the Applicant will:

- Monitor the obinutuzumab process and product quality attributes to ensure that both remain within a controlled state post-approval;
- Update the obinutuzumab control system as necessary based on further process and product knowledge;
- Manage changes to process parameter targets within the design space.

Monitoring program

The obinutuzumab monitoring program can be adapted during the product lifecycle.

Monitoring activities for obinutuzumab comprise routine elements and additional elements which are required by the QbD approach used for the development of the control system.

Management of process parameters within the design space

Changes within the design space will be managed in the Applicant's quality system.

2.2.5. Discussion on chemical, pharmaceutical and biological aspects

ACTIVE SUBSTANCE

Raw materials

Raw materials used throughout the manufacture of obinutuzumab are carefully addressed in relation to their possible impact. Objections concerning raw material variability were well addressed with the Applicant´s Day 120 and Day 180 responses.

Control of critical steps and intermediates

Appropriate in-process controls (IPCs) are in place for the obinutuzumab active substance manufacturing process.

Process validation and/or Evaluation

Process verification was conducted on full-scale and at site consecutive batches. All acceptance criteria were met.

Consistency for all obinutuzumab active substance batches manufactured by the commercial scale has been verified by manufacturing scale data at commercial site. All batches were produced in accordance with the acceptance ranges stated in the dossier. All acceptance criteria were met, supporting that the manufacturing process is robust and consistent.

Data for the removal of raw materials qualified as CQAs were provided and consistent removal has been demonstrated.

Hold times of intermediates have been carefully studied and supported by several multivariate studies.

The data provided by the Applicant support the conclusion that the obinutuzumab cell culture, harvest and purification process, covered by the proposed design space, is capable of producing product of acceptable and consistent quality.

Design Space

Quality by Design (QbD) principles have been applied during the development of obinutuzumab. The design space of obinutuzumab includes all the unit operations, the process parameters describing the operation of each of the unit operations, and the raw materials used. The design space is limited by the Multivariate Acceptable Ranges (MARs) for all process parameters (CPPs and non-CPPs) described in the dossier. Changes to the targets for all process parameters within their MARs are considered to be movement within the design space. Changes to the MARs of CPPs or non-CPPs would be considered to be movement outside the design space.

Even though a huge quantity of data was provided by the Applicant, a sum of uncertainties at all steps of the building of the design space led to doubts, at Day 120, on its suitability.

Following the Applicant´s Day 120 and Day 180 responses, the management of remaining uncertainties was sufficiently addressed.

Especially the final proposed control strategy, which does take into account remaining uncertainties led to the overall conclusion that the claimed design space is considered acceptable.

Manufacturing process development

The changes introduced to the obinutuzumab manufacturing process during its development are sufficiently detailed in the dossier. Three processes have been used in the non-clinical and clinical studies. Pivotal clinical studies have used material produced by the final process. Overall, comparability has been demonstrated.

Characterisation

Obinutuzumab is considered thoroughly characterised in relation to structural, physicochemical- and biological properties. The methods used are considered state of the art.

Obinutuzumab is a Type II CD20 monoclonal antibody, whereas rituximab is a Type 1 monoclonal antibody. The two subtypes differ in their mechanism of depleting B-cells. The mechanism of action of anti-CD20 monoclonal antibodies including rituximab and obinutuzumab involves a combination of (1) antibody-dependent cell-mediated cytotoxicity and phagocytosis (ADCC and ADCP) (2) caspase-independent apoptosis or direct cell death induction and (3) complement-dependent cytotoxicity (CDC) to different degrees.

Both subtypes (Type I and II) recruit immune effector cells and mediate ADCC. Type I antibodies such as rituximab mediate potent CDC. In contrast, Type II antibodies such as obinutuzumab induce enhanced direct cell death while CDC activity is strongly reduced. The latter statement has been further justified by the Applicant in their Day 120 responses. The conclusion drawn by the Applicant, that the obinutuzumab bioactivity is considered not to rely on CDC, is endorsed.

CQA assessment

Detailed information and careful explanations are provided on the Risk Ranking and Filtering (RRF) tool used to define quality attributes of obinutuzumab as critical or not.

The RRF tool used for the attribute criticality designation is acceptable. It is considered that a conservative approach has been taken by the Applicant in the criticality assessment of product-related variants and process-related impurities. Raw materials and leachables as well as so-called “obligatory” CQAs have all been sufficiently addressed.

The overall approach applied for identification of CQAs is generally acceptable. Most CQAs for obinutuzumab are typical of monoclonal antibodies produced in CHO cells.

Control of active substance

The test methods and acceptance criteria included in the obinutuzumab active substance release specification and the release-relevant in-process controls are in general acceptable. Concerns raised at Day 120 and Day 180 were considered resolved.

The control strategy for obinutuzumab active substance is well described and justified. Like the process development, characterisation and validation, the control strategy is also developed by a systematic QbD approach. Attributes to be tested are identified by an Attribute Testing Strategy (ATS) tool.

Development of the attribute testing strategy is a consecutive process comprising the following key steps: CQA identification, establishment of CQA-ACs, outcomes of the process evaluation studies as well as stability studies against predefined limits, the probability to exceed the CQA-TRs leading to the definition of a proposed attribute testing strategy, and finally a robustness assessment on the proposed testing strategy, thereby generating the final attribute testing strategy.

The control strategy does not only take into account the influence that a single CQA may have on the bioactivity, PK, safety and immunogenicity, it also defines a total acceptable change for the product as a whole: the specification for the individual CQAs also takes into account the total “sum of change”.

The proposed control strategy is considered conservative and following the additional information provided in the Day 120 responses, it is considered acceptable.

The CQAs identified for inclusion in the specification are considered acceptable as well as their acceptance criteria. For some CQAs, the acceptance criteria are slightly above the clinical experience. However, it is sufficiently justified, for example by experience with other relevant monoclonal antibody products or by the WHO recommendation.

Finally a number of CQAs are tested, without further control strategy assessment, due to their nature, by which regulatory testing is obligatory (for example Ph. Eur. requirements). This is acceptable and did not call for comments.

Stability

On the basis of the primary stability data derived from registration batches and representative data, a shelf life of 36 months is considered acceptable for the commercial obinutuzumab active substance.

FINISHED PRODUCT

Pharmaceutical Development

Thorough manufacturing process development has been conducted for each of the steps in the process. Development studies were conducted using worst-case process parameter settings, i.e. beyond normal operation ranges, or based on scientific principles and/or platform knowledge. Studies were either full scale studies and / or small-scale studies.

Control of finished product

The specification, including the acceptance criteria, were developed using the enhanced understanding that QbD offers. A QbD approach has been applied to develop the control strategy for obinutuzumab. The general assessment of quality attributes for the finished product control system is performed identically to that performed for the active substance.

Stability

The proposed shelf life of Gazyvaro finished product is 36 months at 2-8°C. On the basis of the stability data provided, this shelf life is considered acceptable. The proposed in-use shelf life is also acceptable.

Adventitious agents safety evaluation

Safety in relation to non-viral and viral adventitious agents has been sufficiently demonstrated.

Acceptable virus removal and inactivation capacity of the obinutuzumab active substance manufacturing process have been demonstrated.

Post-Approval Lifecycle Management (PALM) Plan

The PALM plan is described in the dossier which specifies how the obinutuzumab process and product quality attributes will be monitored, how changes within the design space will be handled, and how update of the control system will be implemented based on further process and product knowledge.

Overall, the PALM plan is considered acceptable.

2.2.6. Conclusions on the chemical, pharmaceutical and biological aspects

Overall, the quality of Gazyvaro is considered to be in line with the quality of other approved monoclonal antibodies. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The fermentation and purification of the active substance are adequately described, controlled and validated. The active substance is well characterised with regard to its physicochemical and biological characteristics, using state-of-the-art methods, and appropriate specifications are set. The manufacturing process of the finished product has been satisfactorily described and validated. The quality of the finished product is controlled by adequate test methods and specifications. Viral safety and the safety concerning other adventitious agents including TSE have been sufficiently assured.

The overall Quality of Gazyvaro is considered acceptable.

2.2.7. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommended two points for investigation.

2.3. Non-clinical aspects

2.3.1. Introduction

The nonclinical testing strategy was designed to demonstrate and characterize the pharmacology, pharmacokinetics/toxicokinetics, and toxicology of obinutuzumab. All pivotal toxicology studies were conducted using IV administration. Obinutuzumab binds to Cynomolgus monkey (but not rodent) CD20 with an affinity and ADCC potency similar to that of human CD20; consequently, the Cynomolgus monkey was considered the only appropriate species in which to assess the safety of obinutuzumab. Pivotal toxicology/toxicokinetics studies were performed according to the GLP principles.

EMA Scientific Advice was sought to confirm the acceptability of assessing safety pharmacology as part of the repeat dose toxicity studies, of avoiding standard genotoxicity and carcinogenicity studies, on the 6-month duration of repeat-dose toxicity studies, and to agree on the design of reproductive toxicity studies.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Epitope mapping and crystal structure analysis of the CD20-obinutuzumab complex showed that obinutuzumab binds CD20 in a different orientation than rituximab. While the epitopes for rituximab and obinutuzumab are not identical they overlap (Niederfellner et al. 2011). In vitro, obinutuzumab and rituximab competed for binding to CD20 (Report 1025130, 1025238). Obinutuzumab exhibited bivalent binding to the CD20 epitope (Report 1043641). Obinutuzumab and rituximab had comparable affinity to CD20 expressed on the surface of a panel of B-cell lymphoma cell lines (Report 1025238).

In contrast to rituximab and ofatumumab, which carry a human wildtype and non-glycoengineered and thus fucosylated IgG1 Fc portion, obinutuzumab has been glycoengineered to produce an afucosylated Fc region that substantially enhances the affinity of this antibody for both the FcγRIIIA-158F and FcγRIIIA-158V variants.

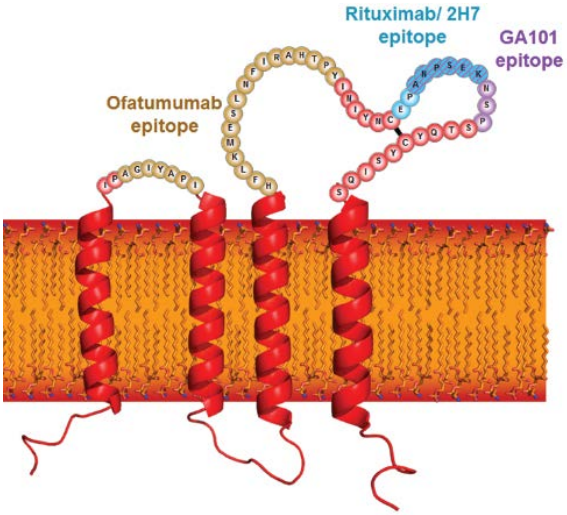


Figure 2: The structure and topology of CD20 and the epitopes recognized by ofatumumab, rituximab and obinutuzumab (GA101) (From Klein et al. 2013).

Most existing anti-CD20 antibodies, including rituximab, veltuzumab, ocrelizumab and ofatumumab, are Type I anti-CD20 antibodies. Type I antibodies induce a translocation of CD20 into large lipid microdomains or 'lipid rafts' within the plasma membrane upon binding, leading to complement-dependent cytotoxicity (CDC).

Obinutuzumab, like tositumomab, can be classified as a type II CD20 antibody. Obinutuzumab did not induce accumulation of CD20 upon antibody binding (Report 1025127) and was more potent than Type I antibodies in inducing homotypic adhesion and direct cell death (Report 1038406).

Obinutuzumab displayed reduced CDC relative to rituximab, in particular, in the presence of physiological levels of human immunoglobulins (Report 1025235). Obinutuzumab had a diminished binding capacity for C1q compared to rituximab (Report 1053171) and ofatumumab (Report 1043692). While complement in serum blocked Natural Killer cell (NK) activation induced by rituximab, it had no effect on NK cell activation induced by obinutuzumab (Report 1053171).

Obinutuzumab (1, 10 µg/mL) was superior to rituximab in inducing early-stage (Annexin V positive) and late-stage (Annexin V/propidium iodide positive) apoptosis in a panel of CD20 expressing B-cell lymphoma cell lines (Report 1025131) and in peripheral blood mononuclear cells obtained from patient samples (Report 1025237). Cell-death induction by obinutuzumab required bivalent binding and is independent of both the Fc region and the glycoengineering of the Fc region (Reports 1025131, 1025240, 1043691, 1038406 and 1043692). Obinutuzumab-induced cell death was dependent on actin reorganization and lysosome disruption, could be abrogated by inhibitors of actin polymerization, and was independent of Bcl-2 overexpression and caspase activation (Alduaij et al. 2011).

The efficacy of rituximab was higher in patients homozygous for the "high-affinity" allele of FcγRIIIa, that is characterized by a valine at position 158 (FcγRIIIa[V158]), than in patients heterozygous or homozygous for the "low-affinity" allele of FcγRIIIa, which has a phenylalanine residue at this position (FcγRIIIa[F158]) and a lower affinity for IgG (Koene et al., 1997). Obinutuzumab binding (K_D of 55.5 nM) to the high-affinity FcγRIIIa[V158] receptor was around 12-fold stronger than for rituximab (K_D of 666 nM). Moreover, obinutuzumab displayed 4.5-fold higher affinity towards the low affinity FcγRIIIa[F158] receptor than rituximab (K_D (obinutuzumab) 457 nM, K_D (rituximab) 2070 nM) (Report 1025340). Obinutuzumab and rituximab displayed comparable affinity for the FcγIIIb receptor (Report 1053422), the FcγIIb receptor (Report 1034799), and the FcRn receptor (Report 1053425).

Obinutuzumab was associated with a significantly enhanced potency in ADCC assays using NK cells as compared to rituximab. Overall, obinutuzumab exhibited approximately 5- to 100-fold enhanced ADCC potency against a panel of B cell lymphoma cell lines in comparison to rituximab (Reports 1043692 and 1025241). However, in Study 1038388, no evidence of obinutuzumab- or rituximab-mediated ADCC with either resting or M-CSF-activated monocytes was seen in a special 3D co-culture model. In subsequent studies, it was investigated whether obinutuzumab triggers macrophage-mediated phagocytosis (ADCP) and cytotoxicity (ADCC) (Report 1053079). In the Cell ELISA assays, the observed superiority of obinutuzumab over rituximab and ofatumumab in monocyte- or macrophage-mediated elimination of tumor cells was primarily due to a contribution of antibody-mediated direct effects and ADCP, but only to a minor extent due to ADCC (1053079, Herter et al., submitted, 2013b).

Follow up experiments using both monocyte and macrophage populations showed that monocyte or macrophage-mediated ADCC is an inefficient process, whereas phagocytosis occurs rapidly and is more efficient (Herter et al., submitted, 2013b).

While obinutuzumab, non-glycoengineered obinutuzumab and rituximab displayed comparable binding to monocyte-derived M1 and M2c macrophage subsets in the absence of competing endogenous IgGs, obinutuzumab displayed superior binding in the presence of competing immunoglobulins. Moreover, the phagocytic activity and nitric oxide release of M1 and in particular M2c macrophage subsets treated with glycoengineered obinutuzumab was superior to that of its wild-type non-glycoengineered counterpart in the presence of competing immunoglobulins.

Obinutuzumab was associated with superior depletion of normal B cells from blood of healthy volunteers as well as of malignant B cells from blood in comparison to rituximab (Report 1049394; Report 1049395; Report 1025239). At concentrations above 1 µg/mL, obinutuzumab was superior to rituximab as well as alemtuzumab in depleting CLL cells in patient whole blood samples (n=23, Report 1053423). The maximal effect obtained was a 55% reduction in CD19+ cells following 8 hours incubation with 10 µg/mL obinutuzumab. The effect of different degree of non-fucosylation (5-50%) in the IgGs heavy chain has on B cell depletion was evaluated in whole blood of healthy human donors. A stepwise improvement of B cell depleting potency was observed with increasing non-fucosylation which reached a plateau at around 20% non-fucosylation. The level of N-glycans lacking core-fucose ranges from 42.0–48.4% in the obinutuzumab registration batches. V

The *Cynomolgus* monkey was considered an appropriate species for the toxicologic assessment of obinutuzumab. CD20 expression on *Cynomolgus* monkey B cells was found to be about 2-fold higher than on human B cells (Report 1025343). The determination of relative binding affinity showed that obinutuzumab bound with comparable nanomolar affinity to human CD20 on normal B cells and to CD20 on B cells from peripheral blood mononuclear cells (PBMCs) from *Cynomolgus* monkeys (Reports 1025242 and 1025343).

The anti-tumour efficacy of obinutuzumab was evaluated in numerous xenograft studies performed in female SCID beige mice. IV Q7D obinutuzumab displayed superior anti-tumour efficacy in SCID mice carrying tumours derived from SUDHL-4 DLBCL, OCI-Ly-18 NHL, Z138 MCL, RL NHL and WSU-DLCL2 B cell lymphoma cell lines when compared to rituximab. Comparable anti-tumour efficacy was seen in the Raji NHL xenograft model. A significant effect was observed in small as well as large tumours and following other treatment schedules.

Second line treatment with obinutuzumab of advanced xenografts was able to control SU-DHL-4 progression in the presence of residual amounts of rituximab whereas rituximab treated tumours were refractory and did not respond to rituximab therapy alone any longer (Report 1029348). The anti-tumour activity of obinutuzumab as second line treatment to rituximab was observed in other studies in the SU-DHL-4 xenograft model (Reports 1038394, 1051515) but not in a mouse xenograft model with RL NHL tumours resistant to rituximab (Report 1049396).

In *Cynomolgus* monkeys, obinutuzumab appeared to be more active at depleting B-cells than rituximab (Report 10301398; Report 1030199 Report 1035992). Vaccination studies in huCD20 mice and *Cynomolgus* monkeys showed that the enhanced efficacy in terms of B-cell depletion of obinutuzumab translated into stronger suppression of *de novo* antibody responses, but left the protective humoral memory responses intact (Report 1053638).

No specific secondary pharmacodynamics studies have been conducted. *In vitro* tissue cross reactivity studies were conducted with obinutuzumab using a full panel of human and *Cynomolgus* monkey tissues (Reports 1024158, 1024159). Expected obinutuzumab-specific membrane staining was present in resident lymphocytes in lymphoid tissues (mammary gland, GALT in the small intestine and stomach, lymph node, spleen, thymus, and tonsil), lymphocytes or hematopoietic cells in bone marrow, and trafficking lymphocytes in other tissues (thyroid). Similar binding patterns were seen with obinutuzumab in the *Cynomolgus* monkey tissue study.

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Safety pharmacology programme

The potential effect of obinutuzumab on CNS, respiratory and cardiovascular systems was evaluated as part of the IV 26-week repeat-dose toxicity study in *Cynomolgus* monkeys (Report 1036190). No treatment-related effects on neurobehavioral parameters, respiration rate or blood pressure were noted during the scheduled dosing or recovery phase assessments. No rhythm abnormalities or qualitative ECG changes attributed to obinutuzumab were observed on Day 78 or 169 of the dosing phase or Day 254 of the recovery phase as part of the qualitative assessment of the ECGs. IV administration of obinutuzumab was not associated with electrocardiographic evidence of cardiotoxicity or arrhythmogenesis or effects on blood pressure when evaluated as part of the 13-week repeat-dose toxicity study in *Cynomolgus* monkeys (Report 1024830).

Pharmacodynamic drug interactions

Using isolated human PBMCs pre-incubated with 5 nM or 5 µM chlorambucil, no impact on the ADCC function of obinutuzumab was observed (Report 1050168). In the Z138 xenograft tumour model, obinutuzumab (1 mg/kg) in combination with chlorambucil (4 mg/kg) resulted in superior efficacy compared with obinutuzumab monotherapy or the combination of rituximab and chlorambucil (Report 1043607).

The applicant also submitted a number of studies addressing the anti-tumour activity of obinutuzumab in combination with various regimens in SCID mice tumour xenograft models Including cyclophosphamide, cyclophosphamide/vincristine, doxorubicin, bendamustine, fludarabine, rituximab (Reports 1029351, 1029347, 1034644, 1036132, 1025317; data not shown). In vitro prednisolone (1-100 µg/mL) decreased ADCC and NK activity (Report 1027588).

2.3.3. Pharmacokinetics

Validated ELISA assays with colorimetric detection were applied for the quantification of obinutuzumab and anti-obinutuzumab antibodies (ADAs) in Cynomolgus monkey serum. The performance of the assays is considered adequate.

Single dose studies were conducted in male mice and Cynomolgus monkeys. Following IV administration, obinutuzumab half-life was 5 and 12 days in mice administered 1 and 10 mg/kg, respectively. In Cynomolgus monkeys, the half-life varied from 7 to 8 days following IV treatment with 1 and 10 mg/kg obinutuzumab while the half-life was 2-3 days after SC treatment with 20 mg/kg obinutuzumab. The volume of distribution in mice and monkeys were small and approximately equal to the vascular volume.

After repeated dosing (4-week SC, 13- and 26-week IV) to monkeys, the systemic exposures generally increased in a dose-proportional manner. The drug accumulation ranged from 2- to 3-fold at the end of the studies. No gender differences were apparent. Formation of ADAs was confirmed in all three studies and was associated with a more rapid clearance of obinutuzumab (Reports 1024838, 1024830, and 1036190).

The in vivo distribution of obinutuzumab has not been studied (see discussion on non-clinical aspects). The Vss values indicated limited tissue distribution of obinutuzumab in animals and were consistent with the value (Vss of 6.62 L/person, 94.6 mL/kg for a 70-kg person) reported for rituximab in humans (Dirks and Meibohm 2010). Monkeys were the only relevant non-clinical responder species tested. Obinutuzumab can cross the blood-placental barrier in monkeys as shown in an enhanced pre- and post-natal development study (ePPND) (Report 1045612).

No specific metabolism studies were performed for obinutuzumab. The expected consequence of metabolism of biotechnology-derived pharmaceuticals is the degradation to small peptides and individual amino acids (ICH S6). In the disposition of mAbs, the FcRn receptor serves as a salvage receptor regulating mAb and/or endogenous IgGs catabolism. Obinutuzumab was shown to have similar binding affinity to the human and cynomolgus FcRn. FcRn could recycle a certain amount of obinutuzumab back to circulation, resulting in long terminal t1/2 in both monkeys and humans.

No specific excretion studies were performed for obinutuzumab in accordance with ICH S6 guideline. Secretion of obinutuzumab in milk appeared to be very limited in monkeys based on the result from the ePPND study (Report 1045612).

No dedicated nonclinical drug interaction study has been performed with obinutuzumab (see discussion on non-clinical aspects).

Table 4: Pharmacokinetic parameters after intravenous single administration

Species (Study reference)	**Assay**	**N**	**Dose (mg/kg)**	**$AUC_{0\text{-}inf}$ (µg.h/mL)**	**Cmax (µg/mL)**	**Cl (mL/hr/kg)**	**Vc (mL/kg))**	**Vss (mL/kg)**	**t½ (h)**
Mouse (1024804)	Sandwich ELISA	20/dose 2/timepoint	1	1540	21.1	0.648	45.3	89.4	125
			10	35600	232	0.281	42.1	107	288
Monkey (1020938)	Sandwich ELISA	2M/dose	1	3640	28.8	0.275	34.0	63.2	172
			10	40800	324	0.245	31.3	58.9	194

Table 5: Pharmacokinetic parameters in monkeys after repeated administration

Species (Study reference)	Route	Sampling time	Dose (mg/kg)	N/sex	Tmax (h)	Cmax (µg/mL)	AUC_{0-168} (µg.h/mL)
Monkey 1024830	IV	D1	10	3M	NA	268	22000
				3F	NA	273	20100
			30	3M	NA	907	69100
				3F	NA	966	72700
			100	5M	NA	3080	219000
				5F	NA	3350	226000
		D29	10	3M	NA	588	37400
				3F	NA	299	7410
			30	3M	NA	1320	134000
				3F	NA	1470	118000
			100	5M	NA	4970	465000
				5F	NA	4460	368000
		D78	10	3M	NA	606	59900
				3F	NA	332	10900
			30	3M	NA	1610	154000
				3F	NA	1470	139000
			100	5M	NA	5110	470000
				5F	NA	5210	462000
Monkey 1036190	IV	D1	5	6M	1	178	12700
				6F	1	174	13300
			25	6M	1	902	70000
				6F	1	907	68200
			50	6M	1	1800	137000
				6F	1	1800	128000
		D85	5	3M	1	327	32100
				4F	1	429	41600
			25	6M	1	1620	171000
				5F	1	1700	172000
			50	6M	7	3230	335000
				6F	1	2900	260000
		D176	5	3M	1	309	33400
				4F	1	427	44500
			25	6M	1	1770	220000
				4M	1	1170	128000
			50	6M	4	3170	379000
				6F	1	2670	303000
Monkey 1024838	SC	D1	30	5M	72	48.5	6660
				5F	72	64.4	8890
			120	5M	72	205	29800
				5F	72	267	35000
		D22	30	5M	72	40.9	5380
				5F	24	43.9	5700
			120	5M	24	291	39700
				5F	24	371	46500
Pregnant Monkey 1045612	IV	D20 pc	25	19F	7	709	66900
			50	17F	7	1460	122000
		D139 pc	25	12F	9.83	1220	125000
			50	14F	7	2470	250000

2.3.4. Toxicology

Single dose toxicity

No dedicated single-dose toxicity studies were performed with obinutuzumab (see discussion on non-clinical aspects).

Repeat dose toxicity

Repeat-dose toxicity studies applying weekly dosing were conducted in Cynomolgus monkeys (Table 6). The route of application was IV (9, 13 and 26-weeks duration) and SC (4-week), thus reflecting the clinical route of administration in the pivotal 26-week study. A 37-week treatment free period was included after the 13 week and 26 week IV studies, respectively.

No off-target toxicity was observed in Cynomolgus monkeys following IV and SC administration of obinutuzumab at AUC exposures up to 6-fold those observed in humans following administration of the maximum recommended dose of 1000 mg.

Obinutuzumab at doses ≥1 mg/kg induced B cell depletion in peripheral blood, lymph nodes and spleen. By the end of a 37-week recovery period, the level of peripheral B cells varied among the treated animals and represented from 7% to 152% of baseline values. Following initiation of treatment, a transient decrease in NK cell levels was observed.

In two cases an anaphylactoid response was observed post-dose and in one of the cases, the incident was lethal. Mortality due to infections secondary to B cell depletion was also observed in two cases.

Table 6: Summary of the results from the repeat-dose toxicity studies performed in Cynomolgus monkeys.

Study ID **Duration** **N** **GLP status**	**Dose (mg/kg)** **Frequency** **Route**	**Major findings**
1024829 3 animals/group 9 weeks Non-GLP	1, 10 mg/kg Day 1 and 8 IV (bolus)	**≥1 mg/kg**: B-cell depletion of the peripheral blood, spleen and lymph node, T cell expansion in lymph nodes **10 mg/kg**: T cell expansion in the spleen, reduced cellularity of lymphoid follicles of lymph nodes
1024838 4 weeks + 28 weeks recovery Main: 3 sex/group Recovery: 2/sex/group GLP	0, 30, 120 mg/animal/week Q7Dx5 SC	**≥30 mg/animal** Haematology: Depletion of B cells from peripheral blood, spleen and lymph nodes, reduction in NK cells Microscopy: lack of germinal centers in the follicles of spleen and lymph nodes **120 mg/animal** Mortality 1♂ during recovery phase (due to infection) Body weight 1♂ had significant body weight los Clinical pathology increased creatinine & fibrinogen Organ weight increased spleen weight **Recovery**: full recovery of B-cell population at 30 mg/animal/week and at least 50% recovery at 120 mg/animal/week. Reduction in NK cell levels was still evident in 1/4 120 mg/kg recovery animals. NOAEL= 10mg/kg
1024830 13 weeks + 37-week recovery Main: 3/sex/group Recovery: 2/sex/group from low and high dose GLP	0, 10, 30, 100 mg/kg Q7Dx IV (30 min infusion)	**≥10 mg/kg** Haematology depletion of B cells and a transient reduction of NK cells Microscopy Lack of germinal centers in the follicles of spleen and lymph nodes **100 mg/kg** Mortality 1 ♂ & 1♀ during recovery phase (one (♂)considered due to immunosuppression and secondary infection, the second (♀) due to low body weight/severe menstrual bleeding) **Recovery** Peripheral B-lymphocyte numbers started to recover 17 and 23 weeks after the last treatment in the male and female high-dose monkey, respectively. At the end of the recovery period, B-cells had recovered to a level around 50% of pre-dose values.
1036190	0, 5, 25, 50	**≥5 mg/kg** Mortality: 1♂ prior to necropsy (due to anaphylactoid response

Study ID Duration N GLP status	Dose (mg/kg) Frequency Route	Major findings
26 weeks + 37 week recovery Main: 4/sex/group Recovery: 2/sex/group GLP	mg/kg Q7Dx26 0 and 50 mg/kg: IV infusion 30 min 5 and 25 mg/kg: IV bolus	immediately after dosing) Physical examination: increased incidence of gingivitis in males Haematology: B cell values in peripheral blood, spleen and lymph nodes were undetectable or close to zero throughout the dosing phase, with the exception of individual animals that developed anti-obinutuzumab antibodies. A transient marginal decrease in natural killer cell numbers was noted on Day 3. Microscopy: lack of germinal centers in lymph nodes due to B cell depletion, immune-complex induced arteritis/periarteritis, and an increased incidence and/or severity of mononuclear infiltrates/inflammation in many tissues and organs. **≥25 mg/kg** Mortality: 2♂ & 1♀ during recovery phase (all due to chronic hypersensitivity reactions *i.e.* immune-complex glomerulonephritis and/or inflammation of other tissues, including serosa/adventitia). Clinical signs: 1♀ had an anaphylactoid response post-dose which was successfully treated Microscopy: immune-complex glomerulonephritis and kidney inflammation. IHC staining revealed glomerular, tubular epithelial cell, interstitial and/or peritubular capillary granular deposits containing monkey IgG, IgM, and/or C3. Electron microscopy showed electron dense deposits in the glomerular basement membrane of animals with glomerulonephritis. **50 mg/kg** Mortality: 1♀ prior to necropsy, 1♀ during recovery phase (both due to chronic hypersensitivity reactions *i.e*. immune-complex glomerulonephritis and/or inflammation of other tissues, including serosa/adventitia). **Recovery** B cell depletion (blood and lymphoid tissues) was completely reversed at the end of the recovery phase, except for 1 animal given 5 mg/kg/dose that exhibited only a partial recovery. Partial recovery of the inflammatory changes. NOAEL<5mg/kg

Genotoxicity

Genotoxicity studies with obinutuzumab were not performed (see discussion on non-clinical aspects).

Carcinogenicity

No carcinogenicity studies have been conducted with obinutuzumab (see discussion on non-clinical aspects).

Reproduction Toxicity

No adverse effects on male and female reproductive organs were observed via organ weight measurements and histopathological analysis conducted as part of the 26-week repeat-dose toxicity study in Cynomolgus monkeys. No treatment-related effect on menstrual cyclicity, sperm count, sperm morphology/motility, and reproductive hormone levels were observed.

No direct maternal toxicity, embryo-foetal toxicity or teratogenicity was observed following treatment of cynomolgus monkey dams with obinutuzumab at dose levels of 25 or 50 mg/kg/week from Day 20 post coitum until birth (table 7). Still, six dams were euthanized during the gestation period due to secondary opportunistic infections and hypersensitivity to obinutuzumab. With regard to the offspring, a complete depletion of B-lymphocytes was observed at both tested dose-levels. B-lymphocyte counts and immunologic function (TDAR) in the infants returned to almost normal levels within 6 months following birth.

Table 7: Summary of reproductive and developmental toxicity study

Study type / Study reference / GLP	Species; Number / sex / group	Dose (mg / kg / day) Route	Study design	NOAEL (mg / kg / day)	Major findings
Enhanced pre- and postnatal development 1045612	Monkey/ Cynomolgus 18 or 19 pregnant female/gp	0, 25, 50 IV Weekly	D20 *post coitum* until birth	NOAEL (F0) < 25 NOAEL (F1 general toxicity) < 25 NOAEL (F1 development) ≥ 50	**F0 females** **⩾ 25 mg/kg**: Mortality (3 at LD and 3 at HD) due to opportunistic infections and/or immunogenicity reactions (immune-complexe mediated serosal and parenchymal insterstitial inflammation of the liver, gallbladder, kidney and glomerulonephritis). Presence of ADA: 5/37 treated females were positive. **F1 generation** 13, 9 and 12 infants were born the in control, 25 and 50 mg/kg groups respectively. **≥ 25 mg/kg**: - Complete B lymphocytes depletion on D28 post-partum that returned to normal by D112 (25 mg/kg) or D168 (50 mg/kg) post-partum. - Mortality (1 at LD and 2 at HD) due to opportunistic infections and/or immunogenicity reactions. - Increased incidence of inflammatory cell foci in the kidney. **50 mg/kg**: Slightly lower infants body weight No effect on development or neurobevioural parameters. No effect on immune function on D181 and 212. Presence of ADA: 3/18 infants were positive.

No treatment-related adverse effects were observed on growth, development, immune function, and hematology and neurobehavioral parameters in the offspring when evaluated up to post-natal Day 240. The mean infant serum levels represented around 76 and 244% of the maternal obinutuzumab serum level at post-partum day 28 showing that obinutuzumab crosses the blood-placental barrier. The concentration of obinutuzumab in the milk was extremely low compared to the corresponding maternal serum concentration. Specifically the milk-to-maternal serum ratios were all less than 0.5% from all animals in both dose groups. The maximal dose tested in the enhanced pre- and post-natal development study gave rise to a plasma exposure level approximately 2.4-fold higher than obtained clinically at the recommended maximal dose of 1000 mg. Chlorambucil is considered a probable genotoxicant and can cause fetal harm when administered to pregnant women.

Toxicokinetic data

The $AUC_{0\text{-}168h}$ values obtained in the 26-week IV repeat-dose toxicity study conducted in Cynomolgus monkeys as well as the animal: human exposure margins are summarised in Table 8.

Table 8: Obinutuzumab AUC0-168h values from the 26-week IV repeat-dose toxicity study.

Species	Dose (mg/kg)	$AUC_{(0–168\ hr)}$ (µg • hr/mL)	AUC_{4wk} [a] (µg•day/mL)	Exposure Margin [b]
Cynomolgus monkey	5	39800	6630	0.39
	25	183000	30500	1.8
	50	344000	57300	3.4

[a] Extrapolated AUC4wk by $AUC_{(0–168\ hr)}$ x4 ÷24 hr

[b] Based on population predictions for 1000 mg clinical dose every 28 days (Cycle 6), AUC_{tau} = 17040 µg.day/mL, (see 5.3.3.5 Population PK Study Report)

Local Tolerance

Dedicated studies of local tolerance have not been submitted (see discussion on Non-clinical aspects).

Other toxicity studies

Obinutuzumab (in concentrations up to 5 mg/mL) was compatible with human whole blood samples and plasma samples, as assessed by lack of haemolysis (whole blood) and no plasma flocculation or changes in plasma turbidity (Report 1025140; data not shown).

In vitro studies showed that obinutuzumab has the potential to cause first infusion related cytokine release (Reports 1025124, 1045703), following 2 and 24 hours treatment of samples with up to 200 or 100 µg/ml obinutuzumab, respectively. Following obinutuzumab treatment of human whole blood samples for 2 hours, no signs of a potential to cause cytokine release similar to the positive controls were observed. However, following 24 hours incubation of the samples (Study 104703), obinutuzumab in concentrations 1-10 µg/ml showed similar potential as the positive controls to induce cytokine release. The results from the samples treated with obinutuzumab showed a bell-shaped curve, with the maximum cytokine release in the interval 1-10 µg/ml, whereas at higher doses of obinutuzumab, lower levels of cytokines were seen.

The tissue cross-reactivity observed in human tissues was similar to the *Cynomolgus* monkey tissues (Reports 1024158, 1024159; data not shown).

2.3.5. Ecotoxicity / environmental risk assessment

No ERA was submitted (see discussion on non-clinical aspects).

2.3.6. Discussion on non-clinical aspects

Obinutuzumab is a recombinant monoclonal humanised and glycoengineered Type II anti-CD20 antibody of the IgG1 isotype. It specifically targeted the extracellular loop of the CD20 transmembrane antigen on the surface of non-malignant and malignant pre-B and mature B-lymphocytes, but not on haematopoietic stem cells, pro-B-cells, normal plasma cells or other normal tissue. Glycoengineering of the Fc part of obinutuzumab resulted in higher affinity for FcγRIII receptors on immune effector cells such as natural killer (NK) cells, macrophages and monocytes as compared to non-glycoengineered antibodies (SmPC, section 5.1).

The exact mechanism of action of obinutuzumab remains to be confirmed. At least three different effector mechanisms may be involved: 1) cell death (also described as direct cell death or apoptosis), 2) antibody dependent cellular cytotoxicity (ADCC) or antibody dependent cellular phagocytosis (ADCP), and 3) complement dependent cytotoxicity (CDC).

ADCC/ADCP is considered as the most important mechanism of action of rituximab in patients, with CDC and cell death playing a less important role. In nonclinical studies, obinutuzumab induced direct cell death and mediated ADCC and ADCP through recruitment of FcγRIII positive immune effector cells. In addition, in vivo, obinutuzumab mediated only a low degree of CDC. In animal models obinutuzumab mediated potent B-cell depletion and antitumour efficacy. Obinutuzumab was characterised by enhanced ADCC as a consequence of the glycoengineering (SmPC, section 5.1).

The contribution of CDC activity of obinutuzumab mechanism of action seemed to be low as the neutralization of complement did not impact its efficacy in an in vivo xenograft study and no activation of complement was observed in patients. CDC activity does not seem to be a major mechanism of action of rituximab either (Alduaij and Illidge 2011; Beers et al. 2010; Glennie et al. 2007; Lim et al. 2010)

The mechanism of direct cell death induction has not been clearly elucidated. Cell death induction by obinutuzumab coincided with homotypic aggregation but was not dependent on mechanical disruption (Cragg et al. 2010, Herter et al. 2013a). Obinutuzumab could induce an immunogenic cell death that may lead to a secondary immune response against lymphoma/leukemia cells in vivo and in patients (Cheadle et al., 2013). Ex vivo studies with CLL patient samples showed that cell death induction in peripheral slowly-proliferating CLL cells was lower than for example in proliferating DLBCL cell lines (data not shown).

During the review, the applicant submitted two new studies investigating the contribution of direct cell death induction to obinutuzumab mechanism of action and using a variant of obinutuzumab with strongly reduced FcgR and effector function (obinutuzumab N297D; data not shown). The variant of obinutuzumab lacked FcgR binding by removal of the N-glycosylation site by introduction of a N297D mutation resulting in complete absence of the carbohydrate moiety of the antibody. As a consequence FcgR binding and C1q binding was strongly reduced rendering the mutated antibody effector dead. In vitro, the variant of obinutuzumab showed comparable direct cell death induction as compared to obinutuzumab and non-glycoengineered (GE) obinutuzumab; a residual ADCC activity; no CDC activity. In a B cell depletion assay, obinutuzumab N297D induced an inferior cell depletion compared to obinutuzumab and to non-GE obinutuzumab to a lesser extent but a greater cell depletion than rituximab or ofatumumab. In an in vivo study in sc SU-DHL4 xenograft model, obinutuzumab N297D induced tumor stasis but not complete tumor remission as seen with obinutuzumab and non-GE obinutuzumab. These data indicated that direct cell death induction significantly contributed to obinutuzumab mechanism of action but that both cell death induction and ADCC were necessary to achieve maximal efficacy.

The validations of the bioanalysis methods used for quantification of obinutuzumab in *Cynomolgus* monkey serum were not performed according to GLP. However, the analytical method was validated according to the guidance valid at the time of study performance, which was consistent with the FDA Guidance on Bioanalytical Method Validation and best industry practices (Kelley M et al. 2007, Viswanathan CT et al. 2007) with regards to the tested validation parameters and pre-defined acceptance criteria; thus, the lack of GLP compliance of the bioanalysis validation was considered acceptable.

The in vivo distribution of obinutuzumab has not been studied. This is deemed acceptable due to 1) the fact that obinutuzumab is specific for CD20 whose tissue expression is characterized 2) the fact that pharmacokinetic data indicate limited distribution beyond the plasma compartment and 3) the human cross-reactivity study indicates no potential for off-target binding. In accordance with the ICH S6 guideline, it is also acceptable that the metabolism and excretion of obinutuzumab has not been studied.

No dedicated nonclinical drug interaction study has been performed with obinutuzumab. Due to its nature as an antibody, obinutuzumab is not expected to have direct effect on the activity or expression of cytochrome P450 enzymes or drug transporters.

Information on potential acute effects of obinutuzumab was obtained from the repeat-dose safety studies in *Cynomolgus* monkeys, which included detailed assessments of clinical pathology, cytokine release, immunophenotyping, and/or cardiovascular safety after the first dose. Results showed no overt toxicity after the first dose. According to ICH guidance M3(R2), the results of these studies are considered appropriate to address acute toxicity aspects. Therefore, the lack of dedicated single-dose toxicity studies was considered acceptable.

In a 26 week cynomolgus monkey study, hypersensitivity reactions were noted and attributed to the foreign recognition of the humanised antibody in cynomolgus monkeys (0.7-6 times the clinical exposure based on Cmax and AUC at steady state after weekly administration of 5, 25, and 50 mg/kg). Findings included acute anaphylactic or anaphylactoid reactions and an increased prevalence of systemic inflammation and infiltrates consistent with immune complex mediated hypersensitivity reactions, such as arteritis/periarteritis, glomerulonephritis, and serosal/adventitial inflammation. These reactions led to unscheduled termination of 6/36 animals treated with obinutuzumab during dosing and recovery phases; these changes were partially reversible. No renal toxicity with a causal relationship to obinutuzumab has been observed in humans.

The lack of genotoxicity studies with obinutuzumab is acceptable because antibodies do not have the potential to cross the cell membrane.

No studies have been performed to establish the carcinogenic potential of obinutuzumab (SmPC, section 5.3). The lack of carcinogenicity studies is considered acceptable based ICH S6 guidance. It should be noted that the present application concerns obinutuzumab co-treatment with chlorambucil, which is a human carcinogen.

An enhanced pre and postnatal development (ePPND) toxicity study in pregnant *Cynomolgus* monkeys showed no evidence of teratogenic effects. However, weekly obinutuzumab dosing from post-coitum day 20 to delivery resulted in complete depletion of B cells in infants at weekly intravenous obinutuzumab doses of 25 and 50 mg/kg (2-5 times the clinical exposure based on Cmax and AUC). Offspring exposure on day 28 post-partum suggested that obinutuzumab can cross the blood-placenta -barrier. Concentrations 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 (less than 0.5% of the corresponding maternal serum levels) suggesting that exposure of infants must have occurred in utero. The B- cell counts returned to normal levels, and immunologic function was restored within 6 months post-partum (SmPC, section 5.3 and 4.6).

There are no data from the use of obinutuzumab in pregnant women. Obinutuzumab should not be administered to pregnant women unless the possible benefit outweighs the potential risk (SmPC, section 4.6).

Women of childbearing potential have to use effective contraception during and for 18 months after treatment with obinutuzumab (SmPC, section 4.6).

In case of exposure during pregnancy, depletion of B cells may be expected in newborns due to the pharmacological properties of the product. Consequently, newborns should be monitored for B cell depletion and vaccinations with live virus vaccines should be postponed until the infant's B cell count has recovered (SmPC, sections 4.4 and 4.6).

Animal studies have shown excretion of obinutuzumab in breast milk (SmPC, section 4.6). Because human immunoglobulin G (IgG) is excreted in human milk and the potential for absorption and harm to the infant is unknown, women should be advised to discontinue breast-feeding during obinutuzumab therapy and for 18 months after the last dose of obinutuzumab (SmPC, section 4.6).

Due to the potential depletion of B cells in newborns following exposure to obinutuzumab during pregnancy, virus vaccines should be postponed until the infant's B cell count has recovered (SmPC, section 4.4, see discussion on clinical safety).

No specific studies in animals have been performed to evaluate the effect of obinutuzumab on fertility. In repeat-dose toxicity studies in *Cynomolgus* monkeys obinutuzumab had no adverse effects on male and female reproductive organs (SmPC, section 5.3). The same conclusion has been reached for other CD20 antibodies, *i.e.*, rituximab and ofatumumab. However, in the clinical setting obinutuzumab will be co-administered with chlorambucil which has induced reversible and permanent sterility in men and women.

Obinutuzumab is not indicated for treatment of the paediatric population and Obinutuzumab has been granted a waiver for paediatric development. The lack of studies in juvenile animals is considered acceptable.

Since the clinically intended route of administration (IV) was also applied in the pivotal toxicity studies, the lack of dedicated studies of local tolerance is considered acceptable.

Renal changes have been observed with obinutuzumab in intravenous toxicity studies in *Cynomolgus* monkeys. Based on light microscopic evaluations, the main kidney findings were glomerulonephritis, interstitial inflammation and tubular degeneration/regeneration. Glomerulonephritis was considered to be immune-complex mediated, as confirmed by immunofluorescence detection of IgG deposits and the observation of sub-epithelial and intra-membranous electron dense regions in the glomeruli by electron microscopy. These findings are considered specific to non-human primates. No evidence for an association between obinutuzumab treatment and renal toxicity was identified. A few patients showed >grade 2 shift in creatinine, however, this appeared to be transient as mean creatinine values remained stable during treatment.

Antibodies, as other peptides and proteins, are exempted from environmental risk assessment (ERA) based on the EMA 2006 Guideline on Environmental Risk Assessment (ERA) for Non-GMO Human Medicinal Products (EMEA/CHMP/SWP/4447/00).

2.3.7. Conclusion on the non-clinical aspects

Overall, the non-clinical documentation submitted was considered adequate. The relevant information has been included in the SmPC (sections 4.4, 4.6, 5.1, 5.3).

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant. The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 9: Clinical Studies Contributing Safety and Efficacy Data Supporting the Application for Registration of Obinutuzumab in CLL

Study [Ref]	Target Population	Treat.	No. and type of obinutuzumab-treated patients included	
			CLL patients	NHL patients
Pivotal Study				
BO21004/ CLL11 Phase III	Previously untreated CLL with comorbidities and/or renal impairment	G+Clb (Clb) (R+Clb †)	Safety run-in 6 Stage 1a: GClb arm: 240 * Cross-over from Clb to GClb: 22	–
Supporting Studies				
BO21000 (GAUDI) Phase Ib	Part I Relapsed/refractory fNHL	G+FC G+CHOP	–	56 fNHL
	Part II Previously untreated fNHL	G+CHOP G+benda	–	81 fNHL
BO20999 (GAUGIN) Phase I/II	Relapsed/refractory NHL or CLL	G	Phase I: 13 * Phase II: 20 *	Phase I: 21 NHL Phase II: 40 iNHL 40 aNHL
BO21003 (GAUSS) Phase I/II	Phase I:CD20+ disease (lymphoma or CLL) Phase II: relapsed iNHL	G	Phase I: 5 *	Phase I: 17 NHL Phase II: 87 iNHL
JO21900 Phase I	CD20+ relapsed/refractory NHL	G	–	12 NHL
			306	354
Total no. of patients treated with obinutuzumab in safety database			660	

aNHL=aggressive non-Hodgkin's lymphoma; benda,=bendamustine; CHOP=cyclophosphamide, doxorubicin (hydroxy-daunorubicin), vincristine, and prednisone; Clb=chlorambucil; CLL=chronic lymphocytic leukemia; FC=fludarabine and cyclophosphamide; fNHL=follicular non-Hodgkin's lymphoma; G=obinutuzumab; iNHL=indolent non-Hodgkin's lymphoma; R=rituximab.

* Efficacy based on 238 patients in the randomized GClb arm of study BO21004/CLL11 (see Section 4.1.3). End-of-treatment response rates from 38 CLL patients in BO20999 and BO21003 studies are described in Section 4.2.

† Data from the RClb arm will not be used to support this application.

2.4.2. Pharmacokinetics

Plasma samples were collected for PK investigation purposes in five clinical studies. In three studies (Phase I/II BO20999, Phase I/II BO21003, and Phase I JO21900 studies), obinutuzumab was administered as a single agent. In two others studies (Phase Ib BO21000 and Phase III pivotal BO21004/CLL11 studies) obinutuzumab was administered in combination with chemotherapy in CD20-positive malignant disease patients.

A population pharmacokinetic model was developed to analyse the PK data in 678 NHL and CLL patients from Phase I, Phase II and Phase III studies who received obinutuzumab. This population PK model was used to describe the PK characteristics of obinutuzumab in patients with CLL.

Absorption

Obinutuzumab is administered intravenously, therefore absorption is not applicable. There have been no clinical PK studies performed with other routes of administration. From the population PK model, after the Cycle 6 Day 1 infusion in CLL patients, the estimated median C_{max} value was 473.2 µg/mL and AUC(τ) value was 9516 µg•d/mL (SmPC section 5.2).

Tables 10-11 present the PK exposure data for obinutuzumab following first dose and at the end of treatment for studies BO20999 and BO21000 and the end of induction for study BO21003.

Table 10: Comparison of Obinutuzumab PK parameters following First Dose (Cycle 1 Day 1) in Studies BO20999, BO21000 and BO21003

Dose (mg)	Study	C_{max} (µg/mL)	AUC_{last} (µg • day/mL)
100	BO20999 (N=3)	39.4 (21.3)	149 (43.8)
	BO21003 (N=3)	38.9 (23.2)	111 (94.5)
200	BO20999 (N=2)	63.2–91.2	257–361
	BO21003 (N=3)	68.8 (47.8)	294 (53.7)
400	BO20999 (N=4)	134 (27.1)	457 (64.9)
	BO21003 (N=3)	85.5 (69.4)	270 (108)
800	BO20999 (N=6)	234 (63.1)	1016 (28.3)
	BO21003 (N=2)	395–267	1487–1027
1200	BO20999 (N=6)	307 (30.6)	1025 (59.4)
	BO21003 (N=2)	332–342	1688–1365
1000	BO20999 (N=3)	210 (74.0)	790 (102)
	BO21000 (N=32)	302 (29.1)	1162 (144)
	BO21003 (N=3)	328 (30.9)	897 (81.3)

Data presented as geometric Mean (%CV) or as individual values for dose cohorts where N=2.

Table 11: Comparison of Obinutuzumab PK parameters for 1000 mg in Studies BO20999, BO21000 and BO21003 at the End of Treatment / Induction

Study	C_{max} (µg/mL)	AUC_{7d} (µg • day/mL)	AUC_{last} (µg • day/mL)
BO20999 Phase I CLL patients [a] (N=3)	573 (73.2)	3040 (118)	21300 (207)
BO20999 Phase II CLL patients [a] (N=12)	741 (43.8)	3870 (55.6)	36000 (69.8)
BO21003 Phase I [b] (N=6)	510 (63.6)	8847 (216)	NC
BO21003 Phase II [b] (N=6)	649 (43.9)	20100 (80.3)	
BO21000 Bendamustine [c] (N=30)	619 (31.1)	3270 (32.3)	20400 (46.2)
BO21000 CHOP [d] (N=28)	609 (30.5)	3240 (28.2)	19200 (41.9)

Data presented as geometric mean (CV%)

[a] CLL patients only received 1000 mg dose in BO20999.

[b] Induction period of 4 doses at weekly intervals.

[c] Obinutuzumab + bendamustine cohort.

[d] Obinutuzumab + CHOP cohort.

Distribution

There are no data on protein binding of obinutuzumab. Following intravenous administration, the volume of distribution of the central compartment (2.76 L), approximated serum volume, which indicates that distribution, is largely restricted to plasma and interstitial fluid (SmPC section 5.2).

Elimination

The metabolism of obinutuzumab has not been directly studied. Antibodies are mostly cleared by catabolism (SmPC section 5.2).

Obinutuzumab elimination comprised a time varying clearance model with two parallel pathways which described clearance, a linear clearance pathway and a non-linear clearance pathway which changed as a function of time. During the initiation of treatment, the non-linear time-varying clearance pathway was dominant and accounted for the major clearance pathway. As treatment progressed, the impact of this pathway diminished and the linear clearance pathway predominated. This was indicative of target mediated drug disposition (TMDD), where the initial abundance of CD20 cells caused a rapid depletion of obinutuzumab. However, once the majority of CD20 cells were bound to obinutuzumab, there was reduced impact of TMDD on PK (SmPC section 5.2).

For a female patient with CLL weighing 75 kg and with baseline tumor size less than 1750 mm^2, the time varying clearance (CLT = 0.231 L/day) was estimated to be 2.8-times higher than steady-state clearance (CLinf = 0.0828 L/day). Time-dependent clearance declined with a half-life of 17 days, and concentrations approached steady-state levels after approximately 4 months of dosing (for Study BO21004/CLL). Median elimination t½ was 30.3 days.

Obinutuzumab steady-state clearance and central volume increased with body weight as power functions with the power coefficients of 0.602 (95% CI: 0.404–0.800) and 0.403 (95% CI: 0.307–0.499), respectively. Obinutuzumab steady-state clearance and central volume were respectively 23% (95% CI: 14–32%) and 18% (95% CI: 13–22%) higher in males (see special populations). Initial time-dependent clearance was 52% (95% CI: 23–87%) higher in males.

Decline of time-dependent clearance was 87% (95% CI: 44−125%) faster in NHL compared to CLL patients, and 148% (95% CI: 93−219%) faster in patients with low baseline tumor size (below 1750 mm^2). At the same dose, patients with high baseline tumor size generally had lower exposure.

Dose proportionality and time dependencies

Table 12: Comparison of Obinutuzumab PK parameters following First Dose (Cycle 1 Day 1) in Studies BO20999, BO21000 and BO21003.

Dose (mg)	Study	C_{max} (µg/mL)	AUC_{last} (µg • day/mL)
100	BO20999 (N=3)	39.4 (21.3)	149 (43.8)
	BO21003 (N=3)	38.9 (23.2)	111 (94.5)
200	BO20999 (N=2)	63.2–91.2	257–361
	BO21003 (N=3)	68.8 (47.8)	294 (53.7)
400	BO20999 (N=4)	134 (27.1)	457 (64.9)
	BO21003 (N=3)	85.5 (69.4)	270 (108)
800	BO20999 (N=6)	234 (63.1)	1016 (28.3)
	BO21003 (N=2)	395–267	1487–1027
1200	BO20999 (N=6)	307 (30.6)	1025 (59.4)
	BO21003 (N=2)	332–342	1688–1365
1000	BO20999 (N=3)	210 (74.0)	790 (102)
	BO21000 (N=32)	302 (29.1)	1162 (144)
	BO21003 (N=3)	328 (30.9)	897 (81.3)

Data presented as geometric Mean (%CV) or as individual values for dose cohorts where N=2.

Special populations

In the population pharmacokinetic analysis, gender was found to be a covariate which explained some of the inter-patient variability, with a 22% greater steady state clearance (CLss) and an 18% greater volume of distribution (V) in males. However, results from the population analysis have shown that the differences in exposure were not significant (with an estimated median AUC and C_{max} of 11282 µg•d/ml and 578.9 µg/ml in females and 8451 µg•d/mL and 432.5 µg/mL in males, respectively at Cycle 6), indicating that there is no need to dose adjust based on gender (SmPC section 5.2).

The population pharmacokinetic analysis of obinutuzumab showed that age did not affect the pharmacokinetics of obinutuzumab. No significant difference was observed in the pharmacokinetics of obinutuzumab among patients < 65 years (n=265), patients between 65-75 years (n=197) and patients > 75 years (n=128) (SmPC section 5.2). No dose adjustment is required in elderly patients (see section 4.2).

No studies have been conducted to investigate the pharmacokinetics of obinutuzumab in paediatric patients (SmPC section 5.2). The safety and efficacy of Gazyvaro in children and adolescents aged below 18 years has not been established. No data are available (SmPC, section 4.2).

No difference in AUC exposure between Caucasians and Japanese subjects was apparent.

The population pharmacokinetic analysis of obinutuzumab showed that creatinine clearance did not affect pharmacokinetics of obinutuzumab. Pharmacokinetics of obinutuzumab in patients with mild creatinine clearance (CrCl 50-89 mL/min, n=306) or moderate (CrCl 30 to 49 mL/min, n=72) renal impairment were similar to those in patients with normal renal function (CrCl ≥90 mL/min, n=207). Pharmacokinetic data in patients with severe renal impairment (CrCl 15-29 mL/min) is limited (n=5), therefore no dose recommendations can be made (SmPC section 5.2; see Risk Management Plan).

No dose adjustment is required in patients with mild to moderate renal impairment (creatinine clearance [CrCl] 30-89 mL/min) (see SmPC section 5.2). The safety and efficacy of Gazyvaro has not been established in patients with severe renal impairment (CrCl < 30 mL/min).

No formal pharmacokinetic study has been conducted in patients with hepatic impairment (SmPC section 5.2; see Risk Management Plan). The safety and efficacy of Gazyvaro in patients with impaired hepatic function has not been established. No specific dose recommendations can be made (SmPC, section 4.2).

Nine patients in the PK database had obinutuzumab human anti-human antibody (HAHA) detected after treatment initiation, all from the pivotal phase III study BO21004/CLL11 during the follow-up period. The PK of these patients was similar to the PK of the other patients during treatment. The most recent analysis of immunogenicity data for study BO21004/CLL11 was performed at the data cut-off for the Stage 2 analysis; the incidence of HAHA-positive patients was 2% at 6 months follow-up, 3% at 9 months follow-up, and 6% at 12 months follow-up.

Pharmacokinetic interaction studies / Pharmacokinetics using human biomaterials

No in vitro or in vivo studies on pharmacokinetic drug interactions have been submitted.

No differences in obinutuzumab PK behaviour were observed between study BO21004/CLL in which obinutuzumab was administered in combination with chlorambucil and those studies in which chlorambucil was not used.

2.4.3. Pharmacodynamics

Mechanism of action

No clinical pharmacodynamic studies were submitted. In the pivotal clinical study BO21004/CLL11, 91% (40 out of 44) of evaluable patients treated with obinutuzumab were B- cell depleted (defined as CD19+ B -cell counts < 0.07 x 10^9/L) at the end of treatment period and remained depleted during the first 6 months of follow up. Recovery of B- cells was observed within 12-18 months of follow up in 35% (14 out of 40) of patients without progressive disease and 13% (5 out of 40) with progressive disease (SmPC, section 5.1).

Primary and Secondary pharmacology

PD data supportive to the suggested mechanism of action have been submitted (data not shown).

2.4.4. Discussion on clinical pharmacology

Overall the PK profile is best described by a two-compartment model with two different clearance mechanisms: one time dependent (suggesting a target-mediated mechanism) and one linear. The time-varying target mediated component inherently suggests lack of dose-proportionality.

Data from phase I/II studies are from different study populations with in fact most data from patients suffering from follicular/indolent non-Hodgkin's lymphoma. Based on simulations (data not shown) predicted clearance was about 19% lower in patients with BCL/DLBCL compared to patients with CLL, and AUC (tau) was 27% (BCL) and 39% (DLBCL) higher than in patients with CLL. These differences are unlikely to be of clinical relevance.

A population pharmacokinetic (PK) model was developed to analyse the PK data in 678 non-Hodgkin's lymphoma (NHL) and CLL patients from Phase I, Phase II and Phase III studies who received obinutuzumab. This population PK model was used to describe the PK characteristics of obinutuzumab in patients with CLL (SmPC, section 5.2).

Estimates of PK parameters from the population PK model were a central volume of distribution of around 2.76 L; initial clearance values (for a female patient with CLL weighing 75 kg and with baseline tumor size less than 1750 mm2) of around 0.23 L/day and steady-state clearance 0.083 L/day. The relevance of the population PK models with respect to differences in the target expression among the different diseases was investigated.

In accordance with current guideline on therapeutic proteins, no studies on metabolism have been submitted.

From population PK model with a target-specific clearance component, a lack of dose-proportionality and time-dependency is expected to some extent. This model suggested moderate effects of gender, low- and high weight on PK parameters with an order of magnitude of about 30%. This is unlikely to be of clinical relevance. No effects of impaired renal function, age or race were apparent.

Interindividual variability appeared to be high with CV% around 100. No covariable was identified as a key element explaining the large inter-individual variability of obinutuzumab PK, and so no recommendations can be drawn for the dosage adjustment by the PK population modelling. The need for individualization of dose or drug monitoring has been considered. Whilst clinical efficacy has been observed at 1000 mg in the pivotal study BO21004/CLL11, there was no evidence from the phase I/II studies that a lower dose would have been equally effective. An exploratory graphical analysis in the Population PK Report did not indicate that there was any relationship between obinutuzumab exposure and adverse events such as infusion-related reactions and neutropenia. Thus, dose individualization and drug monitoring are not necessary.

No formal drug - drug interaction (DDI) studies were undertaken with obinutuzumab. Specific drug interaction studies are generally not required for this type of drug. Due to the fact that it is an antibody, obinutuzumab is not a substrate, inhibitor, or inducer of cytochrome P450 (CYP450), uridine diphosphate glucuronyltransferase (UGT) enzymes and transporters such as P-glycoprotein. Therefore, no pharmacokinetic interaction is expected with drugs known to be metabolised by these enzyme systems (SmPC, section 4.5).

The effect of a co-treatement with chlorambucil on the PK of obinutuzumab has been investigated in the population PK model. Chlorambucil seemed to have no clinically relevant effect on the PK of obinutuzumab (data not shown).

Cytokine modulation as an indirect mechanism appears unlikely given the transient nature of these changes (data not shown). Data from clinical trials do not suggest that concomitant chemotherapy has clinically relevant effect on obinutuzumab pharmacokinetics (data not shown). Data from ongoing trials are elucidating the possible effect of obinutuzumab on the PK of concomitant chemotherapeutic treatment, including CHOP (study GAO4915g) and bendamustine (study GAO4753g). The applicant will submit these data when available (see Risk Management Plan). Potential interaction between obinutuzumab and chlorambucil linked to metabolization / excretion pathways is unlikely.

Anti-CD20 antibodies are not considered to be cardiotoxic, and there is no plausible mechanism of direct cardiotoxicity for these drugs as cardiac cells do not express the CD20 antigen. Obinutuzumab is not expected to induce QT prolongation. The co administration of obinutuzumab with drugs known to prolong QTc and inducing Torsades de Pointes was discussed. As obinutuzumab is a monoclonal antibody, it would not be capable of interacting directly with ion channels, including the hERG channel. See also discussion on clinical safety (worsening of pre-existing cardiac conditions).

Likewise, obinutuzumab induced serious neutropenia and knowing the safety profile of chlorambucil towards blood cells, the mention of a risk of hematologic adverse effects potentiation was included in the product information (see SmPC section 4.5).

Vaccination with live virus vaccines is not recommended during treatment and until B cell recovery because of the immunosuppressive effect of obinutuzumab (SmPC, sections 4.4 and 4.5, see discussion on non-clinical safety).

The suggested mechanism of action appears biologically plausible based on in vitro- and animal studies. No additional clinical pharmacodynamic studies are considered necessary.

Immunogenicity of obinutuzumab did not appear to present a clinically relevant issue from the data available. However the amount of data available on this subject is limited and does not allow for definite conclusions. From a visual inspection of data of exposure (Cmean) against efficacy outcomes, it is not possible to draw clinically meaningful conclusions on an association between exposure and outcome. Immunogenicity has been categorized as a potential risk (see discussion on clinical safety and Risk Management Plan).

During development, three different manufacturing processes were established for obinutuzumab: the first generation (G1/DP1), the second generation (G2/DP2), and the third generation (G3/DP3) process. The applicant has demonstrated comparability between the different drug product DS/DP generations in vitro and in the population-PK analysis (data not shown).

Limited data are available on the effect of Fc gamma receptor polymorphisms on the efficacy of obinutuzumab (Risk Management Plan). In Study BO21004, subgroup analysis confirmed no difference in PFS, the primary endpoint of the study, between patients with the low affinity and high affinity variants FcγRIIa and FcγRIIIa. For rituximab, no clear dependency of response or outcome according to the FcγRIIIA/IIA polymorphism has been established in CLL, follicular lymphoma and diffuse large B-cell lymphoma.

2.4.5. Conclusions on clinical pharmacology

The PK of obinutuzumab has been reasonably well investigated and generally in accordance with the current guideline on therapeutic proteins.

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

Thirteen (13) patients received obinutuzumab at doses of 400 mg up to and including 2000 mg (given as a flat dose) in study BO20999. There were no dose-limiting toxicities (DLTs) and no requirement for dose reductions. Five patients experienced CTC Grade 4 neutropenia as the maximum severity and four patients experienced NCICTC Grade 3 neutropenia as the maximum severity. The overall response rate with obinutuzumab monotherapy as assessed by the International Workshop on CLL criteria observed was in the region of 60-70%. There was no clear dose-response relationship.

The Phase I study together with modelling and simulation indicated that the same levels of obinutuzumab exposure and saturation of target could be achieved with a more practical schedule of 1000 mg used throughout a treatment course and an additional dose given at Day 15 of the first cycle for the CLL patients. In the phase II trial BO20999 a dose of 1000 mg of GA101 to be administered on Days 1, 8 and 15 of the first cycle and then on Day 1 of Cycles 2 - 8 for a maximum of eight cycles (10 infusions in total). Based on the combined Phase I and II results, modelling and simulation, the Phase III dose of 1000 mg has been selected to take forward in both CLL and NHL. All patients randomized to the GClb treatment arm were to receive 1000 mg of obinutuzumab as an IV infusion on Day 1, Day 8 and Day 15 of the first treatment cycle (Cycle 1). For each subsequent cycle, patients received obinutuzumab (1000 mg) as an IV infusion on Day 1 only (Cycle 2−6).

2.5.2. Main study(ies)

BO21004/CLL11 - Stage 1a (GClb vs. Clb) – An open-label, multi-center, three arm randomized, phase III study to compare the efficacy and safety of RO5072759 + chlorambucil (GClb), rituximab + chlorambucil (RClb) or chlorambucil (Clb) alone in previously untreated CLL patients with comorbidities

Methods

Study Participants

Inclusion criteria

Patients had to meet the following criteria:

- Have documented CD20+ B−CLL according to National Cancer Institute (NCI) criteria;
- Previously untreated CLL requiring treatment according to the NCI criteria;
- Total cumulative illness rating scale (CIRS) Score >6 or creatinine clearance <70 mL/min
- or both;
- Absolute neutrophil count (ANC) ≥1.5 x 109/L and platelets ≥75 x 109/L unless cytopenia is caused by the underlying disease, i.e., no evidence of additional bone marrow dysfunction (e.g., myelodysplastic syndrome [MDS], hypoplastic bone marrow);
- Age 18 years or older;
- Life expectancy >6 months;
- Able and willing to provide written informed consent and to comply with the study protocol procedures.

Exclusion criteria

Any patient who met any of the following criteria was excluded:

- Patients who have received previous CLL therapy;
- Transformation of CLL to aggressive NHL (Richter's transformation);
- 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;
- Inadequate renal function: creatinine clearance <30 mL/min;
- Inadequate liver function: NCI Common Toxicity Criteria (NCI CTC) Grade 3 liverfunction tests (aspartate transaminase [AST], alanine transaminase [ALT] >5 × upper limit of normal [ULN] for >2 weeks; bilirubin >3 × ULN) unless due to underlying disease;

- History of other malignancies which could affect compliance with the protocol or interpretation of results. Patients with a history of malignancy that had been treated, but not with curative intent, were excluded, unless the malignancy had been in remission without treatment for ≥2 years prior to enrolment. Patients with a history of adequately treated carcinoma in situ of the cervix; basal or squamous cell skin cancer; low grade, early stage localized prostate cancer treated surgically with curative intent; good prognosis ductal carcinoma in situ (DCIS) of the breast treated with lumpectomy alone with curative intent were eligible.
- Patients with active bacterial, viral, or fungal infection requiring systemic treatment;
- Patients with known infection with human immunodeficiency virus (HIV) or Human T Cell Leukemia Virus 1 (HTLV-1);
- Positive hepatitis serology: Hepatitis B (HBV) : Patients with positive serology for Hepatitis B defined as positivity for Hepatitis B surface antigen (HBsAg) or Hepatitis B core antibody (anti-HBc). Patients positive for anti−HBc may be included if Hepatitis B viral DNA is not detectable.
- Hepatitis C (HCV): Patients with positive Hepatitis C serology unless HCV (RNA) is confirmed negative;
- History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies. Known sensitivity or allergy to murine products;
- Hypersensitivity to Clb or to any of the excipients;
- Women who are pregnant or lactating;
- Fertile men or women of childbearing potential unless: (1) surgically sterile or ≥2 years after the onset of menopause (2) willing to use a highly effectivecontraceptive method (Pearl Index <1) such as oral contraceptives, intrauterine device, sexual abstinence or barrier method of contraception in conjunction with spermicidal jelly during study treatment and in female patients for 12 months after end of antibody treatment and male patients for 6 months after end of chlorambucil treatment;
- Vaccination with a live vaccine a minimum of 28 days prior to randomization.

Treatments

Prior to randomization, 6 eligible patients who fulfilled the inclusion and exclusion criteria entered an open−label, safety run−in phase with GClb. After review of the safety data from these 6 patients by the DSMB, the randomized phase was opened.

Obinutuzumab

Prior to treatment, all patients received pre-medication. All 6 patients entering the safety run-in and all patients randomized to the GClb treatment arm received 1000 mg of obinutuzumab as an IV infusion on Day 1, Day 8 and Day 15 of the first treatment cycle (Cycle 1, see also discussion on clinical safety on amendments introducing the splitting of the Day 1 dose). For each subsequent cycle, patients received obinutuzumab (1000 mg) as an IV infusion on Day 1 only (Cycle 2−6).

Obinutuzumab was administered with full emergency resuscitation facilities immediately available and patients were closely supervised by the investigator at all times.

Originally, for patients with a high white blood cell (WBC) count, the infusion could be given extremely slowly over a longer period of time, or the dose could be split (2 × 500 mg) and given over two consecutive days.

Rituximab

Prior to treatment, all patients received pre-medication. Rituximab was administered according to standard institutional practice.

All patients randomized to the RClb arm received 375 mg/m2 of rituximab as an IV infusion on Day 1 of the first treatment cycle (Cycle 1).

For each subsequent cycle, patients received rituximab (500 mg/m2) as an IV infusion on Day 1 (Cycles 2−6). Thus, the licensed dose of rituximab for use in B-CLL was used.

Rituximab was administered with full emergency resuscitation facilities immediately available and patients were closely supervised by the investigator at all times.

Chlorambucil

The rationale for the Clb dosing is primarily based on the findings from the German GCLLSG CLL5 trial. All patients received 0.5 mg/kg body weight of Clb given orally on Day 1 and Day 15 of all treatment cycles (Cycles 1−6). The interval between each cycle was 28 days. In patients with a Body Mass Index (BMI) >35 (Grade 2 obesity) the dose of Clb was capped at a maximum limit associated with a BMI of 35.

Anti-pyretic and Anti-histaminic Prophylaxis

Because some patients may develop hypersensitivity or other IRRs to obinutuzumab or rituximab, premedication with oral acetaminophen/paracetamol (650 mg to 1000 mg) and an anti−histamine such as diphenhydramine (50 mg to 100 mg) was administered to all patients approximately 30 minutes prior to the start of the first infusion (unless contraindicated). For subsequent obinutuzumab infusions, pre−medication with oral acetaminophen/paracetamol was administered. If the previously administered obinutuzumab infusion did not result in an IRR greater than an NCI CTCAE Grade 1 adverse event (i.e., no medication was required to treat the IRR and there was no interruption to the infusion), the anti−histamine pre−medication could be omitted. Pre−medication with an antipyretic and an antihistaminic was administered before each infusion of rituximab.

Corticosteroid Premedication

Initially, the protocol outlined that pre−medication with corticosteroids (e.g., 100 mg IV prednisolone or equivalent) could be given to obinutuzumab−treated patients who were considered at high risk for a severe IRR (e.g., high circulating lymphocyte count).

Pre−medication with corticosteroids (e.g. 100 mg IV prednisolone or equivalent) was also recommended for rituximab patients whose lymphocyte counts are > 25 × 10^9/L. The option of pre−medication with corticosteroids was later amended making it mandatory that all obinutuzumab- and rituximab−treated patients received corticosteroids at least 1 hour prior to the first infusion and that an equivalent dose of dexamethasone (20 mg) or methylprednisolone (80 mg) was permitted but hydrocortisone was not used.

For subsequent infusions with obinutuzumab and rituximab, corticosteroid premedication was given to patients who experienced a Grade 3 IRR with the previous infusion, patients with lymphocyte counts >25 × 109/L, and at the investigator's discretion.

Concomitant Anti-hypertensive Medications

Originally in the protocol under the warning and precautions section for both ritixumab and obinutuzumab the recommendation was given that since hypotension could occur as a result of an IRR, consideration was to be given to withholding anti−hypertensive medications for 12 hours prior to the infusion.

In protocol amendment G, this guidance was moved to the concomitant medications section to emphasize the importance and the wording for obinutuzumab was slightly amended: Anti−hypertensive drugs used to control underlying hypertension were not given on the morning of, and throughout the first infusion of, obinutuzumab. Of note, anti−hypertensive treatment could still be used to treat IRR−triggered hypertension, if required.

Tumor Lysis Syndrome

Patients with a high tumor burden (WBC >25 × 109/L or bulky lymphadenopathy) received prophylaxis for tumor lysis syndrome (TLS) prior to the initiation of treatment. These patients were to be well hydrated. It was requested that a fluid intake of approximately 3 liters per day was maintained, 1−2 days before the first dose of obinutuzumab or rituximab. All patients with high tumor burden were treated with allopurinol, or a suitable alternative treatment, starting 12−24 hours prior to the first infusion. Patients continued to receive repeated prophylaxis with allopurinol and adequate hydration prior to each subsequent infusion, if deemed appropriate by the investigator.

Infection Prophylaxis

In patients with neutropenia, or at risk of neutropenia, it was strongly recommended to give antibiotic prophylaxis (e.g., co−trimoxazole) throughout the treatment period.

Choice of antibiotic, dose and schedule was according to standard institutional practice.

Antiviral and antifungal prophylaxis was given at the discretion of the investigator.

Objectives

The primary objective of study BO21004 (also known as study CLL11) was to demonstrate clinically relevant statistical superiority in PFS with obinutuzumab + Clb (GClb) compared to rituximab + Clb (RClb) and Clb alone and RClb compared to Clb (GClb vs. Clb; GClb vs. RClb; RClb vs. Clb) in previously untreated CLL patients with comorbidities. The Clinical Study Report (CSR) initially submitted reports the primary analysis of GClb versus Clb (Stage 1a). Subsequently the applicant also submitted the CSR for the primary analysis of GClb versus RClb (Stage 2).

Outcomes/endpoints

Primary endpoint

The primary endpoint was PFS. PFS was defined as the time from randomization to the first occurrence of progression, relapse, or death from any cause as assessed by the investigator. Data for patients without disease progression or death will be censored at the time of the last response assessment, or, if no response assessments were performed after the baseline visit, at the time of randomization plus one day. PFS based on IRC assessments was also analyzed to support the primary analysis. Disease progression was to be assessed by the investigators assessed according to the IWCLL guidelines.

Secondary endpoints

Event-free survival (EFS) was defined as the time between date of randomization and the date of disease progression/relapse, death, or start of a new anti-leukemic therapy. If the specified event (disease progression/relapse, death, start of a new anti-leukemic treatment) did not occur, patients were censored at the date of last tumor assessment. In cases where no tumor assessment is available, patients were conservatively censored at the date of randomization plus one day.

Disease-free survival (DFS) was defined for all patients with complete response at any time from 56 days after end of treatment onwards. DFS extends from the date the complete response was first recorded to the date on which progressive disease (PD) is first noted or the date of death due to any cause.

Only assessments from 56 days after end of treatment onwards were taken into account. Patients with no documented progression after CR/CR with incomplete bone marrow recovery (CRi) were censored at the last date at which they are known to have been in CR/CRi.

Duration of response (DOR) was defined similarly for complete and partial responders at any time from 56 days after end of treatment onwards. DOR starts at the date the response (either CR or PR) was first recorded until the date on which PD is first noted or the date of death due to any cause.

Only assessments from 56 days after end of treatment onwards were taken into account. Patients with no documented progression after CR/CRi or PR were censored at the last date at which they are known to have had the CR/CRi or PR.

Time to re-treatment/new anti-leukemic therapy was defined as time between the date of randomization and the date of first intake of re-treatment or new anti-leukemic therapy. Patients who were reported as not having started re-treatment or new anti−leukemic therapy were censored at the last visit date they were assessed with regard to start of new treatment or the date of death.

Overall Survival (OS) was defined as the time between the date of randomization and the date of death due to any cause. Patients who were not reported as having died at the time of the analysis were censored at the date when they were last known to be alive.

End of treatment response was defined as the response occurring at the end of treatment (first assessment that occurred more than 56 days after the end of treatment) before start of new anti−leukemia treatment. If the only response assessment after treatment end is PD, it was included irrespective of when it occurred (i.e., even if earlier than 56 days after the end of treatment). Overall response rate for end of treatment response (end of treatment response rate) is defined as percentage of patients with CR, incomplete CR (CRi), nodular partial response (nPR), or PR at end of treatment response. Patients with no post-baseline response assessment (due to whatever reason) and patients with post-baseline response assessments (excluding PD) but with no end of treatment response available as well as patients with stable disease (SD) or PD as of the end of treatment response were considered non-responders for end of treatment response.

However, if at any time the only response assessment reported for a patient is PD, it was included irrespective of the time point it occurred.

Best overall response was defined as the best response recorded from 56 days after end of treatment onwards before start of new anti-leukemic treatment. Overall response rate for best overall response (best overall response rate) is defined as percentage of patients with CR, CRi, PR, or nPR as best overall response. Patients with no post-baseline response assessment (due to whatever reason) were

considered non-responders for best overall response as well as patients with SD or PD.

Best overall response within 1 year of start of study treatment was defined as the best response recorded from 56 days after end of treatment onwards until disease progression, death, or 6 months (190 days) after last administration of last component of study drug, whichever occurs first. Overall response rate for best overall response (best overall response rate within 1 year of start of study treatment) is defined as percentage of patients with CR, CRi, PR, or nPR as best overall response. Patients with no post-baseline response assessment (due to whatever reason) and patients with post-baseline response assessments but no response assessments up to 6 months after last administration of last component of study drug were considered non-responders for best overall response as well as patients with SD or PD.

Molecular remission was defined as an MRD-negative result at the end of treatment (assessment that occurred between 56 days and 6 months of last treatment).

Sample size

The primary endpoint of investigator-assessed PFS was used to determine the sample size for the study. The median PFS for Clb in this patient population was estimated to be 14 months. At the time the protocol was written, there were no published Phase III data for patients treated with RClb.

However, according to expert opinions, patients treated with RClb would be expected to progress at least 8 to 10 months later than patients treated with Clb alone. Therefore, a hazard ratio (HR) of 0.6 for a RClb versus Clb comparison seemed reasonable. For the comparison of GClb versus RClb, an HR of 0.74 is assumed as a possible treatment effect. Both of these estimated HRs result in an assumed HR of 0.44 for GClb versus Clb alone.

This led to the following assumptions on the treatment effects:

• Median PFS for Clb alone = 12 months

• Effect of RClb versus Clb alone: HR = 0.6 (corresponding to a median PFS for RClb of 20 months)

• Effect of GClb versus RClb: HR = 0.74 (corresponding to a median PFS for GClb of 27 months)

Statistical assumptions for the comparison of GClb versus RClb:

• α= 5% (two-sided test level, for the entire closed-test procedure)

• Power = 80%

• Dropout rate = 10% per year

Thus, 780 patients in total have to be recruited within approximately 36 months assuming non-linear recruitment with the following study start ramp up:

• Months 1−3: 4 patients each

• Month 4: 8 patients

• Month 5: 12 patients

• Month 6: 16 patients

• Month 7: 20 patients

• After Month 7: 24.5 patients until recruitment end

Randomisation

Eligible patients who fulfilled the inclusion and exclusion criteria were randomly assigned to the three treatment arms via a block stratified randomization procedure using an interactive voice/web-based system (IVRS). Patients were stratified by Binet stage and country/region. The country/regions were classified as:

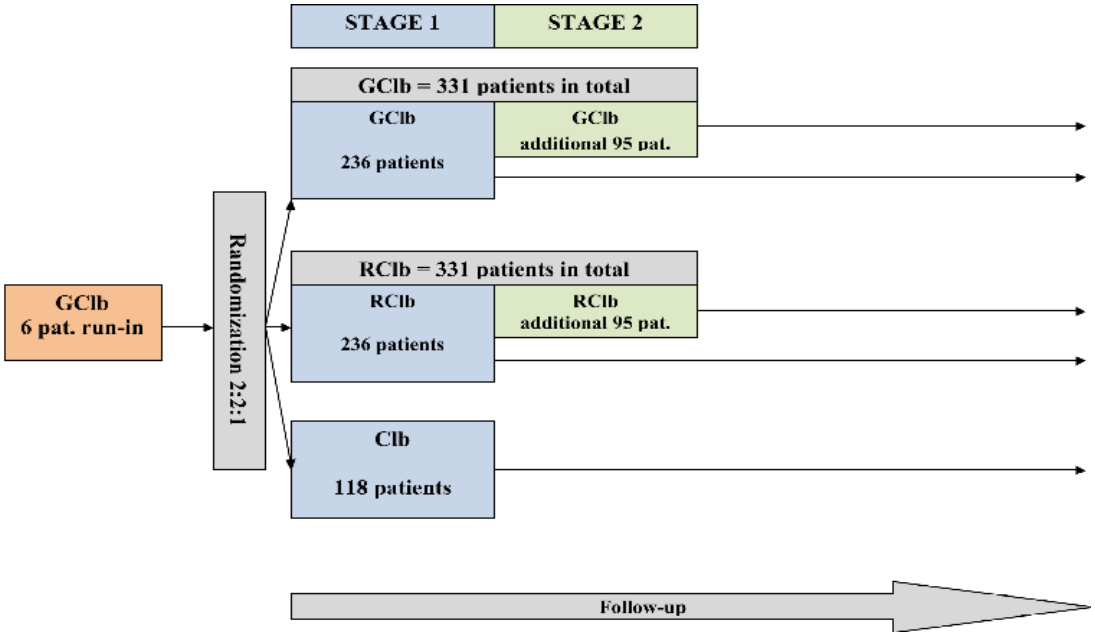
- Asia and Oceania: Hong Kong, China, Thailand, Australia and New Zealand;

- Europe Group 1: United Kingdom, Netherlands, Romania, Bulgaria, Croatia, Estonia, Slovakia, Czech Republic, Italy, France, Russia, Denmark, Spain and Egypt;
- Europe Group 2: Germany, Austria and Switzerland;
- North and Central America and Caribbean: Canada, Mexico and USA;
- South America and South Atlantic: Brazil and Argentina.

Patients were randomized in Stage 1 on a 2:2:1 (GClb:RClb:Clb) basis between the three treatment groups and in Stage 2 on 1:1 (GClb:RClb) basis between the two treatment arms:

- 331 patients in the GClb treatment group
- 331 patients in the RClb treatment group
- 118 patients in the Clb treatment group

Randomization to the Clb arm was stopped once 118 eligible patients were allocated.



Abbreviations: Clb = chlorambucil; GClb = obinutuzumab in combination with chlorambucil; pat. = patients; RClb = rituximab in combination with chlorambucil

Figure 3: Study Design of Pivotal Study BO21004/CLL11

Blinding (masking)

The study was an open–label study.

Statistical methods

The primary objective of the study was to compare the following three hypotheses:

- PFS of GClb versus Clb alone: H0: GClb = Clb versus H1: GClb ≠ Clb (Stage 1a)
- PFS of RClb versus Clb alone: H0: RClb = Clb versus H1: RClb ≠ Clb (Stage 1b)
- PFS of GClb versus RClb: H0: GClb = RClb versus H1: GClb ≠ RClb (Stage 2)

Adjustments for multiplicity were to be done using a three arm closed test procedure. The first test was for any difference between the three treatment groups at an alpha level of 5%. If the null hypothesis of equal PFS distributions for all 3 groups was rejected, pairwise tests for each of the three above mentioned hypotheses were enabled at the 5% alpha level.

Details on sample size and timing of the analysis are provided in Table 14.

Table 13: Analysis timing for stage 1 analysis

Analysis Type	Comparison *(stage)*	Approximate Timing of Analysis Events (%)	Approximate Time (Months)	Number of Events Triggering the Analysis	Two-sided alpha level	Patient Set
Final	GClb vs. RClb vs. Clb (global test, *stage 1a*)	175 (100)	28	GClb + RClb + Clb: 175 (100 [b])	0.05	stage 1 [e]
Final	GClb vs. Clb *(stage 1a)*	105 (100)	28	GClb + RClb + Clb: 175 (100 [b])	0.05	stage 1 [e]
Interim [a] Futility	GClb vs. RClb *(stage 1a)*	125 (30)	28	GClb + RClb + Clb: 175 (100 [b])	0.25 one-sided [d]	stage 1 [e]
Interim [a] Efficacy	GClb vs. RClb *(stage 1a)*	125 (30)	28	GClb + RClb + Clb: 175 (100 [b])	0.0001	stage 1 [e]
Final	RClb vs. Clb *(stage 1b)*	145 (100)	31	GClb + RClb: 155 (38 [c])	0.05	stage 1 [e]

Clb = chlorambucil; GClb = obinutuzumab plus chlorambucil; RClb = rituximab plus chlorambucil; vs. = versus.

[a] At interim efficacy analyses, data will be released only if the efficacy boundary is crossed.

[b] Percent of total stage 1 analysis events.

[c] Percent of total stage 2 analysis events.

[d] See Section 4.9 of statistical analysis plan for details.

[e] Patients randomized in parallel to all three treatment groups.

Table 14: Analysis timing for stage 2 analysis

Analysis Type	Comparison	Approximate Timing of Analysis Events (%)	Approximate Time (Months)	Number of Events Triggering the Analysis	Two-sided alpha level	Patient Set
Interim [a]	GClb vs. RClb	300 (74)	45	GClb + RClb: 300 (74 [b])	0.0182	stage 1 + 2 [c]
Final	GClb vs. RClb	406 (100)	63	GClb + RClb: 406 (100 [b])	0.0445	stage 1 + 2 [c]

Clb = chlorambucil; GClb = obinutuzumab plus chlorambucil; RClb = rituximab plus chlorambucil; vs. = versus.

[a] At interim analyses, data are released only if an efficacy boundary is crossed.

[b] Percent of total stage 2 analysis events.

[c] Patients randomized at any time.

Analysis Populations

Four different patient populations were defined.

Stage 1: Patients randomized in parallel to all three treatment groups (approximately 590 patients). This set of patients was used for the global test of any difference between any of the three treatment groups. For all comparisons of GClb or RClb against Clb, only Stage 1 patients are used.

Stage 1 + 2: Patients randomized at any time during the trial (approximately 780 patients). The patients randomized to GClb and RClb arms (approximately 662 patients) will be used for the Stage 2 analyses of comparison of GClb versus RClb and reported at a later date.

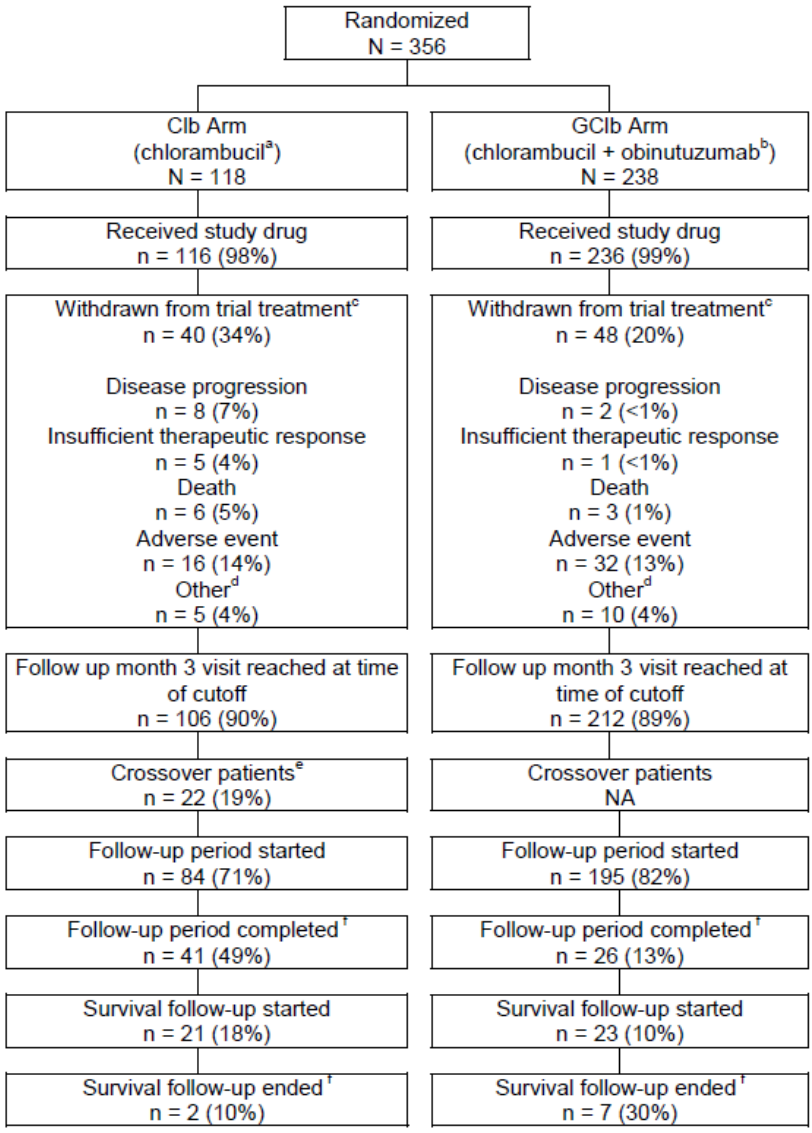
Data for the 6 safety run-in patients administered GClb and the data collected for the 22 patients who crossed over from Clb to GClb by the clinical cutoff were analyzed and reported.

The primary analysis population for efficacy was the ITT population, defined as all randomized patients. Patients were assigned to treatment groups as randomized.

In addition, a per protocol (PP) population was defined for a sensitivity analysis of PFS. The PP population comprised all patients who completed study therapy (defined as having received at least three cycles of study therapy) and patients who terminated treatment before three cycles because of disease progression or death. Patients in this analysis population fulfilled all the inclusion criteria and had no major protocol violations. Patients were assigned to treatment groups as treated. The purpose of the PP population was to assess the robustness of the primary analysis (based on the ITT population) and to quantify more precisely the magnitude of the potential clinical benefit of the treatment in the target population.

Results

Participant flow



NA = not applicable.

[a] Clb was administered orally on Days 1 and 15 of each cycle at 0.5 mg/kg body weight

[b] Patients received 1000 mg of obinutuzumab as an IV. infusion on Day 1, Day 8 and Day 15 of the first treatment cycle (Cycle 1). For subsequent cycles patients received obinutuzumab (1000 mg) as an IV infusion on Day 1 only (Cycle 2 – 6). Following protocol amendment G (dated 9 December, 2011) the first infusion of obinutuzumab was given over two days (100 mg Day 1, 900 mg Day 2)

[c] Includes the two patients in each treatment arm who did not receive study drug.

[d] Includes withdrew consent, administrative/other, other protocol violation, refused treatment/did not cooperate, violation of selection criteria at entry

[e] Patients with PD during Clb treatment or within 6 months of follow-up;

[f] Please note percentages are based on the number of patients entering this period of the study

Figure 4: Disposition of Stage 1a patients (Study BO21004/CLL11)

Recruitment

A total of 781 patients were randomized. The first patient for the safety run in was enrolled on 21 December 2009. The first patient for the Stage 1 analysis was enrolled on 12 April 2010. The last patient was enrolled into the Stage 1 population (i.e., the last patient randomized to Clb) on 24 January 2012 and the last patient was enrolled into Stage 2 on 4 July 2012.

Conduct of the study

The initial protocol, dated 21 July 2009, has been amended 7 times. This included:

- The dose of chlorambucil was capped at a maximum dose associated with a body mass index of 35, antibiotic prophylaxis was strongly recommended (Amendment 3);

- Premedication requirements were modified to include corticosteroids (100 mg prednisolone or 20 mg dexamethasone or 80 mg methylprednisolone) for all patients during the first infusion in an effort to reduce the risk of IRRs (Amendment 5).

- To further reduce the risk and severity of IRRs and on the recommendation of the DSMB, the first infusion of obinutuzumab was to be given over two days (100 mg on Day 1 and 900 mg on Day 2) with a reduced rate of infusion during the first day (Amendment 6; see discussion on clinical safety).

Baseline data

Overall, the majority of patients in the Stage 1a analysis were male (60%), less than 75 years of age (58%) but 65 years or above (81%); the median age of patients was 73.0 years (range: 39 to 88 years, Table 15). Baseline disease information is summarized in tables 16-17. The distribution of prognostic factors at baseline was balanced between the treatment arms; 61% of patients had unmutated *IgVh* gene (Clb arm: 59% patients vs. GClb arm: 61% patients) and 46% patients were ZAP-70 positive (Clb arm: 49% patients vs. GClb arm: 44% patients) (Table 18).

The treatment groups were balanced with respect to cytogenic abnormalities at baseline, although 82% of patients in the Clb arm and 74% of patients in the GClb arm who were tested did not have normal karyotype at baseline. The treatment groups were balanced with respect to the hierarchical model of polymorphisms, apart from the lower percentage of patients with a normal karyotype in the Clb arm (15%) compared to the GClb arm (23%).

Fcγ receptor polymorphism results were available for 330 of 356 patients (93%).The treatment arms were balanced with respect to FcγRIIa and FCγRIIIa polymorphisms with the majority of patients having the 131 HR variant of FCγRIIa (47%) and the 158 FV or FF variant of FCγRIIIa (47% and 42%, respectively). Eight percent of patients in the Clb group and 7% of patients in the GClb group had the 158VV mutation.

The criteria for initiating treatment based on IWCLL criteria were fulfilled by 100% of patients included in the ITT population. According to these criteria a patient who was categorized as Binet C Stage required therapy, while those with Binet Stage A or B required evidence of active or progressive disease.

The treatment groups were balanced with respect to the percentage of patients with Binet Stage C at baseline (Clb arm: 37% patients vs. GClb arm: 36% patients). The treatment arms were also balanced with respect to the reasons why the remaining 74 patients in the Clb group and 153 patients in the GClb group who were not Binet Stage C at baseline, initiated treatment and included severe B symptoms (Clb arm: 47% patients vs. GClb arm: 46% patients), massive symptoms of lymphadenopathy/splenomegaly (45% in each treatment arm), lymphocyte doubling time < 6 months (Clb arm: 43% patients, GClb arm: 38% patients). Additionally, 12% patients in the Clb arm and 18% patients in the GClb arm initiated treatment for reasons other than those above.

Most patients in each treatment arm had comorbidities in four to eight organ systems (Clb arm: 90/118 patients [76%] vs. GClb arm: 192/238 patients [81%]). The majority of patients in each treatment arm had organ system severity scores of < 3 (as assessed by the CIRS definition), 88/118 patients (75%) Clb versus 181/238 (76%) GClb. Overall, 31/118 patients (26%) in the Clb arm and 57/238 (24%) in the GClb arm had comorbidities in all three of the most common organ systems (Hypertension, Endocrine/Metabolic and Cardiac), and most patients in each study arm (Clb arm: 105/118 patients [89%] vs. GClb: 209/238 patients [88%]) had one of the three most common comorbidities.

Table 15: Demographic data (ITT; Study BO21004/CLL11)

Protocol(s): BO21004 (F21004A) - Stage I Population - Stage 1a CSR
Analysis: ITT Center: ALL CENTERS
Snapshot Date: 11OCT2012 Cutoff Date: 11JUL2012

	Clb N = 118	GClb N = 238	Total N = 356
Sex			
FEMALE	43 (36%)	98 (41%)	141 (40%)
MALE	75 (64%)	140 (59%)	215 (60%)
n	118	238	356
Age (years)			
Mean	70.7	72.0	71.6
SD	8.66	8.63	8.65
SEM	0.80	0.56	0.46
Median	72.0	74.0	73.0
Min-Max	43 - 87	39 - 88	39 - 88
n	118	238	356
Age category I (years)			
<75	74 (63%)	131 (55%)	205 (58%)
>=75	44 (37%)	107 (45%)	151 (42%)
n	118	238	356
Age category II (years)			
<65	26 (22%)	42 (18%)	68 (19%)
>=65	92 (78%)	196 (82%)	288 (81%)
n	118	238	356
Race			
WHITE	108 (92%)	229 (96%)	337 (95%)
BLACK	1 (<1%)	-	1 (<1%)
ASIAN	6 (5%)	4 (2%)	10 (3%)
AMERICAN INDIAN OR ALASKA NATIVE	1 (<1%)	-	1 (<1%)
OTHER	2 (2%)	5 (2%)	7 (2%)
n	118	238	356
Ethnicity			
HISPANIC	3 (11%)	6 (12%)	9 (11%)
NON-HISPANIC	24 (89%)	46 (88%)	70 (89%)
n	27	52	79
Height (cm)			
Mean	167.0	166.4	166.6
SD	8.79	10.00	9.61
SEM	0.81	0.65	0.51
Median	168.0	167.0	167.0
Min-Max	149 - 188	142 - 194	142 - 194
n	118	238	356
Weight (kg)			
Mean	75.58	72.86	73.76
SD	15.158	13.950	14.395
SEM	1.401	0.904	0.764
Median	73.00	72.05	72.90
Min-Max	44.9 - 120.0	40.0 - 140.0	40.0 - 140.0
n	117	238	355

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
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Table 16: Baseline disease information (ITT; Study BO21004/CLL11)

Protocol(s): BO21004 (F21004A) - Stage I Population - Stage 1a CSR
Analysis: ITT Center: ALL CENTERS
Snapshot Date: 11OCT2012 Cutoff Date: 11JUL2012

	Clb N = 118	GClb N = 238	Total N = 356
Time from diagnosis to randomization [yrs]			
Mean	3.77	3.61	3.67
SD	4.082	3.723	3.841
SEM	0.376	0.242	0.204
Median	2.75	2.50	2.60
Min-Max	0.0 - 22.9	0.0 - 22.9	0.0 - 22.9
n	118	237	355
Time from diagnosis to randomization cat.			
<=12 months	33 (28%)	59 (25%)	92 (26%)
13-24 months	14 (12%)	45 (19%)	59 (17%)
>24 months	71 (60%)	133 (56%)	204 (57%)
n	118	237	355
Binet Stage at first diagnosis			
A	61 (68%)	129 (71%)	190 (70%)
B	22 (24%)	35 (19%)	57 (21%)
C	7 (8%)	17 (9%)	24 (9%)
n	90	181	271
Binet Stage at Baseline			
A	24 (20%)	55 (23%)	79 (22%)
B	50 (42%)	98 (41%)	148 (42%)
C	44 (37%)	85 (36%)	129 (36%)
n	118	238	356
Areas of involvement at baseline: Cervical			
YES	85 (72%)	158 (66%)	243 (68%)
NO	33 (28%)	80 (34%)	113 (32%)
n	118	238	356
Axillary			
YES	84 (71%)	156 (66%)	240 (67%)
NO	34 (29%)	82 (34%)	116 (33%)
n	118	238	356
Inguinal			
YES	64 (54%)	127 (53%)	191 (54%)
NO	54 (46%)	111 (47%)	165 (46%)
n	118	238	356
Liver			
YES	19 (16%)	49 (21%)	68 (19%)
NO	99 (84%)	189 (79%)	288 (81%)
n	118	238	356
Spleen			
YES	62 (53%)	120 (50%)	182 (51%)
NO	56 (47%)	118 (50%)	174 (49%)
n	118	238	356
B-symptom fever at Baseline?			
YES	2 (2%)	8 (3%)	10 (3%)
NO	114 (98%)	228 (97%)	342 (97%)
n	116	236	352
B-symptom night sweats at Baseline?			
YES	37 (32%)	83 (35%)	120 (34%)
NO	79 (68%)	152 (65%)	231 (66%)
n	116	235	351
B-symptom weight loss at Baseline?			
YES	18 (16%)	30 (13%)	48 (14%)
NO	98 (84%)	206 (87%)	304 (86%)
n	116	236	352
CD5/CD20 (%) available at baseline			
YES	97 (82%)	197 (83%)	294 (83%)
NO	21 (18%)	41 (17%)	62 (17%)
n	118	238	356
CD20 (%) available at baseline			
YES	116 (98%)	234 (98%)	350 (98%)
NO	2 (2%)	4 (2%)	6 (2%)
n	118	238	356

CD19/CD5 (%) available at baseline			
YES	111 (94%)	225 (95%)	336 (94%)
NO	7 (6%)	13 (5%)	20 (6%)
n	118	238	356
No CD5/CD20, CD20, CD19/CD5 available at BL			
YES	-	1	1
n	0	1	1
Calc. Creat. Clearance			
<50 ml/min	25 (21%)	69 (29%)	94 (26%)
>=50 ml/min	92 (79%)	169 (71%)	261 (74%)
n	117	238	355

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
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Table 17: Disease assessment at baseline (ITT; Study BO21004/CLL11)

Protocol(s): BO21004 (F21004A) - Stage I Population - Stage 1a CSR
Analysis: ITT Center: ALL CENTERS
Snapshot Date: 11OCT2012 Cutoff Date: 11JUL2012

	Clb N = 118	GClb N = 238	Total N = 356
SPD for rad. assessed lesions at BL [mmxmm]			
Mean	3812.6	7493.4	6270.1
SD	7717.59	36847.28	30460.49
SEM	726.01	2445.64	1651.95
Median	1854.0	2280.0	2181.0
Min-Max	12 - 65134	10 - 478990	10 - 478990
n	113	227	340
SLD for PE lesions at BL [mm]			
Mean	75.1	91.8	85.9
SD	59.71	99.39	87.80
SEM	5.94	7.27	5.17
Median	60.0	80.0	70.0
Min-Max	2 - 430	3 - 1200	2 - 1200
n	101	187	288
Spleen palpable at BL?			
YES	57 (49%)	115 (49%)	172 (49%)
NO	60 (51%)	122 (51%)	182 (51%)
n	117	237	354
Spleen dist. below costal margin at BL [cm]			
0-2	14 (28%)	33 (32%)	47 (31%)
3-4	8 (16%)	28 (27%)	36 (24%)
>4	28 (56%)	42 (41%)	70 (46%)
n	50	103	153
Liver palpable at BL?			
YES	21 (18%)	53 (22%)	74 (21%)
NO	96 (82%)	184 (78%)	280 (79%)
n	117	237	354
Liver dist. below costal margin at BL [cm]			
0-3	16 (80%)	38 (78%)	54 (78%)
4-6	3 (15%)	7 (14%)	10 (14%)
>6	1 (5%)	4 (8%)	5 (7%)
n	20	49	69
Circulating lymphocyte count at BL (cat. 1)			
<25x10**9 cells/L	18 (16%)	58 (24%)	76 (22%)
>=25x10**9 cells/L	98 (84%)	179 (76%)	277 (78%)
n	116	237	353
Circulating lymphocyte count at BL (cat. 2)			
<100x10**9 cells/L	73 (63%)	179 (76%)	252 (71%)
>=100x10**9 cells/L	43 (37%)	58 (24%)	101 (29%)
n	116	237	353

n represents number of patients contributing to summary statistics.
Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
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Table 18: Prognostic factors: IgVh expression, VH3-21 mutational status, ZAP-70, CD38, P53 and t(11;1) (ITT; Study BO21004/CLL11)

Protocol(s): BO21004 (F21004A) - Stage I Population - Stage 1a CSR
Analysis: ITT Center: ALL CENTERS
Snapshot Date: 11OCT2012 Cutoff Date: 11JUL2012

	Clb N = 118	GClb N = 238	Total N = 356
IGVH mutational status			
MUTATED	36 (36%)	76 (36%)	112 (36%)
UNMUTATED	58 (59%)	129 (61%)	187 (61%)
NVR	5 (5%)	3 (1%)	8 (3%)
NOA	-	2 (<1%)	2 (<1%)
n	99	210	309
VH3-21 usage			
YES	10 (13%)	21 (13%)	31 (13%)
NO	62 (81%)	140 (84%)	202 (83%)
NOA	-	2 (1%)	2 (<1%)
NVR	5 (6%)	3 (2%)	8 (3%)
n	77	166	243
P 53 mutation status			
POSITIVE	2	1 (7%)	3 (14%)
NEGATIVE	4	14 (93%)	18 (86%)
n	6	15	21
ZAP-70 expression			
POSITIVE	48 (49%)	83 (44%)	131 (46%)
NEGATIVE	49 (51%)	106 (56%)	155 (54%)
n	97	189	286
CD38 expression			
POSITIVE	36 (37%)	81 (43%)	117 (41%)
NEGATIVE	62 (63%)	107 (57%)	169 (59%)
n	98	188	286
t(11;14)			
POSITIVE	2 (3%)	-	2 (<1%)
NEGATIVE	70 (93%)	154 (96%)	224 (95%)
NOA	3 (4%)	7 (4%)	10 (4%)
n	75	161	236
Beta2-microglobulin [mg/L]			
< 3.5 mg/L	70 (61%)	158 (68%)	228 (66%)
>= 3.5 mg/L	45 (39%)	73 (32%)	118 (34%)
n	115	231	346
Thymidinkinase [U/L]			
< 10 U/L	56 (49%)	121 (52%)	177 (51%)
>= 10 U/L	59 (51%)	110 (48%)	169 (49%)
n	115	231	346

Percentages are based on n (number of valid values). Percentages not calculated if n < 10.
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Note: NOA: not available; NVR: no valid result
Of note t(11;14) was tested to exclude patients with mantle cell lymphoma.

Numbers analysed

The primary population for the Stage 1a analyses was the ITT population which comprised all patients randomized to the Clb and GClb arms, regardless of whether they received treatment or not, and included 118 patients in the Clb arm and 238 patients in the GClb arm.

The primary population for the Stage 1b analyses was the ITT population which comprised all patients randomized to the Clb and RClb arms, regardless of whether they received treatment or not, and included 118 patients in the Clb arm and 233 patients in the RClb arm.

Outcomes and estimation

The efficacy results for Stage 1a are summarized in

Table 19 and Figure 5 (investigator's assessment; cut-off 11 July 2012),

Table 20 and 6 (independent review committee).

The overall median observation time (randomization to last available assessment), at the time of data cutoff was 14.2 months overall; 13.6 months (range: 0.2-26.8 months) for patients in the Clb arm and 14.5 months (range: 0.1-26.7 months) for patients in the GClb arm. There were 65/118 patients (55%) in the Clb arm and 141/238 patients (59%) in the GClb arm who had been followed for at least 12 months. At data cutoff, a total of 16/356 patients (4%) had been followed for more than 2 years.

Closed Test Procedure

At the time of the Stage 1a analysis, a global test was conducted by the independent Data Coordinating Center (iDCC), and the p-value was communicated to the Sponsor through the DSMB in order to protect the integrity of the trial (i.e., the Sponsor did not have access to RClb data at the time of the Stage 1a analysis).

The p-value of the global test for any difference between the three treatment arms, via a three-arm log-rank test was <0.0001. According to the closed test principle, the adjusted p-value for the pairwise comparison is defined as the maximum of the p-value of the global test and the p-value of the pairwise comparison. In this case, both p-values are <0.0001 which means that the adjusted p-value is <0.0001.

Sensitivity Analyses

All pre-specified sensitivity analyses conducted were supportive of the results from the primary analysis of PFS (data not shown); the HRs for the sensitivity analyses ranged from 0.12 to 0.26.

Progression-Free Survival Subgroup Analyses

A summary of efficacy subgroup analyses is presented in Figures 7-8.

In order to assess the impact of potential prognostic factors on the treatment effect, pre−defined baseline characteristics and prognostic factors were analyzed. Univariate and multivariate Cox regression analyses for PFS confirmed the advantage of GClb over Clb. The HR was 0.14 in a multivariate Cox regression including all covariates listed in Fig. 6 and ranged from 0.13−0.16 for the univariate Cox regressions (including each covariate and treatment, no interaction term).

Updated results

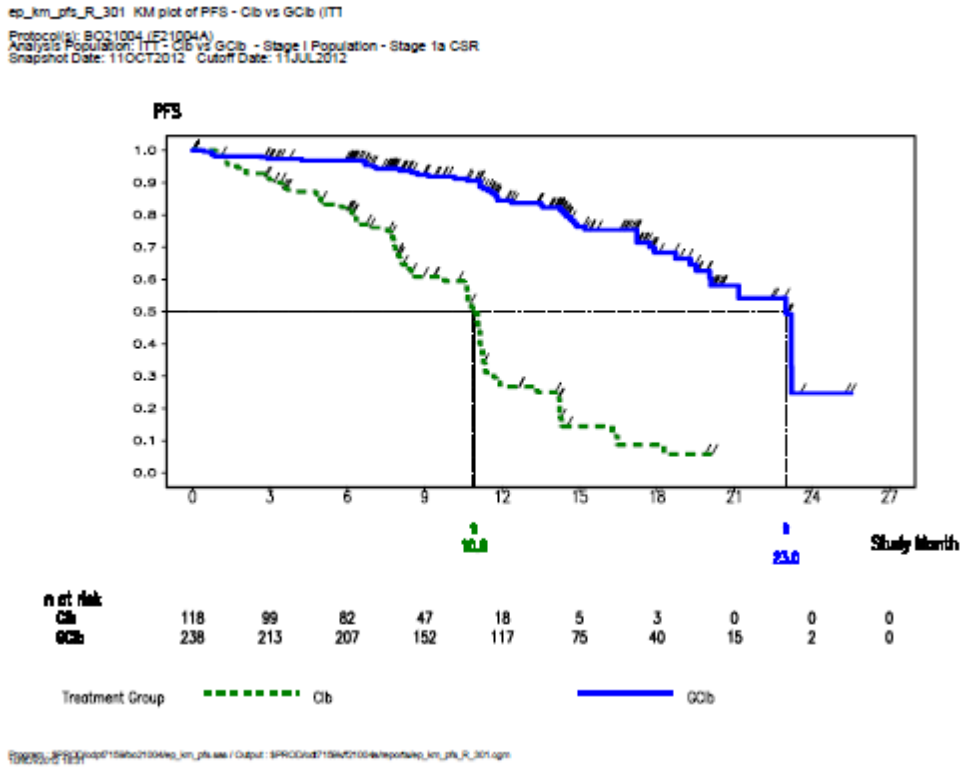
Updated Stage 1a results (ITT; cut-off 9 May 2013, 22.8 months median observation time) are summarized in Table 21 and Figure 9.

Table 19: Summary of efficacy results Clb vs. GClb – primary analysis Stage 1a (ITT, cut-off 11 July 2012, Study BO21004/CLL11)

Protocol(s): BO21004 (F21004A)
Analysis Population: ITT - Clb vs GClb - Stage I Population - Stage 1a CSR
Snapshot Date: 11OCT2012 Cutoff Date: 11JUL2012

	Clb N = 118		GClb N = 238
Primary Efficacy Parameter			
Progression free survival			
Patients with event	71 (60.2 %)		52 (21.8 %)
Patients without event**	47 (39.8 %)		186 (78.2 %)
Time to Event (months)			
Median###	10.9		23.0
P-Value (Log-rank Test, stratified##)		<.0001	
Hazard Ratio (stratified##)		0.14	
95% CI		[0.09;0.21]	
Hazard Ratio (unstratified)		0.14	
95% CI		[0.10;0.21]	
Progression free survival based on IRC data			
Patients with event	66 (55.9 %)		52 (21.8 %)
Patients without event**	52 (44.1 %)		186 (78.2 %)
Time to Event (months)			
Median###	11.1		23.0
P-Value (Log-rank Test, stratified##)		<.0001	
Hazard Ratio (stratified##)		0.16	
95% CI		[0.11;0.24]	
Hazard Ratio (unstratified)		0.15	
95% CI		[0.10;0.23]	
Key Secondary Efficacy Parameters			
Event free survival			
Patients with event	79 (66.9 %)		64 (26.9 %)
Patients without event**	39 (33.1 %)		174 (73.1 %)
Time to Event (months)			
Median###	10.6		23.0
P-Value (Log-rank Test, stratified##)		<.0001	
Hazard Ratio (stratified##)		0.18	
95% CI		[0.13;0.26]	
Overall survival			
Patients with event	9 (7.6 %)		13 (5.5 %)
Patients without event**	109 (92.4 %)		225 (94.5 %)
Time to Event (months)			
Median###	.		.
P-Value (Log-rank Test, stratified##)		0.3820	
Hazard Ratio (stratified##)		0.68	
95% CI		[0.29;1.60]	
End of Treatment Response			
Patients included in analysis	106 (100.0 %)		212 (100.0 %)
Responders$	32 (30.2 %)		160 (75.5 %)
95% CI for Response Rates*	[21.7; 39.9]		[69.1; 81.1]
Difference in Response Rates		45.28	
95% CI for Difference in Response Rates#		[34.3; 56.3]	
p-Value (Chi-squared Test)		<.0001	
Complete Response (CR)	0 (0.0 %)		47 (22.2 %)
Partial Response (PR)	32 (30.2 %)		113 (53.3 %)
Stable Disease(SD)	23 (21.7 %)		10 (4.7 %)
Progressive Disease (PD)	27 (25.5 %)		8 (3.8 %)
Missing (No Response Assessment)	24 (22.6 %)		34 (16.0 %)
End of Treatment Response not reached£	12		26
MRD status at end of treatment (blood and bone marrow combined)			
Patients included in analysis	80 (100.0 %)		142 (100.0 %)
MRD negative	0 (0.0 %)		28 (19.7 %)
MRD positive^	80 (100.0 %)		114 (80.3 %)
95% CI for negative MRD*	[0.0; 4.5]		[13.5; 27.2]
Difference in MRD rates		19.72	
95% CI for difference in MRD rates#		[12.5; 26.9]	
Missing	26		70
End of Treatment Response not reached£	12		26

$ Patients with end of treatment response of CR, CRi, PR or nPR
Complete Response (CR) includes CR and CRi; Partial Response (PR) includes PR and nPR
* 95% CI for one sample binomial using Pearson-Clopper method
# Approximate 95% CI for difference of two rates using Hauck-Anderson method
** censored
stratified by Binet stage at baseline
Kaplan-Meier estimates
£ Follow up month 3 visit not reached by the cut off date; patients are not included in the analysis
^ Includes MRD positive patients and patient who progressed or died before end of treatment
MRD negativity is defined as a result below 0.0001
Program : $PROD/cdpt7159/bo21004/et_overall.sas
Output : $PROD/cdt7159k/f21004a/reports/et_overall_R_301.out
26FEB2013 11:54 Source: page 696



Note: The most common reason for disease progression based on investigator assessment was increasing lymphocyte count (Clb: 45%; GClb: 40%); increasing/new lymphadenopathy (Clb: 25%; GClb: 37%) was also a common reason. Other reasons of disease progression experienced by less than 10% of the patients were increasing new hepatomegaly or splenomegaly and progressive cytopenia. No disease progressions were due to transformation to new histology.

Figure 5: Kaplan-Meier plot of progression-free survival (investigator's assessedl) Clb vs. GClb – primary Stage 1a analysis (ITT, cut-off 11 July 2012, Study BO21004/CLL11)

Table 20: Progression-free survival (independent review committee)– Stage 1a (ITT, cut-off 11 July 2012, Study BO21004/CLL11)

Protocol(s): BO21004 (F21004A)
Analysis Population: ITT - Clb vs GClb - Stage I Population - Stage 1a CSR
Snapshot Date: 11OCT2012 Cutoff Date: 11JUL2012

	Clb (N=118)		GClb (N=238)
Patients with event	66 (55.9 %)		52 (21.8 %)
Patients without event*	52 (44.1 %)		186 (78.2 %)
Time to event (months)			
Median#	11.1		23.0
95% CI for Median#	[10.6;11.3]		[20.1;23.2]
25% and 75%-ile#	7.9;14.1		14.9;23.2
Range##	0.0 to 20.1		0.0 to 25.5
P-Value (Log-rank Test, stratified**)		<.0001	
Hazard Ratio (stratified**)		0.16	
95% CI		[0.11;0.24]	
P-Value		<.0001	
1 year duration			
Patients remaining at risk	21		111
Event Free Rate	0.36		0.83
95% CI for Rate	[0.25;0.47]		[0.77;0.89]

* censored
# Kaplan-Meier estimates
including censored observations
** Stratified by Binet stage at baseline

Program : $PROD/cdpt7159/bo21004/et_time_pfsirf.sas
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31JAN2013 16:51 et_time_pfsirf_R_301

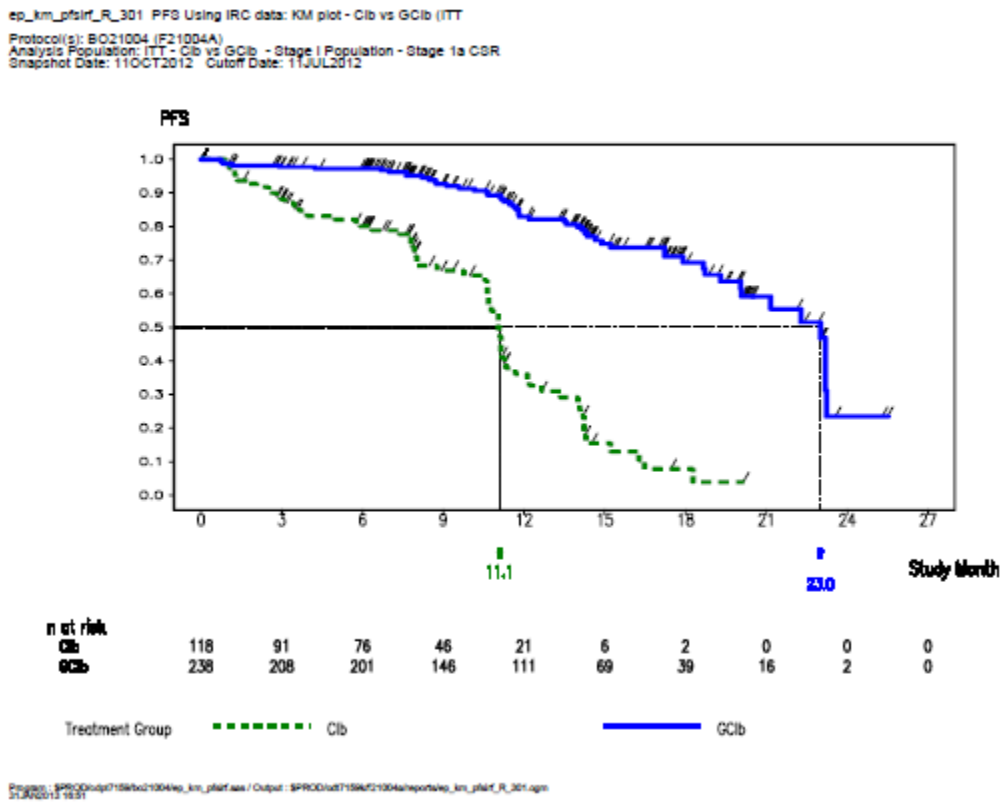
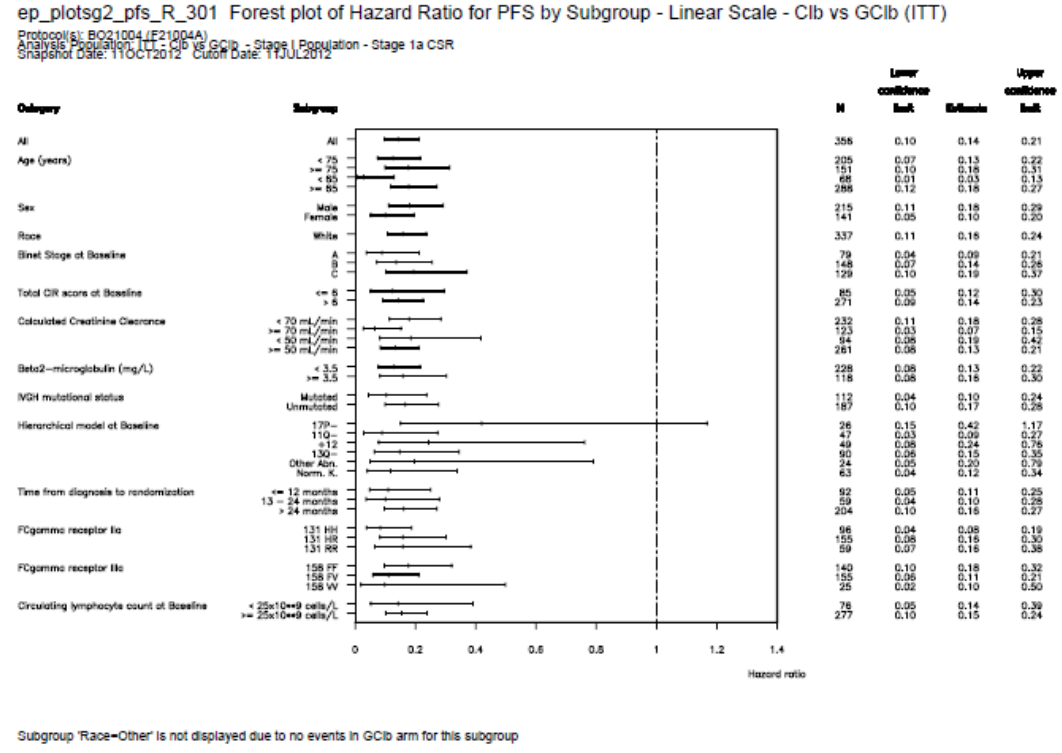


Figure 6: Kaplan-Meier plot of progression-free survival (independent review committee) Clb vs. GClb – Stage 1a (ITT, cut-off 11 July 2012, Study BO21004/CLL11)



Subgroup 'Race=Other' is not displayed due to no events in GClb arm for this subgroup

Figure 7: Forest plot of HR for PFS by subgroup (ITT, cut-off 11 July 2012, Study BO21004/CLL11)

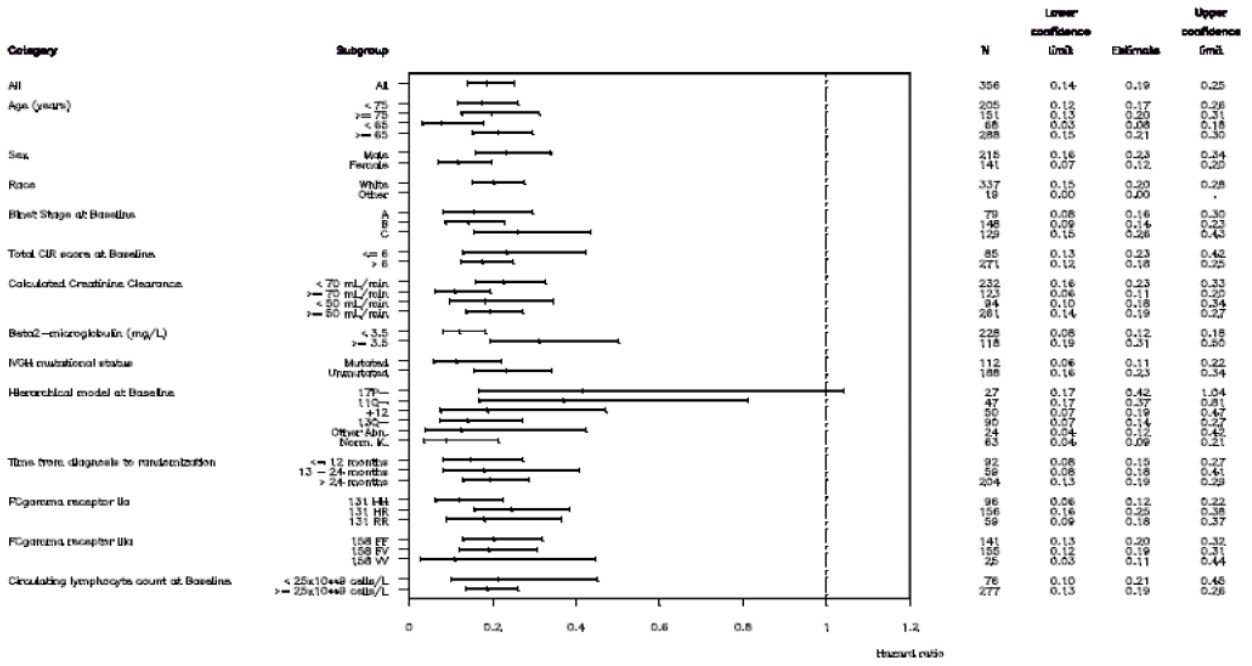
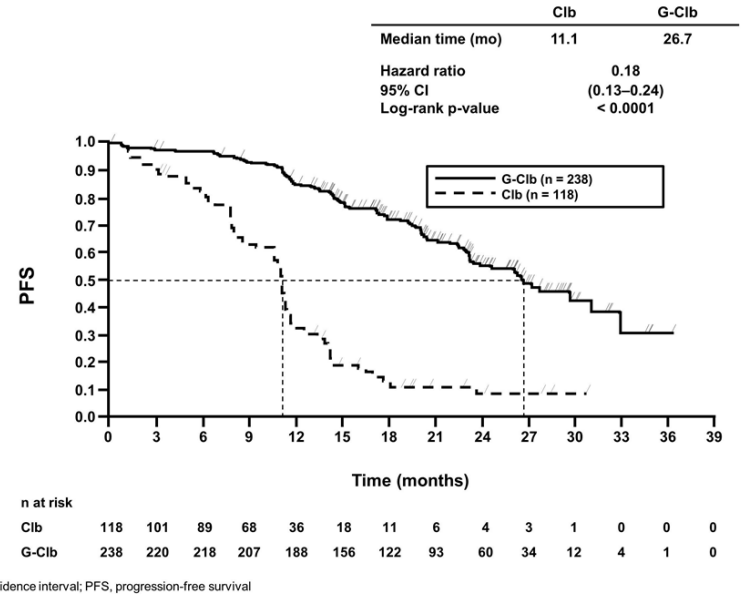


Figure 8: Forest plot of HR for PFS by subgroup (ITT, cut-off 9 May 2013, Study BO21004/CLL11)

Table 21: Summary of efficacy results Clb vs. GClb –Stage 1a Update (ITT; cut-off 9 May, 2013, Study BO21004/CLL11)

	Clb N = 118		GClb N = 238
Primary Efficacy Parameter			
Progression free survival			
Patients with event	96 (81.4 %)		93 (39.1 %)
Patients without event**	22 (18.6 %)		145 (60.9 %)
Time to Event (months)			
Median###	11.1		26.7
P-Value (Log-rank Test, stratified##)		<.0001	
Hazard Ratio (stratified##)		0.18	
95% CI		[0.13;0.24]	
Hazard Ratio (unstratified)		0.19	
95% CI		[0.14;0.25]	
Progression free survival based on IRC data			
Patients with event	90 (76.3 %)		89 (37.4 %)
Patients without event**	28 (23.7 %)		149 (62.6 %)
Time to Event (months)			
Median###	11.2		27.2
P-Value (Log-rank Test, stratified##)		<.0001	
Hazard Ratio (stratified##)		0.19	
95% CI		[0.14;0.27]	
Hazard Ratio (unstratified)		0.20	
95% CI		[0.14;0.27]	
Key Secondary Efficacy Parameters			
Event free survival			
Patients with event	103 (87.3 %)		104 (43.7 %)
Patients without event**	15 (12.7 %)		134 (56.3 %)
Time to Event (months)			
Median###	10.8		26.1
P-Value (Log-rank Test, stratified##)		<.0001	
Hazard Ratio (stratified##)		0.19	
95% CI		[0.14;0.25]	
Overall survival			
Patients with event	24 (20.3 %)		22 (9.2 %)
Patients without event**	94 (79.7 %)		216 (90.8 %)
Time to Event (months)			
Median###	.		.
P-Value (Log-rank Test, stratified##)		0.0022	
Hazard Ratio (stratified##)		0.41	
95% CI		[0.23;0.74]	
End of Treatment Response			
Responders$	37 (31.4 %)		184 (77.3 %)
95% CI for Response Rates*	[23.1; 40.5]		[71.5; 82.5]
Difference in Response Rates		45.95	
95% CI for Difference in Response Rates#		[35.6; 56.3]	
p-Value (Chi-squared Test)		<.0001	
Complete Response (CR)	0 (0.0 %)		53 (22.3 %)
Partial Response (PR)	37 (31.4 %)		131 (55.0 %)
Stable Disease(SD)	27 (22.9 %)		12 (5.0 %)
Progressive Disease (PD)	32 (27.1 %)		8 (3.4 %)
Missing (No Response Assessment)	22 (18.6 %)		34 (14.3 %)
MRD status at end of treatment (blood and bone marrow combined)			
Patients included in analysis	90 (100.0 %)		168 (100.0 %)
MRD negative	0 (0.0 %)		45 (26.8 %)
MRD positive^	90 (100.0 %)		123 (73.2 %)
95% CI for negative MRD*	[0.0; 4.0]		[20.3; 34.2]
Difference in MRD rates		26.79	
95% CI for difference in MRD rates#		[19.5; 34.1]	
Missing	28		70

$ Patients with end of treatment response of CR, CRi, PR or nPR
Complete Response (CR) includes CR and CRi; Partial Response (PR) includes PR and nPR
* 95% CI for one sample binomial using Pearson-Clopper method
# Approximate 95% CI for difference of two rates using Hauck-Anderson method
** censored
stratified by Binet stage at baseline
Kaplan-Meier estimates
^ Includes MRD positive patients and patient who progressed or died before end of treatment
MRD negativity is defined as a result below 0.0001
Program : $PROD/cdpt7159/bo21004/et_overall.sas
Output : $PROD/cdt7159k/f21004f/reports/et_overall_M.out 07OCT2013 23:16



CI, confidence interval; PFS, progression-free survival

Figure 9: Kaplan-Meier plot of progression-free survival (local evaluation) - Stage 1a Update (ITT; cut-off 9 May 2013, Study BO21004/CLL11)

SECONDARY EFFICACY ENDPOINTS

Table 22: End of treatment response Clb vs. GClb –Stage 1a (ITT; cut-off 11 July 2012, Study BO21004/CLL11)

Protocol(s): BO21004 (F21004A)
Analysis Population: ITT - Clb vs GClb - Stage I Population - Stage 1a CSR
Snapshot Date: 11OCT2012 Cutoff Date: 11JUL2012

	Clb N = 118	GClb N = 238
Patients included in analysis	106 (100.0 %)	212 (100.0 %)
Responders$	32 (30.2 %)	160 (75.5 %)
Non-Responders	74 (69.8 %)	52 (24.5 %)
95% CI for Response Rates*	[21.7; 39.9]	[69.1; 81.1]
Difference in Response Rates	45.28	
95% CI for Difference in Response Rates#	[34.3; 56.3]	
p-Value (χ^2 test)	<.0001	
Odds Ratio	7.12	
95% CI for Odds Ratio	[4.23;11.96]	
Complete Response (CR)	0 (0.0 %)	36 (17.0 %)
95% CI for CR Rates*	[0.0; 3.4]	[12.2; 22.7]
Complete Response incomplete (CRi)	0 (0.0 %)	11 (5.2 %)
95% CI for CRi Rates*	[0.0; 3.4]	[2.6; 9.1]
Partial Response (PR)	30 (28.3 %)	90 (42.5 %)
95% CI for PR Rates*	[20.0; 37.9]	[35.7; 49.4]
Nodular Partial Response (nPR)	2 (1.9 %)	23 (10.8 %)
95% CI for nPR Rates*	[0.2; 6.6]	[7.0; 15.8]
Stable Disease (SD)	23 (21.7 %)	10 (4.7 %)
95% CI for SD Rates*	[14.3; 30.8]	[2.3; 8.5]
Progressive Disease (PD)	27 (25.5 %)	8 (3.8 %)
95% CI for PD Rates*	[17.5; 34.9]	[1.6; 7.3]
Missing (No Response Assessment)	24 (22.6 %)	34 (16.0 %)
End of Treatment Response not reached£	12	26

* 95% CI for one sample binomial using Pearson-Clopper method
\# Approximate 95% CI for difference of two rates using Hauck-Anderson method
$ Patients with end of treatment response of CR, CRi, PR or nPR
£ Follow up month 3 visit not reached by the cut off date; patients are not included in the analysis
End of treatment response assessment is the first response assessment after 56 days from last dose

Table 23: End of treatment response Clb vs. GClb –Stage 1a (ITT; cut-off 9 May 2013, Study BO21004/CLL11)

	Clb N = 118		GClb N = 238
Responders$	37 (31.4 %)		184 (77.3 %)
Non-Responders	81 (68.6 %)		54 (22.7 %)
95% CI for Response Rates*	[23.1; 40.5]		[71.5; 82.5]
Difference in Response Rates		45.95	
95% CI for Difference in Response Rates#		[35.6; 56.3]	
p-Value (Chi-squared Test)		<.0001	
Odds Ratio		7.46	
95% CI for Odds Ratio		[4.56;12.22]	
Complete Response (CR)	0 (0.0 %)		41 (17.2 %)
95% CI for CR Rates*	[0.0; 3.1]		[12.7; 22.6]
Complete Response incomplete (CRi)	0 (0.0 %)		12 (5.0 %)
95% CI for CRi Rates*	[0.0; 3.1]		[2.6; 8.6]
Partial Response (PR)	34 (28.8 %)		114 (47.9 %)
95% CI for PR Rates*	[20.8; 37.9]		[41.4; 54.4]
Nodular Partial Response (nPR)	3 (2.5 %)		17 (7.1 %)
95% CI for nPR Rates*	[0.5; 7.3]		[4.2; 11.2]
Stable Disease (SD)	27 (22.9 %)		12 (5.0 %)
95% CI for SD Rates*	[15.7; 31.5]		[2.6; 8.6]
Progressive Disease (PD)	32 (27.1 %)		8 (3.4 %)
95% CI for PD Rates*	[19.3; 36.1]		[1.5; 6.5]
Missing (No Response Assessment)	22 (18.6 %)		34 (14.3 %)

* 95% CI for one sample binomial using Pearson-Clopper method
\# Approximate 95% CI for difference of two rates using Hauck-Anderson method
$ Patients with end of treatment response of CR, CRi, PR or nPR
End of treatment response assessment is the first response assessment after 56 days from last dose

Table 24: Best overall response Clb vs. GClb –Stage 1a (ITT; cut-off 11 July 2012, Study BO21004/CLL11)

Protocol(s): BO21004 (F21004A)
Analysis Population: ITT - Clb vs GClb - Stage I Population - Stage 1a CSR
Snapshot Date: 11OCT2012 Cutoff Date: 11JUL2012

	Clb N = 118		GClb N = 238
Patients included in analysis	106 (100.0 %)		212 (100.0 %)
Responders$	34 (32.1 %)		161 (75.9 %)
Non-Responders	72 (67.9 %)		51 (24.1 %)
95% CI for Response Rates*	[23.3; 41.8]		[69.6; 81.5]
Difference in Response Rates		43.87	
95% CI for Difference in Response Rates#		[32.8; 55.0]	
Odds Ratio		6.69	
95% CI for Odds Ratio		[3.99;11.19]	
Complete Response (CR)	0 (0.0 %)		52 (24.5 %)
95% CI for CR Rates*	[0.0; 3.4]		[18.9; 30.9]
Complete Response incomplete (CRi)	1 (0.9 %)		7 (3.3 %)
95% CI for CRi Rates*	[0.0; 5.1]		[1.3; 6.7]
Partial Response (PR)	31 (29.2 %)		88 (41.5 %)
95% CI for PR Rates*	[20.8; 38.9]		[34.8; 48.5]
Nodular Partial Response (nPR)	2 (1.9 %)		14 (6.6 %)
95% CI for nPR Rates*	[0.2; 6.6]		[3.7; 10.8]
Stable Disease (SD)	21 (19.8 %)		9 (4.2 %)
95% CI for SD Rates*	[12.7; 28.7]		[2.0; 7.9]
Progressive Disease (PD)	27 (25.5 %)		8 (3.8 %)
95% CI for PD Rates*	[17.5; 34.9]		[1.6; 7.3]
Missing (No Response Assessment)	24 (22.6 %)		34 (16.0 %)
End of Treatment Response not reached£	12		26

* 95% CI for one sample binomial using Pearson-Clopper method
\# Approximate 95% CI for difference of two rates using Hauck-Anderson method
$ Patients with best overall response of CR, CRi, PR or nPR
£ Follow up month 3 visit not reached by the cut off date; patients are not included in the analysis

Table 25: Best overall response Clb vs. GClb –Stage 1a (ITT; cut-off 9 May 2013, Study BO21004/CLL11)

	Clb N = 118		GClb N = 238
Responders$	39 (33.1 %)		186 (78.2 %)
Non-Responders	79 (66.9 %)		52 (21.8 %)
95% CI for Response Rates*	[24.7; 42.3]		[72.4; 83.2]
Difference in Response Rates		45.10	
95% CI for Difference in Response Rates#		[34.7; 55.5]	
p-Value (Chi-squared Test)		<.0001	
Odds Ratio		7.25	
95% CI for Odds Ratio		[4.43;11.85]	
Complete Response (CR)	0 (0.0 %)		67 (28.2 %)
95% CI for CR Rates*	[0.0; 3.1]		[22.5; 34.3]
Complete Response incomplete (CRi)	2 (1.7 %)		6 (2.5 %)
95% CI for CRi Rates*	[0.2; 6.0]		[0.9; 5.4]
Partial Response (PR)	36 (30.5 %)		107 (45.0 %)
95% CI for PR Rates*	[22.4; 39.7]		[38.5; 51.5]
Nodular Partial Response (nPR)	1 (0.8 %)		6 (2.5 %)
95% CI for nPR Rates*	[0.0; 4.6]		[0.9; 5.4]
Stable Disease (SD)	25 (21.2 %)		10 (4.2 %)
95% CI for SD Rates*	[14.2; 29.7]		[2.0; 7.6]
Progressive Disease (PD)	32 (27.1 %)		8 (3.4 %)
95% CI for PD Rates*	[19.3; 36.1]		[1.5; 6.5]
Missing (No Response Assessment)	22 (18.6 %)		34 (14.3 %)

* 95% CI for one sample binomial using Pearson-Clopper method
\# Approximate 95% CI for difference of two rates using Hauck-Anderson method
$ Patients with best overall response of CR, CRi, PR or nPR

Table 26: Molecular remission, MRD at end of treatment, blood and bone marrow combined; Clb vs. GClb – Stage 1a (ITT; cut-off 11 July 2012, Study BO21004/CLL11)

Protocol(s): BO21004 (F21004A)
Analysis Population: ITT - Clb vs GClb - Stage I Population - Stage 1a CSR
Snapshot Date: 11OCT2012 Cutoff Date: 11JUL2012

	Clb N = 118		GClb N = 238
Patients included in analysis	80 (100%)		142 (100%)
MRD negative	0 (0%)		28 (20%)
MRD positive£	80 (100%)		114 (80%)
95% CI for MRD negative*	[0.0; 4.5]		[13.5; 27.2]
Difference in MRD rates		19.72	
95% CI for difference in MRD rates#		[12.5; 26.9]	
MRD positive	64 (80%)		107 (75%)
95% CI for MRD positive*	[69.6; 88.1]		[67.4; 82.2]
PD or death before end of treatment	16 (20%)		7 (5%)
95% CI for PD or death*	[11.9; 30.4]		[2.0; 9.9]
Missing	26		70
End of Treatment Response not reached$	12		26

* 95% CI for one sample binomial using Pearson-Clopper method
\# Approximate 95% CI for difference of two rates using Hauck-Anderson method
£ Includes MRD positive patients and patient who progressed or died before end of treatment
MRD negativity is defined as a result below 0.0001
$ Follow up month 3 visit not reached by the cut off date; patients are not included in the analysis

Note: Molecular remission at end of treatment was to be assessed for all patients using a blood sample. Additionally, a bone marrow sample was obtained from patients whom the investigator assumed to have a complete response, consistent with the IWCLL guidelines. A combined analysis of blood and bone marrow results was conducted and an MRD-positive patient was defined as a patient who was positive in either blood or bone marrow. MRD was considered negative if result was less than 1 CLL cell in 10000 leukocytes (MRD value < 0.0001) based on the method of allele specific polymerase chain reaction (ASO-PCR). Patients for whom no end of treatment MRD result was available but who had progressed or died before end of treatment were counted as positive. Patients with a missing result but who had not experienced PD or death, were not included in the MRD-positive patients; they were excluded from the analysis (26/118 patients [22%] in the Clb arm and 70/238 patients [29%] in the GClb arm). The reasons for missing samples included early discontinuation/withdrawal of therapy or consent, samples not taken or analyzed due to issues with a particular sample or assay. In addition, 12/118 patients (10%) in the Clb arm and 26/238 patients (11%) in GClb arm were excluded from the analyses of response rates and MRD due to not reaching the end of treatment response assessment at the time of clinical cutoff.

Table 27: Overall survival Clb vs. GClb –Stage 1a (ITT; cut-off 11 July 2012, Study BO21004/CLL11)

Protocol(s): BO21004 (F21004A)
Analysis Population: ITT - Clb vs GClb - Stage I Population - Stage 1a CSR
Snapshot Date: 11OCT2012 Cutoff Date: 11JUL2012

	Clb (N=118)		GClb (N=238)
Patients with event	9 (7.6 %)		13 (5.5 %)
Patients without event*	109 (92.4 %)		225 (94.5 %)
Time to event (months)			
Median#	.		.
95% CI for Median#	[.;.]		[.;.]
25% and 75%-ile#	.;.		.;.
Range##	0.2 to 26.7		0.0 to 26.7
P-Value (Log-rank Test, stratified**)		0.3820	
Hazard Ratio (stratified**)		0.68	
95% CI		[0.29;1.60]	
P-Value		0.3836	
1 year duration			
Patients remaining at risk	65		139
Event Free Rate	0.93		0.95
95% CI for Rate	[0.87;0.98]		[0.92;0.98]

* censored
# Kaplan-Meier estimates
including censored observations
** Stratified by Binet stage at baseline

Table 28: Overall survival Clb vs. GClb –Stage 1a (ITT; cut-off 9 May 2013, Study BO21004/CLL11)

	Clb (N=118)		GClb (N=238)
Patients with event	24 (20.3 %)		22 (9.2 %)
Patients without event*	94 (79.7 %)		216 (90.8 %)
Time to event (months)			
Median#	.		.
95% CI for Median#	[.;.]		[.;.]
25% and 75%-ile#	27.9;.		.;.
Range##	0.2 to 35.2		0.0 to 36.9
P-Value (Log-rank Test, stratified**)		0.0022	
Hazard Ratio (stratified**)		0.41	
95% CI		[0.23;0.74]	
P-Value		0.0030	
1 year duration			
Patients remaining at risk	102		215
Event Free Rate	0.93		0.95
95% CI for Rate	[0.88;0.98]		[0.92;0.98]

* censored
# Kaplan-Meier estimates
including censored observations
** Stratified by Binet stage at baseline

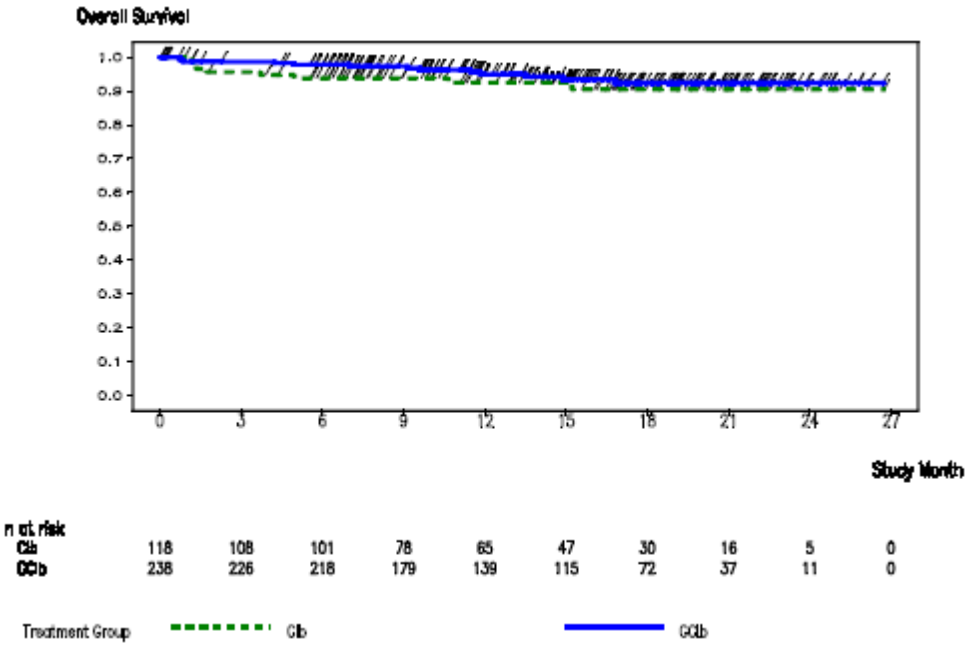
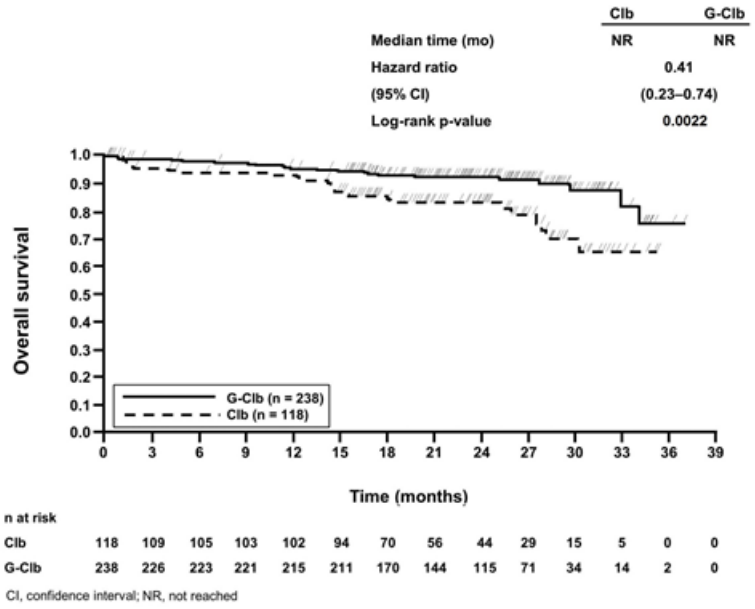
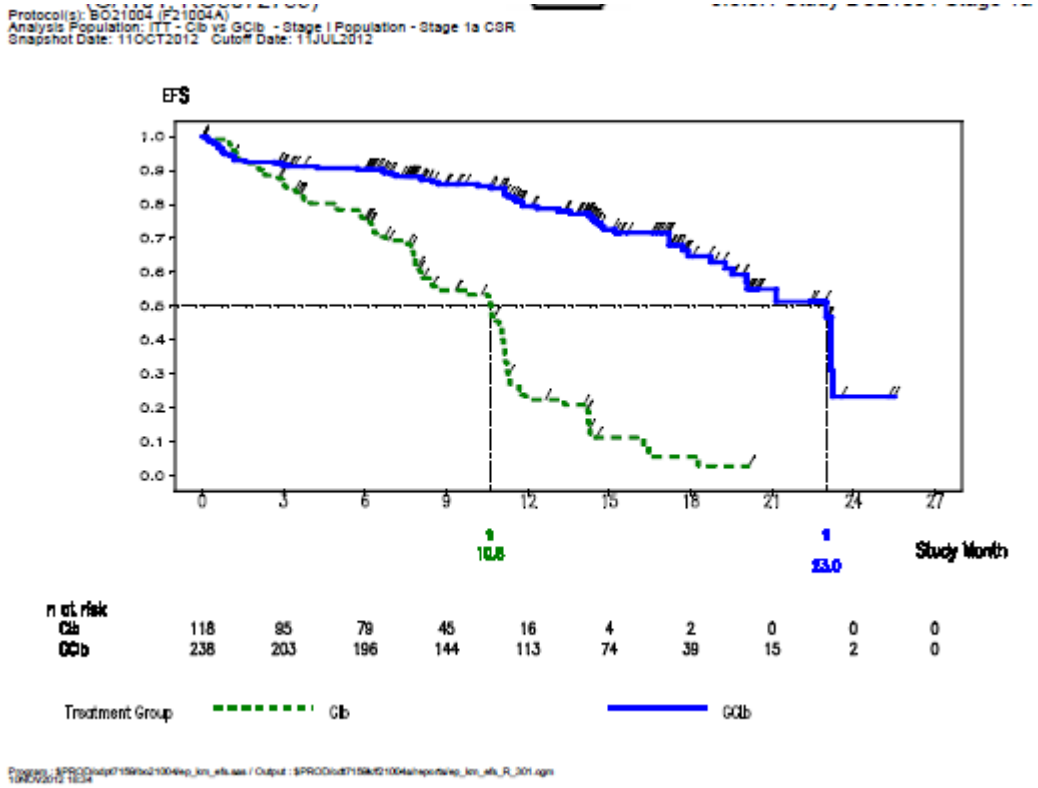


Figure 10: Kaplan-Meier plot of overall survival - Stage 1a (ITT; cut-off 11 July 2012, Study BO21004/CLL11)



Note: In the updated analysis at the clinical data cut-off date, a total of 46 randomized patients had died; 24/118 patients (20.3%) in the Clb arm and 22/238 patients (9.2%) in the GClb arm. The median survival time was not reached in either treatment arm and the overall survival data are therefore still preliminary due to the low number of events. The stratified hazard ratio was 0.41 (95% CI [0.23; 0.74], stratified log-rank test p-value 0.0022).

Figure 11: Kaplan-Meier plot of overall survival - Stage 1a Update (ITT; cut-off 9 May 2013, Study BO21004/CLL11)



Note: In the Clb arm, 79/118 patients (66.9%) had experienced an EFS event (PD, death or start of new anti-leukemic treatment) compared to 64/238 patients (26.9%) in the GClb arm). HR: 0.18 [CI: 0.13, 0.26]. The median EFS was 23.0 months in the GClb arm compared to 10.6 months in the Clb arm.

Figure 12: Event-free survival Clb vs. GClb –Stage 1a (ITT; cut-off 11 July 2012, Study BO21004/CLL11)

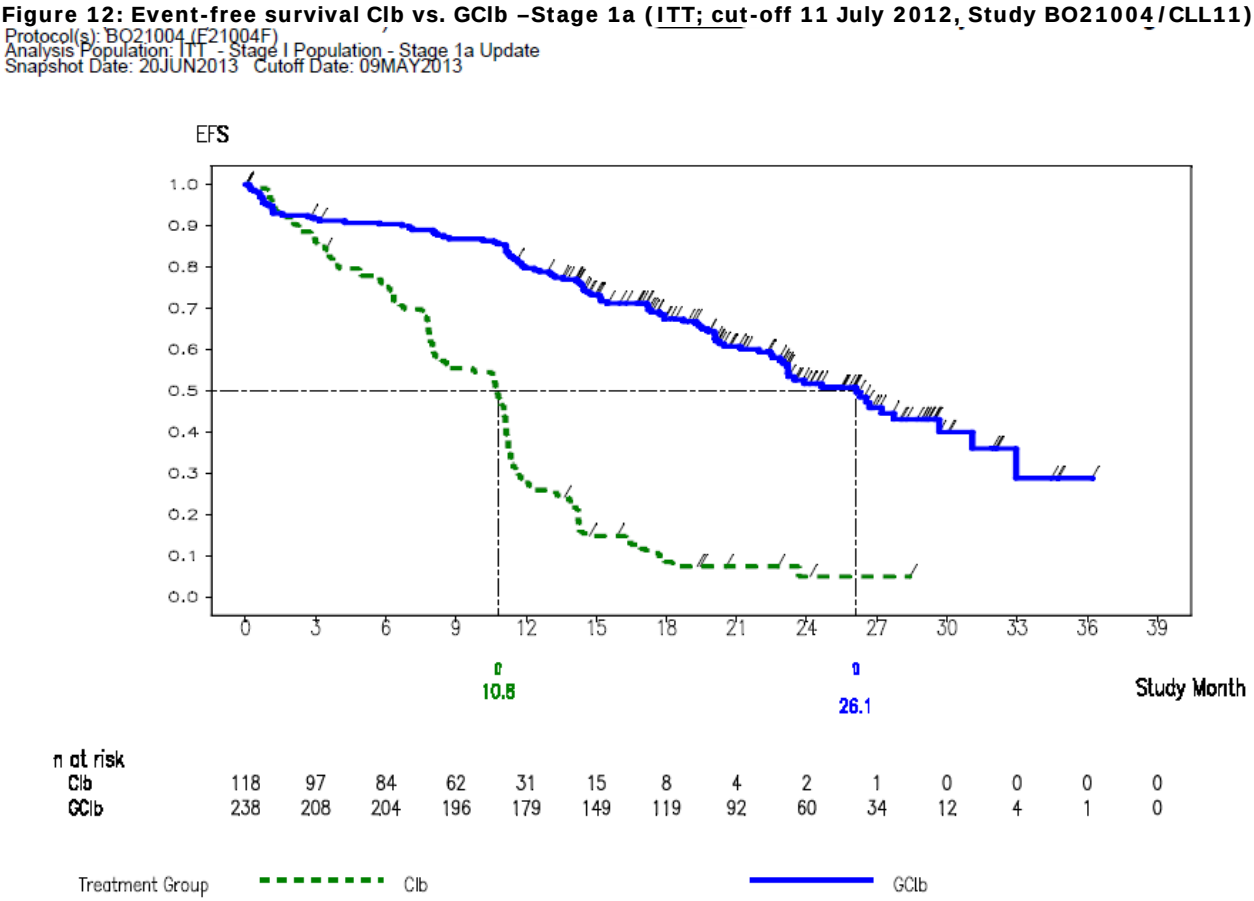
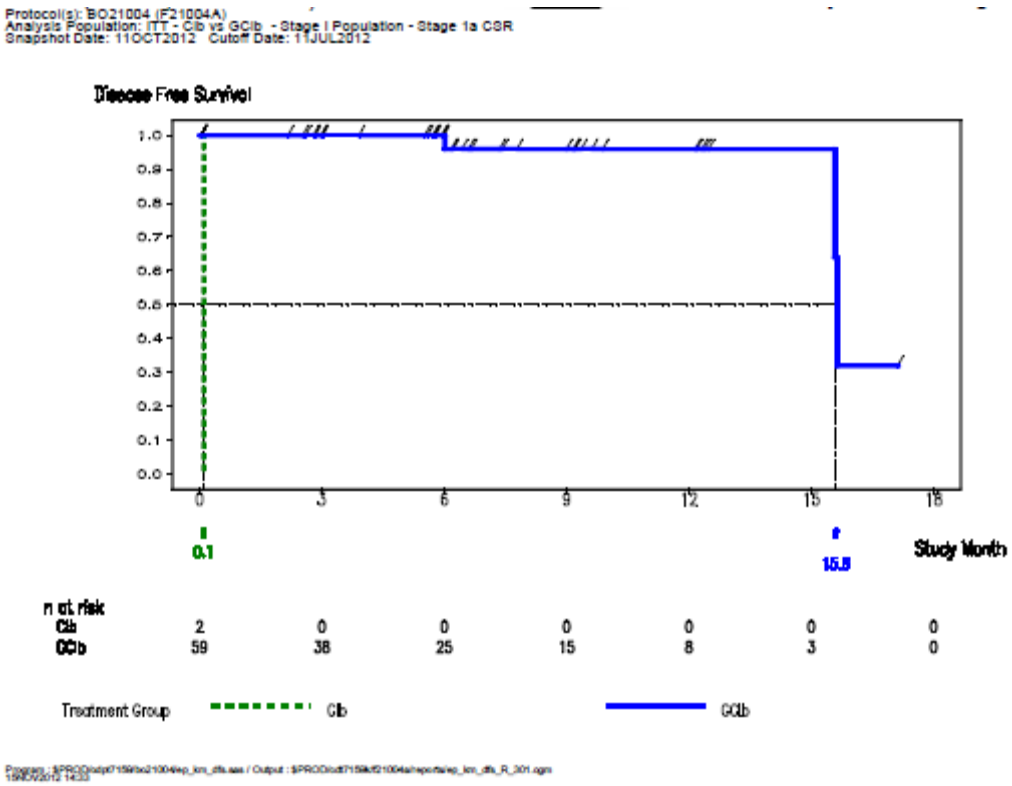


Figure 13: Event-free survival Clb vs. GClb –Stage 1a (ITT; cut-off 9 May 2013, Study BO21004/CLL11)



Note: The disease-free survival was assessed in patients with a best response of CR/Cri at anytime from 56 days after end of treatment. Two out of 118 patients in the Clb arm and 59 out of 238 patients in the GClb arm were included in the DFS analysis. In the Clb arm, one patient out of 2 and in the GClb arm, 3 out of 59 patients (5.1%) had progressed by the clinical cutoff date.

Figure 14: Disease-free survival Clb vs. GClb –Stage 1a (ITT; cut-off 11 July 2012, Study BO21004/CLL11)

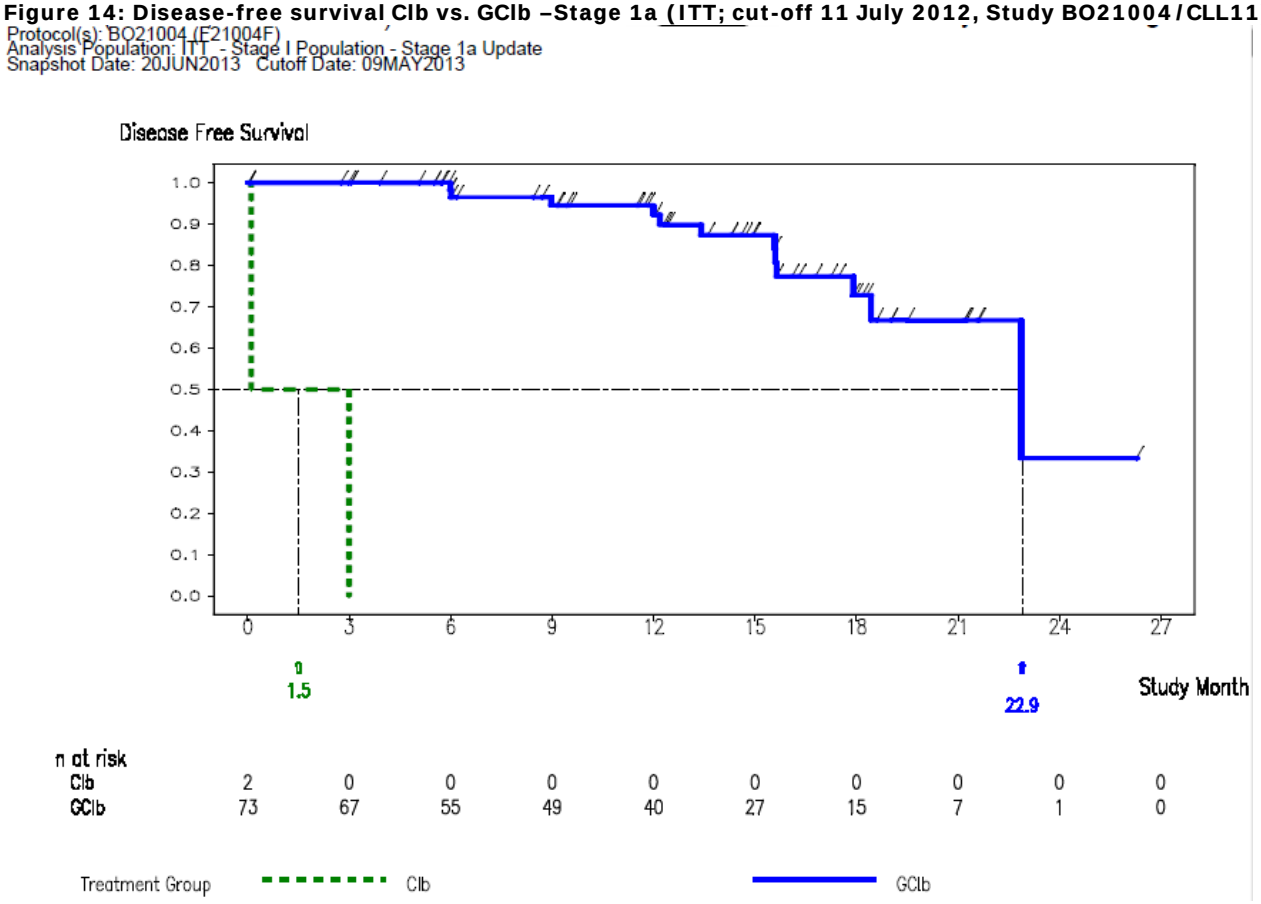


Figure 15: Disease-free survival Clb vs. GClb –Stage 1a (ITT; cut-off 9 May 2013, Study BO21004/CLL11)

Table 29: Duration of response Clb vs. GClb –Stage 1a (ITT; cut-off 11 July 2012, Study BO21004/CLL11)

Protocol(s): BO21004 (F21004A)
Analysis Population: ITT - Clb vs GClb - Stage I Population - Stage 1a CSR
Snapshot Date: 11OCT2012 Cutoff Date: 11JUL2012

	Clb (N=118)		GClb (N=238)
Patients included in analysis	96 (100.0 %)		165 (100.0 %)
Patients with event	20 (55.6 %)		31 (18.8 %)
Patients without event*	16 (44.4 %)		134 (81.2 %)
Duration of response (months)			
Median#	3.5		15.2
95% CI for Median#	[3.0;6.4]		[12.5;15.6]
25% and 75%-ile#	3.0;8.3		9.7;15.6
Range##	0.0 to 11.5		0.0 to 17.4
P-Value (Log-rank Test, stratified**)		<.0001	
Hazard Ratio (stratified**)		0.10	
95% CI		[0.05;0.20]	
P-Value		<.0001	
1 year duration			
Patients remaining at risk	.		26
Event Free Rate	.		0.70
95% CI for Rate	[.;.]		[0.59;0.81]

* censored
# Kaplan-Meier estimates
including censored observations
** Stratified by Binet stage at baseline

Table 30: Duration of response Clb vs. GClb –Stage 1a (ITT; cut-off 9 May 2013, Study BO21004/CLL11)

	Clb (N=118)		GClb (N=238)
Patients included in analysis	41 (100.0 %)		189 (100.0 %)
Patients with event	35 (85.4 %)		67 (35.4 %)
Patients without event*	6 (14.6 %)		122 (64.6 %)
Duration of response (months)			
Median#	5.1		22.4
95% CI for Median#	[3.3;6.7]		[17.1;.]
25% and 75%-ile#	3.0;8.9		12.2;.
Range##	0.1 to 19.8		0.0 to 27.4
P-Value (Log-rank Test, stratified**)		<.0001	
Hazard Ratio (stratified**)		0.16	
95% CI		[0.10;0.25]	
P-Value		<.0001	
1 year duration			
Patients remaining at risk	4		100
Event Free Rate	0.14		0.76
95% CI for Rate	[0.03;0.25]		[0.69;0.82]

* censored
# Kaplan-Meier estimates
including censored observations
** Stratified by Binet stage at baseline

Table 31: Time to new anti-leukemic treatment (ITT; Stage 1a update, cut-off 9 May, 2013, Study BO21004/CLL11)

Protocol(s): BO21004 (F21004F)
Analysis Population: ITT - Stage I Population - Stage 1a Update
Snapshot Date: 20JUN2013 Cutoff Date: 09MAY2013

	Clb (N=118)		GClb (N=238)
Patients with event	65 (55.1 %)		51 (21.4 %)
Patients without event*	53 (44.9 %)		187 (78.6 %)
Time to event (months)			
Median#	14.8		.
95% CI for Median#	[11.7;18.8]		[31.5;.]
25% and 75%-ile#	9.0;28.4		26.9;.
Range##	0.0 to 31.4		0.0 to 36.2
P-Value (Log-rank Test, stratified**)		<.0001	
Hazard Ratio (stratified**)		0.24	
95% CI		[0.16;0.35]	
P-Value		<.0001	
1 year duration			
Patients remaining at risk	55		190
Event Free Rate	0.58		0.89
95% CI for Rate	[0.48;0.68]		[0.85;0.93]

* censored
# Kaplan-Meier estimates
including censored observations
** Stratified by Binet stage at baseline

Program : $PROD/cdpt7159/bo21004/et_time_ttall.sas
Output : $PROD/cdt7159k/f21004f/reports/et_time_ttall_M.out
13AUG2013 12:18 Page 1 of 1

Note: At the time of the primary efficay analysis (cut-off 11 July 2012), 41/118 patients (34.7%) in the Clb arm and 29/238 patients (12.2%) in the GClb arm had started a new anti-leukemia treatment. The risk of receiving a new anti-leukemia therapy was significantly reduced in the GClb arm compared to the Clb arm (stratified HR = 0.26 [95% CI: 0.16, 0.42]; p-value < 0.0001, logrank test). The median time to new anti-leukemia treatment could not be estimated in the GClb arm. In the Clb arm, it was 14.8 months. After disease progression, 30/118 patients (25%) in the Clb arm and 12/238 patients (5%) in the GClb arm received new anti-leukemic treatments, mainly monoclonal antibodies (Clb arm: 19% patients vs. GClb arm: 2% patients), alkylating agents (Clb arm: 10% patients vs. GClb arm: 3% patients) and anti-neoplastic agents (including combination therapies of treatments in these classes) (Clb arm: 7% patients vs. GClb arm: <1% patients). Eleven of the 118 patients (9%) in the Clb arm and 17/238 patients (7%) in the GClb arm received new anti-leukemic treatments before progression, mainly alkylating agents (Clb arm: 7% patients vs. GClb arm: 6% patients) and monoclonal antibodies (Clb arm: 3% patients vs. GClb arm: 2% patients), including combination therapies of treatments in these classes.

Patient reported outcomes

In the EORTC QLQC30 and QLQ-CLL-16 questionnaires conducted during the treatment period, no substantial difference in any of the subscales was observed (data not shown). Data during follow up, especially for the chlorambucil alone arm, were limited. However, no notable differences in quality of life during follow up have been identified to date (SmPC, section 5.1). Health-related quality of life assessments, specific to fatigue through treatment period, showed no statistically significant difference suggesting that the addition of obinutuzumab to a chlorambucil regimen did not increase the experience of fatigue for patients (SmPC, section 5.1). Immunogenicity Patients in the pivotal study BO21004/CLL11 were tested at multiple time-points for anti therapeutic antibodies (ATA) to obinutuzumab. In patients treated with obinutuzumab 8 out of 140 patients in the randomized phase and 2 out of 6 in the run in phase tested positive for ATA at 12 months of follow up. Of these patients, none experienced anaphylactic or hypersensitivity reactions that were considered related to ATA, nor was clinical response affected (SmPC, section 5.1).

Immunogenicity assay results are highly dependent on several factors including assay sensitivity and specificity, assay methodology, assay robustness to quantities of obinutuzumab in the circulation, sample handling, timing of sample collection, concomitant medicines and underlying disease. For these reasons, comparison of incidence of antibodies to obinutuzumab with the incidence of antibodies to other products may be misleading (SmPC, section 5.1).

High level results of Stage 1b analysis (Clb *vs.* RClb)

Updated Stage 1b results (ITT; cut-off 9 May 2013) are summarized in Table 33 and Figure 16.

Table 32: Overview of efficacy results – Clb vs. RClb (ITT; Stage 1b, cut-off 9 May, 2013, Study BO21004/CLL11)

	Clb N = 118		RClb N = 233
Primary Efficacy Parameter			
Progression free survival			
Patients with event	96 (81.4 %)		164 (70.4 %)
Patients without event**	22 (18.6 %)		69 (29.6 %)
Time to Event (months)			
Median###	11.1		16.3
P-Value (Log-rank Test, stratified##)		<.0001	
Hazard Ratio (stratified##)		0.44	
95% CI		[0.34;0.57]	
Hazard Ratio (unstratified)		0.44	
95% CI		[0.34;0.57]	
Progression free survival based on IRC data			
Patients with event	90 (76.3 %)		151 (64.8 %)
Patients without event**	28 (23.7 %)		82 (35.2 %)
Time to Event (months)			
Median###	11.2		16.1
P-Value (Log-rank Test, stratified##)		<.0001	
Hazard Ratio (stratified##)		0.46	
95% CI		[0.35;0.61]	
Hazard Ratio (unstratified)		0.45	
95% CI		[0.35;0.59]	
Key Secondary Efficacy Parameters			
Event free survival			
Patients with event	103 (87.3 %)		169 (72.5 %)
Patients without event**	15 (12.7 %)		64 (27.5 %)
Time to Event (months)			
Median###	10.8		15.4
P-Value (Log-rank Test, stratified##)		<.0001	
Hazard Ratio (stratified##)		0.39	
95% CI		[0.30;0.51]	
Overall survival			
Patients with event	24 (20.3 %)		34 (14.6 %)
Patients without event**	94 (79.7 %)		199 (85.4 %)
Time to Event (months)			
Median###	.		.
P-Value (Log-rank Test, stratified##)		0.1129	
Hazard Ratio (stratified##)		0.66	
95% CI		[0.39;1.11]	
End of Treatment Response			
Responders$	37 (31.4 %)		153 (65.7 %)
95% CI for Response Rates*	[23.1; 40.5]		[59.2; 71.7]
Difference in Response Rates		34.31	
95% CI for Difference in Response Rates#		[23.5; 45.1]	
p-Value (Chi-squared Test)		<.0001	
Complete Response (CR)	0 (0.0 %)		17 (7.3 %)
Partial Response (PR)	37 (31.4 %)		136 (58.4 %)
Stable Disease(SD)	27 (22.9 %)		32 (13.7 %)
Progressive Disease (PD)	32 (27.1 %)		28 (12.0 %)
Missing (No Response Assessment)	22 (18.6 %)		20 (8.6 %)
MRD status at end of treatment (blood and bone marrow combined)			
Patients included in analysis	90 (100.0 %)		169 (100.0 %)
MRD negative	0 (0.0 %)		4 (2.4 %)
MRD positive^	90 (100.0 %)		165 (97.6 %)
95% CI for negative MRD*	[0.0; 4.0]		[0.6; 5.9]
Difference in MRD rates		2.37	
95% CI for difference in MRD rates#		[-0.5; 5.2]	
Missing	28		64

$ Patients with end of treatment response of CR, CRi, PR or nPR
Complete Response (CR) includes CR and CRi; Partial Response (PR) includes PR and nPR
* 95% CI for one sample binomial using Pearson-Clopper method
# Approximate 95% CI for difference of two rates using Hauck-Anderson method
** censored
stratified by Binet stage at baseline
Kaplan-Meier estimates
^ Includes MRD positive patients and patient who progressed or died before end of treatment
MRD negativity is defined as a result below 0.0001
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07OCT2013 23:22

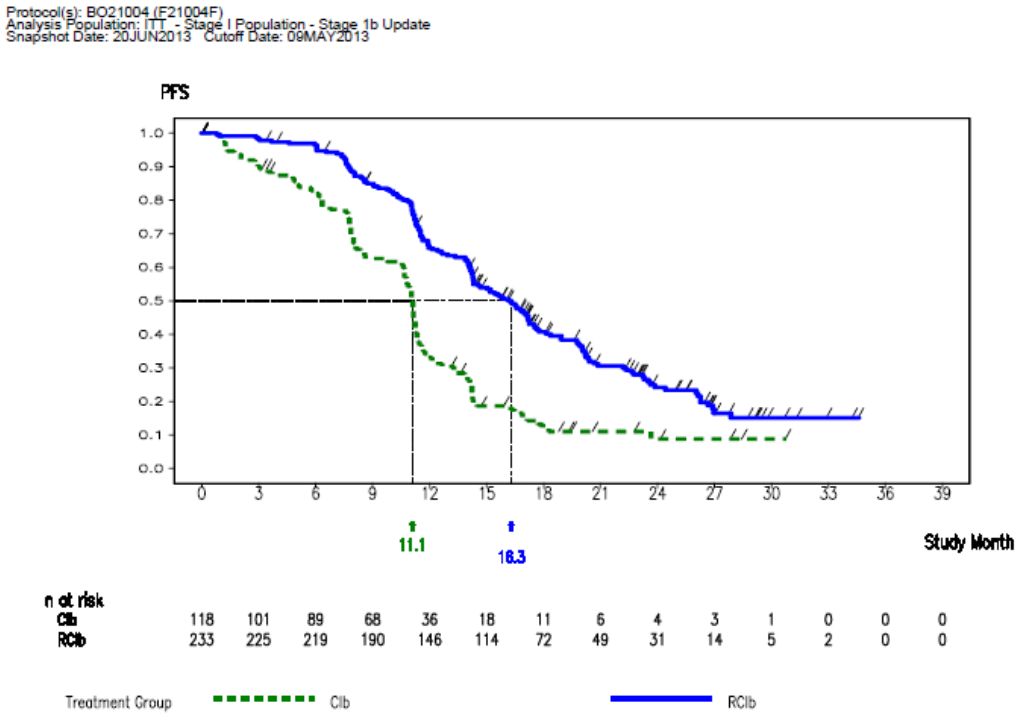

Figure 16: Progression-free survival – Clb vs. RClb (ITT; Stage 1b, cut-off 9 May, 2013, Study BO21004/CLL11)

High level results of Stage 2 analysis (RClb vs. GClb)

The Stage 2 results, which compare GClb to a more aggressive treatment (RClb), became available in July 2013 after a preplanned interim analysis. The efficacy results presented below are based on the ITT population and reflect the primary analysis of the study (18.7 months median follow-up).

Table 33: Overview of efficacy results – RClb vs. GClb (ITT; Stage 2, cut-off 9 May, 2013, Study BO21004/CLL11)

Protocol(s): BO21004 (F21004F)
Analysis Population: ITT - Stage II Population - Stage 2
Snapshot Date: 20JUN2013 Cutoff Date: 09MAY2013

	RClb N = 330		GClb N = 333
Primary Efficacy Parameter			
Progression free survival			
Patients with event	199 (60.3 %)		104 (31.2 %)
Patients without event**	131 (39.7 %)		229 (68.8 %)
Time to Event (months)			
Median###	15.2		26.7
P-Value (Log-rank Test, stratified##)		<.0001	
Hazard Ratio (stratified##)		0.39	
95% CI		[0.31;0.49]	
Hazard Ratio (unstratified)		0.39	
95% CI		[0.31;0.49]	
Progression free survival based on IRC data			
Patients with event	183 (55.5 %)		103 (30.9 %)
Patients without event**	147 (44.5 %)		230 (69.1 %)
Time to Event (months)			
Median###	14.9		26.7
P-Value (Log-rank Test, stratified##)		<.0001	
Hazard Ratio (stratified##)		0.42	
95% CI		[0.33;0.54]	
Hazard Ratio (unstratified)		0.42	
95% CI		[0.33;0.54]	
Key Secondary Efficacy Parameters			
Event free survival			
Patients with event	208 (63.0 %)		118 (35.4 %)
Patients without event**	122 (37.0 %)		215 (64.6 %)
Time to Event (months)			
Median###	14.3		26.1
P-Value (Log-rank Test, stratified##)		<.0001	
Hazard Ratio (stratified##)		0.43	
95% CI		[0.34;0.54]	
Overall survival			
Patients with event	41 (12.4 %)		28 (8.4 %)
Patients without event**	289 (87.6 %)		305 (91.6 %)
Time to Event (months)			

Median###	.		.
P-Value (Log-rank Test, stratified##)		0.0849	
Hazard Ratio (stratified##)		0.66	
95% CI		[0.41;1.06]	
End of Treatment Response			
Patients included in analysis	329 (100.0 %)		333 (100.0 %)
Responders$	214 (65.0 %)		261 (78.4 %)
95% CI for Response Rates*	[59.6; 70.2]		[73.6; 82.7]
Difference in Response Rates		13.33	
95% CI for Difference in Response Rates#		[6.4; 20.3]	
p-Value (Chi-squared Test)		0.0001	
Complete Response (CR)	23 (7.0 %)		69 (20.7 %)
Partial Response (PR)	191 (58.1 %)		192 (57.7 %)
Stable Disease(SD)	50 (15.2 %)		17 (5.1 %)
Progressive Disease (PD)	35 (10.6 %)		12 (3.6 %)
Missing (No Response Assessment)	30 (9.1 %)		43 (12.9 %)
End of Treatment Response not reached£	1		0
MRD status at end of treatment (blood and bone marrow combined)			
Patients included in analysis	244 (100.0 %)		239 (100.0 %)
MRD negative	6 (2.5 %)		61 (25.5 %)
MRD positive^	238 (97.5 %)		178 (74.5 %)
95% CI for negative MRD*	[0.9; 5.3]		[20.1; 31.5]
Difference in MRD rates		23.06	
95% CI for difference in MRD rates#		[17.0; 29.1]	
Missing	85		94
End of Treatment Response not reached£	1		0

$ Patients with end of treatment response of CR, CRi, PR or nPR
Complete Response (CR) includes CR and CRi; Partial Response (PR) includes PR and nPR
* 95% CI for one sample binomial using Pearson-Clopper method
# Approximate 95% CI for difference of two rates using Hauck-Anderson method
** censored
stratified by Binet stage at baseline
Kaplan-Meier estimates
£ Follow up month 3 visit not reached by the cut off date; patients are not included in the analysis
^ Includes MRD positive patients and patient who progressed or died before end of treatment
MRD negativity is defined as a result below 0.0001
Figure 3 Kaplan-Meier curve of iInvestigator assessed progression-free survival from Stage 2

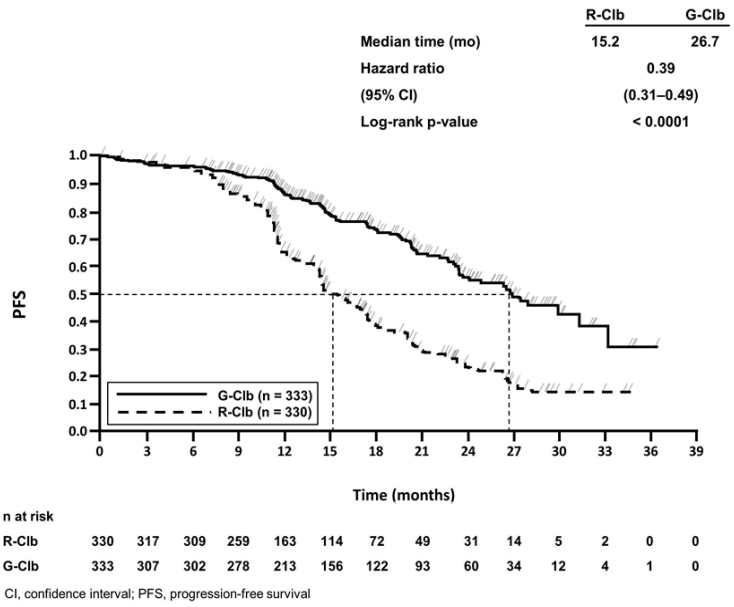

Figure 17: Progression-free survival – RClb vs. GClb (ITT; Stage 2, cut-off 9 May, 2013, Study BO21004/CLL11)

Table 34: Time to new anti-leukemic treatment – RClb vs. GClb (ITT; Stage 2, cut-off 9 May 2013, Study BO21004/CLL11)

Protocol(s): BO21004 (F21004F)
Analysis Population: ITT - Stage II Population - Stage 2
Snapshot Date: 20JUN2013 Cutoff Date: 09MAY2013

	RClb (N=330)		GClb (N=333)
Patients with event	86 (26.1 %)		55 (16.5 %)
Patients without event*	244 (73.9 %)		278 (83.5 %)
Time to event (months)			
Median#	30.8		.
95% CI for Median#	[27.2;32.7]		[31.5;.]
25% and 75%-ile#	18.4;.		27.4;.
Range##	0.0 to 34.6		0.0 to 36.2
P-Value (Log-rank Test, stratified**)		0.0018	
Hazard Ratio (stratified**)		0.59	
95% CI		[0.42;0.82]	
P-Value		0.0021	
1 year duration			
Patients remaining at risk	195		218
Event Free Rate	0.85		0.91
95% CI for Rate	[0.81;0.89]		[0.87;0.94]

* censored
# Kaplan-Meier estimates
including censored observations
** Stratified by Binet stage at baseline

Analysis performed across trials

Table 35: Summary of Efficacy (PFS) in Frail and Unfit Patients in Stage 1a, Stage 1b and Stage 2 of Study BO21004

	Stage 1a (GClb vs Clb) (data cutoff = 11 July, 2012)				Stage 1b (RClb vs Clb) (data cutoff = 10 August, 2012)				Stage2 (GClb vs. RClb) (data cutoff = 9 May, 2013)			
PFS (ITT)	HR 0.14 [95% CI: 0.09, 0.21], p-value < 0.0001, log-rank test				HR 0.32, 95% CI [0.24; 0.44], p-value < 0.0001, log-rank test				HR=0.39, 95% CI=(0.31; 0.49), p-value < 0.0001, log-rank test			
Subgroup	**FRAIL[a]**		**UNFIT[b]**		**FRAIL[a]**		**UNFIT[b]**		**FRAIL[a]**		**UNFIT[b]**	
Treatment pt. number (ITT)	Clb N=46	GClb N=113	Clb N=72	GClb N=125	Clb N=46	RClb N=91	Clb N=72	RClb N=142	RClb N=131	GClb N=150	RClb N=199	GClb N=183
Primary Efficacy Endpoint - Investigator assessed PFS												
Median (months)	10.7	23.0	11.1	23.2	10.6	13.3	11.1	17.2	13.9	23.2	16.9	27.7
PFS HR (95% CI) P-value [c d]	0.20 (0.12; 0.36) < 0.0001		0.11 (0.06;0.20) < 0.0001		0.39 (0.24; 0.64) 0.0002		0.28 (0.18; 0.43) < 0.0001		0.42 (0.29; 0.59) < 0.0001		0.33 (0.23; 0.46) < 0.0001	

Note: [a] Frail patients = patients with CIRS score >6 and CrCl <70 ml/min;
[b] Unfit patients = patients with CIRS score >6 or CrCl <70 ml/min;
[c] Log-Rank test [d] stratified by Binet Stage at Baseline

CI: confidence interval; Clb: chlorambucil; ITT: intent-to-treat; GClb: obinutuzumab +chlorambucil; HR: hazard ratio; RClb: rituximab + chlorambucil; PFS: progression-free survival;

Data sources:
Stage 1a PFS: et_time_pfs_R_832; et_time_pfs_R_838; et_time_pfs_R_301

Stage 1b PFS: et_time_pfs_N_832; et_time_pfs_N_838, et_time_pfs_R

Clinical studies in special populations

Not available.

Supportive study(ies)

Supportive Phase I/II Studies (BO20999, BO21003, BO21000, JO21900)

Supportive clinical safety, PK and pharmacodynamic data come from the pivotal BO21004/CLL11 study in CLL and from four other Phase I/II studies of obinutuzumab in CD20-positive hematological malignancies, as monotherapy or in combination with chemotherapy:

- Study BO20999: an open-label dose-escalating Phase I/randomized Phase II study of obinutuzumab as monotherapy in patients with relapsed/refractory CD20-positive malignancies. The objective of the Phase II part was to compare the efficacy and safety of obinutuzumab in relapsed/refractory iNHL/aNHL (2 doses) or relapsed/refractory CLL (1 dose).

- Study BO21003: an open-label dose-escalating Phase I/randomized Phase II study of obinutuzumab as monotherapy in patients with relapsed/refractory CD20-positive malignant disease. The objective of the Phase II was to compare the efficacy of obinutuzumab versus rituximab in patients with CD20-positive relapsed iNHL.

- Study BO21000: an open-label Phase Ib study of obinutuzumab in combination with cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) or FC as treatment for patients with CD20-positive B-cell relapsed/refractory follicular lymphoma and the combination of obinutuzumab with CHOP or bendamustine in patients with previously untreated follicular lymphoma.

- Study JO21900: a Phase I study conducted in Japan by Chugai Pharmaceutical Co. Ltd of obinutuzumab as monotherapy in patients with relapsed/refractory CD20-positive B-cell NHL only (design similar to Phase I part of study BO20999).

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 36: Summary of Efficacy for trial BO21004

Title: A phase III, open-label, multi-center, three-arm randomized, parallel-group, comparative study of GClb *versus* Clb alone and RClb in previously untreated CLL patients with coexisting medical conditions : Focus on stage 1a results

Study identifier	BO21004 – stage 1a		
Design	Phase III open-label multicenter 3 arm randomized (GClb-Clb-RClb). Stage 1a focuses on the comparison between GClb and Clb alone (only these results are presented in this table). For information, stage 1b focuses on the comparison between RClb and Clb alone. Stage 2 is still ongoing and will compare GClb *versus* RClb.		
	Duration of main phase:		6 cycles of treatment (each of 28 days) and follow up until new untileukemic treatment.
	Duration of Run-in phase:		6 subjects received 6 x 28 day-cycles of GClb
	Duration of Extension phase:		not applicable
Hypothesis	Superiority		
Treatments groups	Chlorambucil (Clb)		Clb 0.5mg/kg on day 1 and 15 of all treatment cycles (1-6), n=118
	Chlorambucil + Obinutuzumab (GClb)		Clb 0.5mg/kg on day 1 and 15 of all treatment cycles (1-6) + 1000 mg of obinutuzumab (IV) on Day 1, Day 8 and Day 15 of the first treatment cycle (Cycle 1), For each subsequent cycle, patients received obinutuzumab (1000 mg) IV on Day 1 only (Cycle 2 – 6), Protocol amendment G specified that the first infusion of obinutuzumab was split over two days in order to reduce the potential risk and severity of infusion-related reactions, n = 238
	Chlorambucil + rituximab (RClb)		Clb 0.5mg/kg on day 1 and 15 of all treatment cycles (1-6) + 375 mg/m2 of rituximab IV on Day 1 of the first treatment cycle (Cycle 1), For each subsequent cycle, patients received rituximab (500 mg/m2) as an IV infusion on Day 1 (Cycles 2 – 6), n= 236
Endpoints and definitions	Primary endpoint	PFS (Inv)	Progression Free Survival assessed by the investigators is defined as the time from randomization to the first occurrence of progression, relapse, or death from any cause as assessed by the investigator.
	Secondary endpoint	PFS (IRC)	Progression Free Survival assessed by the Independent Review Committee
	Secondary endpoint	OS	Overall survival
	Secondary endpoint	RR (nPR, PR, CR, CRi)	Response rate (nodular partial response, partial response, complete response, complete response incomplete)
	Secondary endpoint	End of treatment response	is defined as the response occurring at the end of treatment (first assessment that occurred more than 56 days after the end of treatment) before start of new anti–leukemia treatment.

	Secondary endpoint	EFS	Event-Free-Survival is defined as the time between date of randomization and the date of disease progression/relapse, death, or start of a new anti-leukemic therapy
	Secondary endpoint	DFS	Disease Free Survival is defined for all patients with complete response at any time from 56 days after end of treatment onwards.
	Secondary endpoint	DOR	Duration of response is defined similarly for complete and partial responders at any time from 56 days after end of treatment onwards.
	Secondary endpoint	Time to new anti-leukemia treatment	Time between the date of randomization and the date of first intake of re-treatment or new anti-leukemic therapy
Database lock	Data cutoff : 11 July 2012 ; database lock date : 11 October 2012 Data cutoff : 09 May 2013 ; database lock date : 20 June 2013 –results from this update are included in *italics*		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat 175 PFS events (all 3 treatment arms)		
Descriptive statistics and estimate variability and effect estimate per comparison	**Treatment group**	**Clb**	**GClb**
	Number of subject	**118**	**238**
	PFS (inv) **No of patients with an event (%)**	71 (60.2%) *96 (81.4%)*	52 (21.8%) *93 (39.1%)*
	Median PFS in months (95% CI)	10.9 (7.8 ; 11.2) *11.1 (10.6 ; 11.3)*	23.0 (20.0 ; 23.2) *26.7 (23.2 ; 33.0)*
	P-value (log-rank test)	< 0.0001	
	Hazard ratio (stratified)	0.14 (0.09 ; 0.21) *0.18 (0.13 ; 0.24)*	
	PFS (IRC) **No of patients with an event (%)**	66 (55.9%) *96 (81.4%)*	52 (21.8%) *93 (39.1%)*
	Median PFS in months (95% CI)	11.1 *11.1*	23.0 *26.7*
	P-value (log-rank test)	<0.0001	
	Hazard ratio (stratified)	0.16 (0.11 ; 0.24) *0.19 (0.14 ; 0.27)*	
	OS **No of patients with an event (%)**	9 (7.6%) *24 (20.3%)*	13 (5.5%) *22 (9.2%)*

	Median OS in months (95% CI)	-	-
	P-value (log-rank test)	0.3820 *0.0022*	
	Hazard ratio (stratified)	0.68 (0.29 ;1.60)	
	Disease free survival time to event (months)	0.1 *1.5*	15.6 *22.9*
	p-value	0.0005 *<0.0001*	
	EFS **No of patients with an event (%)**	79 (66.9%) *103 (87.3%)*	64 (26.9%) *104 (43.7%)*
	Median EFS in months (95% CI)	10.6 *10.8*	23.0 *26.1*
	P-value (log-rank test)	<0.0001	
	Hazard ratio (stratified)	0.18 (0.13;0.26) *0.19 (0.14;0.25)*	
	Responders (end of treatment response)	32 (30.2%) *37 (31.4%)*	160 (75.5%) *184 (77.3%)*
	P-value (Chi-squared test)	<0.0001	
	Complete response	0 (0.0%) *0 (0.0%)*	47 (22.2%) *53 (22.3%)*
	Partial response	32 (30.2%) *37 (31.4%)*	113 (53.3%) *131 (55.0%)*
	Stable disease	23 (21.7%) *27 (22.9%)*	10 (4.7%) *12 (5.0%)*
	Progressive disease	27 (25.5%) *32 (27.1%)*	8 (3.8%) *8 (3.4%)*
	Missing (No response assessment)	24 (22.6%) *22 (18.6%)*	34 (16.0%) *34 (14.3%)*
	End of treatment response not reached	12 -	26 -

	MRD negative	0 (0%) *0 (0%)*	28 (19.7%) *45 (26.8%)*
	Duration of response (median in months)	3.5 *5.1*	15.2 *22.4*
	Hazard ratio (stratified)	0.10 (95%CI : 0.05 ; 0.20) *0.16 (95%CI : 0.10 ; 0.25)*	
	p-value	<0.0001	
	No of patients starting a new anti-leukemic treatment (%)	41 (34.7%) *65 (55.1%)*	29 (12.2%) *51 (21.4%)*
	Stratified HR	0.26 (0.16 ; 0.42) *0.24 (0.16 ; 0.35)*	
	p-value (log rank test)	<0.0001	
	Median time to a new anti-leukemic treatment (months)	14.8 *14.8*	- -

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

A Phase III international, multicentre, open label, randomiszed, two-stage, three-arm clinical study (BO21004/CLL11) investigating the efficacy and safety of Gazyvaro plus chlorambucil (GClb) compared to rituximab plus chlorambucil (RClb) or chlorambucil (Clb) alone was conducted in patients with previously untreated chronic lymphocytic leukaemia with comorbidities (SmPC, section 5.1).

A total of 781 patients were randomized 2:2:1 to receive Gazyvaro plus chlorambucil, rituximab plus chlorambucil or chlorambucil alone. Stage 1a compared Gazyvaro plus chlorambucil to chlorambucil alone in 356 patients and Stage 2 compared Gazyvaro plus chlorambucil to rituximab plus chlorambucil in 663 patients (SmPC, section 5.1).

Stratification was performed based on the most important factors that were considered to have the potential to impact the safety and efficacy analyses i.e. Binet stage (A, B or C), which is acknowledged as the most important prognostic factor for CLL patients and region to ensure a balance across the treatment arms with respect to clinical practice. With only 118 patients randomized to the Chlorambucil arm, it would not have been efficient to include additional stratification factors (e.g., CIRS > 6 and ClCr <70 ml/min versus CIRS > 6 or ClCr <70 ml/min). Nevertheless, important imbalances in prognostic factors were not observed and adjusted analyses showed no important differnces in the estimation of the treatment effect.

There was a difference of 5% between the treatment arms in the proportion of patients with ZAP 70 positive disease. This small imbalance of a negative prognostic factor (ZAP 70 positivity) in Clb-treated patients was considered unlikely have biased the results in favour of obinutuzumab. Updated PFS results for ZAP 70 positive and ZAP 70 negative subgroups of patients were consistent with the ITT population (data not shown). In the ZAP 70 positive subgroup (i.e. prognostically potentially worse), there was a trend in favor of GClb, (HR=0.81; 95% CI: 0.33; 1.99, stratified log-rank test p-value 0.6448). The CHMP considered that a possible benefit in OS should be confirmed and that the mature data should be submitted when available (see conclusions on clinical efficacy).

For the positioning of obinutuzumab a comparison with rituximab was necessary since it is now widely recognized that the addition of rituximab to any effective chemotherapy for CLL will improve PFS, ORR (and in some settings also OS). In that respect the comparator arm with chlorambucil was considered of reduced clinical interest.

In the majority of patients, Gazyvaro was given intravenously as a 1,000 mg initial dose administered on Day 1, Day 8 and Day 15 of the first treatment cycle. In order to reduce the rate of infusion reactions in patients, an amendment was implemented and 140 patients received the first Gazyvaro dose administered over 2 days ([Day 1 [(100 mg]) and Day 2 [(900 mg]))] (see section 4.2 and 4.4). For each subsequent treatment cycle (Cycles 2 to 6), patients received Gazyvaro 1,000 mg on Day 1 only. Chlorambucil was given orally at 0.5 mg/kg body weight on Day 1 and Day 15 of all treatment cycles (1 to 6).

The demographics data and baseline characteristics were well balanced between the treatment groups. The majority of patients were Caucasian (95%) and male (61%). The median age was 73 years, with 44% being 75 years or older. At baseline, 22% of patients had Binet Stage A, 42% had Binet Stage B and 36% had Binet Stage C.

Efficacy data and additional analyses

Part 1a of study BO21004 has provided convincing evidence of efficacy of obinutuzumab with a clinically meaningful and statistically significant improvement in the primary endpoint PFS, compared to chlorambucil alone, in previously untreated CLL patients with coexisting medical conditions and/or renal impairment. The risk of disease progression or death was reduced by 86% when obinutuzumab was given with chlorambucil (HR = 0.18, 95% CI [0.13; 0.24]; log-rank p-value < 0.0001). There was a good concordance between investigator and IRC assessment of PFS, and the finding of primary analysis was supported by all relevant sensitivity analyses. Thus, the efficacy results were considered robust.

All secondary endpoints with mature data, including EFS, overall response rates, CR rates, achievement of MRD-negative status, duration of response and time to new treatment, supported the primary efficacy endpoint and favored the GClb arm compared to the Clb arm.

OS data were still immature but the stratified hazard ratio was 0.41 (95% CI [0.23; 0.74], stratified log-rank test p-value 0.0022).

Overall, the baseline demographics and prognostic factors were well balanced although some imbalances were noted. It seems unlikely that such imbalances should influence the overall very convincing efficacy results.

The BO21004/CLL11 study population included patients with varying coexisting medical conditions with one defining common characteristic; the patients were physically fit enough to tolerate an anti-CD20 antibody infusion but they were not fit enough to tolerate the toxicity associated with full dose fludarabine. Prior to enrolment, patients had to have documented CD20+ CLL, and one or both of the following measures of coexisting medical conditions: comorbidity score (Cumulative Illness Rating Scale (CIRS)) of greater than 6 or reduced renal function as measured by CrCl <70 mL/min. Patients with inadequate liver function (National Cancer Institute – Common Terminology Criteria for Adverse Events Grade 3 liver function tests (AST, ALT > 5 x ULN for > 2 weeks; Bbilirubin > 3 x ULN) and renal function (CrCl < 30 mL/min) were excluded. Patients with one or more individual organ/system impairment score of 4 as assessed by the CIRS definition, excluding Eeyes, Eears, nose, throat and larynx organ system, were excluded. The median comorbidity score was 8 and 76% of the patients enrolled had a comorbidity score above 6. The median estimated CrCl was 62 mL/min and 66% of all patients had a CrCl < 70 mLl/min. Forty-two percent of patients enrolled had both a CrCl < 70 mLl/min and a comorbidity score of > 6. Thirty-four percent of patients were enrolled on comorbidity score alone, and 23% of patients were enrolled with only impaired renal function.

The most frequently reported coexisting medical conditions (using a cut off of 30% or higher), in the MedDRA body systems were: vascular disorders (73%), cardiac disorders (46%), gastrointestinal disorders (38%), metabolism and nutrition disorders (40%), renal and urinary disorders (38%), musculoskeletal and connective tissue disorders (33%)(SmPC, section 5.1). To reflect this, the indication (SmPC, section 4.1) has been restricted to treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) and with co morbidities making them unsuitable for full-dose fludarabine based therapy. A cross reference to the SmPC section 5.1 has been included in the indication to describe the key inclusion criteria of the pivotal study.

During the initial evaluation, the CHMP raised a major objection about the indication needing to be further discussed, with reference to “frail” patients (CIRS score >6 and CrCl <70 ml/min) and “unfit” patients (CIRS score >6 or CrCl <70 ml/min; these patients could, according to the some treatment guidelines, have received a more aggressive treatment than Cbl alone, in particular RCbl, or other drugs, like bendamustine or reduced dose RFC). However, it was also acknowledged that Clb was an acceptable comparator treatment for these patients since there was no phase III evidence that the addition of an anti-CD20 antibody to Clb would improve outcome. Based on further subgroup analyses in the “frail” and “unfit” patients, a strongly positive effect was observed with GClb against Cbl alone and RCbl throughout a number of efficacy analyses and endpoints without major differences in toxicity.

To further support this, the Applicant will submit the OS mature data when available in order to confirm the benefit of GClb over RClb for this endpoint (see conclusions on clinical efficacy).

Results of the PFS subgroup analysis (i.e. sex, age, Binet stages, CrCl, CIRS score, beta2-microglobulin, IGVH status, chromosomal abnormalities, lymphocyte count at baseline) were consistent with the results seen in the overall Intent-to-Treat population. The risk of disease progression or death was reduced in the GClb arm compared to the RClb arm and Clb alone arm in all subgroups except for the subgroup of patients with deletion 17p, for which no benefit was observed compared to RClb. For subgroups, reduction of the risk of disease progression or death ranged from 92% to 58% for GClb versus Clb and 72% to 29% for GClb versus RClb (SmPC, section 5.1).

There were strict criteria for crossing over to the GClb arm and cross over was at the Investigator's discretion. At the cutoff date for the primary Stage 1a analysis (11 July, 2012), 22/118 patients (19%) had crossed over from Clb to receive GClb. At the cutoff date for the updated Stage 1a analysis (9 May, 2013), a further 8 patients had crossed over from Clb to GClb, increasing the final number of patients who crossed over from Clb to GClb to 30/118 patients (25%). There were 27 patients (23% patients overall) who, despite fulfilling the criteria, did not cross over to receive GClb of which 16 received alternative treatments like bendamustine and rituximab.

Although only 26 patients with del17p were included in the stage 1 a study (10 in Clb arm and 16 in GClb arm) the results indicate that GClb has limited activity in that subpopulation (SmPC, section 5.1). The availability of newer agents with reported high activity in del(17p) CLL such as ibrutinib and idelalisib further strengthen the need for information on the activity of obinutuzumab in that particular subset.

The chlorambucil dose in BO 21004 trial was relatively low (0.5 mg/kg body weight of Clb given orally on Day 1 and Day 15 of all treatment cycles, Cycle 1 – 6). Dose escalation could have been medically indicated in 4 of the 9 patients who experienced PD prior to receiving 6 cycles of chlorambucil and in 7 patients with stable disease. Although dosing could have been suboptimal in these patients, this is not expected to lead to significant over-estimation of the treatment effect associated with obinutuzumab.

HRQoL data are of limited value due to the open-label design of the study. Blinding was considered impractical due to the different regimens for obinituzumab (given three times in Cycle 1 at a flat dose of 1000 mg and on Day 1 of subsequent cycles) and rituximab (given once per cycle at 375 mg/m²). Despite their limited value the HRQoL data can still be a useful part of the overall benefit-risk estimation. While certain safety events occurred in a higher incidence in the 'frail' population, thus potentially impacting QoL, these safety events are well-known and therefore manageable. Together with the maintenance of the HRQoL outcomes one could conclude that treatment with Obinutuzumab did not negatively impact QoL. However, an improvement of QOL in the study population has not been established.

2.5.4. Conclusions on the clinical efficacy

Study BO21004 has provided convincing evidence of clinical efficacy of obinutuzumab in terms of the primary endpoint PFS, compared to chlorambucil alone, in previously untreated CLL patients with coexisting medical conditions and/or renal impairment. The addition of obinutuzumab to Clb resulted in a clinically meaningful and statistically significant improvement in the primary endpoint of PFS compared to RClb.

The CHMP considers the following measures necessary to address issues related to efficacy:

The applicant will submit by 31 January 2016, the OS mature data of stage 2 in order to confirm the benefit of GClb for this endpoint. Subgroup OS analyses in the frail and unfit subsets will also be provided.

The Applicant will submit by 31 January 2016 the OS mature data of stage 1a in the ITT population, in the subgroups of ZAP70 positive patients and ZAP70 negative patients (see section 4).

2.6. Clinical safety

Safety data from stage 1 of this pivotal study, BO21004/CLL11, comparing the efficacy and safety of obinutuzumab + chlorambucil (GClb), rituximab + chlorambucil (RClb), or chlorambucil alone (Clb) in previously untreated CLL patients with comorbidities, have been submitted. Four additional supporting studies provided additional safety data using a different treatment approach in a somewhat different population i.e. obinutuzumab as monotherapy in relapsed/refractory CLL patients and relapsed/refractory NHL patients and obinutuzumab + chemotherapy (G-CHOP or G-FC) in follicular lymphoma patients.

Table 37: Summary of Studies Contributing to the Obinutuzumab Safety Evaluation

Protocol	Phase	Study Population	Number of Patients Included in this Report	Treatment regimen
Pivotal BO21004/CLL11	III	Previously untreated CLL patients	6 run-in + 240[b] randomized phase + 22 cross over	Obinutuzumab 1000 mg + chlorambucil (GClb), rituximab +chlorambucil (RClb) or chlorambucil (Clb) alone Obinutuzumab: Day 1, 8 and 15 for Cycle 1, Day 1 for Cycles 2-6 Clb: Days 1 and 15 of each cycle Cycle duration = 28 days
Supporting Studies				
BO20999	I/II	Phase I: patients with CD20+ malignant disease for whom no therapy of higher priority is available Phase II: patients with relapsed/refractory CD20+ malignant disease for whom no therapy of higher priority is available	34 (21 NHL and 13 CLL) 100 (40 iNHL, 40 aNHL and 20 CLL)	Dose-escalation: Six cohorts of 50 mg - 2000 mg of obinutuzumab with Cohort 7 to investigate the safety of the recommended Phase II doses in NHL and CLL; Day 1 and 8 for Cycle 1, Day 1 for Cycles 2-8 Cycle duration = 21 days NHL: 1600 mg / 800 mg or 400 mg; Day 1 and 8 for Cycle 1, Day 1 for Cycles 2-8 CLL: 1000 mg; Day 1, 8 and 15 for Cycle 1, Day 1 for Cycles 2-8 Cycle duration = 21 days
BO21003	I/II	Phase I: male and female adult patients with CD20+ malignant disease Phase II: patients with relapsed CD20+ iNHL	17 NHL and 5 CLL patients 86 patients rituximab[a] 87 patients obinutuzumab	Phase I: iv infusion once weekly for 4 weeks. 5 dose-escalation cohorts (100 mg – 2000 mg) with Cohort 6 (1000 mg) to test safety and tolerability of recommended Phase II dose Phase II Obinutuzumab: 1000 mg
BO21000	Ib	Male and female patients with either a documented CD20+ relapsed/refractory B cell follicular lymphoma or	56 relapsed/refractory patients	relapsed/refractory NHL: low dose: 400mg or high dose: 16008/800 mg: given 3-weekly for 6-8 cycles (G-CHOP arm) or 4 weekly for 4-6 cycles (G-FC arm)

		documented CD20+ B-cell follicular lymphoma with no prior systemic therapy	81 patients with previously untreated NHL	Previously untreated NHL: obinutuzumab: 1000 mg G-CHOP arm - Day 1 for 6-8 cycles + extra dose on Cycle 1 Day 8 G- bendamustine - Day 1 for 4-6 cycles + extra dose on Cycle 1 Day 8
JO21900	I	Patients with CD20+ malignant disease	12 NHL patients	Day 1 and 8 for Cycle 1, Day 1 for Cycles 2-8 Cycle duration = 21 days 1st / subsequent doses: 200 mg / 400 mg 400 mg / 800 mg 800 mg / 1200 mg 1200 mg / 2000 mg

[a] rituximab data are not included in this report

[b] includes 4 patients randomized to RClb who erroneously received GClb

CLL=chronic lymphocytic leukemia, CSR=clinical study report, CHOP = cyclophosphamide, daunorubicin, vincristine, prednisone, FC=fludarabine and cyclophosphamide, G-CHOP=obinutuzumab + CHOP, G-FC=obinutuzumab + FC, GClb = obinutuzumab + chlorambucil, NHL = non-Hodgkin's lymphoma, aNHL = aggressive non-Hodgkin's lymphoma, iNHL = indolent non-Hodgkin's lymphoma, RClb = rituximab + chlorambucil, (cutoff date: 2 July 2012, except for study BO21004/CLL11 with a cutoff date of 11 July 2012)

Patient exposure

All patients in the pivotal study in the GClb arm were treated with the proposed dose of 1000 mg obinutuzumab and 0.5 mg/kg body weight of Clb. More than 75% of the patients received the recommended 8 cycles of treatment with obinutuzumab i.e. approximately 6 months of treatment. A greater percentage of patients in the GClb arm received all 6 cycles of planned treatment compared to the Clb arm (Clb arm: 67% patients vs. GClb arm: 81% patients) (SmPC, section 4.8). The treatment arms were similar with respect to the percentage of patients who received only one cycle of treatment (Clb arm: 10% patients vs. GClb arm: 11% patients). However, a greater proportion of patients in the Clb arm withdrew, particularly at Cycles 2, 3 and 4).

The median cumulative dose of Clb in each treatment arm was similar with 384.0 mg in the Clb arm (range: 28.0–672.0 mg) and 370.0 mg in the GClb arm (range: 22.0 mg–1440.0 mg). The median cumulative dose of obinutuzumab in the GClb arm was 8000.0 mg (range: 2.0–26000.0 mg). The highest reported dose of 26000 mg was a data entry error; this patient was confirmed to have received 8 × 1000 mg infusion rather than 6 × 1000mg plus 2 × 10,000mg. The median exposure time was 6.0 months in the Clb arm (range: 1.0–7.4 months) and 5.6 months in the GClb arm (range: 1.0–9.0 months).

Table 38: Exposure to Obinutuzumab by Study and Analysis Population*

Study	BO21004/CLL11			Pooled Studies BO20999 and BO21003		BO21000
Patient Population	GClb-treated CLL patients safety run-in N=6	GClb-treated CLL patients (randomized phase) N=240	Patients who crossed over to receive GClb N=22	Single agent obinutu-zumab-treated patients with relapsed/ refractory CLL N=38	Single agent obinutu-zumab-treated patients with relapsed/ refractory NHL N=205	Obinutu-zumab + chemotherapy - treated patients with follicular lymphoma N=137
Total No. of Patients				**648**		
Exposure by dose (cumulative dose, mg)						
Mean	8000.0	6968.1	7240.9	8976.987	7767.789	8515.684
SD	0.0	2910.38	1703.68	5860.642	5127.814	3410.481
Median	8000.0	8000.0	8000.0	9382.915	6800.000	9000.000
Min	8000.0	2.0	1000.0	9.000	20.000	15.000
Max	8000.0	26000.0[a]	8000.0	27600.00	21200.00	14400.00

* data from study JO21900 are presented separately.

[a] The highest dose of 26000 mg was a data entry error; this patient was confirmed to have received 8 × 1000 mg infusion rather than 6 × 1000 mg plus 2 × 10,000 mg.

GClb = obinutuzumab in combination with chlorambucil

Adverse events

The intensity of all adverse events was graded according to the NCI CTCAE version 4.0.

Almost all patients in the pivotal study experienced adverse events, 82% in the Clb arm vs. 93% in the GClb arm. The differences in frequency of adverse events between the two arm were mainly due to differences in infusion related adverse events (IRRs), neutropenia, thrombocytopenia and leucopenia. These adverse events were also the most common adverse events along with infections and gastrointestinal disorders. This is not unexpected knowing the safety profile of chlorambucil and anti-CD20 antibodies. Grade 3-5 adverse events occurred more frequently in the GClb arm (69%) vs. Clb arm (47%) and were primarily due to IRRs, neutropenia, thrombocytopenia and leucopenia. However, In study BO21004 Stage 1a, 21% (51/240) patients received prophylactic treatment with anti-infective medications and G-CSF in GClb arm compared to 11% (13/116) in Clb arm. From study Day 1 onwards, a higher proportion of patients in the GClb arm were treated with anti-infective medications and G CSF (74%; 178/240) compared to the Clb arm (56%; 65/116).

The difference in the percentage of patients having received prophylactic treatment with anti-infective medications and G-CSF is the most plausible explanation for infections and febrile neutropenia to have occurred more frequently in the Clb arm, though the fact that GClb is more efficient could also have attributed.

A summary of stage 1a and stage 1b of the pivotal study key safety findings is presented in Table 39.

The adverse events occurring with a ≥2% increased incidence in the GClb arm compared with the Clb arm are shown in Table 40.

In Stage 2 of the pivotal study (GClb vs. RClb) the incidence of all grade adverse events (RClb arm: 89% patients vs. GClb arm: 94% patients), adverse events leading to withdrawal from any study medication (RClb arm: 8% patients vs. GClb arm: 13% patients), serious adverse events (RClb arm: 32% patients vs. GClb arm: 39% patients) and Grade 3-5 adverse events (RClb arm: 55% patients vs. GClb arm: 70% patient) were all higher in the GClb arm. This imbalance was mainly due to IRRs (38% in RClb versus 66% in GClb), neutropenia (32% versus 38%), thrombocytopenia (7% versus 14%), and TLS (0% versus 4%). The majority of IRRs were Grade 1 or 2 and there were no Grade 5 IRRs in this study. The difference in the incidence of neutropenic adverse events between the treatment arms (33% versus 42%) was driven by Grade 4 events (11% versus 18%). No Grade 5 neutropenic events occurred in either arm. The incidence of infection in patients with neutropenic adverse events was comparable in the RClb [48/106 (45%)] and GClb arms [68/141 (48%)]. More patients in the GClb arm (21% or 72/336) received prophylactic treatment with anti-infective medications and G-CSF in GClb arm as compared to the RClb arm (19% or 62/321). The adverse events occurring with a ≥2% increased incidence in the GClb arm compared with the RClb arm are shown in Table 41.

In the supportive studies, the pattern and frequency of Grade 3-5 adverse events in the CLL population was almost identical to that of the CLL population in the pivotal study. In the other populations, monotherapy NHL and chemocombination therapy populations, the frequency of the most common adverse events were different, typically lower. An overview of the safety profile in the supportive studies is shown in table 40.

Table 39: Summary of safety in Stage 1a and 1b (safety population; study BO21004/CLL11)

	Stage 1a		Stage 1b	
	11 July 2012 cut-off		10 August, 2012 cut-off	
	Clb N=116	GClb N=240	Clb N=116	RClb N=225
Grade 3-5 AEs (%)	47%	69%	47%	53%
SAE	32%	37%	32%	29%
AE leading to death	7%	3%	7%	5%
AE leading to withdrawal from treatment	15%	20%	15%	14%
AE leading to withdrawal from obinutzumab/rituximab	–	13%	–	6%
AE of particular interest				
Grade 3-5 IRRs	-	21%	-	4%
Grade 3-5 Neutropenia	16%	34%	16%	26%
Grade 3-5 Infections*	13%	9%	13%	12%

* Based on SOC Infections & Infestations.

Table 40: Adverse events occurring with a ≥2% increased incidence in GClb group compared with the Clb group (safety population; study BO21004/CLL11)

System Organ Class and Preferred Term	All Grades %		Grades 3-5%	
(MedDRA)	Clb n=116	GClb n=240	Clb n=116	GClb n=240
Injury, Poisoning and Procedural Complications				
Infusion related reactions	N/A	68.8	N/A	21.3
Blood and lymphatic system disorders				
Neutropenia	18.1	40.0	15.5	34.2
Thrombocytopenia	6.9	15.0	3.4	10.8
Leukopenia	0	6.7	0	5.4
Infections and infestations				
Urinary tract infection	2.6	4.6	<1	1.3
Oral herpes	<1	3.3	0	0
Rhinitis	<1	2.1	0	0
General disorders and administration site conditions				
Pyrexia	6.9	10.4	0	<1
Respiratory, thoracic and mediastinal disorders				
Cough	6.9	9.6	<1	0
Metabolism and nutrition disorders				
Tumour lysis syndrome	<1	4.2	0	1.7
Hyperuricaemia	0	3.3	0	<1
Musculoskeletal and connective tissue disorders				
Arthralgia	2.6	4.6	<1	<1
Back pain	<1	4.6	0	<1
Musculoskeletal chest pain	0	2.1	0	<1
Investigations				
Neutrophil count decreased	0	2.1	0	2.1
White blood cell count decreased	<1	2.1	0	2.1
Weight Increased	0	2.1	0	0
Gastrointestinal Disorders				
Diarrhea	11.2	10.4	<1	2.5
Skin and subcutaneous tissue disorders				
Alopecia	0	2.1	0	0

Sources: st_aediff2_S, st_aediff234_S, ae11_s, ae11v_s

Table 41: Adverse events occurring with a ≥2% increased incidence in GClb group compared with the RClb group (safety population; study BO21004/CLL11)

Protocol(s): BO21004 (F21004F)
Analysis Population: SAP - Stage II Population - Stage 2
Snapshot Date: 20JUN2013 Cutoff Date: 09MAY2013

Body System/ Adverse Event	RClb N=321 No. (%)	GClb N=336 No. (%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
INFUSION RELATED REACTION	121 (37.7)	221 (65.8)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
NEUTROPENIA	103 (32.1)	128 (38.1)
THROMBOCYTOPENIA	21 (6.5)	48 (14.3)
LEUKOPENIA	6 (1.9)	21 (6.3)
GASTROINTESTINAL DISORDERS		
DIARRHOEA	24 (7.5)	34 (10.1)
CONSTIPATION	16 (5.0)	28 (8.3)
INFECTIONS AND INFESTATIONS		
NASOPHARYNGITIS	10 (3.1)	19 (5.7)
UPPER RESPIRATORY TRACT INFECTION	15 (4.7)	8 (2.4)
URINARY TRACT INFECTION	5 (1.6)	18 (5.4)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
BACK PAIN	9 (2.8)	16 (4.8)
ARTHRALGIA	8 (2.5)	16 (4.8)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
OEDEMA PERIPHERAL	17 (5.3)	11 (3.3)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
RASH	19 (5.9)	8 (2.4)
METABOLISM AND NUTRITION DISORDERS		
TUMOUR LYSIS SYNDROME	-	14 (4.2)

Multiple occurrences of the same adverse event in one individual counted only once.
Only AEs with a missing onset date or an onset date on or after the date of first trial medication are considered.
Program : $PROD/cdpt7159/bo21004/st_aediff2.sas
Output : $PROD/cdt7159k/f21004f/reports/st_aediff2_V.out
31JUL2013 17:42

Table 42: Overview of safety profile – supportive studies

Study	Pooled Studies BO20999 and BO21003		BO21000
	Single agent obinutuzumab-treated patients with relapsed/ refractory CLL N=38	Single agent obinutuzumab-treated patients with relapsed/ refractory NHL N=205	Obinutuzumab + chemotherapy-treated patients with follicular lymphoma N=137
Number of Patients (%) with			
Any adverse event	38 (100)	197 (96)	137 (100)
Grade≥3 adverse event	30 (79)	83 (40)	97 (71)
SAE	17 (45)	53 (26)	52 (38)
Adverse event leading to death	2 (5)	5 (2)	4 (3)
Adverse event leading to obinutuzumab treatment withdrawal	4 (11)	11 (5)	12 (9)
Adverse event leading to obinutuzumab dose modification/interruption	32 (84)	101 (49)	90 (66)
Number of Patients with Adverse Events of Particular Interest (%)			
Neutropenia [a]	18 (47)	17 (8)	73 (53)
Infections	21 (55)	94 (46)	96 (70)
Related adverse events (including detailed symptoms of IRR) which occurred during or within 24 hours of the completion of infusion	38 (100)	168 (82)	105 (77)
Tumor lysis syndrome	1 (3)	5 (2)	0
Number of Patients with Events to Monitor (%)			
Thrombocytopenia (acute)	4 (11)	5 (2)	4 (3)
Secondary malignancy [b]	2 (5)	10 (5)	6 (4)

[a] Based on Roche Standard AEGT – Neutropenia and associated complications.

[b] starting 6 months after first drug intake

Adverse drug reactions

The most frequently observed ADRs in patients receiving obinutuzumab were IRRs, which occurred in the majority of patients during the first cycle. The incidence of infusion-related symptoms decreased substantially from 65% with the infusion of the first 1,000 mg of Gazyvaro to less than 3% with subsequent infusions (SmPC, see section 4.8).

Table 43: Adverse drug reactions by grade (safety population; study BO21004/CLL11)

	Stage 1						Stage 2					
	Grade 1-2		Grade 3-5		All Grade		Grade 1-2		Grade 3-5		All Grade	
SOC/ADR	Clb n (%)	GClb n (%)	Clb n (%)	GClb n (%)	Clb n (%)	GClb n (%)	RClb n (%)	GClb n (%)	RClb n (%)	GClb n (%)	RClb n (%)	GClb n (%)
Injury poisoning and procedural complications												
Infusion related reactions	0 (0)	129 (53.5)	0 (0)	51 (**21.2**)	0 (0)	166 (**68.9**)	114 (35.5)	174 (51.8)	12 (3.7)	67 (19.9)	121 (37.7)	221 (65.8)
Blood and lymphatic system disorders												
Neutropenia	3 (2.6)	31 (12.9)	18 (15.5)	84 (**34.9**)	21 (18.1)	98 (**40.7**)	23 (7.2)	35 (10.4)	91 (28.3)	111 (33.0)	103 (32.1)	128 (38.1)
Thrombocytopenia	4 (3.4)	15 (6.2)	5 (4.3)	27 (**11.2**)	9 (7.8)	37 (**15.4**)	11 (3.4)	18 (5.4)	10 (3.1)	35 (10.4)	21 (6.5)	48 (14.3)

Leukopenia	0 (0)	5 (2.1)	0 (0)	13 (**5.4**)	0 (0)	17 (**7.1**)			3 (0.9)	15 (4.5)	6 (1.9)	21 (6.3)
Anemia				**11 (4.6)**	12 (10.3)	30 (**12.4**)				14 (4.2)		
General disorders administration site conditions												
Pyrexia	8 (6.9)	24 (10.0)		1 (<1)	8 (6.9)	25 (**10.4**)				**1 (<1)**		
Respiratory, Thoraic and mediastinal disorders												
Cough	7 (6.0)	23 (9.5)		0 (0)	8 (6.9)	23 (**9.5**)				0 (0)		
Musculoskeletal and connective tissue disorders												
Back pain	2 (1.7)	11 (4.6)		1 (<1)	2 (1.7)	12 (**5.0**)				**3 (<1)**	9 (2.8)	16 (4.8)
Arthralgia	2 (1.7)	9 (3.7)		2 (<1)	3 (2.6)	11 (4.6)				**3 (<1)**	8 (2.5)	16 (**4.8**)
Musculoskeletal chest pain	0 (0)	5 (2.1)		1 (<1)	0 (0)	6 (**2.5**)				**1 (<1)**		
Infections and infestations												
Urinary tract infection	2 (1.7)	11 (4.6)		4 (1.7)	3 (2.6)	15 (**6.2**)	4 (1.2)	13 (3.9)		5 (**1.5**)	5 (1.6)	18 (5.4)
Oral herpes	1 (0.9)	9 (3.7)		0 (0)	1 (0.9)	9 (**3.7**)				0 (0)		
Pharyngitis	0 (0)	5 (2.1)		0 (0)	0 (0)	5 (**2.1**)				0 (0)		
Nasopharyngitis				1 (<1)			10 (3.1)	18 (5.4)		1 (<**1**)	10 (3.1)	19 (**5.7**)
Metabolism and nutrition disorders												
Hyperuricaemia	0 (0)	8 (3.3)		1 (<1)	0 (0)	8 (**3.3**)				1 (**<1**)		
Tumor lysis syndrome				4 (1.7)	1 (0.9)	10 (4.1)	0 (0)	8 (2.4)		**6 (1.8)**	0 (0)	14 (**4.2**)
Investigations												
Weight increased	0 (0)	5 (2.1)		0 (0)	0 (0)	5 (**2.1**)				0 (0)		
Neutrophil count decreased			0 (0)	**5 (2.1)**	0 (0)	5 (**2.1**)				5 (1.5)		
White blood cell count decreased			0 (0)	**5 (2.1)**		5 (**2.1**)						5 (1.5)
Skin and subcutaneous tissue disorders												
Alopecia	0 (0)	5 (2.1)		0 (0)	0 (0)	5 (**2.1**)				0 (0)		
Vascular disorders												
Hypertension	0 (0)	5 (2.1)		**4 (1.7)**	2 (1.7)	9 (**3.7**)				4 (1.2)		
Cardiac disorders												
Atrial fibrillation				2 (<1)	0 (0)	5 (**2.1**)				**2 (<1)**		
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)												
Squamous cell carcinoma of skin				**3 (1.2)**	0 (0)	5 (**2.1**)				3 (<1)		
Gastrointestinal disorders												
Diarrhoea				**6 (2.5)**			23 (7.2)	32 (9.5)		7 (2.1)	24 (7.5)	34 (**10.1**)
Constipation				0 (0)			16 (5.0)	28 (8.3)		0 (0)	16 (5.0)	28 (**8.3**)

Note: The ADR definition used in the SmPC was an at least 2% higher incidence in the GClb arm compared with the comparator in either all grade or grade 3-5 AEs. All AEs that were observed at least 2% higher incidence in at least one of the four comparisons were included as ADRs in the SmPC. Table 4 in the SmPC includes the information of the frequency always for all grade and grade 3-5; overall frequency assessment is based on the highest frequency of Stage 1a or Stage 2.

Table 44: Infusion related reactions by cycle (study BO21004/CLL11)

st_irrinf_S Infusion Related Reactions by Cycle (SAP)

Protocol(s): BO21004 (F21004A)
Analysis Population: SAP - Stage I Population - Stage 1a CSR
Snapshot Date: 11OCT2012   Cutoff Date: 11JUL2012

	GClb N = 240
Cycle 1 Day 1	
Patients with at least one AE	165 (69%)
Number of episodes	233
n, Patients treated in cycle	240
Cycle 1 Day 8	
Patients with at least one AE	6 (3%)
Number of episodes	6
n, Patients treated in cycle	210
Cycle 1 Day 15	
Patients with at least one AE	3 (1%)
Number of episodes	3
n, Patients treated in cycle	210
Cycle 2 Day 1	
Patients with at least one AE	0 (0%)
Number of episodes	0
n, Patients treated in cycle	213
Cycle 3 Day 1	
Patients with at least one AE	1 (0%)
Number of episodes	1
n, Patients treated in cycle	206
Cycle 4 Day 1	
Patients with at least one AE	2 (1%)
Number of episodes	2
n, Patients treated in cycle	205
Cycle 5 Day 1	
Patients with at least one AE	3 (1%)
Number of episodes	3
n, Patients treated in cycle	202
Cycle 6 Day 1	
Patients with at least one AE	1 (1%)
Number of episodes	1
n, Patients treated in cycle	195
Total	
Patients with at least one AE	165 (69%)
Total number of AEs	165
Total number of episodes	249

- Percentages are based on n (number of patients treated in the respective cycle) except the last block (Total) where the percentages are based on N
- Multiple occurrences of the same adverse event IRR in one individual counted only once for each infusion as well as in the total column (except for 'Total number of episodes')

Program : $PROD/cdpt7159/bo21004/st_irrinf.sas
Output : $PROD/cdt7159k/f21004a/reports/st_irrinf_S.out

Table 45: Infusion related reactions at first infusion before and after amendment G (study BO21004/CLL11)

ae11q2v_s108 Grade 3-5 Infusion Related Reactions At First Infusion Of Cycle 1 Day 1 For Patients Enrolled Before And After Amendment G (SAP)
GA101 patients
Protocol(s): BO21004 (F21004A) - Stage I Population - Stage 1a CSR
Analysis: SAP Center: ALL CENTERS
Snapshot Date: 11OCT2012 Cutoff Date: 11JUL2012

Body System/ Adverse Event	Enrolled before N = 195 No. (%)	Enrolled after N = 45 No. (%)
ALL BODY SYSTEMS		
Total Pts with at Least one AE	46 (24)	9 (20)
Total Number of AEs	109	27
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
Total Pts With at Least one AE	43 (22)	8 (18)
INFUSION RELATED REACTION	43 (22)	8 (18)
Total Number of AEs	43	8
VASCULAR DISORDERS		
Total Pts With at Least one AE	23 (12)	3 (7)
HYPOTENSION	15 (8)	1 (2)
HYPERTENSION	7 (4)	1 (2)
FLUSHING	4 (2)	1 (2)
Total Number of AEs	26	3
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Total Pts With at Least one AE	12 (6)	3 (7)
DYSPNOEA	9 (5)	2 (4)
BRONCHOSPASM	5 (3)	2 (4)
STRIDOR	-	1 (2)
WHEEZING	-	1 (2)
Total Number of AEs	14	6
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Total Pts With at Least one AE	11 (6)	2 (4)
CHILLS	9 (5)	2 (4)
PYREXIA	5 (3)	-
Total Number of AEs	14	2
GASTROINTESTINAL DISORDERS		
Total Pts With at Least one AE	5 (3)	2 (4)
VOMITING	4 (2)	1 (2)
NAUSEA	2 (1)	2 (4)
Total Number of AEs	6	3
NERVOUS SYSTEM DISORDERS		
Total Pts With at Least one AE	3 (2)	1 (2)
HEADACHE	3 (2)	-
DIZZINESS	-	1 (2)
Total Number of AEs	3	1
CARDIAC DISORDERS		
Total Pts With at Least one AE	1 (<1)	2 (4)
TACHYCARDIA	1 (<1)	1 (2)
CYANOSIS	-	1 (2)
Total Number of AEs	1	2
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Total Pts With at Least one AE	2 (1)	1 (2)
MYALGIA	2 (1)	1 (2)
Total Number of AEs	2	1
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Total Pts With at Least one AE	-	1 (2)
HYPERHIDROSIS	-	1 (2)
Total Number of AEs	-	1

Investigator text for Adverse Events encoded using MedDRA version 15.0.
Percentages are based on N.
Multiple occurrences of the same adverse event in one individual counted only once.
Both adverse events reported as infusion related reactions and their symptoms are included.
AE11 23NOV2012:12:12:03 (2 of 2)

Note: For a history of the amendments, see discussion on clinical safety.

Based on the mode of action of obinutuzumab and the established safety profiles of other anti-CD20 mAbs including rituximab, the adverse events of neutropenia, infection, IRRs and tumor lysis syndrome (TLS) were defined as events of particular interest in the obinutuzumab clinical development program. Thrombocytopenia and secondary malignancies occurring within 6 months after first drug intake were considered as additional events to monitor.

Tumour Lysis Syndrome (TLS)

A higher incidence of tumour lysis syndrome (TLS) was observed in the GClb arm (10 patients [4%]; 4 Grade 3-4, 3 serious) than in the Clb arm (1 patient, 1%; Grade 2). Stage 2 results confirmed the higher incidence of TLS observed in the GClb arm during the stage 1. In pooled obinutuzumab monotherapy studies (BO20999 and BO21003) in relapsed/refractory patients, four serious events of TLS were reported; 3 (1%) in the NHL population and 1 (3%) in the CLL population. One serious event of TLS was reported in each of the two Phase III blinded studies BO21223 and BO21005 in the NHL population and in Study GAO4779g in the CLL population. Most TLS events were either Grade 3 or Grade 4. There were no Grade 5 events of TLS (Risk Management Plan).

Neutropenia, late onset and prolonged neutropenia

Severe and life-threatening neutropenia including febrile neutropenia has been reported during treatment with obintuzumab. The incidence of neutropenia was higher in the obinutuzumab plus chlorambucil arm compared to the rituximab plus chlorambucil arm with the neutropenia resolving spontaneously or with use of granulocyte-colony stimulating factors. The incidence of infection was 38% in the obinutuzumab plus chlorambucil arm and 37% in the rituximab plus chlorambucil arm (with Grade 3-5 events reported in 12% and 14%, respectively and fatal events reported in < 1% in both treatment arms).

Late onset neutropenia was reported in 37 patients (17%) in the GClb arm and 10 patients (11%) in the Clb arm in Stage 1a of Study BO21004. The median time to recovery was 71 days in the GClb and 55 days in the Clb arm. The maximum time to recovery was 183 days in the GClb arm and 196 days in the Clb arm. By the cut-off date of the Stage 2 analysis, late onset neutropenia had been reported in 47/366 patients (16%) in the GClb arm and 35/321 patients in the RClb arm (12%) (SmPC, section 4.8). The median time to recovery in the patients in the Glb arm was 71 days, while the maximum time to recovery was 183 days. In the RClb arm, the median time to recovery was 63 days, and the maximum time to recovery was 400 days (Risk Management Plan).

Infections and B-cell depletion

Infections were not more frequent in the GClb arm (10%) than in the Clb arm (14%) and there were no deaths in the GClb arm due to infection.

In Study BO21004, fatal infections were reported in 5% of the population receiving Clb. Two cases of infection with a fatal outcome (in 1% of patients) had been reported in the obinutuzumab arm in this study at the time of the Stage 2 analysis. Neutropenic patients in the GClb arm (21%) received prophylaxis and treatment with anti-infective medications and G-CSF more frequently than patients in the Clb (11%) or RClb (19%) arms. Two fatal cases were reported in the pooled monotherapy studies BO20999 and BO21003; one in the CLL (3%) and one in the NHL (< 1%) cohort. In the first line NHL population receiving concomitant bendamustine (GAO4753g, all population, blinded data), 4 out of 188 patients (2.1%) experienced fatal infections. There were two other fatal cases reported in blinded Phase III studies, one in Study BO21005 and one in Study BO21223 (Risk Management Plan).

B-cell depletion, if prolonged, may theoretically increase the risk of infection, including serious infections. In Study BO21004 (Stage 2 analysis), B-cell depletion data was analyzed for all patients in the GClb arm who had B-cell assessments during follow-up. Within 12-18 months after the end of treatment, 52 of 80 GClb patients with available assessments during this period were still depleted. Five patients experienced serious infections and 18 of these 52 patients experienced nonserious infections. However, none started more than 12 months after the end of treatment. The onset date was before this timepoint for all events. Within 18-24 months after the end of treatment, 21 of 29 GClb patients with available assessments during this period were still depleted. One patient had experienced a serious infection (this case was reported within the 12-18 month period) and 8 patients had experienced non-serious infections. Beyond 24 months, 6 of 9 GClb patients with available assessments during this period were still depleted. No serious infections were reported in these patients. Two of these 9 patients experienced non-serious infections (Risk Management Plan).

One case of PML occurred in Study BO21000 (relapsed/refractory follicular lymphoma). B cell depletion could have contributed to this event. B cell depletion could contribute to hepatitis B virus (HBV) reactivation. In the obinutuzumab programme two patients in trial BO21005 exposed to obinutuzumab experienced laboratory hepatitis B reactivation without any signs or symptoms of clinical hepatitis or any liver function test abnormalities.

Thrombocytopenia

Thrombocytopenia occurred more frequently and the incidence of Grade 3-4 thrombocytopenia was higher in the GClb arm than the Clb arm. However, this did result in an increased risk of bleeding. Thrombocytopenia was asymptomatic and resolved spontaneously in the majority of patients. A small number of patients (≤4 patients per study, ≤3%) experienced serious thrombocytopenia across all obinutuzumab trials irrespective of the population and indication (Risk Management Plan). The incidence of serious acute thrombocytopenia (i.e., thrombocytopenia occurring within 24 hours of obinutuzumab infusion) was ≤1% in all studies (Risk Management Plan). Three fatal thrombocytopenia events have been reported, all in patients enrolled in Study BO21005 who received obinutuzumab with concomitant CHOP chemotherapy. All three cases developed during the first cycle (Risk Management Plan). The overall incidence of hemorrhagic adverse events was 7% RClb vs. 8% GClb with the majority of events being of Grade 1 or 2 severity. The number of Grade 5 hemorrhagic events was 3 RClb vs 4 GClb (Risk Management Plan).

Secondary malignancies

Secondary malignancies occurred in all treatment groups in both the pivotal and supportive studies. Meylodysplastic syndrome occurred in almost all treatment groups. Secondary malignancies, in the pivotal study, were diagnosed in 2 patients (2%, lung adenocarcinoma and pancreatic carcinoma) in the Clb arm, and in 7 patients (3%) with 9 second malignancies in the GClb arm: rectal cancer, prostate cancer, myelodysplastic syndrome, keratocanthoma, basal cell carcinoma, squamous cell carcinoma of skin (2 events) and squamous cell carcinoma (2 events). In the supporting studies, the total incidence of second malignancies was 5% in the monotherapy CLL and NHL populations, and 4% in the chemo-combination therapy population.

By the cut-off date for the Stage 2 analysis of Study BO21004 (GClb vs. RClb), the incidence of second malignancies was 4% in the GClb arm, with 17 events reported in 13 patients. The proportion of patients who experienced second malignancies 6 months after starting treatment or later was identical in the GClb and RClb arms (4%), however, more skin cancers were seen in the GClb arm. Of the 8 patients with skin cancers in the GClb arm, 5 had squamous cell carcinoma of the skin, 2 had basal cell carcinoma and 1 patient had keratoacanthoma. Of the 8 patients, three had a medical history of skin cancer. All 8 patients were over 70 years of age and the majority were from countries with a high incidence of skin cancers. Most of the skin lesions were reported in sun-exposed body parts such as ears, forearms, forehead and periocular regions.

Serious adverse event / deaths / other significant events

In the pivotal study, more patients died in the Clb arm (8%) than in the GClb arm (5%) overall. 5% in the Clb arm and 2% in the GClb arm died because of an adverse event. Of these, 3 cases in the Clb arm vs. 1 in the GClb arm were believed to be related to the trial treatment. In the supportive studies only one death was considered related to the study drug.

Serious adverse events (SAEs) were experienced by 32% patients (Clb arm) vs. 37% patients (GClb arm) in the pivotal study. These were as could be expected: infections, neutropenia incl. febrile neutropenia and for the GClb arm, IRRs and tumor lysis syndrome (TLS). The same pattern of SAEs was evident in the supportive studies, most pronounced for the monotherapy CLL population.

61% patients in the GClb arm experienced adverse events leading to dose modification of any study medication compared to 20% in the Clb arm. The most common reason for the differences was more cases of IRRs and neutropenia in the GClb arm. In the supportive studies IRRs were the most common reason for dose modification.

Table 46 presents an overview of the serious adverse events, deaths and withdrawals in the pivotal study Stage 1.

Table 46: Adverse events, death and withdrawals (Stage 1a, study BO21004/CLL11)

Protocol(s): BO21004 (F21004A)
Analysis Population: SAP - Stage I Population - Stage 1a CSR
Snapshot Date: 11OCT2012 Cutoff Date: 11JUL2012

	Clb N = 116	GClb N = 240
Total Pts with at least one AE	95 (82%)	224 (93%)
Total Number of AEs	464	1199
Deaths #	9 * (8%)	13 (5%)
Withdrawals from study treatment due to an AE #	16 (14%)	32 (13%)
Patients with at least one AE leading to Death	8 (7%)	8 (3%)
Serious AE	37 (32%)	88 (37%)
Serious AE leading to withdrawal from treatment	8 (7%)	24 (10%)
Serious AE leading to dose modification/interruption	7 (6%)	26 (11%)
Related serious AE	14 (12%)	51 (21%)
AE leading to withdrawal from treatment	17 (15%)	47 (20%)
AE leading to dose modification/interruption	23 (20%)	147 (61%)
Related AE	63 (54%)	207 (86%)
Related AE leading to withdrawal from treatment	13 (11%)	40 (17%)
Related AE leading to dose modification/interruption	18 (16%)	137 (57%)
Grade 3-5 AE	55 (47%)	165 (69%)

Investigator text for Adverse Events encoded using MedDRA version 15.0
Percentages are based on N
Multiple occurrences of the same adverse event in one individual counted only once
Deaths derived from Death and Survival follow up page, Withdrawals derived from Treatment Completion page
Program : $PROD/cdpt7159/bo21004/st_aedwthd.sas
Output : $PROD/cdt7159k/f21004a/reports/st_aedwthd_S.out
10DEC2012 14:24 st_aedwthd_S

Note: Two deaths in the Clb arm are not included in this table. Please see Section 7.7 of the BO21004/CLL11 CSR for details.

In Stage 2 of the pivotal study (GClb vs. RClb) the incidence of death was lower in the GClb arm (RClb arm: 12% patients vs. GClb arm: 8% patients and the incidence of fatal adverse events was lower in the GClb arm (RClb arm: 6% patients vs. GClb arm: 4% patients).

A total of 102/321 patients (32%) in the RClb arm experienced 172 serious adverse events and 131/336 patients (39%) in the GClb arm experienced 219 serious adverse events. Serious infections were the most frequently reported serious event in each treatment arm (45/321 patients [14%] RClb vs. 42/336 patients [13%] GClb), Serious IRRs occurred in (34/336 patients [10%] in the GClb arm vs. 5/321 patients [2%] in the RClb arm)

Table 48 presents an overview of the serious adverse events, deaths and withdrawals in the pivotal study Stage 2.

Table 47: Adverse events, death and withdrawals (Stage 2, study BO21004/CLL11)
Protocol(s): BO21004 (F21004F)
Analysis Population: SAP - Stage II Population - Stage 2
Snapshot Date: 20JUN2013 Cutoff Date: 09MAY2013

	RClb N = 321	GClb N = 336
Total Pts with at least one AE	286 (89%)	315 (94%)
Total Number of AEs	1261	1644
Deaths #	40 (12%)	28 (8%)
Withdrawals from study treatment due to an AE #	25 (8%)	44 (13%)
Patients with at least one AE leading to Death	20 (6%)	15 (4%)
Serious AE	102 (32%)	131 (39%)
Serious AE leading to withdrawal from treatment	14 (4%)	34 (10%)
Serious AE leading to dose modification/interruption	22 (7%)	41 (12%)
Related serious AE	43 (13%)	70 (21%)
AE leading to withdrawal from treatment	47 (15%)	67 (20%)
AE leading to dose modification/interruption	156 (49%)	211 (63%)
Related AE	223 (69%)	290 (86%)
Related AE leading to withdrawal from treatment	38 (12%)	56 (17%)
Related AE leading to dose modification/interruption	140 (44%)	199 (59%)
Grade 3-5 AE	177 (55%)	235 (70%)

Table 48: Grade 3-5 adverse events that occurred with ≥2% difference between treatment groups (Stage 1a, study BO21004/CLL11)

st_aediff234_S Grade 3-5 AEs That Occurred With >=2% Difference In Incidence Between Treatment Arms (SAP)

Protocol(s): BO21004 (F21004A)
Analysis Population: SAP - Stage I Population - Stage 1a CSR
Snapshot Date: 11OCT2012 Cutoff Date: 11JUL2012

Body System/ Adverse Event	Clb N=116 No. (%)	GClb N=240 No. (%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
NEUTROPENIA	18 (15.5)	82 (34.2)
THROMBOCYTOPENIA	4 (3.4)	26 (10.8)
LEUKOPENIA	-	13 (5.4)
FEBRILE NEUTROPENIA	5 (4.3)	4 (1.7)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
INFUSION RELATED REACTION	-	51 (21.3)
INVESTIGATIONS		
NEUTROPHIL COUNT DECREASED	-	5 (2.1)
WHITE BLOOD CELL COUNT DECREASED	-	5 (2.1)
GASTROINTESTINAL DISORDERS		
DIARRHOEA	1 (<1)	6 (2.5)
INFECTIONS AND INFESTATIONS		
RESPIRATORY TRACT INFECTION	3 (2.6)	2 (<1)
SEPSIS	3 (2.6)	1 (<1)

Multiple occurrences of the same adverse event in one individual counted only once.
Only AEs with a missing onset date or an onset date on or after the date of first trial medication are considered.
Program : $PROD/cdpt7159/bo21004/st_aediff234.sas
Output : $PROD/cdt7159k/f21004a/reports/st_aediff234_S.out
12DEC2012 9:49 Page 1 of 1

Laboratory findings

The change in hematology parameters was similar except for a larger decrease in neutrophils and WBC in the GClb arm in the pivotal study. In the pivotal study, almost 25% of the GClb patients remained B-cell depleted after 18 months. The incidence of B cell depletion at the end of treatment was higher in the GClb arm (91%) compared to the RClb arm (24%) in the pivotal study, Stage 2. Thirty-four (34)% of the patients exposed to GClb had recovered B cells without PD up to Month 24 after end of treatment. The IgG levels were affected in some patients and more so in the GClb arm than in the RClb arm though it did not result in an increase in infections.

Neutropenia and thrombocytopenia occurred in 41% and 15% of patients, respectively, in the pivotal study, with the incidence of Grade 3 5 infection being 16% in the obinutuzumab plus chlorambucil arm (SmPC, section 4.8).

In the chemistry laboratory parameter, no notable differences was evident except for ALAT/ASAT and alkaline phosphatase where more patients in the GClb arm had a slight increase from baseline compared to the Clb arm in the pivotal study (data not shown). In the supportive studies, increased ALAT/ASAT was also seen. However, the increase in ALAT/ASAT was only transient or related to co-morbidity or concomitant administered hepatotoxic medicines.

Renal function was affected more in the GClb arm where 6% of the patients had a shift to Grade 3/4 in low corrected creatinine clearance compared to 3% of the patients in the Clb arm (data not shown). Some adverse effect on corrected creatinine clearance was also seen in the supportive studies. With the updated data submitted it was shown that two patients treated with GClb had proteinuria but in both cases it was unlikely caused by the GClb treatment. Furthermore, patients who had a shift of at least 2 grades in creatinine from baseline to worst value during treatment in the GClb arm all returned to baseline or near baseline creatinine. Obinutuzumab does not seem to cause irreversible changes in creatinine levels and thus presumably in creatinine clearance. With the presented data there is nothing to indicate that obinutuzumab causes glomerulonephritis.

Safety in special populations

Adverse events increased with age and more elderly patients in the GClb arm in the pivotal study experienced AE compared with the Clb but a similar proportion experienced serious AEs and AE that lead to discontinuation. Patients with a creatinine clearance < 50 mL/min experienced a higher frequency of AEs. These were mainly IRRs, thrombocytopenia and neutropenia.

In frail patients (i.e. patients with CIRS > 6 and ClCr <70 mL/min) data form stage 2 of the pivotal study (GClb vs. RClb) showed a higher incidence of IRRs in the GClb arm compared with the RClb and 14% vs. 2% had a serious IRRs. Additionally, the incidence and severity of infections GClb arm was higher in the GClb arm than in the RClb arm (46% vs 39% had an infection and 17% vs 13% had a serious infection). Furthermore, 17% in the GClb arm had an unresolved infection vs. 8% in the RClb arm.

Immunological events

Human Anti-Human Antibodies (HAHA) can develop even if obinutuzumab is a fully humanized antibody. All supportive studies have used a method (first generation assay) for analyzing for HAHAs that was not optimal. A second generation assay was used to detect HAHAs in the pivotal study. Few patients in the supportive studies were positive for HAHAs compared with pivotal study (using the second generation assay) where 9 of 70 patients (13%) had positive HAHA results. The incidence and severity of the IRRs were similar in patients who tested positive for HAHAs and those that did not (data not shown). In stage 2 of the pivotal study 4/243 patients (2%) tested positive at 6 months, 5/183 patients (3%) tested positive at 9 months and 8/140 patients (6%) tested positive at 12 months.

The effect of immunogenicity to an anti-CD20 mAB on re-exposure to the same antibody or other anti-CD20 mAB in patients being treated for hematologic malignancies is unknown but cross-reactivity of HAHA developed for one anti-CD20 mAB towards other anti-CD20 mABs is expected to be very low because of distinct sequences of CDR regions of different anti-CD20 mABs.

Safety related to drug-drug interactions and other interactions

No specific safety issues related to possible drug-drug interaction were identified (see also discussion on clinical pharmacology).

Discontinuation due to adverse events

Fifteen (15)% of patients in the Clb arm and 20% in the GClb arm in the pivotal study experienced at least one adverse event that led to the withdrawal of any study medication. Thirteen (13)% experienced adverse events that led to withdrawal of obinutuzumab. The withdrawals were mainly due to IRRs. A major contributing factor to the difference in withdrawals between the treatment arms was the occurrence IRRs of in the GClb arm which led to the withdrawal of 19/240 patients (8%).

In stage 2 of the pivotal study 47/336 patients [14%]in the GClb arm compared with the RClb arm (24/321 patients [7%] withdrew from treatment. . This imbalance was primarily due to the proportion of patients in the GClb who were withdrawn because of IRRs (25/336 patients [7%]) compared with the RClb arm (3/321 patients [< 1%]).

Post marketing experience

Not applicable.

2.6.1. Discussion on clinical safety

The safety profile of obinutuzumab was not unexpected, as it is an anti-CD20 antibody, with infusion-related reactions (IRRs), neutropenia and infections being the most common adverse events including SEAs and Grade 3-5 AEs. However, most AEs were manageable.

From the safety database a summary of ADRs reported with a higher incidence (difference of ≥2%) in patients receiving obinutuzumab plus chlorambucil as compared to chlorambucil alone or rituximab plus chlorambucil (Study BO21004/CLL11), have been included in the SmPC (see SmPC, section 4.8).

Obinutuzumab + Chlorambucil (GClb) vs. Chlorambucil (Clb) resulted in more adverse events in the GClb treated population but there was almost the same frequency of SAEs in the two arms and fewer patients died due to AE in the GClb arm.

Infusion Related Reactions (IRRs), hypersensitivity reactions including anaphylaxis

The most frequently observed adverse drug reactions (ADRs) in patients receiving obinutuzumab were IRRs, which occurred predominantly during infusion of the first 1,000 mg (SmPC, section 4.4). Most cases of IRRs occurred within the first 5 hours of infusion. The incidence of IRRs was 65% with the infusion of the first 1,000 mg of obinutuzumab (20% of patients experiencing a Grade 3 5 IRR, with no fatal events reported). Overall, 7% of patients experienced an IRR leading to discontinuation of obinutuzumab. The incidence of IRRs with subsequent infusions was 3% with the second 1,000 mg dose and 1% thereafter. No Grade 3 5 IRRs were reported beyond the first 1,000 mg infusions of Cycle 1 (SmPC, section 4.8).

In the majority of patients, IRRs were mild to moderate and could be managed by the slowing or temporary halting of the first infusion, but severe and life threatening IRRs requiring symptomatic treatment have also been reported. IRRs may be clinically indistinguishable from immunoglobulin E (IgE) mediated allergic reactions (e.g. anaphylaxis) (SmPC, section 4.4).

Most frequently reported symptoms associated with an IRR were nausea, chills, hypotension, pyrexia, vomiting, dyspnoea, flushing, hypertension, headache, tachycardia, and diarrhoea. Respiratory and cardiac symptoms such as bronchospasm, larynx and throat irritation, wheezing, laryngeal oedema and atrial fibrillation have also been reported (SmPC, section 4.8).

Anaphylaxis has been reported in patients treated with obintuzumab. Hypersensitivity may be difficult to distinguish from IRRs. If a hypersensitivity reaction is suspected during infusion (e.g. symptoms typically occurring after previous exposure and very rarely with the first infusion), the infusion must be stopped and treatment permanently discontinued. Patients with known IgE mediated hypersensitivity to obinutuzumab must not be treated (SmPC, section 4.4). Gazyvaro is contraindicated in case of hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the SmPC (SmPC, section 4.3).

Several protocol amendments have been made in an attempt to decrease the incidence and severity of IRRs and to also decrease the number of discontinuations due to IRRs. Protocol version G (dated 9 December 2011) was introduced after an amendment to further reduce IRRs. The advice from the DSMB had been that the first obinutuzumab infusion should be administered very slowly. To accommodate the recommendation for a slow initial rate of infusion of the 1000-mg dose on Cycle 1, Day 1, it was decided that the infusion would now be given over two days. Thus, it became mandatory to split the first infusion of obinutuzumab over two days for all patients (100 mg on Day1 and 900 mg on Day 2). The amendment was implemented through a "Dear Healthcare Professional Letter" dated 18 October 2011. Following the introduction of slow infusion rate and mandatory split of the first dose (in addition to other measures previously taken: patients with high circulating lymphocyte count >25 x 109/L received corticosteroids as premedication; premedication requirements were modified to include corticosteroids for all patients during the first infusion; antihypertensive drugs had to be paused, other guidance and optional split dose), the incidence of all grade IRRs decreased. The overall incidence of IRRs in Stage 2 was 52.9% in patients receiving the split dose infusion on C1D1 compared with 61.1% in patients enrolled before this amendment. The incidence of serious IRRs also decreased after this amendment (8.3% vs. 6.4%). In patients who received the combined measures for prevention of IRRs (adequate glucocorticoid, oral analgesic/anti-histamine, omission of antihypertensive medicine in the morning of the first infusion, and the Cycle 1 Day 1 dose administered over 2 days) as described in section 4.2 of the SmPC, a decreased incidence of all Grades IRRs was observed (SmPC, section 4.4).

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 (SmPC, section 4.4). The proportion of patients experiencing Grade 3-4 IRRs was 13.9% vs. 17.1%, before and after implementation of these amendments, respectively; the proportion of patients experiencing IRRs leading to treatment discontinuation was 5.6% vs. 7.1%.

Mitigation measures to reduce IRRs should be followed (see section SmPC, 4.2). The incidence and severity of infusion related symptoms decreased substantially after the first 1,000 mg was infused, with most patients having no IRRs during subsequent administrations of obinutuzumab (see SmPC, section 4.8).

As it is expected to be more convenient for patients to retain the possibility of administering the initial 1000 mg dose of obinutuzumab within one day, section 4.2 of the SmPC under the subheading Dose in Cycle 1 on Day 2 allows the 900 mg dose to be administered on Day 2 or Day 1 continued, provided that the patient does not experience an IRR during infusion of the first 100 mg. This is considered adequate, based on the slow initial infusion rate (25mg/h over 4 hours); the clear recommendation to split the first dose over two days in the event that any modification and/or interruption of the infusion is required within the infusion of the initial 100mg; the recommendation to increase of the rate of infusion for the subsequent 900mg in a stepwise manner; the guidance on how to monitor and treat the patient during the first infusion.

Patients with a high tumour burden (i.e. high peripheral lymphocyte count in CLL [> 25 x 109/L] may be at increased risk of severe IRRs. Patients with renal impairment (CrCl < 50 mL/min) and patients with both Cumulative Illness Rating Scale (CIRS) > 6 and CrCl < 70 mL/min are more at risk of IRRs, including severe IRRs (see SmPC, section 4.4 and 4.8).

Cases of cytokine release syndrome have also been reported with Gazyvaro. For information on prophylaxis see SmPC, section 4.2.

If the patient experiences an IRR, the infusion should be managed according to the grade of the reaction. For Grade 4 IRRs, the infusion must be stopped and therapy permanently discontinued. For Grade 3 IRRs, the infusion must be temporarily interrupted and appropriate medicine administered to treat the

symptoms. For Grade 1 or 2 IRRs, the infusion must be slowed down and symptoms treated as appropriate. Upon resolution of symptoms, the infusion can be restarted, except following Grade 4 IRRs, at no more than half the previous rate and, if the patient does not experience the same adverse event with the same severity, the infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose. If the previous infusion rate was not well tolerated, instructions for the Cycle 1, Day 1 and Day 2 infusion rate should be used (see Table 3 in the SmPC, section 4.2).

Patients must not receive further obinutuzumab infusions if they experience:

- Acute life-threatening respiratory symptoms;
- A Grade 4 (i.e. life threatening) IRR or;
- A second occurrence of a Grade 3 (prolonged/recurrent) IRR (after resuming the first infusion or during a subsequent infusion).

Patients who have pre-existing cardiac or pulmonary conditions should be monitored carefully throughout the infusion and the post-infusion period. Hypotension may occur during obinutuzumab intravenous infusions. Therefore, withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each obinutuzumab infusion and for the first hour after administration. Patients at acute risk of hypertensive crisis should be evaluated for the benefits and risks of withholding their anti-hypertensive medicine (SmPC, section 4.4).

From the presented data of Stage 2 of the pivotal study it is evident that obinutuzumab + Clb cause more IRRs and more severe IRRs than rituximab + Clb. This is not unexpected due to the formulation of obinutuzumab, i.e., reduced levels of core-fucosylations leading to increased ADCC. The incidence of IRRs was highest in cycle 1 day 1 and decreased to ≤1% in subsequent cycles.

The mechanism by which IRRs are triggered is not clearly understood, however, IRRs may be linked to the release of cytokines and/or other chemical mediators from B-cells targeted by obinutuzumab (Wing et al. 1996; Winkler et al. 1999; Dillman and Hendrix 2003; Wing 2008). This seems to be a class effect of monoclonal antibodies in general and those targeting CD20 in particular. Cases of cytokine release syndrome have also been reported with obinutuzumab SmPC, section 4.4). Anaphylactic or hypersensitivity reactions to the intravenous administration of protein may also play a part in some patients. 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 (Risk Management Plan).

Obinutuzumab should be administered under the close supervision of an experienced physician and in an environment where full resuscitation facilities are immediately available (SmPC, section 4.2).

In order to minimise the potential for medication errors, 100 mL and 250 mL infusion bags should be used for the 100 mg and 900 mg dose, respectively (SmPC, section 6.6).

A standard list of MedDRA preferred terms will be used to monitor the identified risk of IRR in the applicant's Global Safety Database as part of the Risk Management Plan.

Tumour Lysis Syndrome (TLS)

Tumor lysis syndrome results from the rapid destruction of malignant cells and the abrupt release of intracellular ions, nucleic acids, proteins and metabolites into the extracellular space. These can

overwhelm the body's normal homeostatic mechanisms, causing life threatening metabolic derangements and renal failure (Risk Management Plan).

Tumour Lysis Syndrome (TLS) has been reported with obinutuzumab. Patients who are considered to be at risk of TLS, e.g. patients with a high tumour burden or a high circulating lymphocyte count (> 25 x 109/L), should receive adequate tumour lysis prophylaxis with uricostatics (e.g. allopurinol) and hydration starting 12-24 hours prior to the infusion of obinutuzumab (see SmPC section 4.2). For treatment of TLS, correct electrolyte abnormalities, renal function and fluid balance should be monitored, and supportive care administered, including dialysis as indicated (SmPC, section 4.4). TLS has been classified as an identified risk in the Risk Management Plan.

Neutropenia, late onset and prolonged neutropenia

Severe and life-threatening neutropenia including febrile neutropenia has been reported during treatment with obinutuzumab (SmPC, section 4.4). Neutropenia in patients with CLL is a known risk with anti-CD20 therapies and is a complex clinical phenomenon to which several distinct mechanisms may contribute (Boxer et al. 2012; Golay et al. 2013). Neutropenia observed during treatment with obinutuzumab may be due to the fact that afucosylated IgG1 binds very strongly to neutrophil FcγRIIIb receptors leading to their activation and, potentially, to activation-induced neutrophil death. In addition, activated PMNs may become re-distributed to the microvasculature of tissues such as the lung (Chopra et al. 2009 [10862]) and thereby disappear from the peripheral circulation (Risk Management Plan).

The mechanism of prolonged neutropenia and late onset neutropenia is not well understood but appears to be different from that of early acute neutropenia. Data from on-going phase III clinical trials with obinutuzumab in patients with both non-Hodgkin's lymphoma (NHL) and CLL will provide information to further characterise and manage the risk of neutropenia, including prolonged and late onset neutropenia (Risk Management Plan).

Patients who experience neutropenia should be closely monitored with regular laboratory tests until resolution. If treatment is necessary it should be administered in accordance with local guidelines and the administration of granulocyte-colony stimulating factors should be considered. Any signs of concomitant infection should be treated as appropriate. Dose delays should be considered in case of severe or life-threatening neutropenia. Cases of late onset neutropenia (occurring 28 days after the end of treatment) or prolonged neutropenia (lasting more than 28 days after treatment has been completed/stopped) have also been reported. Patients with renal impairment (CrCl < 50 mL/min) are more at risk of neutropenia (SmPC, section 4.4).

The combination of obinutuzumab with chlorambucil may increase neutropenia (SmPC, section 4.5).

Neutropenia, late onset and prolonged neutropenia are identified risks in the Risk Management Plan.

Infections and B-cell depletion

Obinutuzumab should not be administered in the presence of an active infection and caution should be exercised when considering the use of obinutuzumab in patients with a history of recurring or chronic infections. Serious bacterial, fungal, and new or reactivated viral infections can occur during and following the completion of obinutuzumab therapy. Fatal infections have been reported (SmPC, section 4.4). Patients with both CIRS > 6 and CrCl < 70 mL/min are more at risk of infections, including severe infections (SmPC, section 4.4).

Prolonged B-cell depletion and infections are identified risks in the Risk Management Plan. Although obinutuzumab had a potent and prolonged effect on B cell depletion and possibly a minor effect on IgG levels during follow up, the adverse events observed in studies BO21004/CLL11, GAO4768g and

GAO4779g did not suggest any clinically relevant effect. The risk will continue to be analyzed in clinical trials (patients are followed for B-cell status for up to 2 years after the last dose of obinutuzumab or until a new anti-cancer therapy is initiated, see Risk Management Plan).

Thrombocytopenia

Severe and life-threatening thrombocytopenia including acute thrombocytopenia (occurring within 24 hours after the infusion) has been observed during treatment with obinutuzumab (SmPC, section 4.4). The incidence of thrombocytopenia was higher in the obinutuzumab plus chlorambucil arm compared to the rituximab plus chlorambucil arm especially during the first cycle. Four (4)% of patients treated with obinutuzumab plus chlorambucil experienced acute thrombocytopenia (occurring within 24 hours after the obinutuzumab infusion).

The overall incidence of haemorrhagic events was similar in the obinutuzumab treated arm and in the rituximab treated arm in Study BO21004/CLL11. The number of fatal haemorrhagic events was balanced between the treatment arms; however, all of the events in patients treated with obinutuzumab were reported in Cycle 1.

Patients with renal impairment (CrCl < 50 mL/min) are more at risk of thrombocytopenia (see section 4.8). Fatal haemorrhagic events have also been reported in Cycle 1 in patients treated with obinutuzumab. A clear relationship between thrombocytopenia and haemorrhagic events has not been established.

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. Transfusion of blood products (i.e. platelet transfusion) according to institutional practice is at the discretion of the treating physician. Use of all concomitant therapies which could possibly worsen thrombocytopenia-related events, such as platelet inhibitors and anticoagulants, should also be taken into consideration, especially during the first cycle. Thrombocytopenia is considered an identified risk in the Risk Management Plan. In this context, the applicant will monitor the risk of haemorrhagic events including the review of unblinded data from clinical trials BO21005, BO21223 and GAO4753g (Risk Management Plan).

Worsening of pre-existing cardiac conditions

In patients with underlying cardiac disease, arrhythmias (such as atrial fibrillation and tachyarrhythmia), angina pectoris, acute coronary syndrome, myocardial infarction and heart failure have occurred when treated with obinutuzumab. These events may have occurred as part of an IRR and could be fatal.

In Stage 1a of Study BO21004, a higher incidence of serious cardiac events was found in patients treated with obinutuzumab and chlorambucil (18/241 patients; 7%) compared with those treated with chlorambucil 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. 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. Seven of the events in the obinutuzumab-treated patients occurred on Day 1; these vents 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). In the Clb arm of Study BO21004, 5 patients experienced six events:

cardiac failure (2), MI (2), angina pectoris (1) and tachyarrhythmia (1). In the Stage 2 data analysis (GClb vs. RClb), a comparable incidence of serious cardiac events was observed in the GClb arm (6%) and the RClb arm (4%) (Risk Management Plan). 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 (SmPC, section 4.4). Worsening of pre-existing cardiac conditions is considered an identified risk in the Risk Management Plan.

Hepatitis B reactivation

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with anti CD20 antibodies including obinutuzumab. At the cut-off date of the Risk Management Plan ver. 1.2 (April 2014), two cases of hepatitis B reactivation had been reported in clinical trials with obinutuzumab, both from Study BO21005 in DLBCL. These patients were found to have raised serum HBV DNA after obinutuzumab therapy, but no clinical manifestations of hepatitis. One patient is reported to have received antiviral therapy. HBV DNA was undetectable in both patients in subsequent tests. Hepatitis B virus screening should be performed in all patients before initiation of treatment with obinutuzumab. At a minimum this should include hepatitis B surface antigen (HBsAg)- status and hepatitis B core antibody (HBcAb) status. These can be complemented with other appropriate markers as per local guidelines. Patients with active hepatitis B disease should not be treated with obinutuzumab. Patients with positive hepatitis B serology should consult liver disease experts before start of treatment and should be monitored and managed following local medical standards to prevent hepatitis reactivation (SmPC, section 4.4). Hepatitis B reactivation is considered an identified risk in the Risk Management Plan.

Progressive Multifocal Leukoencephalopathy (PML)

PML is caused by reactivation of the DNA JC virus, a human polyomavirus that resides in latent form in 70-90% of the adult population worldwide. Long-lasting immunosuppression induced by anti-CD20 antibody treatment, associated chemotherapies and the underlying disease itself are associated with an increased risk of reactivation of this virus. PML is a disease that is always serious, and that is fatal or severely debilitating in the large majority of patients. There is a potential risk that B-cell depletion may have an impact on the incidence and severity of infections. Rituximab has been associated with serious viral infections including PML. As obinutuzumab is more potent in terms of B-cell depletion than rituximab, there may be an increased risk of infections with obinutuzumab compared to rituximab. One case of PML with confirmed presence of JC virus in cerebro-spinal fluid has been reported in Study BO21000 (follicular NHL, obinutuzumab in combination with CHOP, FC or bendamustine) (Risk Management Plan). At the time of this case, the total exposure to obinutuzumab was over 1200 patients. It is not possible to draw any conclusions about the incidence of PML in obinutuzumab treated patients at this time. Progressive multifocal leukoencephalopathy (PML) has been reported in patients treated with obinutuzumab. The diagnosis of PML should be considered in any patient presenting with new-onset or changes to pre-existing neurologic manifestations. The symptoms of PML are unspecific and can vary depending on the affected region of the brain. Motor symptoms with corticospinal tract findings (e.g. muscular weakness, paralysis and sensory disturbances), sensory abnormalities, cerebellar symptoms, and visual field defects are common. Some signs/symptoms regarded as “cortical” (e.g. aphasia or visual-spatial disorientation) may occur. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain magnetic resonance imaging (MRI), and lumbar puncture (cerebrospinal fluid testing for John Cunningham viral DNA). Therapy with obinutuzumab should be withheld during the investigation of potential PML and permanently discontinued in case of confirmed PML. Discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy should also be considered. The patient

should be referred to a neurologist for the evaluation and treatment of PML (SmPC, section 4.4).PML is an identified risk that will be followed through post-marketing surveillance (see Risk Management Plan).

Laboratory abnormalities

Transient elevation in liver enzymes (aspartate aminotransferase, AST; alanine aminotransferase, ALT; alkaline phosphatase) has been observed shortly after the first infusion of obinutuzumab.

Special populations

Elderly: In the pivotal study, 46% (156 out of 336) of patients with CLL treated with obinutuzumab plus chlorambucil were 75 years old or older (median age was 74 years). These patients experienced more serious adverse events and adverse events leading to death than those patients < 75 years of age (SmPC, section 4.8).

Renal impairment: In the pivotal study, 27% (90 out of 336) of patients with CLL treated with obinutuzumab plus chlorambucil had moderate renal impairment (CrCl < 50 mL/min). These patients experienced more serious adverse events and adverse events leading to death than those with CrCl ≥50 mL/min.

Potential risks

Impaired immunization response: The safety of immunisation with live or attenuated viral vaccines following obinutuzumab therapy has not been studied and vaccination with live virus vaccines is not recommended during treatment and until B cell recovery (SmPC, section 4.4). Due to the potential depletion of B cells in newborns following exposure to obinutuzumab during pregnancy, newborns should be monitored for B cell depletion and vaccinations with live virus vaccines should be postponed until the infant's B cell count has recovered (see SmPC section 4.4). In case of exposure during pregnancy, depletion of B cells may be expected in newborns due to the pharmacological properties of the product. Consequently, newborns should be monitored for B cell depletion and vaccinations with live virus vaccines should be postponed until the infant's B cell count has recovered (SmPC, section 4.6).

Immunogenicity: The incidence and severity of the IRRs were similar in patients who tested positive for HAHAs and those that did not. A literature review did not reveal any relevant publications describing the effect of immunogenicity to an anti-CD20 mAB on re-exposure to the same antibody or other anti-CD20 mAB in patients being treated for hematologic malignancies. Cross-reactivity of HAHA developed for one anti-CD20 mAB towards other anti-CD20 mABs is expected to be very low because of distinct sequences of CDR regions of different anti-CD20 mABs. So far there is nothing to indicate cross-reactivity even if this risk cannot be ruled out. Immunogenicity has been categorized as a potential risk (see Risk Management Plan). The Applicant will assess the influence of HAHAs on pharmacokinetics, clinical response, and overall safety (including allergic reactions/hypersensitivity events) through analysis of HAHA-positive patients in Phase III studies BO21004, BO21005 and BO21223 (Risk Management Plan).

Secondary malignancies: Secondary malignancies are known to occur with the use immunomodulators and it is well known that myelodysplastic cancer/syndrome is associated with the use of chlorambucil. No specific pattern regarding other secondary malignancies was evident except for non-melanoma skin cancers that occurred in almost all treatment groups. The incidence of second malignancies in the GClb arm was lower than reported in the literature for CLL patients; however, the mean observation time in Study BO21004 is too short for definitive conclusions to be drawn. However, it is uncertain if non-melanoma skin cancers occurred more frequently than what could be expected for this population.

Second malignancies occurring 6 months after the start of therapy will be considered for monitoring this risk in the post-marketing setting. Second malignancy has been categorized as a potential risk (see Risk Management Plan).

Gastrointestinal perforation: No cases of GI perforation have been reported in CLL patients treated with obinutuzumab. The incidence of GI perforation events reported from studies with obinutuzumab in NHL was 1% or less. A history of GI lymphoma and co-medication with chemotherapy and prednisolone have been identified as risk factors for developing GI perforation. The most common causes of perforation in cancer patients are spontaneous perforation secondary to tumor (either primary or metastatic), iatrogenic perforation secondary to instrumentation (endoscopy) or cancer treatment. Perforation secondary to tumor is mainly relevant in NHL patients, as GI tract involvement is much more frequent in this patient population than in CLL patients; GI tract involvement is rare in CLL patients. Gastrointestinal perforation has been categorized as a potential risk (see Risk Management Plan).

Immune-mediated glomerulonephritis: Although immune-mediated glomerulonephritis has been observed in monkeys, this finding appeared to be species-specific and not relevant in terms of predicting the potential immunogenicity of obinutuzumab in humans. Nevertheless, in line with the EMA guideline on Good Pharmacovigilance Practices, immune-mediated glomerulonephritis has been categorized as a potential risk (see Risk Management Plan).

Effects on ability to drive and use machines

Gazyvaro has no or negligible influence on the ability to drive and use machines. IRRs are very common during the first infusion of Gazyvaro, and patients experiencing infusion related symptoms should be advised not to drive or use machines until symptoms abate. (SmPC, section 4.7).

Overdose

No experience with overdose is available from human clinical studies. In clinical studies with obinutuzumab, doses ranging from 50 mg up to and including 2,000 mg per infusion have been administered. The incidence and intensity of adverse reactions reported in these studies did not appear to be dose dependent. Patients who experience overdose should have immediate interruption or reduction of their infusion and be closely supervised. Consideration should be given to the need for regular monitoring of blood cell count and for increased risk of infections while patients are B cell depleted (SmPC, section 4.9).

Additional expert consultations

Not applicable.

2.6.2. Conclusions on the clinical safety

The safety profile of obinutuzumab was in accordance with what would be expected for an anti-CD20 antibody with infusion-related reactions (IRRs), neutropenia and infections being the most common adverse events.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management system version 1.2 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

This advice is based on the following content of the Risk Management Plan:

Safety concerns

The safety concerns identified in the RMP by the applicant are summarised in Table 50.

Table 49: Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	Infusion-related reactions Tumor lysis syndrome Thrombocytopenia Neutropenia Late onset and prolonged neutropenia Prolonged B-cell depletion Infections Hepatitis B reactivation Progressive multifocal leukoencephalopathy Worsening of pre-existing cardiac conditions
Important potential risks	Impaired immunization response Immunogenicity Second malignancies GI perforation Immune-mediated glomerulonephritis
Missing information	Use in Children Use in pregnancy and lactation

Pharmacovigilance plans

Table 50: Ongoing and planned additional PhV studies / activities in the Pharmacovigilance Plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
Study BO21004: Obinutuzumab + chlorambucil compared to rituximab + chlorambucil or chlorambucil alone in previously untreated CLL patients with comorbidities. 3	Primary: demonstration of clinically relevant statistical superiority in PFS obinutuzumab + Clb compared to rituximab + Clb and Clb alone and RClb compared to Clb in previously untreated CLL patients with comorbidities. Includes secondary objective to evaluate and compare the safety profile of patients.	IRRs (confirmation of decrease in IRRs since protocol amendment introducing split dosing, slow infusion and reinforcing pre-existing risk minimization measures) (complete) Prolonged B-cell depletion Immunogenicity Immune-mediated glomerulonephritis	Study ongoing	Q1 2014 (Stage 2 analysis CSR) Q3 2022 (Final CSR)
Study BO21005: Obinutuzumab in combination with CHOP versus rituximab and CHOP in previously untreated patients with CD20-positive DLBCL 3	Primary: demonstrate superiority in PFS of obinutuzumab plus chemotherapy vs. rituximab plus chemotherapy in previously untreated DLBCL patients Includes secondary objective to evaluate and compare the safety profiles of patients treated with the combination of obinutuzumab and CHOP with	Thrombocytopenia Late onset and prolonged neutropenia Prolonged B-cell depletion Immunogenicity Immune-mediated glomerulonephritis	Study ongoing	Q1 2017

Ongoing and planned additional PhV studies / activities in the Pharmacovigilance Plan (cont.)

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
	rituximab and CHOP			
Study BO21223: Obinutuzumab plus chemotherapy compared with rituximab plus chemotherapy in previously untreated patients with advanced indolent lymphoma followed by GA101[23] or rituximab maintenance therapy in responders 3	Primary: Efficacy of obinutuzumab plus chemotherapy followed by obinutuzumab maintenance therapy compared with rituximab plus chemotherapy followed by rituximab maintenance therapy in previously untreated advanced follicular lymphoma Includes secondary objective to evaluate and compare the safety profiles between the two arms	Thrombocytopenia Late onset and prolonged neutropenia Prolonged B-cell depletion Immunogenicity Immune-mediated glomerulonephritis	Study ongoing	Q4 2017
Study MO28543: Obinutuzumab in combination with chemotherapy in patients with previously untreated or relapsed/refractory CLL 3	Primary: To evaluate the safety and tolerability of obinutuzumab alone or in combination with chemotherapy	IRRs	Study ongoing	Q4 2018
Study GAO4753g: Obinutuzumab in combination with bendamustine compared with	To evaluate clinical benefit in terms of PFS of obinutuzumab in combination with	Thrombocytopenia Prolonged B-cell depletion	Study Ongoing	Q4 2016 (approx.)

Ongoing and planned additional PhV studies/activities in the Pharmacovigilance Plan (cont.)

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
bendamustine in patients with rituximab-refractory indolent NHL 3	bendamustine compared with bendamustine alone in patients with indolent NHL refractory to prior rituximab-containing therapy. Includes secondary objective evaluate and compare the safety profiles of patients treated with bendamustine and obinutuzumab and bendamustine alone.			
Drug Safety Report on hemorrhagic events in the context of thrombocytopenia 3	Evaluation of the incidence of hemorrhagic events and assessment of relationship with thrombocytopenia	Thrombocytopenia	In preparation	Q1 2015 (latest, for submission within PBRER)

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Infusion related reactions	EU SmPC Section 4.2 Section 4.4 Section 4.8	None proposed
Tumor lysis syndrome	EU SmPC Section 4.2 Section 4.4 Section 4.8	None proposed
Thrombocytopenia	EU SmPC Section 4.4 Section 4.8	None proposed
Neutropenia	EU SmPC Section 4.4 Section 4.5 Section 4.8	None proposed

Late onset and prolonged neutropenia	EU SmPC Section 4.4 Section 4.5	None proposed
Prolonged B-cell depletion	EU SmPC Section 4.4	None proposed
Infections	EU SmPC Section 4.4 Section 4.8	None proposed
Hepatitis B reactivation	EU SmPC Section 4.4 Section 4.8	None proposed
Progressive multifocal leukoencephalopathy	EU SmPC Section 4.4 Section 4.8	None proposed
Worsening of pre-existing cardiac conditions	EU SmPC Section 4.4 Section 4.8	None proposed
Impaired immunization response	EU SmPC Section 4.4	None proposed
Immunogenicity	EU SmPC Section 4.4	None proposed
Second malignancies	None	None proposed
GI perforation	None	None proposed
Immune mediated glomerulonephritis	None	None proposed
Use in children	EU SmPC Section 4.2	None proposed
Use in pregnancy and lactation	EU SmPC Section 4.4 Section 4.6	

The CHMP endorsed this advice without changes.

In addition, the CHMP considered that the applicant should take the following minor points into consideration when an update of the Risk management Plan is submitted:

- Part V, Risk Minimisation Measures, does not currently include the section on “Effectiveness of risk minimisation measures”. The applicant should ensure that this is incorporated into table V.1, Risk minimisation measures by safety concern, at the time of the next RMP update.

2.9. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Study BO21004 has provided convincing evidence of clinical efficacy of obinutuzumab in terms of the primary endpoint PFS, compared to chlorambucil alone, in previously untreated CLL patients with coexisting medical conditions and/or renal impairment. At the initial submission, the risk of disease progression or death was reduced by 86% when obinutuzumab was given with chlorambucil (HR=0.14, 95% CI: 0.09, 0.21; log-rank p value = 0.0001). The updated efficacy results from Stage 1a with longer follow-up, now available, support the conclusion drawn from the primary analysis. The Kaplan-Meier estimated median duration of PFS was 11.1 months vs. 26.7 months in the Clb arm and GClb arm, respectively. The proportion of responders at the end of treatment in the GClb arm was more than double that in the Clb arm (77% vs. 31%). A complete response was reported in 22% of patients in the GClb arm versus none in the Clb arm. Forty-five of 168 GClb patients (27%) assessed for molecular remission (blood and bone marrow combined) at the end of treatment were minimal residual disease (MRD) negative. The secondary endpoints with mature data, including EFS, overall response rates (Clb: 30.0% vs. GClb: 75.5%), CR rates (Clb: 0% vs. GClb: 22.2%), time to new treatment, supported the primary efficacy endpoint and favored the GClb arm compared to the Clb arm.

OS data are still immature. However, there is evidence of a survival benefit for patients in the GClb arm compared to the Clb arm with a stratified hazard ratio of 0.41 (95% CI [0.23; 0.74], stratified log-rank test p-value 0.0022).

Meanwhile, stage 2 data where obinutuzumab is directly compared to rituximab (GClb vs RClb), are available. The addition of obinutuzumab to Clb resulted in a clinically meaningful and statistically significant improvement in the primary endpoint of PFS compared to RClb. Statistically significant improvements were observed in all of the secondary efficacy endpoints apart from OS for which the data are immature. In addition, the results were consistent across the pre-specified subgroups for investigator-assessed PFS.

Uncertainty in the knowledge about the beneficial effects

A number of uncertainties were identified during the assessment, including the specific population included in the pivotal trial (co-existing medical conditions and / or renal impairment) and the initially proposed indication, the posology of Clb and its use in 'unfit' patients, the efficacy in the subset of patients with CLL with 17p deletion, and the open label design of the pivotal study; all of these uncertainties were satisfactorily addressed (see discussion on clinical efficacy).

One remaining uncertainty is the treatment effect in terms of OS associated with GClb. The OS data are still immature although it is possible to exclude a detrimental effect. Additional follow-up will further quantify the OS benefit of GClb over Clb and RClb (see discussion on clinical efficacy).

Risks

Unfavourable effects

The safety profile of obinutuzumab is not unexpected, with infusion-related reactions (IRRs), neutropenia and infections being the most common adverse events including SEAs and Grade 3-5 AEs. However, most AEs were manageable. Obinutuzumab + Chlorambucil (GClb) vs. Chlorambucil (Clb) resulted in more adverse events in the GClb treated population but there was almost the same frequency of SAEs in the two arms and fewer died due to AE in the GClb arm. Twenty (20)% of patients withdrew from treatment due to AE in the GClb. Infusion related reactions (IRRs) were the main contributor to this.

In Step 2 of the pivotal trial, the incidence of adverse events, serious adverse events, adverse events of Grade 3-5, and adverse events leading to discontinuation of study treatment was higher in the GClb arm compared with the RClb arm. This difference was mainly due to IRRs and a slightly more cases of neutropenia, thrombocytopenia and TLS. More importantly, fewer patients died overall and fewer patients had fatal adverse events in the GClb arm compared to the RClb arm.

Uncertainty in the knowledge about the unfavourable effects

There are currently limited data to assess the influence of HAHAs on safety. Based on the available data, however, the incidence and severity of the IRRs were similar in patients who tested positive for HAHAs and those that did not. So far there is nothing to indicate cross-reactivity even if this risk cannot be ruled out (see discussion on clinical safety). Immunogenicity has been categorised as a potential risk as evidence to date is based on laboratory data without any clinical signs of immunogenicity (see Risk Management Plan).

CLL occurs almost exclusively in the adult population, with the median age at diagnosis in the USA being 72 years, and has an extremely low incidence in children and adolescents (ages 0-18 years). The incidence of CLL per 100,000 population in the US is < 0.1 in those aged ≤ 29 years and 0.1-1.8 in those aged 30-49 years (Howlader et al. 2013). Thus, data about use of GClb in CLL in children and use in pregnancy and lactation are missing. These have been adequately reflected in the SmPC (see section 4.2, 4.6, 5.1, 5.2 and 5.3) and are reflected in the Risk Management Plan.

The evidence available on the effectiveness of minimising the risk of IRR by dividing the first dose appears limited. The Applicant will continue to assess the effectiveness of minimising the risk of IRRs in the on-going CLL clinical study M028543 (see Risk Management Plan)

Benefit-risk balance

Importance of favourable and unfavourable effects

The clinical efficacy results observed for GClb vs. Clb and RClb are considered of a magnitude that is of clear clinical relevance both in absolute (difference in median PFS in the order of one year) and relative terms (hazard ratios in the order of .14 to .39 in favour of GClb), in delaying progression of the disease. This can be assumed to be delaying worsening of symptoms to a significant extent, and, although data are still immature, possible prolonging of OS. Thus, the observed effects are clearly of importance for the patients. The toxicity associated with GClb, although expected based on the mechanism of action, was also important, including severe, life-threatening or fatal adverse events that occurred more frequently in the GClb arm (69%) vs. Clb arm (47%) and were primarily due to IRRs, neutropenia, thrombocytopenia and leucopenia.

Benefit-risk balance

The safety profile of obinutuzumab included infusion-related reactions (IRRs), neutropenia and infections being the most common adverse events. In view of the large effect in terms of PFS, the lack of a detriment in OS and possibly an improvement in OS, the coherent evidence from secondary efficacy endpoints, the lack of significant uncertainty in terms of efficacy or safety, the toxicity profile is considered acceptable. Therefore, the benefit-risk balance for GClb in the proposed indication is considered positive.

Discussion on the benefit-risk balance

From a regulatory perspective, a submission with only one pivotal study can be accepted but generally requires demonstration of efficacy at levels beyond standard criteria for statistical significance (CHMP/EWP/2330/99). The efficacy data submitted for obinutuzumab were clearly statistically and clinically convincing, and there was enough corroborating evidence from secondary endpoints and non-clinical pharmacodynamic studies to show that the observed results were robust.

Initially, the benefit-risk balance was uncertain in unfit and frail patients. Indeed, at the time of stage 1 cut-off, no direct comparison between GClb and RClb (the standard treatment for unfit patients) was available in terms of efficacy or safety. Similarly, Clb alone was considered an acceptable comparator only in the frailest patients of the pivotal study and the benefit of GClb in a larger set of frail patients was uncertain. Following submission of high-level results from Stage 2 showing a strongly positive effect of GClb against RCbl without major differences in toxicity, and acknowledging that Clb alone was an acceptable comparator at the time the studies were conducted, these uncertainties have been satisfactorily addressed.

There have been major advances in the treatment of CLL over the past decade with the introduction of rituximab, ofatumumab, alemtuzumab, purine analogs, bendamustine and combined chemoimmunotherapy with regimens such as FCR. However, the disease remains incurable and a significant number of patients die of CLL every year. Recently, there have been an increasing number of new compounds in clinical development, including new anti-CD20 monoclonal antibodies such as obinutuzumab, agents targeting BCR signalling (e.g., idelalisib, ibrutinib), etc. Given the high number of new agents, the challenge will be to identify and clinically validate the best combinations and sequences of treatments to achieve the long-term control of CLL with optimal quality of life (Hallek 2013).

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Gazyvaro is not similar to Arzerra within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

Derogation of market exclusivity

Not applicable.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Gazyvaro, in combination with chlorambucil for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) and with comorbidities making them unsuitable for full-dose fludarabine based therapy (see section 5.1.), is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 8 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

Not applicable.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
The Applicant shall submit the OS mature data of stage 2 of study BO21004/CLL11 in order to confirm the benefit of GClb for this endpoint. Subgroups OS analyses in the	31 January 2016

frail and unfit subsets shall also be provided.	
The Applicant shall submit the OS mature data of stage 1a of study BO21004/CLL11 in the ITT population, in the subgroups of ZAP70 positive patients and ZAP70 negative patients	31 January 2016

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that obinutuzumab is qualified as a new active substance.