CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125486Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	BLA
Application Number	125486/0
Priority or Standard	Priority
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Division / Office	DHP/OHOP
Reviewer Name	Hyon-Zu Lee, Pharm.D. (Efficacy) Barry W. Miller, MS, CRNP (Safety)
Review Completion Date	October 1, 2013
Established Name	Obinutuzumab
(Proposed) Trade Name	Gazyva
Therapeutic Class	CD20-directed cytolytic monoclonal antibody
Applicant	Genentech, Inc.
Formulation	1000 mg/40mL (25 mg/mL) single-use vial
Dosing Regimen	1000 mg intravenously every 4 weeks
Indication	Obinutuzumab in combination with chlorambucil for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL)
Intended Population(s)	≥ 18 years of age

Template Version: March 6, 2009

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Table of Abbreviations

ADCC	Antibody-Dependent Cellular Cytotoxicity
ADL	Activities of Daily Living
AE	Adverse Event
ANC	Absolute neutrophil count
Anti-HBc	Hepatitis B virus core Antibody
AUC	Area under the plasma concentration-time curve
BLA	Biologics License Application
CBC	Complete Blood Count
CDC	Complement-Dependent Cytotoxicity
CDn	Cluster of Differentiation "n"
CD20+	B-lymphocyte antigen CD20 positive
CHOP	Cyclophosphamide, Hydroxydaunorubicin, Oncovin, and Prednisone
CIRS	Cumulative Illness Rating Scale
CLL	Chronic Lymphocytic Leukemia
Clb	Chlorambucil
C_{max}	Maximum plasma concentration
CMC	Chemistry, Manufacturing and Controls
COPD	Chronic Obstructive Pulmonary Disease
CR	Complete Response
CRi	Complete Response with incomplete marrow recovery
CT	Computed Tomography
CTCAE	NCI Common Terminology Criteria for Adverse Events
CrCl	Creatinine Clearance
CRF	Case Report Form
DCD	Direct Cell Death
DCLO	Diffusion lung capacity for carbon monoxide
DDI	Drug-drug Interaction
DLBCL	Diffuse large B-cell lymphoma
DSMC	Data Safety Monitoring Committee
DHP	Division of Hematology Products
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCTD	electronic Common Technical Document
EFS	Event Free Survival
EGD	Esophagogastroduodenoscopy
EORTC	European Organization for Research and Treatment of Cancer
FC	Fludarabine, Cyclophosphamide
FCR	Fludarabine, Cyclophosphamide, Rituximab
FEV1	Forced expiratory volume in 1 second
FR	Fludarabine-Rituximab
FDA	Food and Drug Administration

G-CSF	Granulocyte Colony Stimulating Factors
GClb	Obinutuzumab combined with chlorambucil
HAHA	Human anti-human antibodies
HBsAg	Hepatitis B virus surface Antigen
HBV	Hepatitis B Virus
HDMP	High-dose methylprednisolone
HR	Hazard Ratio
Ig	Immunoglobulin
IgV_H	Immunoglobulin V_H
IRC	Independent Review Committee
IRR	Infusion Related Reaction
IV	Intravenous
IWCLL	International Workshop on chronic lymphocytic leukemia
kg	kilogram
MAED	MedDRA Adverse Event Diagnosis
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
ml	milliliter
MRD	Minimal Residual Disease
MRI	Magnetic Resonance Image
n	number, sample size
NCI	National Cancer Institute
NHL	Non-Hodgkin's lymphoma
NK	Natural Killer
nPR	Nodular Partial Response
ORR	Overall Response Rate
ITT	Intent-to-treat
IWG	International Working Group
NYHA	New York Heart Association
ODAC	Oncologic Drugs Advisory Committee
OHOP	Office of Hematology and Oncology Products
OSI	Office of Scientific Investigations
PCR	Pentostatin –Cyclophosphamide-Rituximab
PCR	Polymerase Chain Reaction
PD	Progressive Disease/Pharmacodynamics
PFS	Progression Free Survival
PK	Pharmacokinetic
PR	Partial Response
PREA	Pediatric Research Equity Act
PRO	Patient Reported Outcome
PS	Performance Status
QLQ	Quality of Life Questionnaire
RClb	Rituximab in combination with chlorambucil
REMS	Risk Evaluation and Mitigation Strategy
SAE	Serious Adverse Event

SAP	Safety Analysis Population
SD	Stable Disease
SD	Standard Deviation
SEER	Surveillance Epidemiology and End Results
SOC	System Organ Class
TLS	Tumor Lysis Syndrome
ULN	Upper Limit Normal
USPI	US prescribing information
V_H	Variable Heavy Chain
WBC	White Blood Cell

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This reviewer recommends approval for obinutuzumab in combination with chlorambucil for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL).

1.2 Risk Benefit Assessment

Analysis of Condition

Summary of evidence

Chronic lymphocytic leukemia (CLL) is a lymphoproliferative disorder. The affected lymphocytes are of B-cell lineage in 95% of cases, and the remaining cases involve T-lymphocytes, representing a distinct disorder.

CLL is the most common leukemia in adults in Western countries, accounting for approximately 30% of all leukemias. It is estimated that there will be 15,680 new cases of CLL and 4,580 deaths due to CLL in 2013 in the US. The male to female ratio is approximately 2:1 with median age at diagnosis of 71 years (from the NCI SEER data base, 2006-2010 statistics). Seventy percent of patients are > 65 years of age at diagnosis, and almost 50% of patients are 75 years or older. CLL is rare in younger patients with < 2% of patients < 45 years of age at diagnosis. CLL is asymptomatic at diagnosis in the majority of patients, however when present they include weight loss, fevers and night sweats (B symptoms). Patients often present with symptomatic anemia, thrombocytopenia, increasing hepatosplenomegaly and lymphadenopathy and have a predisposition to repeated infections. Although treatable, there is no established chemotherapy to cure CLL.

Conclusions

CLL is a serious and life-threatening disease. The natural course of CLL is variable with a median survival of 8-10 years (with survival time ranging from 2-20 years or more depending on whether the disease is aggressive or indolent).

Unmet Medical Need

Summary of evidence

Currently, fludarabine, cyclophosphamide, and rituximab (FCR) immunochemotherapy is the standard of care for previously untreated patients with CLL. However, this regimen is not appropriate for older, unfit patients.

Conclusions

There is a medical need for more effective and well-tolerated therapies for the elderly patients and those with significant co-morbidities who do not tolerate the standard regimens well.

Clinical Benefit

Summary of evidence

This BLA was supported by efficacy and safety data primarily from a randomized, open-label, parallel-group, multicenter phase 3 trial (BO21004/CLL11, specifically stage 1a) comparing obinutuzumab in combination with chlorambucil (GClb) to chlorambucil (Clb) alone in previously untreated CLL patients. Trial BO21004/CLL11 was conducted at 155 centers in 24 countries. A total of 356 patients were randomized to Clb (n=118) and GClb (n=238) in stage 1a. Randomization was stratified by Binet stage and region. The primary endpoint was investigator assessed PFS. However, for regulatory decision the primary endpoint of PFS was to be based on the results from the Independent Review Committee (IRC).

At the clinical cutoff on July 11, 2012 the median observation time was 14.2 months and median exposure to the study medications was 6 cycles. The IRC assessed median PFS was 11.1 months in the Clb arm versus 23.0 months in the GClb arm. The hazard ratio (HR) was 0.16 (95% CI: 0.11, 0.24), log-rank p-value <0.0001. At one year, 36% of patients in the Clb arm and 83% of patients in the GClb arm were progression free. All pre-specified sensitivity analyses for PFS were supportive of the primary analysis with HRs ranging from 0.12 to 0.26 and subgroup analyses of PFS were in general consistent with the ITT population (HRs ranged from 0.03 to 0.42).

Secondary endpoints included end of treatment response, best overall response, event free survival, duration of response, disease free survival, time to new anti-leukemic therapy and overall survival and were also supportive of the primary endpoints. However, there was no multiplicity adjustment plan for these endpoints. The best overall response rate was 32.1% in the Clb arm and 75.9% in the GClb arm (with CR rate of 0.9% in the Clb arm and 27.8% in the GClb arm). Among patients who had a response, the median duration of response was 3.5 months in the Clb arm and 15.2 months in the GClb arm [HR: 0.1 (0.05, 0.2), p-value <0.0001].

Conclusions

Trial BO21004/CLL11, stage 1a demonstrated a clinically meaningful and statistically robust improvement in PFS for patients with CLL that received obinutuzumab in combination with chlorambucil, compared with patients who received chlorambucil alone. Obinutuzumab in combination with chlorambucil provides treatment for patients who are elderly or have co-morbidities, who might not otherwise tolerate standard treatment regimens (containing fludarabine). Regular approval is recommended because BO21004/CLL11 was a randomized trial using a primary endpoint of PFS that is routinely accepted in the CLL indications. No other

trials are recommended at this time to further characterize the clinical benefit of ofatumumab in combination with chlorambucil in patients with previously untreated CLL.

Risk

Summary of evidence

The safety population from trial BO21004/CLL11 consisted of 224 patients who received at least one dose of obinutuzumab and 116 patients on the chlorambucil only arm. The main safety issues were infusion reactions and myelosuppression. Symptoms of infusion related adverse events were, in part, gastrointestinal, vascular including hypotension and tachycardia, and respiratory. Infrequent important adverse events included tumor lysis syndrome, thrombocytopenia, and fevers. Though serious infections, such as Hepatitis B and PML, did not occur in this trial, there were cases in patients on other trials of obinutuzumab. The majority of adverse events occurred during the treatment period.

Conclusions

These risks are acceptable for a population with a life-threatening illness for which there is limited available therapy.

Risk Management

Summary of evidence

Multiple interventions were developed prior to trial initiation and during the trial to minimize the risk of adverse events. Infusion reactions adverse events were mitigated by the development of an improved pre-medication regimen and specific directions for adjusting infusion rate and holding infusion. Patients at risk for tumor lysis syndrome were identified and given prophylaxis. Patients were screened for hepatitis B reactivation risk and those at risk were monitored.

Conclusions

The clinical trial experience with obinutuzumab and the known class effect risks were considered in the mitigation strategies. These are similar to the strategies used with other monoclonal antibodies and can be incorporated into the practice of prescribers using obinutuzumab by inclusion in the product label.

Benefit-Risk Summary and Assessment

The addition of obinutuzumab to chlorambucil demonstrated superior efficacy to chlorambucil in this randomized trial. The safety profile is fairly well described in this randomized trial and is bolstered by the experience with agents in this class.

Given the treatment benefit of obinutuzumab in patients with chronic lymphocytic leukemia, the risks associated with obinutuzumab in combination with chlorambucil are acceptable.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Risk Evaluation and Mitigation Strategy (REMS) is not required for obinutuzumab in combination with chlorambucil for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL).

1.4 Recommendations for Postmarket Requirements and Commitments

No clinical PMCs or PMRs are deemed necessary for this BLA.

2 Introduction and Regulatory Background

This review will be concentrated on the results of stage 1a of the applicant's trial, BO21004/CLL11, entitled "An Open-label, Multi-center, Three Arm Randomized, Phase 3 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".

2.1 Product Information

Established Name:	Obinutuzumab (also known as GA101, RO5072759)
Trade Name:	Gazyva
Applicant:	Genentech, Inc. 1 DNA Way South San Francisco, CA 94080-4990
Drug Class:	Anti-CD20 monoclonal antibody
Proposed Indication:	Obinutuzumab in combination with chlorambucil for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL).
Proposed Dosage and Administration:	Obinutuzumab should be administered as an intravenous infusion. The recommended dose and administration of obinutuzumab is as shown in Table 1 below for 6 cycles (1 cycle is 28 days).

Table 1 Obinutuzumab: Proposed Dosage and Administration

Treatment cycle and day		Dose	Rate of infusion (in the absence of infusion reactions/ hypersensitivity during previous infusions)
Cycle 1	Day 1	100 mg	Administer at 25 mg/hr over 4 hours. Do not increase the infusion rate.
	Day 2	900 mg	Administer at 50 mg/hr. The rate of infusion can be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr.
	Day 8	1000 mg	Infusions can be started at a rate of 100 mg/hr and increased by 100 mg/hr every 30 minutes to a maximum rate of 400 mg/hr.
	Day 15	1000 mg	
Cycles 2-6	Day 1	1000 mg	

Drug Product: Obinutuzumab is available in 1000 mg dose in a 50 ml glass vial containing 40 ml of the 25 mg/ml strength liquid concentrate.

2.2 Tables of Currently Available Treatments for Proposed Indications

The applicant's proposed indication is "Obinutuzumab in combination with chlorambucil for the treatment of patients with previously untreated chronic lymphocytic leukemia."

Table 2 below shows FDA approved drugs for CLL and Table 3 describes first-line chemotherapy regimen for chronic lymphocytic leukemia.

Table 2 FDA-Approved Drugs for CLL

Drug	Approval	Indication
Chlorambucil (alkylating agent)	1957	CLL (unspecified)
Cyclophosphamide (alkylating agent)	1959	CLL (unspecified)
Fludarabine (nucleotide analog)	1991	Nucleotide metabolic inhibitor indicated for the treatment of adult patients with B-cell CLL who have not responded to or whose disease has progressed during treatment with at least one standard alkylating-agent containing regimen. Benefit in treatment-naïve or non-refractory CLL patients is not established.
Alemtuzumab (anti-CD52 monoclonal antibody)	2007 (converted to regular approval)	CD52-directed cytolytic antibody indicated as a single agent for the treatment of B-cell CLL.
Bendamustine (alkylating agent)	2008	CLL (unspecified). Efficacy relative to first line therapies other than chlorambucil has not been established.
Ofatumumab (anti-CD20 monoclonal antibody)	2009	For the treatment of patients with CLL refractory to fludarabine and alemtuzumab.

Rituximab (anti-CD20 monoclonal antibody)	2010	In combination with fludarabine and cyclophosphamide for the treatment of patients with previously untreated and previously treated CD20-positive CLL.

Table 3 Chemotherapy Regimens Recommended for First-Line CLL

Regimen	Population
Chlorambucil ± rituximab	CLL without del (11q) or del (17p) [a d] CLL with del (11q) [a]
Bendamustine ± rituximab	CLL without del (11q) or del (17p) [a b] CLL with del (11q) [a b]
Cyclophosphamide, prednisone ± rituximab	CLL without del (11q) or del (17p) [a] CLL with del (11q) [a]
Alemtuzumab	CLL without del (11q) or del (17p) [a] CLL with del (11q) [a]
Rituximab	CLL without del (11q) or del (17p) [a d] CLL with del (11q) [a]
Fludarabine ± rituximab	CLL without del (11q) or del (17p) [a c]
Fludarabine + cyclophosphamide+ rituximab (FCR)	CLL without del (11q) or del (17p) [b] CLL with del (17p) CLL with del (11q) - reduced dose [a c] CLL with del (11q) [b]
Fludarabine + rituximab (FR)	CLL without del (11q) or del (17p) [b] CLL with del (17p)
Pentostatin + cyclophosphamide + rituximab (PCR)	CLL without del (11q) or del (17p) [b] CLL with del (11q) [b]
High-dose methylprednisolone (HDMP) + rituximab	CLL with del (17p)
Alemtuzumab ± rituximab	CLL with del (17p) CLL with del (11q) [a]
Lenalidomide	CLL without del (11q) or del (17p) [a] CLL with del (11q) [a]
Cladribine	CLL without del (11q) or del (17p) [a]
Pulse corticosteroids	CLL without del (11q) or del (17p) [d]

[a] Age ≥70 years or younger patients with comorbidities.
[b] Age <70 or older patients without significant comorbidities.
[c] In patients with ≥70 years of age with comorbidities, fludarabine does not appear to have a benefit for first-line therapy over other therapies including chlorambucil.
[d] Frail patient, significant comorbidity (not able to tolerate purine analog).

2.3 Availability of Proposed Active Ingredient in the United States

Obinutuzumab is not currently marketed in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

Obinutuzumab is an anti-CD20 monoclonal antibody. Other commercially available CD20-directed monoclonal antibodies include Rituximab (rituximab) and Arzerra (ofatumumab). The

table below shows the Warnings and Precautions that are listed in the US prescribing information (USPI) for these drugs.

Table 4 Anti-CD20 Monoclonal Antibodies: USPI Warnings and Precautions

	Rituximab	Ofatumumab
Infusion reactions	X	X
Tumor lysis syndrome	X	
Mucocutaneous reactions	X	
Progressive multifocal leukoencephalopathy	X	X
Hepatitis B virus reactivation	X	X
Infections	X	
Cardiac arrhythmias and angina	X	
Renal toxicity	X	
Bowel obstruction and perforation	X	
Intestinal obstruction		X
Cytopenias	X	X
Do not to administer live viral vaccines	X	X

In addition, rituximab also has the following in the Boxed Warning:

- Fatal infusion reactions within 24 hours of Rituxan infusion occur; approximately 80% of fatal reactions occurred with first infusion. Monitor patients and discontinue Rituxan infusion for severe reactions.
[redacted] (b) (4)
- Severe mucocutaneous reactions, some with fatal outcomes.
- PML resulting in death.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The table below shows the regulatory history pertaining to this BLA.

Table 5 Regulatory History

Date	Event
July 7, 2009	End-of-Phase 2 meeting. FDA stated the following: • FDA does not agree that the study population proposed is [redacted] (b) (4) The study defines patients who are [redacted] (b) (4) as patients having renal failure (creatinine clearance < 70 cc/min) or other general co-morbidities as defined by the Cumulative Illness Rating Scale (CIRS). FDA stated that the eligibility criteria should be revised to include only patients with creatinine clearance < 30 ml/minute as fludarabine is contraindicated in severe renal insufficiency (creatinine clearance < 30 ml/min). With regard to CIRS, this co-morbidity index has not been validated for use in CLL or in any other cancer setting. FDA would consider patients having any of the following

to be unsuitable candidates for fludarabine:

- Impaired performance status requiring assistance with activities of daily living (ADLs), e.g. Karnofsky PS ≤ 60.
- Known hypersensitivity to fludarabine.
- Serious co-morbid condition.

Serious co-morbid conditions would include:

- Chronic active infection.
- History of opportunistic infection.
- Autoimmune disease including hemolytic anemia, thrombocytopenia.
- Grade 3 or higher motor or sensory neuropathy.
- Clinically significant organ dysfunction including :
  - Pulmonary disease (e.g., COPD with FEV1 ≤ 60% predicted or DCLO ≤ 60% predicted).
  - Diabetes mellitus requiring chronic treatment with oral agents or insulin.
  - NYHA Grade 3/4 heart failure or ischemic heart disease.
  - Severe renal insufficiency (CrCl < 30 cc/min).
  - Hepatic insufficiency (Child-Pugh A classification or worse).

All co-morbid conditions which make a patient unsuitable for fludarabine therapy must be clearly documented in the case report form.

Genentech stated their intent to change the proposed indication from (b) (4) FDA requested that Genentech define the term (b) (4) in objective terms as it pertains to the proposed study population and provide data to support the definition. Genentech stated that they plan to use the CIRS scale. Genentech noted that the CIRS is used by the German CLL Study Group and by the 2008 CLL NCI-IWG to identify patients from whom FCR chemotherapy may not be appropriate. FDA advised that use of this scale might result in the inclusion of patients who have multiple conditions that are not incapacitating conditions; classification of these patients as (b) (4) may not be appropriate. FDA advised that the condition(s) that result in the classification of the patient as (b) (4) must be collected on the case report forms. The defined (b) (4) population should be one that would also be considered not appropriate for fludarabine therapy by the US medical community. The label claim sought should be based on characteristics of the population enrolled and rather than the vague term (b) (4)

- FDA does not agree with inclusion of CLL patients defined as Binet B and C: FDA stated that CLL population to be enrolled should meet the criteria for treatment consistent with current clinical practice guidelines. The following inclusion criteria for initiating CLL therapy should be used:
  a. Significant disease-related symptoms (B symptoms):
     1) Fever due to CLL
     2) Night sweats
     3) Weight loss
     4) Extreme fatigue
  b. Bulky disease which would include any of the following (should be documented by CT);
     1) Progressive enlargement of lymph nodes or progression of hepatomegaly or splenomegaly.

	2) Spleen > 6 cm beneath costal margin, lymph nodes > 10 cm unidimensionally 3) Obstructive adenopathy. c. Documented progressive anemia or Hemoglobin < 10 g/dl. d. Documented progressive thrombocytopenia or platelet count < 100,000 cells/mm^3. e. Documented rapid lymphocyte doubling time (< 6 months). f. Evidence of end organ dysfunction requiring treatment. The basis for the decision to treat CLL should be clearly captured in the case report form. • FDA does not agree with the proposed dose/dosing schedule for the chlorambucil only arm: FDA stated that chlorambucil is an acceptable active control treatment for previously untreated B-CLL patients unsuitable for fludarabine-based therapy. The chlorambucil dose of 0.5 mg/kg biweekly for 6 months proposed for the chlorambucil only arm based on review of the literature is a suboptimal dose. FDA asked the Sponsor to provide evidence from the medical literature to support the proposed dose and to discuss the dose titration of chlorambucil generally used in CLL patients receiving chlorambucil. Chlorambucil therapy is generally continued until there is evidence of CR, stable PR, progression or unacceptable toxicity, a treatment period usually much longer than six months. FDA asked to discuss the adequacy of the proposal for only six months of therapy on the chlorambucil only arm and on the combination arms and to provide literature evidence to support the appropriateness of a six month schedule of therapy. *Genentech stated they would treat patients until best response was achieved or until 6 months whichever is sooner. Chlorambucil therapy until CR, or stable PR for one year is considered standard in the US. FDA requested that Genentech provide literature to support the contention that chlorambucil treatment for six months is adequate. Genentech agreed to provide the requested information.* *FDA stated that all patients, including the first six to receive RO5072759 plus chlorambucil should be randomized; thus all patients enrolled can be included in the comparative analyses of safety and efficacy. Genentech and FDA agreed that the safety data from the first twenty-five patients randomized to each arm will be reviewed by an independent data safety monitoring committee to determine if the toxicities of the combination of GClb and Clb are acceptable. The DSMC would then review safety data at 3 to 6 month intervals (interval dependent on prior safety results). The final protocol will also have dose modification and early termination rules for unacceptable toxicity.* • FDA does not agree with the planned crossover to the GClb arm with progression on chlorambucil: FDA recommended that patients treated on this study not be crossed over to another study treatment at documented progression as this will obscure survival results. • FDA does not agree that that the primary analysis of PFS should be based on investigator-assessment: FDA stated that IRC review of PFS should be the primary endpoint. Progression should be assessed by an independent radiologic assessment of

PFS and include correlation with clinical information from the CRFs with the reviewers masked to the therapy that the subject received. IRC review should be done in real time to avoid investigator bias in this unblinded study regarding removal from study of patients who have not actually progressed. For any patient enrolled on this study IRC confirmation of progression should be obtained prior to the initiation of a new CLL therapy.

FDA stated that verification of investigator-determined PFS events by the independent radiologist to occur in real time. Genentech stated that a group of CLL experts, blinded to treatment assignment, would be given data to confirm response or disease progression but not in real time. Genentech stated their intent that the IRC would not review films but would only review the reports of CT scans. FDA stated that use of reports would be acceptable only if the clinical site radiology review was comprehensive (inclusive of all scans from baseline forward) at each reading and that lesions measurements would be described in the report for use in determining percent change in individual lesions and sum of the largest diameters of all measurable disease at each time-point. FDA stated that all CT scans should be available for FDA review and audit and it would be more desirable if these scan were available for review by the IRC. Genentech agreed to store images and have them available for review by the IRC as needed.

- FDA does not agree with the proposed assessment plan for response/progression: FDA stated that although PFS is an acceptable primary endpoint for this study, FDA does not agree that the proposed analysis of PFS should be based on investigator assessment in this open-label trial, (b) (4) The accurate measurement of organomegaly as well as changes in the extent of organomegaly and lymphadenopathy over time by physical examination alone has been shown to be unreliable. Recently the ODAC panel expressed the opinion that determination of disease progression on the basis of organomegaly and/or lymphadenopathy requires confirmation by radiological testing (e.g., CT scan) in the context of a clinical trial for registration purposes. CT scans of the chest, abdomen, and pelvis (and neck if clinically involved) should be scheduled every 3 months while on study to evaluate hepatomegaly, splenomegaly, and lymphadenopathy, and be continued during the follow-up period every 3 months until disease progression.

  FDA stated that CT scans must be performed at baseline (within one month prior to enrollment) for all patients, be obtained to confirm objective response, and to confirm PD in those patients who progress based on physical examination only (i.e., new or increased lymph node size; new or increasing organomegaly). Genentech agreed to require CT scans at these time points. Genentech agreed to provide data to support statements that radiographs contributed to determination of disease progression in only 15% of patients undergoing first-line treatment for CLL. FDA agreed that doubling of lymphocyte counts could be used to define progression.

- FDA stated that patients with AST or ALT > 2.5 x ULN should be excluded unless liver infiltration by leukemia is suspected as should patients with bilirubin > 2 x ULN.

  Genentech agreed to make the requested change. Genentech noted that chlorambucil

	labeling does not specify dose modification for liver toxicity and agreed to provide data to justify the safety of the proposed chlorambucil dosing schedule in patients with abnormal liver function tests. *Genentech will be performing a Coombs test for the detection of autoimmune hemolytic anemia on all patients at entry onto the study.* • FDA stated that molecular confirmation of complete response in CLL is strongly encouraged. • FDA asked to justify the dosing schedule for the proposed RO5072759 in combination with chlorambucil as well as for rituximab in combination with chlorambucil to treat CLL. Specifically, to provide evidence that 6 months of treatment with either combination is likely to provide clinical benefit in CLL and explain why therapy with chlorambucil in both combination arms is not continued until achieving PR or CR. • FDA stated that two phase 3 studies are generally required for licensure. FDA would accept a single pivotal study to support licensure if the results demonstrate a highly significant effect on the primary endpoint that is internally consistent across subgroups. The results of a single pivotal trial must be sufficiently robust and so compelling that if would be unethical to the repeat the study. A second randomized trial could be performed in a different CLL population. • FDA asked to provide sensitivity analyses to study the impact on the analysis of PFS due to any missing data/assessments, and any loss to follow-up or discontinuation of assessments of PFS not due to an event. • FDA stated that independent review of scans and clinical information should occur simultaneously or shortly after the investigator's review. Patients should continue to undergo clinical visit/follow up and CT scans until progression has been confirmed by the independent review committee. *Genentech agreed to perform CT scans at the time of enrollment, and collect, and store them. Images will also be collected at time of response and at time of progression if progression is noted on physical examination (i.e., palpable lymph nodes, new lymph nodes, new or recurrent organomegaly). FDA commented that independent review of scans should be done at real time at least for those patients determined as PD by study investigators. If the independent review committee cannot confirm PD, these patients should continue to be assessed for response until PD is confirmed or the end of study.*
November 29, 2011	Type C meeting to discuss DDI and QTc plans: This meeting was cancelled as all questions were addressed in the FDA's preliminary comments.
June 8, 2012	Type C meeting to discuss the proposed statistical analysis plan: • FDA and Genentech agreed to the submission of the analysis datasets containing the PFS results from all treatment arms in order to assess the global test. FDA stated that submission of the updated (Stage 1b: RClb vs. Clb) data is acceptable provided there is an indicator of the data used for the global test.
October 30,	Type C meeting to discuss the proposed content and format of the BLA:

2012	• FDA asked to include analysis for hypogammaglobulinemia for the proposed safety analysis of B-cell recovery. • FDA asked to submit case report forms (CRFs) for patients who died or experienced any serious adverse event during treatment or within 30 days of treatment discontinuation. Also, to submit case report forms for patients who discontinued treatment due to an adverse event. • FDA asked to submit detailed information on all the components used to determine the Modified Cumulative Illness Rating Scale for all patients. This meeting was cancelled on November 1, 2012 due to hurricane Sandy.
February 22, 2013	Pre-BLA meeting to discuss the clinical trial results of the Stage 1a (GClb against Clb). • FDA stated that the applicant's proposal to include an abbreviated report in the BLA which will contain a high level summary of safety and efficacy results from Stage 1b is acceptable as long as no data or claims from Stage 1b are proposed in the draft labeling.

On March 13, 2013, Genentech, Inc. submitted a request for Breakthrough Therapy Designation for obinutuzumab for previously untreated CLL indication. The FDA Medical Policy Council meeting was held on May 7, 2013 to discuss this request. On May 9, 2013, obinutuzumab was granted Breakthrough Therapy Designation in combination with chlorambucil for the treatment of patients with previously untreated CLL.

2.6 Other Relevant Background Information

Obinutuzumab was given orphan drug designation for the treatment of CLL on February 17, 2012 under the provisions of section 526 of the Federal Food, Drug, and Cosmetic Act. Therefore, obinutuzumab is exempt from the Pediatric Research Equity Act (PREA) requirement.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This BLA was submitted as an electronic Common Technical Document (eCTD) and follows the FDA Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications. The overall quality and integrity of this BLA were adequate.

3.2 Compliance with Good Clinical Practices

Trial BO21004/CLL11 was conducted in accordance with the principles of the "Declaration of Helsinki" and "Guidelines for Good Clinical Practice" as defined by the International Conference on Harmonization (January 1997) Tripartite Guideline or with local law. The trial was reviewed and approved by the appropriate Ethics Committees and Institutional Review Boards.

The Roche Clinical Quality Assurance group or designee conducted audits at seven investigator sites. The applicant reported that no critical audit findings were observed. For all audit findings, appropriate corrective and preventive actions were undertaken.

Upon receipt of the application, two clinical sites were chosen for Office of Scientific Investigations (OSI) inspections. These selections were sites in the Russian Federation based on higher accrual numbers. However, as there was a delay in issuing travel visas to Russia, the sites for inspections were changed to one site in Austria and one site in France (Table 6).

Table 6 Requested OSI Clinical Site Audits for BO21004/CL11

Site ID	Number of enrolled patients	Name of the PI	Location
164932	6	Heinz Ludwig	Montleartstrasse 37 Wien, 1160 Austria
166942	6	Katell LeDu	194 Avenue Rubillard Pavillon Le Mans, 72037 France

After a Center Director briefing regarding the status of the application review, it was decided to cancel the clinical site OSI inspections altogether because only 12 patients would be covered by the currently proposed inspections (Austria and France). Significant findings at these sites, covering this few patients could not impact the overall data reliability for the trial. In a trial with enrollment occurring at 155 centers in 24 countries, the potential for fraud or bias is dramatically minimized. Therefore, OSI clinical site inspections were not required to verify the reliability of the data for this trial.

Per Dr. Anthony Orencia's consult review, OSI inspected the applicant site (Genentech, Inc.) in South San Francisco, CA from July 29 to August 2, 2013. The inspection evaluated documents related to study monitoring visits and correspondence, Institutional Review Board approvals, completed Form FDA 1572s, monitoring reports, drug accountability, and training of staff and site monitors.

The conclusions of the inspection report were that the applicant maintained adequate oversight of this clinical trial, no regulatory deficiencies were observed, the preliminary classification was No Action Indicated (NAI), and that the study data collected and submitted by the applicant appear generally reliable in support of the requested indication.

It is noted in his review that the Establishment Inspection Report (EIR) has not been received, findings are based on preliminary communication with the field at the Office of Regulatory Affairs (ORA), and final review of the EIR is pending. An inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.

3.3 Financial Disclosures

The applicant provided FDA financial certification form 3454 signed by the vice president of US regulatory affairs, Michelle H. Rohrer, Ph.D. dated on April 22, 2013.

A total of 1142 principal and sub-investigators participated in the trial. There were two sub-investigators from whom a signed financial disclosure was unable to be obtained as the investigators left the study site and did not provide a forwarding address. Four principal and five sub-investigators had qualifying disclosures. None of the investigators were sponsor employees.

The applicant provided financial disclosures for the nine principal and sub-investigators that participated in the trial at nine different sites.

Table 7 BO21004/CLL11: Financial Disclosures of Investigators

Clinical ID	Investigator	Patient enrollment	Disclosure
		(b) (6)	Roche research foundation grant not related to the conducted study 2008-2009
		(b) (6)	Roche support of other investigator trials; speaker's honoraria
			$80,000 research grant and $3,000 honoraria for speaking
			Honoraria and speakers fees for Roche Global
			Data manager for CLL service evaluation
			Investigator initiated research ($18,000), educational grants ($15,000)
			Lymphoma database ($222,000); multicenter phase 2 clinical trial ($652,152)
			Research grants
			Research grants from Roche and Biogen

Since few patients were enrolled at the affected sites, it is not likely that these financial conflicts of interest affected the overall trial results.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Gazyva (obinutuzumab) is a type II glycoengineered, humanized anti-CD20 monoclonal antibody of the IgG1 subclass. It recognizes a specific epitope of the CD20 molecule found on B-cells. The molecular mass of the antibody is approximately 150 kDa.

Obinutuzumab is produced by mammalian cell (CHO) suspension culture. Obinutuzumab is a sterile, clear, colorless to slightly brown, preservative free liquid concentrate for intravenous administration. Obinutuzumab is supplied at a concentration of 25 mg/mL in 1000 mg single use vials. The product is formulated in 20 mM L-histidine/ L-histidine hydrochloride, 240 mM trehalose, 0.02 % poloxamer 188. The pH is 6.0.

Refer to Chemistry, Manufacturing and Controls (CMC) review for details.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

Refer to Pharmacology/Toxicology review for details.

No genotoxicity or carcinogenicity studies have been performed with obinutuzumab and are not required for the proposed indication.

No specific studies have been conducted to evaluate potential effects on fertility, but in repeat-dose toxicity studies in cynomolgus monkeys, obinutuzumab did not affect reproductive parameters nor embryo-fetal development, parturition, postnatal survival, growth, and development of infants. However, since IgG antibodies cross the placental barrier and B cells are depleted in infants, it is recommended that women of childbearing potential use effective contraceptive methods during and for up to 12 months after treatment with obinutuzumab.

4.4 Clinical Pharmacology

Refer to Clinical Pharmacology review for details.

4.4.1 Mechanism of Action

Obinutuzumab is a glycoengineered, type II monoclonal antibody directed against the CD20 antigen. Obinutuzumab targets the extracellular loop of the CD20 transmembrane antigen

expressed on the surface of pre B- and mature B-lymphocytes. Glycoengineering of the Fc portion of Gazyva results in the absence of a fucose residue, leading to high affinity for FcgRIII receptors on immune effector cells such as natural killer (NK) cells, macrophages and monocytes as compared to non-glycoengineered antibodies.

The Fab portion of obinutuzumab binds to the CD20 molecule and the Fc domain mediates immune effector functions that results in B-cell lysis *in vitro*. Possible mechanisms of cell lysis include direct cell death (DCD) induction, antibody dependent cellular cytotoxicity (ADCC) and antibody dependent cellular phagocytosis (ADCP) through recruitment of FcgRIII positive immune effector cells such as NK cells, macrophages and monocytes, and low degrees of complement mediated cytotoxicity (CDC). As a type II antibody, obinutuzumab is characterized by an enhanced DCD induction with a concomitant reduction in CDC compared to type I CD20 antibodies. As a consequence of the glycoengineering, obinutuzumab is characterized by enhanced ADCC compared to non-glycoengineered CD20 antibodies.

4.4.2 Pharmacodynamics

The effect of obinutuzumab in combination with chlorambucil was evaluated in 44 patients with previously untreated CLL. Out of the 44 patients, 40 patients (91%) were B-cell depleted (CD19+ B-cell < 0.07 x 10^9/L) at the end of treatment and during the 6 months follow-up. Thirteen patients (33%) without progressive disease (PD) and 5 patients (13%) with PD had B-cell recovery within 12-18 months follow up.

4.4.3 Pharmacokinetics

The pharmacokinetics of obinutuzumab were evaluated in phase 1, 2 and 3 studies and a population pharmacokinetics model of 590 Non-Hodgkin's lymphoma (NHL) and CLL patients.

Based on the population PK model, after Cycle 6 Day 1 of obinutuzumab 1000 mg infusion, C_{max} was 510.6 microgram/mL, $AUC_{(0-\infty)}$ was 10,113 microgram.d/mL, volume of distribution of the central compartment was 2.77L (which approximated serum volume), clearance approximated 0.085 L/day with an elimination half-life of approximately 30.4 days in CLL patients. The elimination pathway comprised of two parallel pathways (a non-linear and a linear clearance pathway) which changed as a function of time.

Special Population:
Based on the population pharmacokinetic analysis, gender, age, body weight and renal impairment did not have clinical significant effects on the pharmacokinetics of obinutuzumab. Dose adjustment is not recommended in patients with creatinine clearance > 30 mL/min.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The clinical trials included in this BLA are summarized in the table below.

Table 8 Clinical Trial Reports Included in BLA 125486

Trial ID	Design	Regimen	Objective	No. of Subjects and Sites	Status
BO21004	Phase 3, open-label, multi-center, 3-arm randomized study (GA101 +Clb, Rituximab +Clb, Clb alone)	1000 mg iv q4wk for 6 cycles; additional doses on Days 8 and 15 of Cycle 1.	Efficacy, safety, PK, and PD.	781 randomized (and 6 safety run-in non-randomized patients), 155 sites in 24 countries	Stage 1: completed stage 2: ongoing
BO21000	Phase 1b, open-label, multicenter study in B-cell relapsed/ refractory follicular lymphoma.	IV infusion q3wk for 8 cycles (GA101+CHOP), q4wk for 6 cycles (GA101+FC, GA101+ bendamustine); additional dose on C1D8. -Relapsed or refractory: 1st/subsequent dose either in combination with CHOP (400/400mg or 600/800mg), with FC (400/400 mg or 1600/800 mg) -Previously untreated: with CHOP 1000/1000 mg, with bendamustine 1000/1000 mg.	Efficacy, safety, PK, pharmaco-genetics and PD.	-R/R: 56 (28 GA101 + FC, 28 GA101+ CHOP), 16 sites in 6 countries (all non-US) -1st line patients: 80 (40 GA101 + CHOP, 40 GA101 +bendamus-tine), 26 sites in 5 countries	Ongoing
BO20999	-Phase 1: open-label, multi-center, non-randomized, adaptive dose-escalating in documented CD20+ malignant disease (lymphoma or	-Phase 1: IV infusion q3wk for 8 cycles; additional dose on C1D8, 1st/subsequent doses: 50/100 mg, 100/200 mg, 200/400 mg 400/800 mg, 800/1200 mg 1200/2000mg, 1600/800mg (NHL only) 1000/1000 mg (CLL only) Dose-escalation in B-CLL patients, starting with	-Phase 1: dose escalation (safety and tolerabil-ity), PK. -Phase 2: safety, efficacy, PK and PD.	-Phase 1: 34 (21 NHL, 13 CLL), 7 sites in France -Phase 2: 100 (40 aNHL, 40 iNHL, and 20 B-CLL), 16 sites in Germany and France.	-Phase 1: ongoing -Phase 2: ongoing

	CLL). -Phase 2: open-label, multi-center, randomized in relapsed or refractory DLBCL, or follicular lymphoma, or CLL or MCL.	cohort 4. -Phase 2: iv infusion q3wk for 8 cycles; additional dose on Day 8 of Cycle 1. NHL: 2 doses (400/400 mg, 1600/800 mg) CLL: 1000mg; additional dose on Day 15 of Cycle 1.			
BO21003	-Phase 1: single-arm open-label, multi-center, dose-escalating study in documented CD20+ malignant disease (lymphoma or CLL), -Phase 2: randomized (obinutuzumab vs. rituximab) study in relapsed indolent lymphoma	-Phase 1: 4 iv infusions q wk 1st/subsequent doses: 100/200 mg, 200/400 mg, 400/800 mg 800/1200mg, 1200/2000mg Patients with documented response eligible to enter maintenance therapy regimen (obinutuzumab 1000 mg every 3 months until progression or maximum 2 years) -Phase 2: 1000 mg, 4 iv infusions q wk. Patients with documented response or SD after induction treatment eligible to enter maintenance therapy (rituximab or obinutuzumab every 2 months until progression or for a maximum of 2 years).	-Phase 1: dose escalation (safety, tolerability and PK) -Phase 2: efficacy, safety and PK.	199 -Phase 1: 22 (17 NHL, 5 B-CLL), 5 sites in Canada -Phase 2: 175 (149 follicular lymphoma, 26 non-follicular lymphoma), 54 sites in 15 countries. The largest sites were in New Jersey, Belgium and Milan.	Phase 1 is complete, Phase 2 is ongoing
JO21900	Phase 1, open-label, multi-center non-randomized dose-escalation study in documented CD20+malignant disease (NHL)	IV infusion q3wk for 8 cycles; additional dose on C1D8. Dose levels were 200/400 mg, 400/800 mg 800/1200 mg and 1200/2000 mg.	Dose escalation (safety and tolerability)	12 NHL, 3 sites in Japan.	Complete

5.2 Review Strategy

The clinical review was primarily based on the efficacy and safety of stage 1a of the BO21004/CL11 trial to support the proposed indication and included the following:

- Four phase 1 and 2 trials (BO21000, BO20999, BO21003, and JO21900) were reviewed to support the safety of obinutuzumab;
- Electronic submission with clinical study reports and other relevant portions of the BLA;
- Efficacy and safety data were audited or reproduced;
- Regulatory history of ofatumumab;
- Applicant's presentation to FDA on June 10, 2013;
- Applicant's responses to FDA information requests;
- Relevant published literature in CLL; and
- The 120-day safety update submitted on July 19, 2013.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Clinical Trial

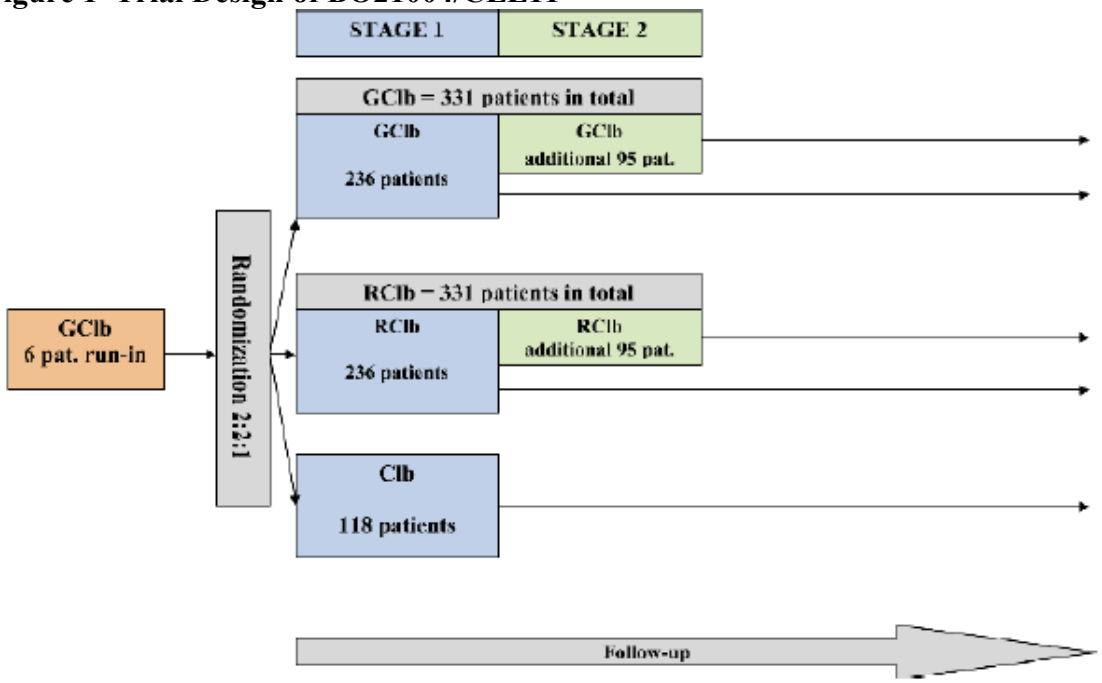
Trial ID and Title:
BO21004/CL11: An Open-label, Multi-center, Three Arm Randomized, Phase 3 Study to Compare the Efficacy and Safety of RO5072759 + Chlorambucil (GClb), Rituximab + Chlorambucil (RClb) or Chlorambucil (Clb) Alone in Previously Untreated CLL Patients with Comorbidities.

5.3.1.1 Trial Design

This was an open-label, three-arm randomized, parallel-group, multicenter phase 3 trial of obinutuzumab in combination with chlorambucil (GClb) versus rituximab in combination with chlorambucil (RClb) versus chlorambucil (Clb) alone in previously untreated CLL patients. The trial was conducted in collaboration with the German CLL Study Group (GCLLSG).

The trial was divided into two stages. In stage 1, patients were randomized to Clb alone, GClb, or RClb (1:2:2 ratio). In stage 2, the randomization continued between GClb and RClb (1:1 ratio). The randomization part of the trial was preceded by a safety run-in phase where 6 enrolled patients were treated with GClb. The 6 run-in patients were analyzed for safety separately and not included in the randomization part of the trial. Patients were to be stratified by Binet stage, and country/region.

Figure 1 Trial Design of BO21004/CLL11



Clb = chlorambucil; GClb = obinutuzumab + chlorambucil; pat. = patients; RClb = rituximab + chlorambucil
Source: Pre-BLA meeting package, page 33

For the purpose of analysis, stage 1 was further divided into stages 1a and 1b.

- Obinutuzumab + chlorambucil (GClb) vs. chlorambucil (Clb) - Stage 1a
- Rituximab + chlorambucil (RClb) vs. chlorambucil (Clb) - Stage 1b

Patients in the Clb arm who had clearly documented disease progression during or within 6 months of end treatment with Clb could cross-over to the GClb treatment arm at the discretion of the investigator. At the stage 1a analysis cutoff date, 22 out of 118 patients (19%) in the Clb treatment arm had crossed over to GClb arm after disease progression. For cross over patients, unscheduled laboratory and lesion assessments were to be performed maximum of 28 days prior to entry into the cross-over arm to establish a 're-baseline' and a CT scan was recommended pre-crossover to confirm progressive disease.

The stage 1 population was used to conduct the stage 1a (GClb versus Clb; futility analysis of RClb versus GClb; Global Test) and stage 1b (RClb versus Clb) analyses. The analysis of this BLA is based on the stage 1a data. The applicant included the clinical study report of stage 1b in the BLA submission. However since it is not relevant to the sought indication, stage 1b is not included in this review.

Response was assessed by the investigator according to standard NCI/International Workshop on CLL (IWCLL) guidelines which was considered primary for all endpoints. An independent review committee (IRC) composed of at least three CLL experts (two reviewers and one adjudicator) also assessed response and progression based on peripheral blood counts, bone

marrow biopsy results, reports of physical examination, and radiology reports. Though not formally reviewed by IRC, the CT scan images were collected and stored should a radiology review be required in the future.

Safety data were reviewed by a Data Safety Monitoring Board (DSMB) regularly during the trial. The safety analyses were performed monthly until 50 patients (at least 20 on the GClb arm) had completed 3 cycles of therapy, withdrawn due to toxicity, or died. After this initial review, the DSMB reviews were to occur twice per year. For each review, the DSMB reviewed general toxicity (grade 3 and 4 AEs and all SAEs); laboratory data (hematology and chemistry), any adverse events requiring discontinuation of the study drug; patient deaths, and concomitant medications. After the DSMB met, they were to recommend to the applicant whether the trial should continue according to the protocol, or suggest changes in the protocol based upon the review of the data.

The DSMB also evaluated the interim efficacy analyses according to the schedule outlined in the statistical analysis plan (SAP).

End of trial was defined as 8 years after the last patient enrollment (unless all patients died).

Trial Objectives:
The primary objective was to demonstrate clinically relevant statistical superiority in progression-free survival (PFS) with GClb compared to 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 secondary objectives were as follows:

- To evaluate PFS based on independent review committee (IRC)
- To evaluate PFS censoring in patients who started new anti-leukemic therapy before showing signs of disease progression
- To evaluate and compare in each study arm: overall response rate (ORR), complete response (CR) and partial response (PR) rate after the end of treatment, best ORR within 6 months of end of treatment, event-free survival (EFS), disease-free survival (DFS) in CR/complete response with incomplete marrow recovery (CRi) patients, and duration of response in CR/CRi and PR patients
- To evaluate time to re-treatment/start of new anti-leukemic therapy
- To evaluate and compare the proportion of patients with molecular remission [minimal residual disease (MRD) negative] in each study arm
- To determine and compare, overall survival in each study arm
- To evaluate and compare the safety profile of patients treated with GClb, RClb and Clb alone
- To characterize the pharmacokinetics of RO5072759 in combination with Clb
- To evaluate the relationship between various baseline markers and clinical outcome parameters in patients from all arms of the study.
- To analyze pharmacoeconomics (medical resource utilization) in all arms of the study

- To assess patient-reported outcomes in all arms of the study

Trial Population:
Inclusion criteria:

1. Documented CD20+ B-CLL (NCI criteria).
2. Previously untreated CLL requiring treatment (NCI criteria).
3. Total Cumulative Illness Rating Scale (CIRS) > 6 or creatinine clearance <70 ml/min or both.
4. Absolute neutrophil count (ANC) ≥1.5 x 10^9/L and platelets ≥ 75 x 10^9/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].
5. Age 18 years or older.
6. Life expectancy > 6 months.
7. Able and willing to provide written informed consent and to comply with the protocol procedures.

Exclusion criteria:

1. Patients who have received previous CLL therapy.
2. Transformation of CLL to aggressive NHL (Richter's transformation).
3. 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.
4. Inadequate renal function: Creatinine clearance < 30 ml/min
5. Inadequate liver function: NCICTC Grade 3 liver function tests (AST, ALT >5 x ULN for >2 weeks; bilirubin >3 x ULN) unless due to underlying disease.
6. History of other malignancy which could affect compliance with the protocol or interpretation of results. Patients with a history of malignancy that has been treated but not with curative intent, were to be excluded, unless the malignancy has been in remission without treatment for ≥ 2 years prior to enrollment. 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.
7. Patients with active bacterial, viral, or fungal infection requiring systemic treatment.
8. Patients with known infection with human immunodeficiency virus (HIV) or Human T Cell Leukemia Virus 1 (HTLV-1).
9. 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.
10. History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies. Known sensitivity or allergy to murine products.
11. Hypersensitivity to Clb or to any of the excipients.
12. Women who are pregnant or lactating.

13. Fertile men or women of childbearing potential unless:
    - surgically sterile or ≥2 years after the onset of menopause
    - willing to use a highly effective contraceptive 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.
14. Vaccination with a live vaccine a minimum of 28 days prior to randomization.

Patients with Total Cumulative Illness Rating Scale (CIRS) > 6 or creatinine clearance <70 ml/min or both were eligible for this trial. The CIRS index uses a scoring system that includes 14 body system domains and severity scale (0-4) for each domain. The applicant used the CIRS to quantify the number and the severity of coexisting medical conditions and to allow a separate cumulative evaluation of each organ specific system. Their rationale for selecting a CIRS cutoff of 6 was because a CIRS score of 6 or higher was reached in the presence of multiple comorbidities in a sample of older cancer patients in two trials (by Extermann et al. and Chen et al) and was considered a suitable risk discriminator in CLL patients in this trial. Also, glomerular filtration rate could be a possible surrogate for decline in functional organ reserve (which can be estimated by creatinine clearance). However, CIRS has not been validated for use in CLL or in other cancer setting.

Treatment:
Obinutuzumab: Patients (including the 6 safety-run patients) that were randomized to the GClb treatment arm were to receive obinutuzumab 1000 mg by intravenous (IV) infusion on Day 1, Day 8 and Day 15 of the first treatment cycle (Cycle 1). At each subsequent cycle, patients were to receive obinutuzumab 1000 mg by IV infusion on Day 1 only (Cycles 2 to 6).

Rituximab: Patients randomized to the RClb treatment arm were to receive rituximab 375 mg/m^2 by IV infusion on Day 1 of the first treatment cycle (Cycle 1). At each subsequent cycle, patients were to receive rituximab 500 mg/m^2 mg by I.V. infusion on Day 1 (Cycles 2 to 6).

Chlorambucil: All patients were to receive oral chlorambucil 0.5 mg/kg body weight on Day 1 and Day 15 of all treatment cycles (Cycle 1 to 6). In patients with a Body Mass Index (BMI) >35, the dose were capped to a BMI dose of 35. The recommended chlorambucil dose in the US prescribing information is 0.1 to 0.2 mg/kg body weight daily for 3 to 6 weeks as required or alternatively, intermittent, biweekly, or once-monthly pulse doses of an initial single dose of 0.4 mg/kg to be increased by 0.1 mg/kg until control of lymphocytosis or toxicity.

The dose of 0.5 mg/kg chosen for chlorambucil was based on the findings from the German GCLLSG CLL5 trial. In this trial, a total of 193 patients with a median age of 70 years were randomized to receive fludarabine (25 mg/m^2 for 5 days intravenously, every 28 days, for 6 courses) or chlorambucil (0.4 mg/kg body weight with an increase to 0.8 mg/kg, every 15 days, for 12 months). The ORR and CR were higher in the fludarabine arm (72% vs. 51%, p=0.003 and 7% vs. 0%, p=0.011). However, there was no difference in PFS (fludarabine: 19 months, chlorambucil: 18 months) and fludarabine did not increase the overall survival time

(fludarabine: 46 months, clorambucil: 64 months, p=0.15). In this trial, the median administered chlorambucil dose was 0.5 mg/kg body weight. The maximum chlorambucil dose of 0.8 mg/kg was administered in 20% of the patients and 23% received 12 months of treatment (with median duration of treatment of 6.5 months in the chlorambucil arm).

The table below shows the grading scale used for hematological toxicity for dose modification decisions for patients with cytopenia at baseline.

Table 9 Grading Scale for CLL

Decrease in platelets or Hb from pre-treatment (%)	**Grades**	**ANC (mcL)**
No change to 10%	0	≥ 2000
11%-24%	1	≥ 1500 and <2000
25%-49%	2	≥ 1000 and <1500
50%-74%	3	≥ 500 and <1000
≥ 75%	4	<500

Dose modification of obinutuzumab and rituximab were not allowed. Dose reductions for chlorambucil were allowed and once reduced the dose could not be re-escalated. For chlorambucil, treatment delay of up to 4 weeks for the next cycle Day 1 was permitted to allow recovery of hematologic toxicities to ≤ grade 2 or non-hematologic toxicities to grade 1 or baseline. Chlorambucil was to be discontinued for treatment delay for more than 4 weeks due to toxicity. However, at the discretion of the investigator, the administration of obinutuzumab or rituximab could continue when the toxicity had improved. The patient was to be withdrawn from the trial with the discontinuation of obinutuzumab or rituximab. At the discretion of the investigator, to enable resolution of unrelated adverse events, concurrent diseases or recovery from surgical procedures, treatment could continue when treatment were delayed for longer than 4 weeks for all three treatments.

The table below shows the guidelines for dose delay (Clb and obinutuzumab or rituximab) and dose reduction (Clb only) due to grade 3 or 4 cytopenia.

Table 10 Dose Modification due to Cytopenia

	Chlorambucil	RO5072759 or rituximab
Grade 3 or 4 cytopenia#	Delay dosing for a maximum of 4 weeks Administer G-CSF for neutropenia or platelets or red blood cells as required. First episode: If improvement to ≤ Grade 2*, decrease Clb dose to 75% of initial dose for subsequent cycles Second episode: If improvement to ≤ Grade 2*, decrease Clb dose to 50% of initial dose for subsequent cycles Third episode: Discontinue Clb	If improvement to ≤ Grade 2*, administer full dose If Clb is discontinued RO5072759 or rituximab may continue at the investigator discretion.
Grade 1 or 2 cytopenia#	No dose reduction or delay	No dose reduction or delay

In patients with cytopenia at baseline, dose modifications will be based on the NCI grading scale for haematological toxicity in CLL studies (see Table 7)
*or baseline
Source: Protocol BO21004/CLL11, page 75

When there was evidence of clinically significant hemolytic anemia secondary to chlorambucil, study treatments were to be withdrawn.

Criteria for permanently discontinuing study treatment were as follows:

- Grade 4 infusion related symptom
- Grade 3 infusion related symptom at re-challenge.
- Grade 3 or 4 cytopenia that has not resolved to ≤ grade 2 and delays treatment of the next cycle day 1 dose by 4 weeks
- Grade ≥ 2 non-cytopenic toxicity that does not resolve to ≤ grade 1 or baseline and delays treatment of the next cycle day 1 dose by 4 weeks.

The criteria for re-starting study treatment were as follows:

- No active infection present
- Grade 3 or 4 cytopenia has resolved to ≤ grade 2 (or baseline if ANC $<1.5x10^9$/L, or platelet count <75 $x10^9$/L at study entry)
- Non-hematologic toxicity has resolved to ≤ grade 1 or baseline.

Patients were to be pre-medicated for infusion related reactions (IRR) and tumor lysis syndrome (TLS).

Pre-medications:
As hypotension may occur as a result of an IRR, consideration was given to withholding anti-hypertensive medications for 12 hours prior to rituximab infusion. For obinutuzumab, anti-hypertensive drugs used to control underlying hypertension were not to be given on the morning of, and throughout the first infusion. However, anti-hypertensive treatment could still be used to treat IRR-triggered hypertension, if required.

To prevent hypersensitivity or other IRRs to obinutuzumab or rituximab, premedication with oral acetaminophen/paracetamol (650-1000 mg) and anti-histamine such as diphenhydramine (50-100 mg) were to be administered approximately 30 minutes prior to the start of the first infusion (unless contraindicated). Premedication were to be administered before each infusion of rituximab. Premedication with oral acetaminophen/paracetamol was to be given for subsequent obinutuzumab infusions. However, if the previously administered obinutuzumab infusion did not result in an IRR > grade 1 (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 prednisolone or prednisone 100 mg i.v. at least one hour prior to the first obinutuzumab and rituximab infusion was mandatory. An equivalent dose of dexamethasone (20 mg) or methylprednisolone (80 mg) was permitted but hydrocortisone was not recommended. Corticosteroid premedication was to be given for subsequent infusions to:

- patients who experienced a grade 3 IRR with the previous infusion
- patients with lymphocyte counts >25 $x10^9$/L
- at investigator discretion.

Patients with a high tumor burden (WBC ≥ 25 $x10^9$/L or bulky lymphadenopathy) were to receive prophylaxis for tumor lysis syndrome (TLS) prior to the initiation of treatment. Before the first dose of obinutuzumab or rituximab, it was recommended to maintain a fluid intake of approximately 3 liters per day, 1-2 days. Patients with high tumor burden were to be treated with allopurinol or an alternative treatment starting 12-24 hours prior to the first infusion. Patients were to continue to receive repeated prophylaxis with allopurinol and adequate hydration prior to each subsequent infusion, if deemed appropriate by the investigator.

Obinutuzumab infusion:
Obinutuzumab had to be administered with full emergency resuscitation facilities immediately available and under close supervision of the investigator at all times. The first infusion of obinutuzumab was split between Day 1 and Day 2.

After protocol amendment G, on Day 1, all patients received a fixed dose of 100 mg at a fixed rate of 25 mg/hr with no increase in the infusion rate (total duration of 4 hours). For IRR, medications (including epinephrine for subcutaneous injections, corticosteroids, diphenhydramine for i.v. injection) and resuscitation equipment were to be available for immediate use. Upon complete resolution of IRR symptoms, the obinutuzumab infusion could be restarted at half initial rate (12.5 mg/hour) and increased to 25 mg/hour after an hour but not increased further. On Day 2, all patients were to receive 900 mg starting at the rate of 50 mg/hr. The rate of the infusion was to be escalated in increments of 50 mg/hr every 30-minutes to a maximum rate of 400 mg/hr. After protocol amendment version G was implemented, 45 patients included in stage 1a were enrolled.

If the first obinutuzumab infusion (on Day 1 and Day 2) was well tolerated (defined by an absence of IRRs during a final infusion rate of ≥100 mg/hr), subsequent infusions were to be

administered at an initial rate of 100 mg/hr and increased by 100 mg/hr increments at 30 minute intervals, as tolerated, to a maximum rate of 400 mg/hr.

The obinutuzumab infusions were to be temporarily interrupted or slowed down if a hypersensitivity or IRR developed and concomitant medication administered if deemed appropriate by the investigator. Upon resolution of symptoms, the infusion was to be resumed at one-half the previous rate (the rate being used at the time that the hypersensitivity or infusion-related reaction occurred). In the absence of infusion-related symptoms, the rate of infusion could be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr.

If the patient experienced a life-threatening IRR (which may include pulmonary and cardiac events) or IgE-mediated anaphylactic reaction, obinutuzumab (or rituximab) were to be discontinued. Patients who experienced any of these reactions were to receive aggressive symptomatic treatment and were to be discontinued from study treatment. The table below shows the management guideline used for IRRs.

Table 11 Management of Infusion-related Symptoms (obinutuzumab or rituximab)

Infusion-Related Symptoms	Guidance
Grade 1-2	• Slow or hold infusion • Give supportive treatment • Upon symptom resolution, may resume infusion rate escalation, at investigator discretion
Grade 3	• Discontinue infusion • Give supportive treatment • Upon symptom resolution, may resume infusion rate escalation, at investigator discretion • If same adverse event recurs with same severity, treatment must be permanently discontinued.
Grade 4	• Discontinue infusion immediately, treat symptoms aggressively, and do not restart drug

Supportive Treatment: administer acetaminophen/paracetamol and an antihistamine such as diphenhydramine if not received in the last 4 hours. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, patients may require antihistamines, oxygen, corticosteroids (e.g., 100 mg i.v. prednisolone or equivalent), and/or bronchodilators. For hypotension, patients may require vasopressors.
Source: protocol BO21004/CLL11, page 89

The following was reported regarding IRR:
"Commonly experienced IRRs reported to date were characterized by hypotension, fever, chills, flushing, nausea, vomiting, hypertension, and fatigue, among other symptoms. Respiratory infusion-related symptoms such as hypoxia, dyspnea, bronchospasm, larynx and throat irritation, and laryngeal edema have also been reported. IRRs occurred during the infusion (predominantly during the first hour of the infusion) or shortly after the first infusion had finished.

Their incidence and severity decreased with subsequent infusions. Cases of tumor flare have also been reported with GA101. The CLL11 (BO21004) Data Safety Monitoring Board (DSMB)

identified risk factors associated with an increased risk of severe IRRs with the first GA101 infusion. This review confirmed that patients with high tumor burden may be at increased risk of severe IRRs. Listed below are the specific patient characteristics that were identified by the DSMB as potential risk factors for developing IRRs with GA101:

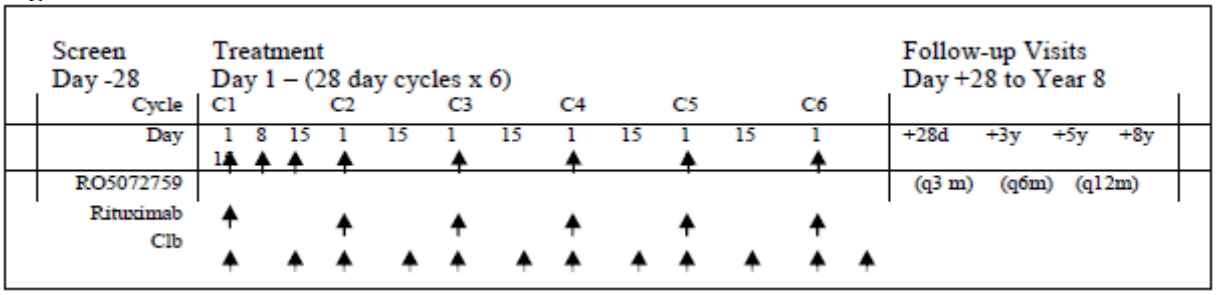
- High tumor burden (circulating lymphocyte count >100 $x10^9$/L)
- Binet stage C CLL at screening (Rai III/IV)
- Low body mass index (BMI <20)
- Hypertension necessitating anti-hypertensive treatment."

For patients with evidence of TLS, obinutuzumab or rituximab were to be discontinued and the patient treated as clinically indicated. Following complete resolution of TLS complications, obinutuzumab or rituximab could be re-administered at the full dose during the next infusion in conjunction with prophylactic therapy.

Prohibited treatments were investigational or unlicensed/unapproved agents, immunotherapy/radio-immunotherapy, chemotherapy and radiotherapy. Treatment with systemic corticosteroids other than intermittent use to control or prevent infusion reactions and initially to treat auto-immune hemolytic anemia (AIHA) was prohibited (also the dose of steroids to treat AIHA had to be reduced gradually once the study treatment started). Non-steroidal hormones administered for non-lymphoma-related conditions (e.g., insulin for diabetes) were allowed.

Patients were to receive a maximum of 6 cycles of study treatment (1 cycle= 28 days). Crossover patients could receive an additional 6 cycles of treatment. After the last treatment, patients were to be followed until disease progression, next leukemia treatment and survival. The figure below summarizes the trial schema.

Figure 2 BO21004/CLL11: Trial Schema



Source: Protocol BO21004, page 50

Schedule of Events:
All patients were to be followed up 28 days after their last dose of trial treatment. The next follow-up visit occurred 3 months after the end of treatment and then every 3 months until 3 years from last treatment. Further follow-up visits were planned to occur every 6 months until 5 years from date of randomization of the last patient entering the trial and then, annually for 8 years after last patient entered the trial. Response was followed at all visits by clinical/laboratory

signs and symptoms until progression was identified. A CT scan was performed in patients who had achieved a CR or PR two to three months after end of treatment.

In those patients who had achieved a CR (or cytopenic CR), a bone marrow aspirate and biopsy was obtained. CT imaging was not be used to determine PD. Only when PD was detected by physical examination in the absence of any objective hematological progression, a CT scan of the involved nodes was performed. The DSMB also evaluated the interim efficacy analyses according to the schedule outlined in the statistical analysis plan.

Table 12 Schedule of Events (Treatment Period)

	Screening	Treatment Period Visits											
		Cycle 1			Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6	
Assessment	Day -28 to −1	D1	D8	D15	D1	15	D1	15	D1	D15	D1	D15	D1	D15
Informed consent	x													
Demographics	x													
Medical History including CIRS score and IADL	x													
Physical Examination(Height /Weight)	x	x							x					
Liver/Spleen (by Physical Exam)	x								x					
Vital Signs	x	x	x		x		x		x		x		x	
ECG 12 lead	x	As clinically indicated												
ECOG – Performance status	x	x	x		x		x		x		x		x	
B symptoms	x	x	x		x		x		x		x		x	
Lymphadenopathy (during Physical Exam)	x								x					
Staging (Binet)	x													
CT scan assessment (or MRI only if contrast enhanced CT not possible)	x													
Bone Marrow – data will be collected only if a sample was collected as part of clinical work-up or if BM is done due to cytopenia	x													
Viral screen – HBV, HCV	x													
Minimal Residual Disease – blood	x#								x					
Serum Pregnancy test (if req)	x													
Coombs test	x													
Hematology/blood chemistry	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Coagulation (aPTT, PT, INR)	x													
Serum Parameters - β-2 microglobulin, Thymidine Kinase	x#													
Creatinine Clearance (Cockcroft and Gault)	x													
Immunoglobulin (IgA, IgG, IgM)		x												
IgV_H mutation status + VH3-21, Cytogenetic aberrations (FISH), P53 alteration	x#													
Lymphocyte immunophenotyping for diagnosis,	x													
ZAP70 expression and CD38 expression	x#													
Lymphocyte immunophenotyping for safety (all patients enrolled prior to 1st 50 patient DSMB safety review)					x		x		x		x		x	
Clinical Genotyping	x#													

	Screening	Treatment Period Visits												
		Cycle 1			Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6	
Assessment	Day -28 to -1	D1	D8	D15	D1	15	D1	15	D1	D15	D1	D15	D1	D15
Metaphase Cytogenetics in subset of 200 patients entered in GCLLSG sites	x#													
Pharmacokinetics (pre and post infusion sample in all GClb pts)		x			x		x		x		x		x	
Additional Pksampling			x	x										
HAHA (GClb patients only)									x					
RCR (Non-DNA) Whole blood (RNA) pre-infusion in all patients. Post infusion (GClb and RClb only and if shipment possible within 48h) Serum (proteomic) pre-infusion in all patients. Post infusion (GClb and RClb only)		x												
RCR (DNA) – Whole blood pre-infusion in all patients	x#													
Drug Administration														
Chlorambucil		x		x	x	x	x	x	x	x	x	x	x	x
Rituximab		x			x		x		x		x		x	
RO5072759		x+ D2	x	x	x		x		x		x		x	
Adverse Events	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Serious AE's and grade 3 and 4 Infections	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Patient reported outcome questionnaire (EORTC)	x#								x					
Response assessment									x					
Follow-up for disease progression									x					

Source: Protocol BO21004, page 51-53.

Table 13 Schedule of Events (Treatment-free Follow-up)

	All patients	Follow-up Visits Duration from last study drug administration until PD				Survival (All Patients)
Assessment	+28 days after last study drug	+3 * month End of treatment response	+ 6m, +9m, +12m from last treatment	Every 3m until 3 years from last treatment	Every 6 m until 5 years from last patient enrolled	Every year until 8 years from last patient enrolled
Physical Examination (Weight)	x	x	x	x	x	
Liver/Spleen (during PE)	x	x	x	x	x	
Vital Signs/Cardio pulmonary exam	x	x	x	x	x	
ECOG – Performance status	x	x	x	x	x	
B symptoms	x	x	x	x	x	
Lymphadenopathy (by Phys. Exam)	x	x	x	x	x	
CT scan assessment (or MRI if performed at screening)		X (CR/PR pts only)				
CT scan of involved nodes at time of PD if PD determined by physical examination alone	x	x	x	x	x	
Bone Marrow Aspirate (MRD) and Biopsy (confirmation of response)		x (if CR / cytopenic CR)*				
Minimal Residual Disease – Blood	x	x	x(just 6 &12m)			
Hematology/blood chemistry	x	x	x	x	x	
Urinalysis (6, 12, **18, 24 month** only)			x	x		
Lymphocyte immunophenotyping B-cell recovery -12, 18, 24 months and then 6 monthly until recovery.		x	x	x		
Immunoglobulin (IgA, IgG, IgM)	x	x	x			
HAHA (all GClb patients only) and Additional PK in 30 GClb patients	x	x	x			
Cytogenetic aberrations (FISH), P53 alteration	x (only if PD	x (only if PD)	x (only if PD)	x (only if PD)	x (only if PD)	
RCR (Non-DNA) Whole blood (RNA) Serum (proteomic) GClb and RClb only and if shipment possible within 24 h	x (only if PD)	x (only if PD)	x (only if PD)	x (only if PD)	x (only if PD)	
RCR (DNA) whole blood	x (only if PD)	x (only if PD)	x (only if PD)	x (only if PD)	x (only if PD)	
Adverse Events	x					

	All patients	Follow-up Visits Duration from last study drug administration until PD				Survival (All Patients)
Assessment	+28 days after last study drug	+3 * month End of treatment response	+ 6m, +9m, +12m from last treatment	Every 3m until 3 years from last treatment	Every 6 m until 5 years from last patient enrolled	Every year until 8 years from last patient enrolled
Unrelated Serious AE's	x	x	x			
Grade 3 and 4 Infections (until 2 years)	x	x	x	x		
Related SAEs and secondary malignancies indefinitely	x	x	x	x	x	x
Concomitant medications	x					
Response assessment	x	x	x			
Follow-up for disease progression/disease transformation	x	x	x	x	x	
After PD continue to Follow-up for next anti-leukemia treatment (NLT)	x	x	x	x	x	
PRO questionnaire (EORTC) until NLT^	x	x	x	x	x	
After PD and NLT follow all patients annually for Survival (and progression if it has not already occurred)	x	x	x	x	x	x

*Visit to have occurred no earlier than 2 and no later than 3 months after end of treatment. If the patient is in CR following the CT scan a bone marrow examination were to be performed a minimum of 3 months after the end of treatment. Source: Protocol BO21004, page 54-55.

An interim staging assessment was to be performed after 3 cycles of treatment. This included an assessment of hematological status and a full physical examination to assess any lymphadenopathy and hepato/splenomegaly. Patients that had a CR by laboratory and physical examination, a bone marrow aspirate and biopsy were to be performed no earlier than 3 months after end of treatment.

5.3.1.2 Clinical trial landmarks and protocol amendments

The clinical trial landmarks and protocol amendments are summarized below.

Table 14 Trial BO21004/CLL11 Landmarks and Protocol Amendments

Date	Trial BO21004/CLL11 Landmark
July 16, 2009	Initial protocol
August 24, 2009	Amendment 1 (version B)
November 20, 2009	Amendment 2 (version C)
December 21, 2009	First patient enrollment into the safety run-in
January 25, 2010	Amendment 3 (version D) • Modified the exclusion criteria to prevent patients who were recently vaccinated with live virus from entering the study. • Modified entry criteria so that patients with the following could participate in the study: - positive HCV serology but who are RNA negative, also - certain malignancies with good prognosis - autoimmune hemolytic anemia • Amended inconsistencies in the definition of partial response. • Clarified laboratory processes. • Updated information to warnings and precautions section because of new safety information providing recommendations for the monitoring of HBV reactivation. • Revised the frequency of the DSMB review of safety data from 3-monthly to monthly (until 50 patients had been randomized). • In response to feedback from investigators, various changes to study drug administration were made including the dose of chlorambucil was capped at a maximum dose associated with a body mass index of 35, antibiotic prophylaxis was strongly recommended. • Secondary malignancies were to be reported irrespective of time elapsed since study completion.
April 12, 2010	First patient enrollment into stage 1
November 26, 2010	Amendment 4 (version E) • The DSMB recommendation to define a clear and consistent cutoff for high circulating lymphocyte count (>25 x 10^9/L) was implemented and it was recommended that all patients above this level received corticosteroids as premedication. • Patients with HBV DNA were to be followed at monthly intervals for

	12 months (instead of 3-monthly intervals for 6 months). • Clarified events that required permanent discontinuation of study therapy. • Some clarifications were made to the response section to avoid ambiguity and also the IRC section was aligned with the IRC charter. • Refinement of the CIRS eligibility criteria. • Clarification of lab procedures and study assessments.
June 13, 2011	Amendment 5 (version F) • Premedication requirements were modified to include corticosteroids for all patients during the first infusion to reduce the risk of IRRs. • The duration of follow up for B-cell recovery and monitoring of infection was extended to 2 years after the end of treatment. • Clarified that not all NCI CTC Grade 4 laboratory parameters are considered serious adverse events since they are not always considered 'life-threatening – at immediate risk of death". • Clarified dose modification criteria.
December 9, 2011	Amendment 6 (version G) • To reduce the risk 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) and hypertensive drugs were not to be given on the morning of and throughout infusion. • Two additional urinalysis samples were added to obtain long term information on proteinuria.
January 24, 2012	Last patient enrollment into stage 1
July 4, 20012	Last patient enrollment into stage 2 (total of 781 patients excluding the 6 run-in patient)
July 11, 2012	Data cutoff for Stage 1a primary analysis
August 10, 2012	Data cutoff for Stage 1b primary analysis
September 20, 2012	Amendment 7 (version H) • Clarified Stage 1a and Stage 1b data release. • Use the stored plasma sample obtained at baseline for the obinutuzumab PK analysis to determine human antibody to humanized antibody (HAHA) at baseline.
October 11, 2012	Database lock date

5.3.1.3 Statistics

Endpoints:
Primary efficacy endpoint was PFS based on investigator's assessment. However, the regulatory decision was to be based on IRC-assessed PFS. Response was according to the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) guidelines.

The primary objective was to compare PFS of the following:

- GClb vs. Clb alone
- GClb vs. RClb
- RClb vs. Clb alone.

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 three groups was rejected, pairwise tests for each of the three hypotheses (i.e., GClb versus Clb alone, GClb versus RClb, and RClb versus Clb alone) were to be enabled at the 5% alpha level. Treatment comparison was to be based on PFS using a two-sided stratified (by Binet stage) log-rank test.

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 were to be censored at the time of the last tumor assessment, or if no tumor assessments were performed after the baseline visit, at the time of randomization plus one day.

Sensitivity analyses for PFS were as follows:

- The impact of patients starting a new anti-leukemic treatment without showing signs of progression was to be assessed by censoring these patients at the start date of the new anti-leukemic treatment. Stopping only one component of the randomized study treatment was not considered as a reason for censoring patients.
- Although there is no reason to believe study investigators will be biased in favor of the GClb or RClb treatment arm when assessing disease progression, an analysis were to be conducted to assess the potential investigator bias on PFS in this trial. For this analysis measurements from the IRC will be used.
- The impact of late death cases were to be assessed for the analysis of PFS based on investigator's as well as IRC assessment. Patients who died more than 6 months after last treatment and showed no sign of progression were to be censored at the last available tumor assessment.

Secondary efficacy endpoints were as follows:

- End of treatment response
- Best overall response
- Molecular Remission (Minimal Residual Disease negative)
- Event-free survival (EFS)
- Duration of response
- Disease-free survival
- Time to re-treatment/new anti-leukemic therapy
- Overall survival

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 to be censored at the date of last tumor assessment. In case no tumor assessment was available, patients were to be censored at the date of randomization plus one day.

Disease-free survival was defined for all patients with complete response at any time from 56 days after end of treatment onward. Complete response was defined from the date the complete response was first recorded to the date on which progressive disease was first noted or the date of death due to any cause. Patients with no documented progression after CR/CR with incomplete blood count recovery (CRi) were to be censored at the last date at which they are known to have been in CR/CRi.

Duration of response was defined similarly for complete and partial responders. Response started at the date the response (either complete or partial) was first recorded to the date on which progressive disease was first noted or the date of death due to any cause. Only assessments from 56 days after end of treatment onwards were to be taken into account.

Partial response was defined from the first date of partial response to the date of the first observation of progressive disease or the date of death due to any cause. Patients with no documented progression after CR/CRi or PR were to be censored at the last date at which they are known to have had the CR/CRi or PR.

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

Overall survival 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 to be censored at the date when they were last known to be alive as documented by the investigator.

End of treatment response was defined as the response occurring at the end of treatment [first assessment that occurred more than 56 days (approximately 8 weeks) after the end of treatment] before start of new anti-leukemia treatment. If the only response assessment after treatment end was PD, it were to be included irrespectively of when it occurred (i.e., even if it earlier than 56 days after the end of treatment). Overall response rate for end of treatment response (end of treatment response rate) was defined as percentage of patients with CR, incomplete CR (CRi), nodular partial response (nPR), or PR as 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 to be considered non-responders for end of treatment response. However, if at any time the only response assessment to be reported for a patient is PD, it was to be 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) was 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 to be 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.

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

Patients who crossed over from Clb to the GClb treatment after clear documented disease progression were to be handled in all time-to-event analyses like patients who started second line therapy on the RClb or GClb arm.

Best overall response rates and end of treatment response rates were to be compared using a chi-square test. The 95% confidence limits for the difference were to be calculated using Anderson-Hauck. Response rates and 95% confidence limits were to be according to Pearson-Clopper.

Patient reported outcomes: Health-related quality of life assessments were to be used to derive pre-specified global and domain scores according to the EORTC QLQC30 and CLL-16 module scoring manuals. (b) (4)

Analyses:
Efficacy analysis:
The primary efficacy analysis was based on the intent-to-treat (ITT) population defined as all randomized patients, regardless of whether the patient received treatment. Patients were assigned to treatment groups as randomized. All efficacy analyses were to be performed using the ITT population.

Per-protocol population was to be used for sensitivity analysis of PFS. The per-protocol population was defined as all patients who have completed study treatment (defined as having received at least three complete cycles of study therapy) unless progressed or died before and all patients who fulfilled the inclusion criteria with no major protocol violations. Patients were assigned to treatment groups as treated. The purpose of the per-protocol analysis was to assess the robustness of the primary analysis (based on the intent-to-treat population).

The following patient populations were to be used for analysis:

- Stage 1: Patients randomized to all three treatment groups (approximately 590 patients) which were to be used for the global test (of any difference between any of the three treatment groups). For all comparisons of GClb and RClb against Clb, only stage 1 patients were to be used.

- Stage 1 + 2: Patients randomized at any time during the trial (approximately 780 patients) which were to be used for the stage 2 analyses of comparison of GClb versus RClb.

Interim analysis:
There were two interim analyses (first one for efficacy/futility at the end of Stage 1a and a second one during the conduct of stage 2 for efficacy of GClb vs. RClb) scheduled and to be conducted by a statistician of the DSMB.

Sample size:
The sample size of 780 patients (118 patients for the Clb arm and 331 patients for each of the GClb and RClb arms) was determined using the primary endpoint of investigator-assessed PFS. The assumed hazard ratio (HR) of GClb vs. Clb alone was 0.44. The statistical assumptions of GClb vs. RClb were based on an alpha of 5% (two-sided test level, for the entire closed-test procedure), power of 80% and a dropout rate of 10% per year.

6 Review of Efficacy

Efficacy Summary

Trial BO21004 was conducted at 155 centers in 24 countries. In stage 1a of the trial, a total of 356 patients were randomized to Clb (n=118) and GClb (n=238). Randomization was stratified by Binet stage and region. The primary endpoint was PFS based on investigator's assessment. However, for regulatory decision the primary endpoint of PFS was to be based on IRC. Secondary endpoints included end of treatment response, best overall response, event free survival, duration of response, disease free survival, time to new anti-leukemic therapy and overall survival.

At the clinical cutoff on July 11, 2012 the median observation time was 14.2 months and median exposure to the study medications was 6 cycles. The efficacy results were as follows:

- The IRC assessed median PFS was 11.1 months in the Clb arm versus 23.0 months in the GClb arm. The hazard ratio was 0.16 (95% CI: 0.11, 0.24), log-rank p-value <0.0001. At one year, 36% of patients in the Clb arm and 83% of patients in the GClb arm were progression free.

- Investigator assessed median PFS was 10.9 months in the Clb arm versus 23.0 months in the GClb arm. The hazard ratio was 0.14 (95% CI: 0.09, 0.21), log-rank p-value <0.0001.

- All pre-specified sensitivity analyses for PFS were supportive of the primary analysis with hazard ratios (HRs) ranging from 0.12 to 0.26.

- Subgroup analyses of PFS by investigator were in general consistent with the ITT population. The HRs ranged from 0.03 to 0.42.

- Secondary endpoints were also supportive of the primary endpoint. However, there was no multiplicity adjustment plan for these endpoints.

Table 15 BO21004/CLL11: Summary of Efficacy Results

	Clb	GClb
Primary endpoint		
Median PFS by IRC (months)	11.1	23.0
Hazard ratio, p-value	0.16 (0.11, 0.24), <0.0001	
Median PFS by investigator (months)	10.9	23.0
Hazard ratio, p-value	0.14 (0.09, 0.21), <0.0001	
Secondary endpoints		
Best overall response	34 (32.1%)	161 (75.9%)
Complete response	1 (0.9%)	59 (27.8%)
Partial response	33 (31.1)	102 (48.1%)
Median event free survival (months)	10.6	23.0
Hazard ratio, p-value	0.18 (0.13, 0.26), <0.0001	
Median duration of response (months)	3.5	15.2
Hazard ratio, p-value	0.1 (0.05, 0.2), <0.0001	
Time to new anti-leukemic treatment (months)	14.8	-
Hazard ratio, 95% CI	0.26 (0.16, 0.42)	
P-value (log-rank test)	<0.0001	

Overall survival data was not yet mature at the clinical cutoff.

The improvement of PFS for patients who received treatment with GClb was both statistically robust and clinically meaningful. The primary endpoint results of PFS demonstrate the efficacy of GClb in patients with CLL who have not received prior therapy for their disease.

6.1 Indication

The applicant's proposed indication is obinutuzumab in combination with chlorambucil for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL).

6.1.1 Methods

The efficacy review was concentrated on the stage 1a data of the BO21004/CLL11 trial and included the review of the following items:

- Clinical study report
- Protocol and statistical analysis plan
- Raw and derived datasets
- Case report forms
- Response to information requests

- Proposed labeling

6.1.2 Demographics

Trial BO21004/CLL11 randomized 781 patients (excluding the 6 run-in patients) from 155 centers in 24 countries. Among the 781 patients, 589 patients were included in stage 1 and 356 patients in stage1a (GClb arm: 238 patients, Clb arm: 118 patients). This review focuses on stage 1a. The table below shows the primary efficacy analysis population (ITT) enrolled in stage 1.

Table 16 BO21004/CLL11: Patient Enrollment in Stage 1 (ITT)

	Stage 1	
	Stage 1a	**Stage 1b**
GClb	238	
Clb	118	
RClb		233
Total	589	

In stage 1a, the highest numbers of enrolled patients were from Germany (18%), Spain (14%), Russian Federation (13%) and France (10%). Only one patient was enrolled in the US site. At randomization, patients were stratified by country/region. The table below shows patient enrollment by country.

Table 17 BO21004, Stage 1a: Patient Enrollment by Country (ITT Population)

	Clb (n=118)	**GClb (n=238)**	**Total (n=356)**
Germany	24	41	65 (18%)
Spain	18	33	51 (14%)
Russian Federation	16	29	45 (13%)
France	12	25	37 (10%)
Italy	7	16	23 (6%)
United Kingdom	6	11	17 (5%)
Austria	5	12	17 (5%)
Australia	2	11	13 (4%)
Czech Republic	3	8	11 (3%)
Canada	3	8	11 (3%)
Bulgaria	2	9	11 (3%)
Romania	4	6	10 (3%)
Others (<10 patients each)	16	29	45 (13%)

In general, patient demographics were well balanced between the treatment arms. The median age was 73 years (range 39 to 88) and both arms contained more males than females. Ninety-five percent of all patients were Caucasian and 89% had a baseline ECOG performance status of 0 or 1. The table below shows the patient demographics in stage 1a by treatment group in the ITT population.

Table 18 BO21004, Stage 1a: Patient Demographics (ITT Population)

	Clb (n=118)	GClb (n=238)	Total (n=356)
Gender			
Female	43 (36%)	98 (41%)	141 (40%)
Male	75 (64%)	140 (59%)	215 (60%)
Age (years)			
Median	72.0	74.0	73.0
Range	43-87	39-88	39-88
Age (by category, years)			
< 75	74 (63%)	131 (55%)	205 (58%)
≥ 75	44 (37%)	107 (45%)	151 (42%)
< 65	26 (22%)	42 (18%)	68 (19%)
≥ 65	92 (78%)	196 (82%)	288 (81%)
Race			
Caucasian	108 (92%)	229 (96%)	337 (95%)
Black	1 (<1%)	-	1 (<1%)
Asian	6 (5%)	4 (2%)	10 (3%)
Other	3 (3%)	5 (2%)	8 (2%)
Baseline ECOG score			
0 to 1	105 (89%)	211 (89%)	316 (89%)
2 to 4	13 (11%)	27 (11%)	40 (11%)

In general, key patient disease characteristics were balanced at baseline between the two treatment arms. Sixty-five percent of patients had a calculated creatinine clearance of < 70 mL/min and the estimated median creatinine clearance was 61 mL/min. The percentage of patients in Binet stage A, B and C were 22%, 42% and 36%, respectively. Disease characteristics that had a lower percentage of patients in the GClb arm included CIRS >6 only (Clb: 39%, GClb: 28%), number of < 4 involved organ system per patient (Clb: 21%, GClb: 14%), circulating lymphocyte count ≥ 25 $x10^9$ cells/L (Clb: 84%, GClb: 76%), circulating lymphocyte count ≥ 100 $x10^9$ cells/L (Clb: 37%, GClb: 24%), short lymphocyte doubling time of < 6 months (Clb: 43%, GClb: 38%) and β_2-microglobulin of ≥ 3.5 mg/L (Clb: 39%, GCLb: 32%).

According to the IWCLL 2008, newly diagnosed patients with asymptomatic early-stage disease (Binet A) should be monitored without therapy unless they have evidence of disease progression whereas patients at Binet stage B or C usually benefit from the initiation of treatment, some of these patients (Binet stage B) can be monitored without therapy until they have evidence for progressive or symptomatic disease. All patients in the ITT population fulfilled the criteria for initiating treatment including patients who were in the Binet stages A and B. There were 74 patients (62%) in Clb and 153 patients (64%) in GClb that were in Binet stage A or B. The criteria for initiating treatment for these patients included severe B symptoms (Clb: 47%, GClb: 46%), massive symptoms of lymphadenopathy/splenomegaly (45% in each treatment arm), lymphocyte doubling time < 6 months (Clb: 43%, GClb: 38%) and other reasons (Clb: 12%, GClb: 18%). An information request was sent to the applicant on July 16, 2013 to provide

reasons for initiating treatment for patients that had 'other reasons'. On July 19, 2013, the applicant provided a table with reasons for treatment initiation and responded as follows:

"Patients enrolled to the study needed to have CLL requiring treatment according to the NCI criteria (Hallek, M; Blood 2008). Investigators were instructed to complete 'reason for initiating treatment' during the screening process. A selection of pre-defined tick boxes were provided: 1) does the patient have symptomatic /massive lymphadenopathy 2) short lymphocyte doubling time, 3) severe B symptoms or 4) other. The 'other' text field was available for Investigators to add any reasons not included in the first 3 tick boxes. One patient may fulfill more than one criteria. Based on the clinical database, a total 36 patients (across both arms) initiated treatment for 'other' reasons (see table below). Out of the 36 that had 'other' in the clinical database, 21 also had at least one of the 3 other pre-defined reasons ticked. Of the 15 patients who did not fulfill any of the first 3 pre-defined criteria and only had the 'other' reason ticked, the reason was recorded in the text field in the screening form. In the majority of cases, one of the pre-defined tick boxes could have been completed rather than using the free text in the 'other' category. Six patients had 'other' in the clinical database, but did not have a reason recorded next to the 'other' field in the screening form. These patients all had at least 1 of the other 3 pre-defined reason ticked as present on the screening form. Based on these data, all 36 patients with 'other' selected as the reason to initiate treatment had valid reason to initiate treatment."

Table 19 BO21004, Stage 1a: Patient Baseline Disease Information (ITT Population)

	Clb (n=118)	GClb (n=238)	Total (n=356)
Time from diagnosis to randomization (years)			
Median (years)	2.75	2.5	2.6
Range (years)	0-22.9	0-22.9	0-22.9
n	118	237	355
Time from diagnosis to randomization (category)			
≤ 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 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
Reason for initiating treatment fulfilled?			
Yes	118 (100%)	238 (100%)	356 (100%)
n	118	238	356
Severe B symptoms?			
Yes	35 (47%)	71 (46%)	106 (46%)

No	39 (53%)	83 (54%)	122 (54%)
n	74	154	228
Massive/symptomatic lymphadenopathy/splenomegaly			
Yes	33 (45%)	70 (45%)	103 (45%)
No	41 (55%)	84 (55%)	125 (55%)
n	74	154	228
Short lymphocyte doubling time (<6 months)?			
Yes	32 (43%)	59 (38%)	91 (40%)
No	42 (57%)	94 (61%)	136 (60%)
Unknown	-	1 (<1%)	1 (<1%)
n	74	154	228
Other reason for treatment requirement?			
Yes	9 (12%)	27 (18%)	36 (16%)
No	65 (88%)	127 (82%)	192 (84%)
n	74	154	228
Estimated creatinine clearance			
Median (mL/min)	63.10	60.00	61.10
n	117	237	354
Calculated creatinine clearance			
Median	63.80	61.40	61.80
n	117	238	355
Calculated creatinine clearance I			
< 70 mL/min	71 (61%)	161 (68%)	232 (65%)
≥ 70 mL/min	46 (39%)	77 (32%)	123 (35%)
n	117	238	355
Calculated creatinine clearance II			
< 50 mL/min	25 (21%)	69 (29%)	94 (26%)
≥ 50 mL/min	92 (79%)	169 (71%)	261 (74%)
n	117	238	355
Circulating lymphocyte count at baseline I			
$< 25 \times 10^9$ cells/L	18 (16%)	58 (24%)	76 (22%)
$\geq 25 \times 10^9$ cells/L	98 (84%)	179 (76%)	277 (78%)
n	116	237	353
Circulating lymphocyte count at baseline II			
$< 100 \times 10^9$ cells/L	73 (63%)	179 (76%)	252 (71%)
$\geq 100 \times 10^9$ cells/L	43 (37%)	58 (24%)	101 (29%)
n	116	237	353
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
IgVH			
Unmutated	58 (59%)	129 (61%)	187 (61%)
Mutated	36 (36%)	76 (36%)	112 (36%)
n	99	210	309
ZAP-70 expression			
Positive	48 (49%)	83 (44%)	131 (46%)
negative	49 (51%)	106 (56%)	155 (54%)
n	97	189	286
β_2-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
Chromosomal abnormalities at baseline			
17P-	10 (10%)	16 (8%)	26 (9%)
11Q-	14 (15%)	33 (16%)	47 (16%)
+12	16 (17%)	33 (16%)	49 (16%)
13Q-	32 (33%)	58 (29%)	90 (30%)
Other abnormal	9 (9%)	15 (7%)	24 (8%)
Normal karyotype	15 (16%)	48 (24%)	63 (21%)
n	96	203	299
FC gamma receptor IIa			
131 HH	36 (33%)	60 (27%)	96 (29%)
131 HR	50 (46%)	105 (47%)	155 (47%)
131 RR	17 (16%)	42 (19%)	59 (18%)
Other	5 (5%)	15 (7%)	20 (6%)
n	108	222	330
FC gamma receptor IIIa			
158 FF	45 (42%)	95 (43%)	140 (42%)
158 FV	53 (49%)	102 (46%)	155 (47%)
158 VV	9 (8%)	16 (7%)	25 (8%)
Other	1 (<1%)	9 (4%)	10 (3%)
n	108	222	330

Percentages are based on n (number of valid values).

In BO21004, stage 1a, 46 patients (39%) in Clb and 113 patients (47%) in GClb had both a CIRS score >6 and creatinine clearance of < 70 mL/min. The most common comorbidity (by CIRS)

was in the hypertension organ system [Clb: 88 patients (75%), GClb: 168 patients (71%)]. The applicant claims that only the most severe disease in each of the 14 organ systems was captured therefore, it is likely that the comorbidity burden may have been underestimated in the population studied. However, CIRS has not been validated for use in CLL or in other cancer setting.

Table 20 BO21004, Stage1a: Cumulative Illness Rating Scale (ITT Population)

	Clb (n=118)	GClb (n=238)	Total (n=356)
Total CIRS score at baseline			
≤ 6	26 (22%)	59 (25%)	85 (24%)
>6	92 (78%)	179 (75%)	271 (76%)
Median	8.0	8.0	8.0
n	118	238	356
CIRS and creatinine clearance			
CIRS >6 only	46 (39%)	66 (28%)	112 (31%)
CIRS >6 and CrCl <70	46 (39%)	113 (47%)	159 (45%)
CrCl <70 only	25 (21%)	57 (24%)	82 (23%)
None	1 (<1%)	2 (<1%)	3 (<1%)
n	118	238	356
No. of organ system per patient			
Median	5.0	5.0	5.0
n	118	238	356
No. of organ system per patient (category)			
< 4	25 (21%)	34 (14%)	59 (17%)
4-8	90 (76%)	192 (81%)	282 (79%)
> 8	3 (3%)	12 (5%)	15 (4%)
n	118	238	356

With regard to baseline comorbidity, the applicant also presented data using the MedDRA coding. In general, the baseline comorbidity (by MedDRA) was balanced between the two treatment arms. The most frequent comorbidities (based on MedDRA) were Vascular Disorders (77%), Cardiac Disorders (48%), Gastrointestinal Disorders (44%), Metabolism and Nutrition Disorders (42%), Renal and Urinary Disorders (37%) and Musculoskeletal and Connective tissue disorders (31%).

Table 21 BO21004, Stage 1a: Baseline Comorbidities with Incidence Rate of ≥ 5% (HLGT) in Body Systems with Incidence Rate ≥ 30% (ITT population)

Body system High Level Group Term	Clb (n=118)	GClb (n=238)	Total (n=356)
Vascular disorders	91 (77%)	182 (76%)	273 (77%)
Vascular hypertensive disorders	82 (69%)	162 (68%)	244 (69%)
Arteriosclerosis, stenosis, vascular insufficiency and necrosis	6 (5%)	21 (9%)	27 (8%)
Venous varices	8 (7%)	18 (8%)	26 (7%)
Cardiac disorders	57 (48%)	115 (48%)	172 (48%)
Coronary artery disorders	29 (25%)	48 (20%)	77 (22%)
Cardiac arrhythmias	13 (11%)	32 (13%)	45 (13%)
Gastrointestinal disorders	54 (46%)	101 (42%)	155 (44%)
Gastrointestinal inflammatory conditions	21 (18%)	25 (11%)	46 (13%)
Gastrointestinal motility and defecation conditions	10 (8%)	31 (13%)	41 (12%)
Gastrointestinal signs and symptoms	8 (7%)	10 (4%)	18 (5%)
Metabolism and nutrition disorders	49 (42%)	100 (42%)	149 (42%)
Glucose metabolism disorders (including diabetes mellitus)	27 (23%)	44 (18%)	71 (20%)
Lipid metabolism disorders	20 (17%)	38 (16%)	58 (16%)
Renal and urinary disorders	40 (34%)	92 (39%)	132 (37%)
Renal disorders (excluding nephropathies)	30 (25%)	76 (32%)	106 (30%)
Musculoskeletal and connective tissue disorders	30 (25%)	79 (33%)	109 (31%)
Joint disorders	16 (14%)	37 (16%)	53 (15%)
Bone disorders (excluding congenital and fractures)	6 (5%)	12 (5%)	18 (5%)

6.1.3 Subject Disposition

In stage 1a, 356 patients (Clb arm: 118, GClb arm: 238) were randomized and comprised the efficacy analysis population (ITT population). Among the 356 randomized patients however, four patients did not receive study medication [two patients in the Clb arm (patient 4384 had a protocol violation and withdrew consent and patient 6420 withdrew consent), two patients in the GClb arm (patients 6400 and 5151) withdrew consent]. The data cutoff date for the stage 1a primary analysis and database lock date were July 11, 2012 and October 11, 2012, respectively.

Overall, a higher percentage of patients in the Clb arm (34%) than in the GClb arm (20%) withdrew from trial treatment; mostly due to differences in disease progression (7% versus <1%), death (5% versus 1%) and insufficient therapeutic response (4% versus <1%). The table below shows the reasons for withdrawal from treatment between the treatment arms.

Table 22 BO21004, Stage 1a: Withdrawal from Study Drug Treatment (ITT Population)

	Clb (n=118)	GClb (n=238)	Total (n=356)
Withdrawn from trial treatment	40 (34%)	48 (20%)	88 (25%)
Reason for withdrawal			
Adverse event or intercurrent illness	16 (14%)	32 (13%)	48 (13%)
Disease progression	8 (7%)	2 (<1%)	10 (3%)
Withdrew consent	2 (2%)	8 (3%)	10 (3%)
Death	6 (5%)	3 (1%)	9 (3%)
Insufficient therapeutic response	5 (4%)	1 (<1%)	6 (2%)
Administrative/other	1 (<1%)	1 (<1%)	2 (<1%)
Refused treatment	-	1 (<1%)	1 (<1%)
Eligibility criteria violation at entry	1 (<1%)	-	1 (<1%)
Other protocol violation	1 (<1%)	-	1 (<1%)

During the follow-up period, higher percentage of patients in the Clb arm (41%) were withdrawn than in the GClb arm (16%) which was mostly due to the difference in disease progression (Clb: 25% vs. GClb: 7%). The table below shows the reasons of withdrawal during follow-up.

Table 23 BO21004, Stage 1a: Withdrawal during Follow-up (ITT Population)

	Clb (n=118)	GClb (n=238)	Total (n=356)
Withdrawn from follow-up	48 (41%)	39 (16%)	87 (24%)
Reason for withdrawal			
Disease progression	30 (25%)	16 (7%)	46 (13%)
Administrative/other	8 (7%)	7 (3%)	15 (4%)
Adverse event or intercurrent illness	4 (3%)	5 (2%)	9 (3%)
Withdrew consent	2 (2%)	6 (3%)	8 (2%)
Death	1 (<1%)	4 (2%)	5 (1%)
Failure to return	2 (2%)	-	2 (<1%)
Refused treatment/did not cooperate	1 (<1%)	1 (<1%)	2 (<1%)

At the stage 1a analysis cutoff date, 22 patients (19%) in the Clb treatment arm had crossed over to GClb arm after disease progression. A higher percentage of patients in the GClb arm entered the follow-up period compared to Clb arm [GClb: 195 patients (82%), Clb: 84 patients (71%)]. The table below shows the actual number of patients that started follow-up and survival follow-up and that completed the follow-up and survival follow-up.

Table 24 BO21004, Stage 1a: Patient Follow-up (ITT Population)

	Clb (n=118)	GClb (n=238)	Total (n=356)
Follow-up started	84 (71%)	195 (82%)	279 (78%)
Completed follow-up period*	41 (49%)	26 (13%)	67 (24%)
Survival follow-up started	21 (18%)	23 (10%)	44 (12%)
Completed survival follow-up period*	2 (10%)	7 (30%)	9 (20%)

*Percentages are based on the number of patients entering the period.

In stage 1a, ITT population defined as all randomized patients included 118 patients in the Clb arm and 238 patients in the GClb arm. The PP was defined as all patients who have completed study treatment (defined as having received at least three complete cycles of study therapy and patients who terminated treatment before three cycles because of disease progression or death) and all patients who fulfilled the inclusion criteria with no major protocol violations. Patients were assigned to treatment groups as treated. PP population was comprised of 99 patients in the Clb arm and 192 patients in the GClb arm. The safety analysis population (SAP) was defined as all patients who received at least one dose of study drug and was comprised of 116 patients in Clb arm and 240 patients in GClb arm. There were two patients in each arm that did not receive the study drug (therefore these four patients were excluded from SAP) and four randomized patients to RClb received a dose of obinutuzumab in error (therefore these patients were included in the GClb arm in the stage 1a SAP). The table below shows the analysis population in stage 1a.

Table 25 BO21004, Stage 1a: Analysis Population (All Population)

	Clb	GClb	RClb	Total
Patients randomized	118	238	4	360
ITT population	118	238	0	356
Excluded from ITT	-	-	4	4
Received other than the randomized treatment	-	-	4	4
PP population	99	192	4	295
Excluded from PP*	19	46	-	65
Less than 3 cycles received and patient did not withdraw due to death or PD	13	30	-	43
Inadequate or no tumor assessment at baseline	5	9	-	14
Unconfirmed diagnosis of B-cell CLL	2	6	-	8
ANC $\geq$1.5 x 10^9/L and platelets $\geq$ 75 x 10^9/L unless cytopenia is caused by the underlying disease	1	2	-	3
Patient does not fulfill the comorbidity criteria	1	2	-	3
Patient does not meet NCI criteria or has received previous treatment for CLL	1	-	-	1
SAP	116	236	4	356
Excluded from SAP	2	2	-	4
No study drug received	2	2	-	4

*Based on the number of patients. Although a patient may have had 2 or more reasons for exclusion, the patient is counted only once. The same patient may appear in different categories.

At the time of clinical cutoff, the median observation time (from randomization to the last available assessment) was 14.2 months (Clb: 13.6 months, GClb: 14.5 months) in the ITT population.

Table 26 BO21004, Stage 1a: Observation Time (ITT Population)

	Clb (n=118)	GClb (n=238)	Total (n=356)
Observation time (months)			
Mean	13.0	14.1	13.7
Median	13.6	14.5	14.2
Range	0.2-26.8	0.1-26.7	0.1-26.8
Patient with ≥ 12 months	65 (55%)	143 (60%)	206 (58%)

In the safety analysis population, the median exposure time was 6.0 cycles and a greater percentage of patients in the GClb arm receive all planned 6 treatment cycles compared to the Clb arm (Clb: 67% of patients, GClb: 81% of patients).

Table 27 BO21004, Stage 1a: Exposure to Study Medications (SAP Population)

	Clb (n=116)	GClb (n=240)
Total number of cycles received		
1	12 (10%)	27 (11%)
2	6 (5%)	7 (3%)
3	10 (9%)	1 (0%)
4	7 (6%)	3 (1%)
5	3 (3%)	7 (3%)
6	78 (67%)	195 (81%)
Median	6.0	6.0
Range	1.0-6.0	1.0-6.0

6.1.4 Analysis of Primary Endpoint(s)

Based on IRC data, 66/118 patients (55.9%) in the Clb arm and 52/238 patients (21.8%) in the GClb arm had a PFS event of death or disease progression at the time of stage 1a analysis. The IRC assessed median PFS was 11.1 months in the Clb arm versus 23.0 months in the GClb arm. However, at the IRC assessed median GClb PFS time of 23.0 months, the remaining percentage of patients at risk was less than 5% (about 10 patients). Because of the low percentage of patients at risk at the median PFS time, this should be interpreted with caution.

The IRC assessed hazard ratio (stratified) was 0.16 (95% CI: 0.11, 0.24), log-rank p-value <0.0001.

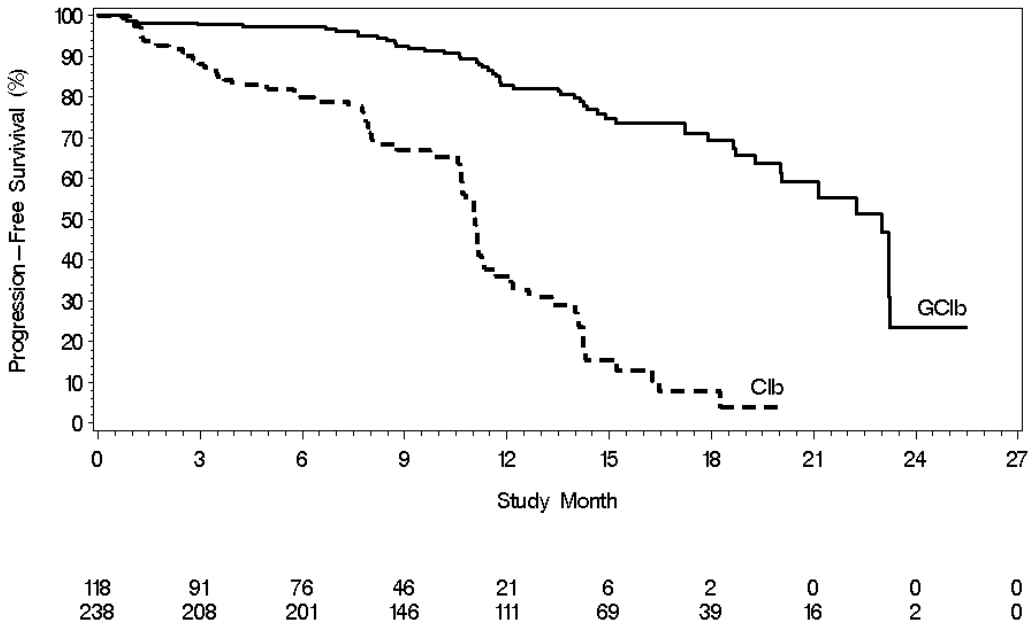
Table 28 BO21004, Stage 1a: Primary Endpoint Analysis (ITT Population)

Progression free survival	**Clb (n=118)**	**GClb (n=238)**
Based on IRC data		
Patients with event	66 (55.9%)	52 (21.8%)
Patients without event [a]	52 (44.1%)	186 (78.2%)
Time to event (months)		
Median [b]	11.1	23.0
Hazard ratio, 95% CI	0.16 (0.11, 0.24)	
P-value	< 0.0001	
Based on investigator's assessment		
Patients with event	71 (60.2%)	52 (21.8%)
Patients without event [a]	47 (39.8%)	186 (78.2%)
Time to event (months)		
Median [b]	10.9	23.0
Hazard ratio, 95% CI	0.14 (0.09, 0.21)	
P-value	< 0.001	

[a] Censored
[b] Kaplan-Meier estimates

Interestingly, IRC and investigator assessed numbers of patients with and without event were exactly the same in the GClb arm (with event: 52 patients, without event: 186 patients) while they were different in the Clb arm. The percentage of patients with event was lower in the GClb arm than in the Clb arm in both the IRC and investigator assessments [by investigator: Clb (60.2%) versus GClb (21.8%), by IRC: Clb (55.9%) versus GClb (21.8%)] and so there was more censoring in the GClb arm than in the Clb arm in both the IRC and investigator assessments [by investigator: Clb (39.8%) versus GClb (78.2%), by IRC: Clb (44.1%) versus GClb (78.2%)].

Figure 3 BO21004, Stage 1a: Kaplan Meier Estimates of IRC-Assessed PFS (ITT)



The percent of patients who were progression free at one year was 36% in the Clb arm versus 83% in the GClb arm based on IRC data.

Table 29 BO21004, Stage 1a: Progression-Free Survival at 1 Year (ITT)

Progression free survival	Clb (n=118)	GClb (n=238)
Based on IRC data		
1 year duration		
Patients remaining at risk	21	111
Event free rate (95% CI)	0.36 (0.25, 0.47)	0.83 (0.77, 0.89)
Based on investigator's assessment		
1 year duration		
Patients remaining at risk	18	117
Event free rate (95% CI)	0.27 (0.17, 0.37)	0.84 (0.79, 0.90)

The applicant performed an analysis of the concordance between the IRC and investigator assessed PFS events (provided below). According to this analysis, the IRC review was in agreement with the investigator that 25% of patients had a progression event, 5% of patients had death as an event and 63% of patients did not have an event (censored). The investigator and the IRC agreed with the PD date in 70 of the 88 patients (within 30 days of each other). The applicant claims that this leads to an overall concordance rate of 93%.

This high rate of concordance indicates that the PFS results by the investigator were not likely to be biased based upon knowledge of the treatment assignment.

Table 30 BO21004, Stage 1a: Agreement between the IRC determined and investigator determined PD dates (ITT)

Progression free survival	Clb (n=118)	GClb (n=238)	Total (n=356)
PD events per IRC	57	41	98
Agreement with investigator PD event	53 (45%)	35 (15%)	88 (25%)
PD event date agreement	43 (36%)	27 (11%)	70 (20%)
PD event later per investigator	5 (4%)	5 (2%)	10 (3%)
PD event earlier per investigator	5 (4%)	3 (1%)	8 (2%)
Censored per investigator	4 (3%)	6 (3%)	10 (3%)
Death as event per IRC	9	11	20
Death as event per investigator	8	10	18
Agreement	8 (7%)	10 (4%)	18 (5%)
Deaths by IRC, PD by investigator	1 (1%)	1 (0%)	2 (1%)
Censored per IRC	52	186	238
Agreement with investigator	43 (36%)	180 (76%)	223 (63%)
PD event by investigator	9 (8%)	6 (3%)	15 (4%)
Difference of time to event in days* (Investigator - IRC timing)			
Mean	3.1	9.9	6.0
Range	-229 to 269	-92 to 281	-229 to 281
Median	0	0	0
N	62	46	108

IRC and investigator dates are considered to be in agreement if they are within 30 days apart to account for potential differences in visit date assignments.
* includes PD events and deaths.
Source: BO21004, stage 1a clinical study report page 704

6.1.4.1 Sensitivity Analysis of the Primary Endpoint

The following sensitivity analyses were conducted for the primary endpoint:

- Analysis of the impact of missing response assessments: Patients who discontinued for any reason other than disease progression or death were counted as having progressed at the time of withdrawal. Also, patients who missed/had an incomplete response assessment prior to a PD or the cutoff for the analysis were counted as having progressed at the time of the missed/ incomplete response assessment.

- Analysis of the impact of patients starting a new anti-leukemic treatment without meeting the criteria of disease progression was assessed by censoring these patients at the start date of the new anti-leukemic treatment.

- Analysis of the impact of late death cases was assessed. Patients who died more than 6 months after last treatment and showed no sign of progression were censored at the last available tumor assessment.

- Analysis of the impact of withdrawal due to IRR with the first infusion of GClb was assessed where, in addition to PFS, an early treatment withdrawal was counted as an event.

- PFS was assessed in the per protocol population where patients with a major protocol violation, and patients who did not complete study therapy (defined as having received less than 3 cycles of study drug when reason of withdrawal was not death or PD) were excluded from the analysis.

The results of the analyses are shown in the table below.

Table 31 BO11004, Stage 1a: Sensitivity Analyses for Investigator-Assessed PFS (ITT)

Sensitivity Analysis	**Clb (n=118)**	**GClb (n=238)**
Missing response assessments		
Patients with an event	86 (72.9%)	77 (32.4%)
Median (months) [95% CI]	10.6 [8.0, 11.1]	20.5 [19.3, 23.2]
Hazard ratio [95% CI]	0.22 [0.15, 0.30]	
Log-rank p-value	< 0.0001	
Early treatment withdrawals		
Patients with an event	87 (73.7%)	84 (35.3%)
Median (months) [95% CI]	9.8 [7.8, 11.0]	20.1 [17.9[a], 23.2]
Hazard ratio [95% CI]	0.26 [0.19, 0.36]	
Log-rank p-value	< 0.0001	
New anti-cancer treatment		
Patients with an event	68 (57.6%)	47 (19.7%)
Median (months) [95% CI]	10.9 [9.8, 11.2]	23.2 [20.1, 23.2]
Hazard ratio [95% CI]	0.12 [0.08, 0.19]	
Log-rank p-value	< 0.0001	
Late death cases		
Patients with an event	71 (60.2%)	48 (20.2%)
Median (months) [95% CI]	10.9 [9.8, 11.2]	23.2 [20.1, 23.2]
Hazard ratio [95% CI]	0.13 [0.09, 0.20]	
Log-rank p-value	< 0.0001	

Per protocol population[b]		
Patients with an event	63 (63.6%)	45 (23.4%)
Median (months) [95% CI]	11.0 [8.6 [c], 11.2]	23.0 [20.0, 23.2]
Hazard ratio [95% CI]	0.13 [0.09, 0.20]	
Log-rank p-value	< 0.0001	

[a] FDA analysis value=17.9, applicant's value=18.7
[b] Based on Clb (n=99), GClb (n=192)
[c] FDA analysis value=8.6, applicant's value=9.8

The hazard ratios (HRs) in the above pre-specified sensitivity analyses ranged from 0.12 to 0.26. The PP population was comprised of 99 patients in the Clb arm and 192 patients in the GClb arm. In this patient population the HR was 0.13 (0.09, 0.20), log-rank p-value <0.0001.

The sensitivity analyses support the results of the primary analysis.

6.1.5 Analysis of Secondary Endpoints(s)

Key secondary efficacy endpoints included the following:

- End of treatment response
- Best overall response
- Event-free survival (EFS)
- Duration of response
- Disease-free survival
- Time to re-treatment/new anti-leukemic therapy
- Overall survival
- Molecular Remission (Minimal Residual Disease negative)

End of treatment response:
End of treatment response included nodular PR (nPR), PR, CR with incomplete bone marrow recovery (CRi) and CR and was higher in the GClb arm than in the Clb arm [Clb: 32/106 (30.2%), GClb: 160/212 (75.5%)]. There were no CRs in the Clb arm at the end of treatment while the CR rate in the GClb arm was 22.2% [CR: 36 patients (17.0%), CRi: 11 patients (5.2%)]. The trial cutoff date was July 11, 2012 and the last patient in stage 1 was randomized in January 2012. The end of treatment response assessment was to occur 3 months after the last dose. Therefore, not all patients had reached this visit at the cutoff date [i.e., 12 of the 118 patients (10%) in the Clb arm and 26 out of 238 patients (11%) in the GClb arm were excluded from the response rates and MRD analyses unless they had already experienced PD].

Table 32 BO21004, Stage 1a: End of Treatment Response Based on Investigator Assessment

	Clb (n=118)	GClb (n=238)
End of treatment response		
Patients included in analysis	106 (100.0%)	212 (100.0%)
Responders [a]	32 (30.2%)	160 (75.5%)
Complete response (CR)	0 (0.0%)	36 (17.0%)
Complete response incomplete (CRi)	0 (0.0%)	11 (5.2%)
Partial response (PR)	30 (28.3 %)	90 (42.5 %)
Nodular partial response (nPR)	2 (1.9 %)	23 (10.8 %)
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

[a] Patients with end of treatment response of CR, CRi, PR or nPR (CR includes CR and CRi, PR includes PR and nPR)

Best overall response:
Best overall response rate was 32.1% (34 out of 106 patients) in the Clb arm and 75.9% (161 out of 212 patients) in the GClb arm. The CR rate was 0.9 % in the Clb arm (CRi: 1 patient) and 27.8% in the GClb arm [CR: 52 patients (24.5%), CRi: 7 patients (3.3%)].

The secondary endpoint of 'best overall response' is supportive of the primary analysis.

Table 33 BO21004, Stage 1a: Best Overall Response Based on Investigator Assessment

	Clb (n=118)	GClb (n=238)
Best overall response		
Patients included in analysis	106 (100.0%)	212 (100.0%)
Responders [a]	34 (32.1 %)	161 (75.9 %)
Complete response (CR)	0 (0.0%)	52 (24.5 %)
Complete response incomplete (CRi)	1 (0.9 %)	7 (3.3 %)
Partial response (PR)	31 (29.2 %)	88 (41.5 %)
Nodular partial response (nPR)	2 (1.9 %)	14 (6.6 %)
Stable disease (SD)	21 (19.8 %)	9 (4.2 %)
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

[a] Patients with end of treatment response of CR, CRi, PR or nPR (CR includes CR and CRi, PR includes PR and nPR)

Event-free survival (EFS):
The median EFS was lower in the Clb arm (10.6 months) than in the GClb arm (23.0 months). The percentage of patients who experienced an event (PD, death or start of a new anti-leukemic

treatment) was higher in the Clb arm (66.9%) compared to GClb arm (26.9%). The hazard ratio was 0.18 (0.13, 0.26). The EFS analysis results are supportive of the primary endpoint.

Overall survival (OS):
The OS data was not yet mature at the clinical cutoff date (July 11, 2012). A total of 22 patients had died at the cutoff date (Clb: 9 patients, GClb: 13 patients). Of note, no one from the 22 Clb patients who crossover to the GClb arm after disease progression had an OS event by the cutoff date but were all censored.

Table 34 BO21004, Stage 1a: Event-free Survival and Overall Survival Based on Investigator Assessment (ITT Population)

	Clb (n=118)	GClb (n=238)
Event free survival		
Patients with event	79 (66.9%)	64 (26.9%)
Patients without event [a]	39 (33.1%)	174 (73.1%)
Time to event (months)		
Median [b]	10.6	23.0
Hazard ratio, 95% CI	0.18 (0.13, 0.26)	
P-value	< 0.0001	
Overall survival (OS)		
Patients with event	9 (7.6%)	13 (5.5%)
Patients without event [a]	109 (92.4%)	225 (94.5%)
Time to event (months)		
Median [b]	-	-
Hazard ratio, 95% CI	0.68 (0.29, 1.60)	

[a] Censored
[b] Kaplan-Meier estimates

This rate of patients without death events is typical for patients with previously untreated CLL.

Disease-free survival (DFS):
Patients with a best response of CR/CRi at any time from 56 days after end of treatment were assessed for disease-free survival. Out of the 59 patients included in the GClb arm for DFS analysis, three patients (5.1%) had an event by the clinical cutoff date. The applicant's analysis included two patients in the Clb arm. However, based on the CR/CRi response from the best overall response, one patient was included in the Clb arm (see table below). Because of the low number of patient included in the Clb arm, this should be interpreted with caution.

Duration of response:
Patients who had a response (CR, CRi, PR or nPR) at any time from 56 days after end of treatment onwards were assessed for duration of response. The applicant analysis included 36/118 patients in the Clb arm and 165/238 patients in the GClb arm. When including only the responders from the best overall response (Clb: 34/118 patients, GClb: 161/238 patients), the

median duration of response was 15.2 months in the GClb arm and 3.5 months in the Clb arm [HR: 0.10 (0.05, 0.20), p-value <0.0001]. The duration of response analysis is supportive of the primary endpoint.

Table 35 BO21004, Stage 1a: Disease-free Survival and Duration of Response Based on Investigator

	Clb	GClb
Disease free survival		
Patients included in analysis	1 (100.0%)	59 (100.0%)
Patients with event	1 (100.0%)	3 (5.1%)
Patients without event [a]	0 (0.0%)	56 (94.9%)
Time to event (months)		
Median [b]	0.1	15.6
Duration of response		
Patients included in analysis	34 (100.0 %)	161 (100.0 %)
Patients with event	20 (58.8 %)	31 (19.3%)
Patients without event [a]	14 (41.2%)	130 (80.7%)
Time to event (months)		
Median [b]	3.5	15.2
Hazard ratio, 95% CI	0.1 (0.05, 0.2)	
P-value (log-rank test)	< 0.0001	

[a] Censored
[b] Kaplan-Meier estimates

Time to re-treatment/new anti-leukemic therapy:
At the time of the analysis, 41 out of 118 patients (34.7%) in the Clb arm and 29 out of 238 patients (12.2%) in the GClb arm had started a new anti-leukemia treatment. The median time to new anti-leukemia treatment in the Clb arm was 14.8 months and this could not be estimated in the GClb arm.

Table 36 BO21004, Stage 1a: Time to New Anti-leukemic Therapy Based on Investigator

	Clb (n=118)	GClb (n=238)
Time to new anti-leukemic treatment		
Patients with event	41 (34.7%)	29 (12.2%)
Patients without event [a]	77 (65.3%)	209 (87.8%)
Time to event (months)		
Median [b]	14.8	-
Hazard ratio, 95% CI	0.26 (0.16, 0.42)	
P-value	<0.0001	

[a] Censored
[b] Kaplan-Meier estimates

Molecular Remission (Minimal Residual Disease negative):

An analysis of the combined blood and bone marrow was conducted and MRD-positive patient was defined when it was positive in either blood or bone marrow. It was considered MRD-negative if the result was less than 1 CLL cell in 10,000 leukocytes (MRD < 0.0001) based on allele specific polymerase chain reaction (ASO-PCR). When a patient had no end of treatment MRD result 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 excluded from the analysis [Clb: 26 out of 118 patients (22%), GClb: 70 out of 238 patients (29%)]. At the end of the treatment, there were no MRD-negative patients in the Clb arm while 28 out of 142 patients (20%) were MRD-negative in the GClb arm. Although MRD was listed as a secondary endpoint, the analysis for MRD status was not alpha-adjusted.

Table 37 BO21004, Stage 1a: Molecular Remission

	Clb (n=80)	GClb (n=142)
MRD status at the 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 [a]	80 (100.0%)	114 (80.3%)
Missing	26	70
End of treatment response not reached [b]	12	26

[a] Includes MRD positive patients and patient who progressed or died before end of treatment MRD negativity is defined as a result below 0.0001.
[b] Follow up month 3 visit not reached by the cutoff date; patients are not included in the analysis.

6.1.6 Other Endpoints

Cause of progression:
Other exploratory endpoints included a comparison of cause of disease progression by the investigator, IRC and a programmed algorithm based on data collected on the eCRF. The most common reasons for disease progression from all three sources were increasing/new lymphadenopathy and increased lymphocyte count. The concordance rates between any two methods ranged from 76% to 89% (source: BO21004/stage 1a, CSR page 748).

Patient reported outcomes:
The trial collected data on QLQ-C30 and QLQ-CLL-16 questionnaires. The applicant reports that in the QLQC30 and QLQ-CLL-16 questionnaires collected, no substantial difference between the two treatment arms was observed during the treatment period. Data during follow up (especially for the Clb arm) is limited. However, no notable differences in quality of life between the two treatment arms during follow up have been identified to date. Additional analysis comparing QLQ-CLL16 fatigue subscale scores during the treatment period revealed no statistically significant difference between patients treated with GClb compared to patients treated with Clb,

(b) (4)

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6.1.7 Subpopulations

Subgroup analysis of PFS by investigator was, in general, consistent with the ITT population. The HRs ranged from 0.03 to 0.42. In the cytogenetics 17p deletion subgroup only, there was no difference between the treatment groups [HR: 0.42 (95% CI: 0.15, 1.17)] with only 26 patients in this subgroup.

Table 38 BO21004, Stage 1a: Hazard Ratio (GClb vs. Clb) for PFS by Subgroup by Investigator Assessment

Category	Hazard Ratio (95% CI)	Total (n)
All	0.14 (0.10, 0.21)	356
Age (years)		
<75	0.13 (0.07, 0.22)	205
≥75	0.18 (0.10, 0.31)	151
<65	0.03 (0.01, 0.13)	68
≥65	0.18 (0.12, 0.27)	288
Sex		
Male	0.18 (0.11, 0.29)	215
Female	0.10 (0.05, 0.20)	141
Race		
White	0.16 (0.11, 0.24)	337
Binet stage		
A	0.09 (0.04, 0.21)	79
B	0.14 (0.07, 0.26)	148
C	0.19 (0.10, 0.37)	129
Total CIRS score at baseline		
≤ 6	0.12 (0.05, 0.30)	85
>6	0.14 (0.09, 0.23)	271
Calculated creatinine clearance		
<70 mL/min	0.18 (0.11, 0.28)	232
≥70 mL/min	0.07 (0.03, 0.15)	123
<50 mL/min	0.19 (0.08, 0.42)	94
≥50 mL/min	0.13 (0.08, 0.21)	261
Circulating lymphocyte count		
<25 x 10^9 cells/L	0.14 (0.05, 0.39)	76
≥25 x 10^9 cells/L	0.15 (0.10, 0.24)	277
Beta 2 microglobulin (mg/L)		
<3.5	0.13 (0.08, 0.22)	228
≥3.5	0.16 (0.08, 0.30)	118
IVGH mutational status		
Mutated	0.10 (0.04, 0.24)	112
Unmutated	0.17 (0.10, 0.28)	187
Hierarchical model at baseline		
17P-	0.42 (0.15, 1.17)	26
11Q-	0.09 (0.03, 0.27)	47
+12	0.24 (0.08, 0.76)	49
13Q-	0.15 (0.06, 0.35)	90
Other abnormal	0.20 (0.05, 0.79)	24
Normal karyotype	0.12 (0.04, 0.34)	63
Time from diagnosis		

≤ 12 months	0.11 (0.05, 0.25)	92
13-24 months	0.10 (0.04, 0.28)	59
>24 months	0.16 (0.10, 0.27)	204
FC gamma receptor IIa		
131 HH	0.08 (0.04, 0.19)	96
131 HR	0.16 (0.08, 0.30)	155
131 RR	0.16 (0.07, 0.38)	59
FC gamma receptor IIIa		
158 FF	0.18 (0.10, 0.32)	140
158 FV	0.11 (0.06, 0.21)	155
158 VV	0.10 (0.02, 0.50)	25

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

The recommended dosing regimen of obinutuzumab was defined from the BO20999 and BO21003 trials in conjunction with the pharmacokinetic (PK) model of obinutuzumab. In BO20999, obinutuzumab was administered over 50 to 2000 mg and in BO21003 over 100 to 2000 mg as monotherapy. The response rate (CR+PR) in BO21003 was zero. In BO20999 phase 2, three out of twenty patients (15%) had a PR with no CR reported in the obinutuzumab 1000 mg relapsed/refractory CLL cohort.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Refer to sections 6.1.4 and 6.1.5.

6.1.10 Additional Efficacy Issues/Analyses

Protocol violations:
In Stage 1a, there were 47 patients [Clb arm: 16 patients (14%) and GClb arm: 31 patients (13%)] that had at least one major protocol violation:

- Fifteen patients had inclusion criteria violations [Clb: 5 patients (4%), GClb: 10 patients (4%)] and were excluded from the per-protocol (PP) population.
- Twenty-one patients had exclusion criteria violations [Clb: 8 patients (7%), GClb: 13 patients (5%)] and were not excluded from the PP population.
- Fourteen patients had on-study violations which were all related to either inadequate or no tumor assessment at baseline [Clb: 5 patients (4%), GClb: 9 patients (4%)] and were excluded from the PP population.

Table 39 BO21044/CLL11: Protocol Violations

Protocol violations*	Clb (16/118)	GClb (31/238)	Exclusion from PP
Patients with inclusion criteria violations	Clb (5/118)	GClb (10/238)	
Unconfirmed diagnosis of B-cell CLL	2	6	Yes
Patient does not meet NCI criteria or has received previous treatment for CLL	1	0	Yes
Patient does not fulfill the comorbidity criteria	1	2	Yes
ANC $\geq$1.5 x 10^9/L and platelets $\geq$ 75 x 10^9/L unless cytopenia is caused by the underlying disease	1	2	Yes
Patients with exclusion criteria violations	Clb (8/118)	GClb (13/238)	
Creatinine Clearance of < 30 mL/min	1	7	No
History of other malignancy which could affect compliance with the protocol or interpretation of results	0	1	No
Patient has positive hepatitis serology	7	3	No
Patient of childbearing potential without contraception	0	1	No
Patients with active bacterial, viral, or fungal infection	0	1	No
Patients with on-study violations	Clb (5/118)	GClb (9/238)	
Inadequate or no tumor assessment at baseline	5	9	Yes

*Based on the number of patients, not the number of violations. Although a patient may have had 2 or more violations, the patient is counted only once. The same patient may appear in different categories.
** Patient 2620 (Clb arm) had positive hepatitis serology, ANC $\geq$1.5 x 10^9/L and platelets $\geq$ 75 x 10^9/L unless cytopenia is caused by the underlying disease, inadequate or no tumor assessment at baseline and was excluded from the per-protocol population.
***Patient 4080 (GClb arm) had creatinine clearance of < 30 mL/min, unconfirmed diagnosis of B-cell CLL and was excluded from the per-protocol population.

Overall, because of the small numbers and equality between treatment arms, it is not likely that these protocol violations affected the overall efficacy analysis of the primary endpoint (see table 31 Sensitivity Analyses).

7 Review of Safety

Safety Summary

The safety of obinutuzumab was evaluated in a randomized trial of 356 patients with previously untreated chronic lymphocytic leukemia. Stage 1a of trial BO21004 consisted of 224 patients on the obinutuzumab plus chlorambucil arm (GClb) and 116 patients on the chlorambucil arm (Clb). A summary of the important safety results from this clinical trial follow.

- In the experimental arm, obinutuzumab was given in 28 day cycles, with 1000mg IV infusion weekly times three in the first cycle followed by 1000mg every cycle times five. In both arms, chlorambucil was given orally at 0.5 mg/kg on day 1 and 15 of each of 6 cycles.

- The incidence of deaths within 30 days of the last treatment dose was lower in the obinutuzumab plus chlorambucil arm (1%) compared to the chlorambucil only arm (5%).
- Infusion related reactions were common with obinutuzumab occurring in 69% of patients. Grade 3 or 4 infusion reactions were experienced by 21% of patients. There were no infusion reaction related deaths.
- Symptoms of infusion related reactions (>20%) included nausea, chills, pyrexia, hypotension, and vomiting.
- Obinutuzumab pre-medication (instituted mid-trial) which included a corticosteroid, acetaminophen, and an antihistamine reduced the incidence of infusion reactions to 46%.
- Neutropenia occurred in 58% of patients in the obinutuzumab plus chlorambucil arm compared to 37% in the chlorambucil only. The incidence of infections was not higher in the obinutuzumab plus chlorambucil arm, though 23% of patients in the obinutuzumab plus chlorambucil arm received GCSF compared to 14%.
- Tumor Lysis syndrome occurred in 4% of the patients in the obinutuzumab plus chlorambucil arm. There were no deaths from tumor lysis syndrome.
- Other common adverse events (>5%) were cough, fever, arthralgias, and musculoskeletal pains.

7.1 Methods

The safety evaluation for this application is based on Stage 1a of trial BO21004 which consisted of two randomized arms in patients with untreated chronic lymphocytic leukemia. Refer to Section 5.3.1.1 for inclusion and exclusion criteria. Safety was monitored over the course of the trial by an independent data safety monitoring board.

Adverse events (AE) and serious adverse events (SAE) were captured on case report forms from the time of informed consent up to 28 days after completion of study treatment. Grade 3 and 4 AEs that developed during the trial were reported until 6 months after the end of study treatment. Unrelated SAEs were reported to one year. Grade 3 and 4 infections were reported to 2 years post-treatment or until another anti-leukemic therapy was started. All related SAEs and all secondary malignancies were and will be reported until the end of the study (8 years after the last patient was enrolled).

Safety assessments included physical examination, ECOG performance status, vital signs, ECG, and laboratory tests (CBC with differential, serum chemistry and electrolytes). Human anti-human antibodies (HAHA) were also assessed routinely in patients on the obinutuzumab arm. Patients who were HBsAg negative and Anti-HBc positive with undetectable serum HBV DNA were monitored monthly for HBV DNA by PCR until 12 months after completing study treatment. Refer to Section 5.3.1.1 for a detailed schedule of safety assessments.

The safety dataset includes 240 patients who received one or more doses of obinutuzumab plus chlorambucil and 116 patients who received chlorambucil only.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The safety review for obinutuzumab was performed by review of the following items for trial BO21004/CLL11 submitted by the Applicant, Genentech:

- Summary of Clinical Safety/Integrated Summary of Safety
- Trial protocol
- Clinical study reports
- Raw and derived datasets
- Case report forms
- Narratives for deaths, SAEs, and withdrawals due AEs
- Responses to Division Information Requests
- Proposed labeling for Gazyva

This trial was conducted under U.S. IND 104405. Additional trials of obinutuzumab below provided support for this application to aid in identification of rare adverse reactions:

- BO21003, a Phase 1/2, randomized trial compared to rituximab in patients with relapsed CD20+ indolent B-cell non-Hodgkin lymphoma
- BO21000, a Phase 1, randomized trial in combination with CHOP or FC in patients with relapsed/refractory CD20+ B-cell follicular non-Hodgkin lymphoma
- BO20999, a Phase 1/2 trial in patients with CD20+ malignant disease
- JO21900, a Phase 1 trial in patients with CD20+ B-cell non-Hodgkin lymphoma

7.1.2 Categorization of Adverse Events

MedDRA terminology, version 15.0, was used to categorize all adverse events in BO21004. Adverse event grading was performed using the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.

Adverse event categorization and grading was verified by this reviewer. Mapping of verbatim terms (AETXT) to MedDRA Preferred Term (AEPT) was acceptable. Grading of laboratory toxicities conformed to the CTCAE. AE analysis datasets containing full MedDRA hierarchy were provided on request.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Trial BO21004 was the only randomized trial available and therefore the best evidence of the clinical experience of obinutuzumab. No pooled analyses of the single arm trials were performed.

7.2 Adequacy of Safety Assessments

The data submitted to this BLA is adequate to perform the safety review. Raw and derived datasets were provided so that pertinent analyses could be repeated by this reviewer.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

As identified in Section 6.1.3, 81% of patients received all six treatment cycles, with a median cumulative dose of 8,000mg. Refer to Table 27 for exposure by cycle.

There were more dose modifications and interruptions of study medications on the obinutuzumab plus chlorambucil arm (39%) compared to the chlorambucil only arm (15%); specifics shown in Table 40 below. Chlorambucil dose modifications were either delays or reductions as specified in the protocol. Chlorambucil doses in both arms were comparable. Based on the protocol chlorambucil dosing, one would expect each patient to receive a cumulative dose of approximately 420mg upon completing six cycles. Obinutuzumab dose modifications were either infusion interruptions or infusion rate reductions as specified in the protocol.

Table 40 Dose Modifications in BO21004

	Clb (n=116)	GClb (n=240)
Chlorambucil dose modification Median cumulative dose	17 (15%) 384 mg	76 (32%) 370 mg
Obinutuzumab dose modification Infusion interruptions Infusion rate reductions		 127 (53%) 40 (17%)

The summary of demographic parameters for the safety population in BO21004 is shown below in Table 41. Overall, the participant demographic characteristics were well-balanced between the two arms. Over 75% of patients were 65 years of age or older with a mean age of 71-72. More than 90% of the patients were Caucasian, reflecting the population in the predominantly European and Russian trial sites. Refer to Section 6.1.2 for additional patient characteristics.

Table 41 Demographics of Safety Population in BO21004

Demographic Parameter	Clb (N=116)	GClb (N=240)
Age (years)		
Mean (SD)	71 (9)	72 (9)
Range	43, 87	39, 88
Groups		
<40	0	1
40-64	26	40
≥65	90	199
Sex		
Female	74 (64%)	141 (59%)
Male	42 (36%)	99 (41%)
Race		
Caucasian	106 (91%)	231 (96%)
Non-Caucasian	10 (9%)	9 (4%)
Weight (kg)		
Mean (SD)	75.6 (15.3)	73.1 (14.0)
Range	44.9, 120.0	40.0, 140.0
ECOG Performance Status		
0-1	103 (89%)	211 (88%)
2-4	13 (11%)	29 (12%)
CIRS (a)		
≤6	25 (22%)	61 (25%)
>6	91 (78%)	179 (75%)

(a) Cumulative Illness Rating Scale, modified by Salvi et al (2008) and specified in protocol

7.2.2 Explorations for Dose Response

The Applicant did not examine different doses of obinutuzumab in trial BO21004. There was no variation in dosing per protocol. An exploration for dose-response could not be performed.

7.2.3 Special Animal and/or In Vitro Testing

Refer to the Pharmacology/Toxicology review.

7.2.4 Routine Clinical Testing

Routine clinical testing assessments in BO21004 included physical examination, ECOG performance status, vital signs, ECG, and laboratory tests (CBC with differential, serum chemistry and electrolytes). Human anti-human antibodies (HAHA) were also assessed routinely in patients on the obinutuzumab arm. Patients who were HBsAg negative and Anti-HBc positive with undetectable serum HBV DNA were monitored monthly for HBV DNA by PCR until 12 months after completing study treatment. Refer to Table 12 for a detailed schedule of safety assessments.

7.2.5 Metabolic, Clearance, and Interaction Workup

Pharmacokinetic and pharmacodynamic effects of obinutuzumab were analyzed in three clinical trials of patients with chronic lymphocytic leukemia. Obinutuzumab is administered by intravenous infusion and is distributed intravascularly. As protein agents are degraded into amino acids, metabolism and elimination studies were not performed. As monoclonal antibodies do not interact directly with CYP450 or other metabolizing enzymes, *in vitro* studies were not performed. Refer to the Clinical Pharmacology review for additional details.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Obinutuzumab is a monoclonal antibody specific for human CD20. Class effects include infusion reactions, cytopenias, tumor lysis syndrome, infections including Hepatitis B reactivation and progressive multifocal leukoencephalopathy, mucocutaneous reactions, cardiac arrhythmias, renal toxicity, bowel obstruction and perforation. Of these class effects, infusion reactions, cytopenias, and tumor lysis syndrome were observed in the BO21004 trial.

7.3 Major Safety Results

7.3.1 Deaths

Twenty-two deaths occurred in trial BO21004 Stage 1a (data cutoff 11 July 2012); 9 of 116 patients on the Clb arm and 13 of 240 on GClb arm. Deaths during treatment or follow-up are listed in Table 42.

Table 42 Deaths in BO21004

Deaths	Clb (n=116)	GClb (n=240)
Within 30 days of the last treatment dose	6 (5.2%)	3 (1.3%)
During follow-up	3 (2.6%)	10 (4.2%)

Based on this trial, there was no evidence of additional mortality with obinutuzumab in patients with chronic lymphocytic leukemia. As borne out in the narratives that follow, patients with chronic lymphocytic leukemia tend to be older and have multiple co-morbidities.

Narratives for the patients who died within 30 days of the last dose of obinutuzumab:

Subject number 165896-2981 was an 81 year old male with a past medical history of Bowen's disease, back pain, edema, polyuria, constipation, glaucoma, nystagmus, cataract, hypercholesterolemia, thrombosis, gastritis, osteoarthritis, spinal column stenosis, nasopharyngitis, and pleural effusion. The last dose (#2) of obinutuzumab was on study day 8. On day (b) (6), the patient was hospitalized with hemorrhagic stroke. Platelet count was 104,000/µL. The patient died on day (b) (6) due to hemorrhagic stroke.

Subject number 164624-1605 was a 73 year old male with a past medical history of atrial fibrillation, diabetes mellitus, benign prostatic hyperplasia, hypertension and myocardial ischemia. The last dose (#3) of obinutuzumab was on study day 15. The patient had a history of ischemic heart disease, atrial fibrillation and hypertension, and died on day (b) (6) due to cerebrovascular accident.

Subject number 164815-5405 was a 70 year old female with a past medical history of acoustic neuroma, hypertension, pancreatic cyst, renal failure, cardiac myxoma, diabetes mellitus, and thalassemia. The last dose (#1) of obinutuzumab was on study day 1. The patient had grade 3 hypotension during the obinutuzumab infusion for which the infusion was interrupted. After restarting the infusion, hypotension occurred a second time. On day 16, the patient had an accident at home and hit her head. On day (b) (6), the patient developed seizures, and a subdural hematoma was identified. Platelet count was 121,000/µL, prothrombin time was normal. The patient died on day (b) (6) due to subdural hematoma.

Of the ten patients on the obinutuzumab arm that died during follow-up, four died from progressive disease or related physical deterioration. There was a mean of 151 days and a median of 106 days (range 47-344) from the last dose of obinutuzumab to death.

Narratives for the six patients who died from other causes:

Subject number 166939-2581 was a 76 year old male with a past medical history of prostate cancer, hip arthroplasty, anemia, intestinal diverticulum, obesity, renal failure, hypertensive heart disease, atrial fibrillation and hypertension. The last dose of obinutuzumab was on day 113. On about day (b) (6) the patient was hospitalized with a colon perforation, peritonitis, and septic shock. On day (b) (6) the patient underwent EGD and colonoscopy, was subsequently diagnosed with colon cancer, and was treated with oxaliplatin. The patient died on day (b) (6) due to colon cancer.

Subject number 164559-1240 was an 81 year old male. The last dose of obinutuzumab was on study day 1. The patient died of chronic obstructive pulmonary disease on day (b) (6).

Subject number 164930-1404 was a 71 year old female with a past medical history that included knee arthroplasty, thyroidectomy, polyarthritis, gastroesophageal reflux disease, and tachycardia. The last dose (#4) of obinutuzumab was on study day 43. On day (b) (6) the patient developed symptoms of lung cancer and was diagnosed with squamous cell carcinoma of the lung on day (b) (6) The patient died on day (b) (6) due to squamous cell carcinoma of the lung.

Subject number 166939-2582 was an 83 year old female with a past medical history of heart failure, ischemic cardiomyopathy, renal impairment, dyspnea, anemia (folate deficiency), and hypothyroidism. The last dose (#8) of obinutuzumab was on study day 141. On day (b) (6) the patient developed Grade 2 anemia, was diagnosed myelodysplastic syndrome on day (b) (6) and with rectal carcinoma on day (b) (6). The patient died on day (b) (6) of unknown cause.

Subject number 166019-3682 was a 76 year old male with a past medical history of coronary artery disease, Borrelia infection, erysipelas, hypertension, and thrombocytopenia. The last dose of obinutuzumab was on study day (b) (6). On day (b) (6), the patient died due to myocardial infarction.

Subject number 202500-6780 was an 80 year old female. The last dose of obinutuzumab was on study day 155. On day (b) (6) the patient died of unknown cause.

7.3.2 Nonfatal Serious Adverse Events

Treatment emergent serious adverse events (SAE) with ≥1% overall incidence occurring during treatment defined as up to 28 days from last treatment are summarized in Table 43. The most common SAE was infusion related reactions. Evaluation of SAEs at the System Organ Class level did not detect an increased difference between arms >2%.

Table 43 Treatment emergent SAEs with ≥1% overall incidence

	Chlorambucil n=116		Obinutuzumab + chlorambucil n=240	
Adverse Event	(n)	(%)	(n)	(%)
Injury, Poisoning and Procedural Complications	0	0.0	30	12.5
Infusion Related Reaction	0	0.0	27	11.3
Infections and Infestations	14	12.1	16	6.7
Pneumonia	3	2.6	5	2.1
Blood and Lymphatic System Disorders	7	6.0	10	4.2
Anemia	0	0.0	3	1.3
Neutropenia	0	0.0	3	1.3
Metabolism and Nutrition Disorders	0	0.0	4	1.7
Tumor Lysis Syndrome	0	0.0	3	1.3

There were no SAEs during the follow-up period with ≥5% overall incidence and ≥2% difference between the two arms.

7.3.3 Dropouts and/or Discontinuations

Of the 356 patients in the safety population, 46 (19%) patients in the obinutuzumab plus chlorambucil arm and 39 (33%) patients in the chlorambucil arm withdrew from trial treatment. In the obinutuzumab arm, 34 (14%) of these patients withdrew due to an AE and 7 (3%) patients withdrew consent. In the chlorambucil arm, 17 (15%) patients withdrew due to an AE, 8 (7%) withdrew to progression of disease, and 6 (5%) died.

Of the patients who completed treatment and withdrew early from study, 39 (16%) were in the obinutuzumab arm and 49 (42%) patients were in the chlorambucil arm. In the obinutuzumab arm, 19 (8%) were due to progression of disease, 7 (3%) withdrew consent, 5 (2%) were due to

an AE or intercurrent illness, and 4 (2%) died. In the chlorambucil arm, 36 (31%) were due to progression of disease, 7 (6%) withdrew consent, and 4 (3%) were due to an AE or intercurrent illness.

7.3.4 Significant Adverse Events

Infusion Related Reactions

Infusion Related Reactions (IRR) occurred in 69% of patients receiving obinutuzumab. Grade 3 and 4 IRRs were experienced by 21% of patients. These events occurred at some point after the initiation of the obinutuzumab infusion and within 24 hours of completion of the infusion. The most common were nausea, hypotension, chills, pyrexia, and respiratory symptoms. These are shown in Table 44. There were no Grade 5 IRRs.

Table 44 Symptoms of Infusion Related Reactions with a ≥2% incidence

	Obinutuzumab + chlorambucil n=240			
	Grades 1-4		Grades 3&4	
Adverse event	n	%	n	%
Gastrointestinal Disorders	136	56.7	37	15.4
Nausea	67	27.9	18	7.5
Vomiting	48	20.0	15	6.3
Diarrhea	21	8.8	4	1.7
General Disorders and Administration Site Conditions	111	46.3	30	12.5
Chills	56	23.3	18	7.5
Pyrexia	55	22.9	12	5.0
Vascular Disorders	104	43.3	41	17.1
Hypotension	53	22.1	23	9.6
Hypertension	18	7.5	6	2.5
Flushing	33	13.8	12	5.0
Cardiac Disorders	18	7.5	9	3.8
Tachycardia	17	7.1	8	3.3
Nervous System Disorders	35	14.6	4	1.7
Dizziness	15	6.3	2	0.8
Headache	20	8.3	2	0.8
Respiratory, Thoracic and Mediastinal Disorders	60	25.0	31	12.9
Dyspnea	33	13.8	16	6.7
Bronchospasm	12	5.0	9	3.8
Throat Irritation	5	2.1	2	0.8
Musculoskeletal and Connective Tissue Disorders	13	5.4	5	2.1
Myalgia	8	3.3	4	1.6
Skin and Subcutaneous Tissue Disorders	20	8.3	7	2.9
Rash	9	3.8	5	2.1
Pruritus	6	2.5	1	0.4

All patients who experienced an infusion reaction did so with the first dose. Ten of 240 patients (4.2%) also experienced an infusion reaction with the second dose. At subsequent cycles (3-6), <2% of patients experienced an infusion reaction. All infusion reactions after the first dose were Grade 1 or 2.

Dose delays of obinutuzumab occurred 163 times in 104 patients (43%). The majority (143) of these dose delays were due to adverse events in 94 patients (39%).

Prevention of infusion reactions evolved over the course of the protocol. The percentage of patients who experienced infusion reactions was 46% with the final iteration of prevention. This included a required dose of a corticosteroid (prednisolone or prednisone 100mg IV,

dexamethasone 20mg IV, or methylprednisolone 80mg IV) one hour prior to the first infusion of obinutuzumab. Also required, approximately 30 minutes before the first infusion, was premedication with 650 to 1000mg PO acetaminophen and an antihistamine such as diphenhydramine 50-100mg.

Management and prevention of infusion reactions should be iterated in the label using the last protocol amendment as guidance.

There were two cases of investigator identified anaphylaxis in patients receiving obinutuzumab. Review of the narratives reveals that one case was likely related to another drug. The other case is difficult to categorize as anaphylaxis; the symptoms listed were consistent with monoclonal antibody class infusion reactions and were likely exacerbated by pre-infusion administration of a beta blocker; this patient did not receive pre-treatment with a corticosteroid, and did not receive epinephrine.

Narratives for the two patients who had anaphylaxis:

Subject number 104608-7361: After pre-medication with prednisolone and clemastine and initiation of obinutuzumab infusion, the patient developed 'circulatory collapse which was considered a Grade 3 anaphylaxis. He was treated with corticosteroids, IV fluids, and supplemental oxygen, with resolution of symptoms without sequelae. The patient was taken off protocol treatment. Two weeks later, prior to starting a rituximab-based regimen, the patient had a positive re-challenge to clemastine with similar anaphylactic symptoms occurring during the clemastine infusion.

Subject number 166942-2642: After pre-medication with bisoprolol and furosemide and initiation of obinutuzumab infusion, the patient developed a Grade 3 infusion reaction consisting of chest tightness, hypotension, and malaise. Symptoms resolved with supplemental oxygen. The infusion was restarted at half the rate and soon after, the patient developed a Grade 4 infusion reaction consisting of the same symptoms as earlier. He was treated with terbutaline, hydrocortisone and methylprednisolone. This patient was started on protocol prior to the amendment that required corticosteroids.

There is no evidence for the Applicant's inclusion of a contraindication for IgE mediated allergic reactions to obinutuzumab in the label.

<u>Neutropenia</u>
Neutropenia defined as a Treatment Emergent AE or as a Treatment Emergent laboratory AE occurred in 58% of patients receiving obinutuzumab plus chlorambucil compared to 37% of patients receiving chlorambucil only. On the obinutuzumab plus chlorambucil arm, there was a 35% incidence of Grade 3 and 4 neutropenia compared to 22% on the chlorambucil only arm. These are shown in Table 47 and Table 48. There was no Grade 5 neutropenia.

The use of granulocyte colony stimulating factor (G-CSF) was not specified for the obinutuzumab plus chlorambucil arm in the protocol. Investigators were advised to give G-CSF

for neutropenia "as required" to patients on the chlorambucil arm. Analysis of the medication dataset for trial BO21004 revealed that 77 patients (32%) on the obinutuzumab plus chlorambucil arm received G-CSF while on trial, compared to 16 patients (14%) on the chlorambucil arm. The median time to the first dose of G-CSF was 24 days for obinutuzumab plus chlorambucil arm and 34 days for the chlorambucil only arm.

Late onset neutropenia has been reported as an uncommon effect of another monoclonal antibody, rituximab. It can occur several months after the last dose and is usually not clinically relevant and is self-limited. In trial BO21004, there were 204 patients (85%) on the obinutuzumab plus chlorambucil arm and 86 patients (74%) in the chlorambucil arm who had neutrophil counts available between 28 and 200 days after completing treatment. Of these patients, 33 (16%) on the obinutuzumab plus chlorambucil arm and 10 (12%) on the chlorambucil only arm had late onset neutropenia.

Tumor lysis syndrome

Tumor lysis syndrome (TLS) is a preventable and treatable metabolic complication, while uncommon, of chronic lymphocytic leukemia and other malignancies. Prevention of tumor lysis syndrome (TLS) was addressed in the protocol for trial BO21004. The investigators were advised to provide adequate hydration of approximately three liters per day for 1-2 days and give allopurinol or similar anti-hyperuricemic 12-24 hours prior to the first dose of obinutuzumab. The incidence of TLS was less than 5%. An evaluation of the AEs that are part of the definition of laboratory TLS reveal a higher incidence in the obinutuzumab plus chlorambucil arm. These are shown in Table 45 below. There were no deaths from tumor lysis syndrome.

Table 45 Incidence of Tumor Lysis Syndrome and related laboratory parameters

	Chlorambucil n=116				Obinutuzumab + chlorambucil n=240			
	Grades 1-4		Grades 3&4		Grades 1-4		Grades 3&4	
Adverse event	n	%	n	%	n	%	n	%
Metabolism and Nutrition Disorders								
Tumor Lysis Syndrome	1	0.9	0	0.0	10	4.2	4	1.7
Hyperuricemia	0	0.0	0	0.0	7	2.9	1	0.4
Hyperkalemia	2	1.7	0	0.0	4	1.7	2	0.8
Hypophosphatemia	0	0.0	0	0.0	1	0.4	0	0.0
Hypercalcemia	0	0.0	0	0.0	1	0.4	0	0.0

Even though the incidence of TLS is low, prescribers must be aware of this risk in the label. Identification of patients considered at risk, prophylaxis for those that are, and timely management of TLS are imperative.

7.3.5 Submission Specific Primary Safety Concerns

Cardiac

In trial BO21004, investigators were advised to more closely monitor patients who had pre-existing cardiac conditions while receiving obinutuzumab infusion. Analysis of the cardiac disorders that occurred on trial, are presented in Table 46 below. Even when grouping dysrhythmias, there does not appear to be a significant difference between the two arms. As mentioned before, there were no infusion related cardiovascular deaths.

Table 46 Cardiac Disorders

	Chlorambucil n=116				Obinutuzumab + chlorambucil n=240			
	Grades 1-4		Grades 3&4		Grades 1-4		Grades 3&4	
Adverse event	n	%	n	%	n	%	n	%
Cardiac Disorders								
Acute Coronary Syndrome	0	0.0	0	0.0	1	0.4	1	0.4
Angina Pectoris	1	0.8	0	0.0	2	0.8	0	0.0
Coronary Artery Disease	1	0.8	0	0.0	0	0.0	0	0.0
Dysrhythmias (a)	1	0.8	1	0.8	5	2.1	0	0.0
Heart Failure (b)	1	0.8	0	0.0	4	1.7	1	0.4
Myocardial Infarction	1	0.8	1	0.8	1	0.4	0	0.0
Tachycardia	0	0.0	0	0.0	1	0.4	0	0.0

(a) Includes the Preferred Terms: Atrial Fibrillation, Atrial Tachycardia, Tachyarrhythmia, Ventricular Arrhythmia
(b) Includes the Preferred Terms: Cardiac Failure, Cardiac Failure Congestive

Rather than identify in the label "worsening of pre-existing cardiac conditions" as the Applicant proposes in the label, inclusion of the cardiac or vascular related symptoms that were identified should be a part of the description of infusion reactions.

Thrombocytopenia

Evaluation of the Treatment Emergent AEs from trial BO21004 reveal a significantly higher incidence of thrombocytopenia on the obinutuzumab plus chlorambucil arm (15% compared to 7%). Analysis of the Treatment Emergent AEs from the laboratory dataset revealed that there was a less than 5% difference between the two arms, with the obinutuzumab plus chlorambucil arm having a lower incidence. Clinically relevant differences may be seen in the difference in severity of thrombocytopenia between the two arms. On the obinutuzumab plus chlorambucil arm 14% of patients experienced thrombocytopenia Grade 3 or 4 compared to 11% on the chlorambucil only arm. As the applicant noted, this occurred in 11 patients (4.6%) within 24 hours of the obinutuzumab infusion.

B-cell depletion
B-cell depletion is defined here as CD19+ B-cell counts < 0.07 x 10^9/L. In a subset of 44 patients on the obinutuzumab plus chlorambucil arm on trial BO21004, 40 (91%) were B-cell depleted at the end of treatment. Recovery of B-cells occurred between 9-18 months with the majority (46%) recovering between 12-18 months post-treatment. At the end of 18 months, 9 patients (23%) remained B-cell depleted. In the chlorambucil only arm, 2 of 20 patients tested were B-cell depleted at the end of treatment; both patients recovered their B-cells by 9 months.

Infection
Given the concerns for infections seen with other agents in this class, an exploratory analysis was done for infection. When Preferred Terms were grouped by the System Organ Class of Infections and Infestations, 44% of patients on the obinutuzumab plus chlorambucil arm experienced an AE (16% of these were Grade 3 or 4) compared to 45% in the chlorambucil only arm (27% of these were Grade 3 or 4). There were no infection related deaths on the obinutuzumab plus chlorambucil arm and there were 3 on the chlorambucil arm, one each from sepsis, pneumonia, and respiratory infection. There were 17 Serious AEs in 7% of patients on the obinutuzumab plus chlorambucil arm and 17 (15%) on the chlorambucil only arm. On the obinutuzumab plus chlorambucil arm, these were primarily comprised of pneumonia and respiratory tract infections. There appeared to be an increased incidence of herpes simplex infections on the obinutuzumab plus chlorambucil arm (3% vs. 1%).

While there were no incidences of Hepatitis B infection or progressive multifocal leukoencephalopathy on trial BO21004, there was a single incidence of hepatitis B reactivation in a patient with large cell lymphoma being treated on protocol with CHOP and obinutuzumab. There was one case of fatal PML two years after a patient with relapsed or refractory follicular lymphoma was exposed to obinutuzumab combined with other chemotherapy.

Regarding the label, Hepatitis B and PML are significant risks that should be identified so that prescribers can screen and evaluate their patients.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

As addressed earlier, infusion related reactions to obinutuzumab were the most common AE. Table 47 below provides details on the adverse events that occurred more often in the obinutuzumab plus chlorambucil arm.

Table 47 Treatment-emergent Adverse Events with ≥5% incidence and ≥2% difference between the two arms

	Chlorambucil n=116				Obinutuzumab + chlorambucil n=240			
	Grades 1-4		Grades 3&4		Grades 1-4		Grades 3&4	
Adverse event	n	%	n	%	n	%	n	%
Injury, Poisoning and Procedural Complications								
Infusion Related Reaction	0	0.0	0	0.0	165	68.8	50	20.8
Blood and Lymphatic System Disorders								
Neutropenia	20	17.2	17	14.7	96	40.0	82	34.2
Thrombocytopenia	8	6.9	4	3.4	36	15.0	26	10.8
Leukopenia	0	0.0	0	0.0	15	6.3	12	5.0
Respiratory, Thoracic and Mediastinal Disorders								
Cough	9	7.8	1	0.9	22	9.2	0	0.0
General Disorders and Administration Site Conditions								
Pyrexia	8	6.9	0	0.0	23	9.6	1	0.4
Musculoskeletal and Connective Tissue Disorders								
Arthralgias (a)	3	2.6	1	0.8	13	5.4	2	0.8
Musculoskeletal Pains (b)	8	6.9	0	0.0	23	9.6	2	0.8

(a) Includes the Preferred Terms: Arthralgia, Gouty Arthritis, Arthritis, Osteoarthritis
(b) Includes the Preferred Terms: Musculoskeletal Pain, Musculoskeletal Chest Pain, Bone Pain, Myalgia Intercostal, Neck Pain, Pain In Extremity, Back Pain

Exploratory analyses including Standardized MedDRA Queries using MAED and evaluation of combinations of Preferred Terms with little clinical difference did not reveal new safety concerns with significant differences between the two arms.

7.4.2 Laboratory Findings

Treatment Emergent laboratory adverse events derived from the LAB41ALL dataset are summarized in Table 48. There are several notable differences from the investigator identified adverse event profile. On the obinutuzumab plus chlorambucil arm, there was a greater incidence of decreased white cell types and greater electrolyte and transaminase abnormalities. The clinical implications of these lab abnormalities were not borne out in adverse events such as infections or renal or liver dysfunction.

Table 48 Maximum Post-Baseline Treatment Emergent Laboratory Abnormalities by CTCAE Grade with ≥5% incidence and ≥2% difference between the two arms

	Chlorambucil n=116				Obinutuzumab + chlorambucil n=240			
	Grades 1-4		Grades 3&4		Grades 1-4		Grades 3&4	
Adverse event	n	%	n	%	n	%	n	%
Hematology								
White Blood Cell Count Decreased	10	8.6	1	0.9	147	61.3	66	27.5
Neutrophils Decreased	43	37.1	25	21.6	140	58.3	83	34.6
Platelets Decreased	58	50.0	13	11.2	112	46.7	33	13.8
Lymphocytes Decreased	1	0.9	1	0.9	42	17.5	40	16.7
Chemistry								
Calcium Decreased	31	26.7	1	0.9	73	30.4	8	3.3
Potassium Increased	18	15.5	2	1.7	71	29.6	11	4.6
Sodium Decreased	13	11.2	2	1.7	67	27.9	18	7.5
Creatinine Increased	21	18.1	2	1.7	66	27.5	2	0.8
AST (SGOT) Increased	14	12.1	0	0.0	64	26.7	1	0.4
ALT (SGPT) Increased	16	13.8	0	0.0	56	23.3	2	0.8
Albumin Decreased	16	13.8	1	0.9	46	19.2	0	0.0
Alkaline Phosphatase Increased	12	10.3	0	0.0	37	15.4	0	0.0
Potassium Decreased	5	4.3	1	0.9	31	12.9	3	1.3

There were no cases that met Hy's Law in patients on the obinutuzumab plus chlorambucil arm.

7.4.3 Vital Signs

Other than the clinical adverse events that occurred as part of an infusion reaction, there were no significant changes in blood pressure, pulse rate, temperature, or weight over the course of the treatment period.

7.4.4 Electrocardiograms (ECGs)

Baseline ECGs only were obtained on trial BO21004 per protocol. QT/QTc interval evaluation was done in early Phase 1 studies and did not identify a pattern that could be considered evidence of QTc prolongation for obinutuzumab. The Applicant proposed a QT/QTc interval sub-study in another trial of obinutuzumab in patients with indolent non-Hodgkin lymphoma, with which the Agency agreed.

7.4.5 Special Safety Studies/Clinical Trials

There were no special safety studies.

7.4.6 Immunogenicity

Human anti-human antibody (HAHA) response was evaluated in 238 patients on the obinutuzumab plus chlorambucil arm. Four patients tested positive before the first infusion; all were subsequently negative with additional testing, and likely represents false positive results. No other positive HAHA results were obtained until the six month follow-up visit. Between 6 and 12 months post follow-up 7 of 64 patients (11%) were positive. Given the limited number of patients with a HAHA response, no clinical relevance can be determined. Exploration of AEs and disease response in these patients did not yield any patterns, e.g. 5 of 7 patients experienced Grade 1 or 2 infusion reactions, 0 of 7 experienced tumor lysis syndrome.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Dose dependency for adverse events was not evaluated because the Applicant did not examine different doses of obinutuzumab in trial BO21004. There was no variation in dosing of obinutuzumab per protocol.

7.5.2 Time Dependency for Adverse Events

Obinutuzumab is administered for 6 cycles and is not a chronically administered therapy.

Section 7.3.4 contains a discussion on the time dependency for infusion related reactions. In brief, patients who experienced an infusion related AE did so with the first dose with very few reactions with subsequent doses.

Section 7.3.4 also contains a discussion on the time dependency for neutropenia while on treatment and for late-onset neutropenia in trial BO21004.

7.5.3 Drug-Demographic Interactions

Trial BO21004 did not enroll an adequate number of patients to allow for adequate analysis of adverse events for most demographic parameters e.g., age, race. Evaluating the frequency of AEs by sex reveals no significant difference; 92% of males and 95% of females on the obinutuzumab plus chlorambucil arm experienced an AE compared to 86% of males and 74% of females on the chlorambucil only arm.

7.5.4 Drug-Disease Interactions

Patients with chronic lymphocytic leukemia tend to be older with a median age at diagnosis of 71 years. As such, many patients have comorbidities affecting excretory and metabolic functions. As addressed in the review by Clinical Pharmacology, there were no differences in obinutuzumab exposure in patients with mild, moderate, or normal renal function. Obinutuzumab was not evaluated in patients with a creatinine clearance of <30mL/min/1.73m^2. There is very limited data on the use of obinutuzumab in patients with hepatic impairment. Monoclonal antibodies tend to be catabolized through non-hepatic pathways but the impact of hepatic impairment is unknown.

The major cause of death in patients with chronic lymphocytic leukemia is from complications of pancytopenia, including hemorrhage and infection. Immunologic abnormalities i.e. hemolytic anemia, depressed immunoglobulin are also frequent. In trial BO21004, there was a higher incidence of infections in the chlorambucil arm which may be the result of improved chronic lymphocytic leukemia disease control in the obinutuzumab plus chlorambucil arm or may be a result of the greater use of G-CSF in the obinutuzumab plus chlorambucil arm. Refer also to the neutropenia portion of Section 7.3.4 for details.

7.5.5 Drug-Drug Interactions

Refer to the Clinical Pharmacology Review.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

There was a higher incidence of cancers on the obinutuzumab plus chlorambucil arm, primarily skin cancers. This may simply be an artifact of a greater proportion of patients in the obinutuzumab arm in longer term follow-up.

Table 49 Neoplasms during the follow-up period

Adverse Event	Chlorambucil n=116		Obinutuzumab + chlorambucil n=240	
	(n)	(%)	(n)	(%)
Neoplasms Benign, Malignant and Unspecified (incl. Cysts and Polyps)	2	1.7	9	3.8
Squamous Cell Carcinoma	0	0.0	2	0.8
Squamous Cell Carcinoma Of Skin	0	0.0	2	0.8
Basal Cell Carcinoma	0	0.0	1	0.4
Keratoacanthoma	0	0.0	1	0.4
Myelodysplastic Syndrome	0	0.0	1	0.4
Prostate Cancer	0	0.0	1	0.4
Rectal Cancer	0	0.0	1	0.4
Lung Adenocarcinoma	1	0.9	0	0.0
Pancreatic Carcinoma	1	0.9	0	0.0

The overall difference in the percentage of post-treatment neoplasms is 2.1%. The two neoplasms that are the most life-threatening (lung and pancreatic carcinoma) were reported in the control arm. These events should be monitored in the post-marketing setting.

7.6.2 Human Reproduction and Pregnancy Data

There are no adequate and well-controlled trials of obinutuzumab in pregnant women. Based on the mechanism of action and on findings in animals, obinutuzumab can cause fetal harm when administered to pregnant women.

7.6.3 Pediatrics and Assessment of Effects on Growth

The safety and effectiveness of obinutuzumab was not been established in pediatric patients. Clinical trials of obinutuzumab have not included sufficient numbers of pediatric patients to determine whether they respond differently than adult patients.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There were no cases of overdose of obinutuzumab on trial. There is typically no abuse potential for anti-cancer agents due to the adverse toxicity profile. The highest dose studied in patients with chronic lymphocytic leukemia was 2000mg in two Phase 1 trials with no differences noted in the incidence of AEs.

7.7 Additional Submissions / Safety Issues

Applicant submitted a 90 day safety report with a data cutoff date of March 19, 2013. No new safety issues were identified during the review of the safety update.

8 Postmarket Experience

Obinutuzumab is a new molecular entity and is not approved for marketing in any country at this time. There is no post-marketing experience with obinutuzumab.

9 Appendices

9.1 Literature Review/References

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Howlader N, Noone AM, Krapcho M, Garshell J, Neyman N, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Cho H, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2010, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2010/, based on November 2012 SEER data submission, posted to the SEER web site, 2013.

Huntley AL, Johnson R, Purdy S, et al. Measures of multimorbidity and morbidity burden for use in primary care and community settings: a systematic review and guide. Ann Fam Med. 2012;10(2):134-141.

9.2 Labeling Recommendations

The label is under development. Refer to the final version of the label. Safety review comments pertaining to labeling are throughout Section 7.

9.3 Advisory Committee Meeting

This application was not taken to ODAC (Oncologic Drugs Advisory Committee) because the trial design was acceptable and the Division has experience with the PFS endpoint in CLL. The results clearly demonstrated a positive risk: benefit ratio, so advice from ODAC was not needed for this application.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HYON-ZU LEE
10/01/2013

BARRY W MILLER
10/01/2013

VIRGINIA E KWITKOWSKI
10/01/2013
Concur.

CLINICAL FILING CHECKLIST FOR BLA

BLA Number: 125486/0 **Applicant: Genentech, Inc.** **Stamp Date: April 22, 2013**

Drug Name: Gazyva (obinutuzumab) **BLA Type: NME**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			X	351(a)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: BO20999 Study Title: An open-label, multicentre, non-randomized, dose-escalating Phase 1/2 study, with a randomized Phase 2 part, to investigate the safety and tolerability of RO5072759 (GA101) given as monotherapy in patients with CD20+ malignant disease. Sample Size: 134 (phase 1: 34, phase 2: 100) Arms: Phase 1 (single-arm), phase 2 (5 arms: iNHL 400mg, aNHL 400mg, iNHL 1600/800mg, aNHL 1600/800mg, CLL 1000mg)	X			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR BLA

	Content Parameter	Yes	No	NA	Comment
	Location in submission: eCTD 5.3.3.2 Study Number: BO21003 Study Title: An open-label, multicentre, dose escalating, Phase 1 / randomized Phase 2 study to investigate the safety and tolerability of RO5072759 (GA101) given as monotherapy in patients with CD20+ malignant disease. Sample Size: 200 (phase 1: 20, phase 2: 180) Arms: Phase 1 (single-arm), phase 2 (2 arms: RO5072759 and rituximab) Location in submission: eCTD 5.3.3.2				
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: BO21004/CLL11 Study title: An Open-label, Multi-center, Three Arm Randomized, Phase 3 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. Sample Size: 781 Arms: GClb, Clb, and RClb Location in submission: eCTD 5.3.5.1 Pivotal Study #2: None.	X			In general, 2 adequate and well-controlled trials are required. However, Congress amended section 505(d) to allow FDA to consider single pivotal trial and confirmatory evidence (FDAMA).
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?		X		Joseph Grillo (Clin Pharm) requested add'l info from sponsor, including an update on the status of the QT/QTc substudy of Study BO25454.
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate			X	

CLINICAL FILING CHECKLIST FOR BLA

	Content Parameter	Yes	No	NA	Comment
	number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?				
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	Orphan designation for CLL received on 2/17/12.
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR BLA

	Content Parameter	Yes	No	NA	Comment
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE?
Yes.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1) Provide the number of investigators in the BO21004/CLL11 trial who are sponsor employees (including both full-time and part-time employees).

Barry Miller
Clinical Reviewer of Safety

Hyon-Zu Lee
Clinical Reviewer of Efficacy

Virginia Kwitkowski
Clinical Team Leader

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HYON-ZU LEE
05/24/2013