CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125486Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	See Electronic Stamp
From	Virginia Kwitkowski, MS, RN, ACNP-BC
Subject	Cross-Discipline Team Leader Review
BLA #	BLA 125486
Applicant	Genentech
Date of Submission	April 22, 2013
PDUFA Goal Date	December 22, 2013
Proprietary Name / Established (USAN) names	Gazyva Obinutuzumab
Dosage forms / Strength	Liquid single-use vial; 1000 mg/40 mL (25 mg/mL)
Proposed Indication(s)	For the treatment of patients with previously untreated chronic lymphocytic leukemia
Recommended:	*Regular Approval*

1. Introduction

On April 22, 2013, Genentech submitted Biological License Application (BLA) 125486 under section 351(a) of the Public Health Service Act for their anti-CD20 monoclonal antibody, obinutuzumab (previously known as GA101 and R05072759), to the Division of Hematology Products. The application was complete upon submission and was filed as a priority review. Obinutuzumab is an anti-CD20 cytolytic antibody.

The Applicant proposed the following indication: "For the treatment of patients with previously untreated chronic lymphocytic leukemia".

To support the proposed indication, Genentech conducted a single randomized, multi-center 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. Background

Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia is the most common adult leukemia in Western countries with 15,680 new cases and 4,580 deaths estimated for 2013 in the United States[1]. CLL is characterized by progressive accumulation of these leukemic cells in the peripheral blood, bone marrow, and lymphoid tissues. CLL and small lymphocytic lymphoma (SLL) are different manifestations of the same disease and are managed in much the same way[2]. The

major difference is that in CLL, a significant number of the abnormal lymphocytes are also found in the bone marrow and blood, while in SLL the abnormal lymphocytes are predominately found in the lymph nodes[3].

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. (Source: Hyon-Zu Lee, Clinical Efficacy Review)

Because the median overall survival of patients with CLL ranges from 8-10 years, the Agency has not required overall survival data for approval of agents for CLL. PFS is an acceptable endpoint for regular approval in CLL indications.

Prior approvals of drugs/biologics for chronic lymphocytic leukemia (CLL) have been granted based upon clinically relevant and statistically robust prolongation of PFS as the primary endpoint. The table below provides a list of products that have been granted FDA approval for the treatment of CLL.

Approved Products for the Treatment of CLL	
Drug Name ***Date of Approval***	***Indication***
Chlorambucil/Leukeran 1957	CLL (unspecified)
Cyclophosphamide/Cytoxan 1959	CLL (unspecified)
Fludarabine/Fludara 1991	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/Campath 2007	Treatment of B-cell CLL
Bendamustine/Treanda 2008	CLL (unspecified)
Ofatumumab/Arzerra 2009	Treatment of patients with CLL refractory to fludarabine and alemtuzumab
Rituximab/Rituxan 2010	In combination with fludarabine and cyclophosphamide for the treatment of patients with previously untreated and previously treated CD20-positive CLL

Published treatment guidelines include the following regimens for the treatment of first-line CLL:

- Chlorambucil ± rituximab
- Bendamustine ± rituximab
- Cyclophosphamide, prednisone, ± rituximab
- Alemtuzumab
- Rituximab
- Fludarabine ± rituximab (FR)
- Fludarabine, cyclophosphamide, ± rituximab (FCR)
- Pentostatin, cyclophosphamide, rituximab (PCR)
- High-dose methylprednisone + rituximab
- Alemtuzumab ± rituximab
- Lenalidomide
- Cladribine
- Pulse corticosteroids

Treatment modalities for CLL have evolved from the use of single-agent alkylating agents to purine analog-containing regimens and chemoimmunotherapy combinations. The CALGB 9011 trial randomized 509 patients with previously untreated CLL to receive fludarabine, chlorambucil, or the combination of the two. The combination arm was stopped early due to excessive toxicity. Response rates between the fludarabine + chlorambucil and the fludarabine alone arm were similar. Fludarabine, compared with chlorambucil alone, provided a higher CR rate (20% vs. 4%), PR rate (43% vs. 33%), median response duration (25 mos. vs. 14 mos.), and median PFS (20 mos. vs. 14 mos.). There was no statistically significant difference in median OS between the two arms (66 mos. vs. 56 mos.), though crossover data was included in this analysis[4].

A European frontline CLL trial comparing fludarabine with the CAP (cyclophosphamide, doxorubicin, and prednisone) and CHOP regimens (n=938). Fludarabine and CHOP produced similar results in overall remission rates (ORR; 71%) compared to CAP (58%); CR rates were higher with fludarabine (40%) vs. 30% for CHOP and 15% with CAP. Median survival times were similar (69, 67, and 70 months, respectively). Fludarabine was found to have a more preferable tolerability profile than CHOP.

Chlorambucil is a frequently used treatment for patients with CLL who are not likely to tolerate higher intensity therapies. A Phase 3 randomized trial (CLL5) was conducted by the German CLL Study Group comparing fludarabine with chlorambucil in previously untreated patients >65 years with CLL (n=193). Fludarabine resulted in a significantly higher overall response rate (ORR) [72% vs. 51%] and median time to treatment failure [18 mos. vs. 11 mos.] than chlorambucil. However, no advantage for fludarabine was observed for PFS [19 vs. 18 mos.] or OS [46 mos. vs. 64 mos.][5]. Chlorambucil remains a viable treatment option for patients with CLL who are elderly or with comorbidities for whom more intensive regimens are not appropriate.

The median age at diagnosis of CLL is 72 years, with approximately 70% of patients diagnosed at age ≥65 years[6]. Due to the increased incidence of co-morbidities in patients in

this age group, the tolerability of CLL regimens is an important treatment selection decision factor.

Since 2007, four new agents have been approved for the treatment of CLL. Elderly patients predominate the population with CLL, and elderly patients are subject to an increased incidence of co-morbidities that may impact their ability to tolerate intensive chemotherapy. Therefore, the patients who enrolled in the trial are consistent with patients in the broad CLL indication.

The Applicant's selected comparator of chlorambucil for this trial is acceptable, given the population selected.

The Division of Hematology Products and the previous review division (Division of Biologic Oncology Products) met with Genentech on several occasions to discuss this trial. The reader is referred to the primary clinical review by Dr. Lee and Mr. Miller for a detailed review of the interactions that occurred between the Applicant and FDA regarding this indication and the pivotal trial. One main area of disagreement was regarding how to define a population of patients with CLL who were unsuitable for fludarabine. The Agency did not agree to the use of the vague term (b) (4) or use of the Cumulative Illness Rating Scale (CIRS) to identify this population, because of a lack of validation for this purpose. The Agency advised the Sponsor to ensure that the patients enrolled met the criteria for "need for treatment". The Agency did not agree with the planned primary endpoint of PFS by investigator, and recommended that the primary endpoint be PFS by IRC. There was agreement that CT scans would be performed at baseline, to confirm objective response, and to confirm progressive disease in those patients who progress based on physical exam only (new or increased lymph node size or new/increasing organomegaly).

During the pre-BLA meeting (02/22/13), the Agency strongly encouraged Genentech to work to ensure that obinutuzumab product development (CMC) would be prepared for launch at the time of expedited action. Genentech stated that based upon information available at this time, BA-101 product should be available by December 1, 2013.

On May 9, 2013, obinutuzumab was granted Breakthrough Therapy Designation in combination with chlorambucil for the treatment of patients with previously untreated CLL. The full advantages of Breakthrough Therapy Designation were not available to the Applicant because the designation was submitted so close to the BLA submission.

3. CMC

Due to the Agency plan to expedite the review of the BLA and the lack of availability of (b) (4) on that timeline, the Agency worked with the Applicant to develop a plan for (b) (4) obinutuzumab. Genentech stated early in the BLA review that they had (b) (4) . The CMC review team confirmed that the (b) (4) . Without this agreement, (b) (4) .

The CMC review team members assigned to this application are:

Product Quality Team: Mate Tolnay, Ph.D. (Traditional Elements Reviewer)
Chikako Torigoe, Ph.D. (Quality by Design Reviewer)
Laurie Graham, M.S. (Quality by Design Team Leader)
Marjorie Shapiro, Ph.D., (Traditional Elements Team Leader)

BMAB: Don Obenhuber, Kalavati Suvarna and Colleen Thomas; Patricia Hughes (Team Leader)

The primary review by Mate Tolnay, Ph.D. and Chikako Torigoe, Ph.D. states that approval is recommended. The summary of recommendations from their review are noted below:

A. Recommendation on Traditional Elements:
We recommend approval of the BLA. The data submitted in this Biologics License Application support the conclusion that the manufacture of Gazyva (obinutuzumab) is well controlled, and leads to a product that is pure and potent. The product is free of endogenous and adventitious infectious agents sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product has been manufactured form multiple production runs. It is recommended that Gazyva (obinutuzumab) be approved for human use (under conditions specified in the package insert).

We recommend an expiration dating period of (b) (4) for obinutuzumab drug substance when stored at (b) (4)

We recommend an expiration dating period of 36 months for obinutuzumab drug product when stored at 2-8 C.

We recommend approval of the proposed release and shelf-life test methods and specifications for obinutuzumab drug substance and drug product.

B. QbD: We recommend the approval of the proposed design space and the Post-Approval Lifecycle Management (PALM) plan for obinutuzumab manufacturing. Revisions to the testing strategy, PALM plan, and design space were agreed to during the review cycle.

II. List Of Deficiencies To Be Communicated
There are no CMC-related deficiencies precluding approval of this BLA.

III. List Of Post-Marketing Commitments/Requirement
A formal verification for hold times of (b) (4) from manufacturing scale samples for up to (b) (4) will be completed in December 2013. The final study report will be submitted to the Agency by February 28, 2014.

IV. Review Of Common Technical Document-Quality Module 1

A. A categorical exclusion is claimed from the requirement to prepare an environmental assessment in accordance with 21 CFR 25.31(c). ***The claim of categorical exemption is accepted.***

V. Primary Container Labeling Review
The initial CMC review of the Drug Product Label was generated under a separate consult to Kimberly Rains. The final review incorporating Genentech's response to recommendations for changes to the container and carton labels was performed by Mate Tolnay.

VI. Review Of Common Technical Document-Quality Module 3.2
The review of module 3.2 is provided below. A review of the product immunogenicity assays is included at the end of the primary review document.

VII. Review Of Immunogenicity Assays – Module 5.3.1.4
The current second generation immunogenicity assay has sufficient sensitivity (18.4 ng/mL) and it has acceptable drug tolerance (500 ng/mL HAHA can be determined to be positive in a sample containing up to 47.8 µg/mL drug).

The immunogenicity assay is adequately validated. No inconclusive HAHA results were obtained in assessing clinical samples with both the first and second generation HAHA assay. No neutralizing antibody assay exists. Instead, neutralizing potential is evaluated using a complex approach based on correlation of several parameters.

The recommendations and conclusions on approvability from Marjorie Shapiro's Team Leader's Executive Summary are as follows:

> The Division of Monoclonal Antibodies, Office of Biotechnology Products, OPS, CDER, recommends approval of STN 125486 for obinutuzumab (Gazyva™) manufactured by Genentech. The data submitted in this application are adequate to support the conclusion that the manufacture of obinutuzumab (Gazyva™) is well controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use (under conditions specified in the package insert).

One Post-Marketing Commitment is Identified for CMC:

PMC #1
A formal verification for hold times of (b) (4) from manufacturing scale samples for up to (b) (4) will be completed in December 2013. The final study report will be submitted to the Agency by February 28, 2014.

Description of Obinutuzumab (Gazyva™) drug substance and drug product
Obinutuzumab is a full length recombinant, humanized, immunoglobulin IgG1, monoclonal antibody (GA101, huMAb <CD20>, RO5072759) that is directed to CD20, a membrane protein expressed on B lymphocytes. Obinutuzumab is comprised of (b) (4)

[redacted] The total molecular weight of obinutuzumab is approximately [redacted] Da, with [redacted]

Obinutuzumab drug product is supplied as a sterile, preservative-free liquid solution at 25 mg/ml in 50 mL single-dose vials. Obinutuzumab drug product is formulated in 20 mM L-histidine (L-histidine and L-histidine hydrochloride [redacted]), 240 mM trehelose [redacted] and 0.02% (w/v) poloxamer 188, pH 6.0. The inclusion of 20 mM L-histidine [redacted] while 240 mM trehelose [redacted] poloxamer 188 at 0.02% (w/v) [redacted] As supplied, the solution of obinutuzumab drug product has a clear to slightly opalescent, colorless to slightly brownish appearance [redacted]. It is supplied in single-use, 50 mL vials containing 1000 mg (nominal) obinutuzumab for intravenous (IV) infusion. The extractable volume of each vial is a minimum 40 mL.

The intended long term storage temperature for obinutuzumab drug product is 2-8 C.
The primary packaging components for obinutuzumab drug product consist of a USP/Ph. Eur./JP Type 1, 50 ml colorless [redacted] glass vial that is sealed with a 20 mm [redacted] rubber stopper [redacted] and crimped with a 20 mm aluminum seal, then fitted with a slip off plastic cap.

Obinutuzumab is diluted into 250 mL 0.9% saline PVC or non-PVC polyolefin infusion bags immediately prior to administration. The diluted infusion solution can be stored at 2-8°C for up to 24 hours. The obinutuzumab drug product vial does not contain any overages.
A claim for a categorical exclusion from the Environmental Assessment (EA) requirement has been submitted under 21CFR section 25.31(c), which states that any application for marketing approval of a biologic product for substances that occur naturally in the environment, or supplement to such an application, is categorically excluded and ordinarily does not require an EA or an Environmental Impact Statement when there is not a significant alteration of the concentration or distribution of the substance, its metabolites or degradation product in the environment. The Sponsor states that no extraordinary circumstances exist with respect to this product. There is no indication that additional environmental information is warranted. The claim of categorical exclusion is deemed acceptable.

The Product Quality Microbiology Review was conducted by Colleen Thomas, Ph.D. (Team Leader, Patricia Hughes, Ph.D.) and Don Obenhuber, Ph.D. (Branch Chief, Zhihao Peter Qiu, Ph.D).

The summary recommendation for approvability in Dr. Thomas's primary review was as follows:
The BLA was reviewed from a product quality microbiology perspective. Approval cannot be recommended until acceptable microbial retention data for the [redacted] has been

provided. The study data will be submitted to the BLA the week of 7 October 2013. The study data will be reviewed in an addendum to this memo.

Dr. Thomas submitted an amendment to her review on 10/15/13 after completion of her review of Amendment 0040 that was submitted on 10/09/13 providing additional microbial retention data for the (b) (4). Her conclusions in this amendment to her review are as follows:

Conclusion
I. The BLA, as amended, was reviewed from a product quality microbiology perspective and is recommended for approval.
II. Product quality aspects other than microbiology should be reviewed by OBP.
III. No inspection follow-up items were identified.

With this amendment, no further CMC deficiencies exist that would preclude the approval of the BLA.

Donald Obenhuber's primary review concludes that "the BLA, as amended, is recommended for approval from a product quality microbiology perspective."

He recommends the following PMC #2: *Submit a protocol for* (b) (4) *The protocol should include bioburden and endotoxin limits to demonstrate continued microbial control over* (b) (4). *The protocol should be submitted as a CBE-30 by 31 Dec 2013. Execute the protocol and provide the results in the annual report following the approval of the CE-30.*

(b) (4)

Review comment (From Dr. Obenhuber's review): *During the pre-license manufacturing inspection on* (b) (4), *a CDER request was made to review the GMP compliance of* (b) (4)

Several changes were introduced (b) (4).

Reviewer comment: *(b) (4) lots met the same established criteria for microbial control as the (b) (4) lots.*

Review Conclusions:
I. This BLA, as amended, is recommended for approval from a product quality microbiology perspective.
II. Information and data in this submission not related to the product quality microbiology was not evaluated and should be reviewed by an OBP reviewer.
III. No additional inspectional follow-up items were identified.

The Product Quality Microbiology Review of the Leptospira PCR assay validation and testing was conducted by Kalavati Suvarna, Ph.D. The Team Leader was Patricia Hughes, Ph.D.

The Executive Summary and Conclusion from this review states:

> The subject of this BLA is obinutuzumab, a recombinant humanized anti-CD20 monoclonal antibody produced in Chinese Hamster Ovary (CHO) cells. This review only covers the *Leptospira* PCR assay validation and testing applied during drug substance manufacture as described in the original BLA and amendments (eCTD sequences 0013 dated 7/25/2013; 0015 dated 8/1/2013, and 0022 dated 8/22/2013). For a review of the microbial controls in drug substance manufacture, please see the review by Donald Obenhuber. The drug substance is manufactured and released at Roche Diagnostics GmbH, Nonnenwald 2, D-82377 Penzberg, Germany, Inc. (FEI No. 3002806560).
>
> The Leptospira real time PCR assay will be implemented (b) (4) in the commercial obinutuzumab manufacturing process for the detection of *Leptospira* (b) (4). The applicant indicated that the assay is being implemented (b) (4) in response to the *Leptospira* contamination observed in Rituxan manufacturing process at the Vacaville facility in California. The real time Leptospira PCR assay was validated to detec (b) (4) *Leptospira* (b) (4). Appropriate positive and negative controls were used. The validation assessed the specificity, sensitivity, and robustness of the assay. Overall, the real time qualitative PCR assay is acceptable for the detection of *Leptospira* in the Obinutuzumab (b) (4) samples.

- **Facilities review/inspection**
  The pre-license inspection of the drug substance manufacturing site at Roche Diagnostics GmbH, Penzberg, Germany was conducted on August 7-14, 2013 by Donald C. Obenhuber, BMAB and Kurt Brorson, Mate Tolnay and Chikako Torigoe,

DMA. The inspection covered the manufacturing of drug substance at the (b) (4) The inspection was system-based and covered Quality, Production, Laboratory Control, and Facilities and Equipment Systems. In addition, the inspection included extensive coverage of the QbD aspects of the manufacturing process. No Form FDA483 was issued. It was recommended that the inspection be classified as no action indicated. The pre-license inspection of the drug product manufacturing site was waived.

On 10/17/13, the Office of Compliance (Christinea A Capacci-Daniel) issued a Therapeutic Biological Establishment Evaluation in which they stated that "there are no pending or ongoing compliance actions that prevent approval of this supplement".

- **Other notable outstanding issues**
  None. There are two PMCs for this BLA, both regarding CMC (#1 is final and agreed upon by the FDA and Genentech and #2 is being sent to Genentech on the date of this review).

4. Nonclinical Pharmacology/Toxicology

The nonclinical pharmacology/toxicology review was conducted by M. Stacey Ricci, M.Eng, Sc.D., Pedro L. Del Valle, Ph.D., Armaghan Emami, Ph.D., and Natalie E. Simpson, Ph.D. The reviews were supervised/team led by Haleh Saber, Ph.D. Concurrence was obtained from the DHOT Division Director, John K. Leighton, Ph.D., D.A.B.T.

The nonclinical review team concluded that the submitted pharmacology and toxicology studies using obinutuzumab (Gazyva) support the safety of its use in patients with previously untreated CLL, and that no further nonclinical studies were necessary for the proposed indication. There are no proposed Pharm/Tox Post-Marketing Commitments or Requirements.

The italicized information below is summarized from the primary Pharmacology / Toxicology review.

Obinutuzumab binds to the extracellular loop of the CD20 transmembrane antigen expressed on the surface of pre B and mature B lymphocytes (B-cells). The CD20 antigen is present on both normal and malignant B-cells, and there are multiple anti-CD20 antibody therapies approved for treatment of B-cell malignancies.2 The proposed mechanism of action of obinutuzumab is that upon binding to CD20, obinutuzumab mediates B-cell lysis through (1) engagement of immune effector cells that mediate B-cell cytolysis, (2) activation of the complement cascade, and/or (3) by directly activating intracellular death signaling pathways. The immune effector cell mechanisms include antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP), both activities mediated through binding of the Fc region of obinutuzumab with Fc gamma receptor (i.e., FcγRIIIa) receptor positive effector cells, such as natural killer (NK) cells and macrophages/monocytes. Complement-mediated

cytotoxicity (complement-dependent cytotoxicity; CDC) can also mediate obinutuzumab induced cell death. The mechanism of directly activated cell death is still under investigation but data provided suggests that it is independent of caspase activation, involves homotypic aggregation of CD20 molecules and is dependent on actin reorganization and lysosome disruption.

The manufacturing of obinutuzumab involves the manipulation of its pattern of glycosylation (termed glycoengineering), a process that reduces fucosylation of the Fc region of the mAb and results in an increased affinity for FcγRIII receptors and subsequent activation of antibody-dependent cellular cytotoxicity.

Pharmacology studies demonstrated that obinutuzumab has a high selectivity and affinity for human CD20 ($K_D \approx 4.0$ nM). Mechanistic studies identified that obinutuzumab can induce cell death in three ways: (1) autonomously, by directly activating internal cell death signaling pathways; (2) through Fc receptor-mediated immune effector cell activated pathways (ADCC/ADCP); and (3) antibody activation of the complement cascade (CDC).

Toxicology studies were conducted solely using cynomolgus monkeys because other species available for toxicity testing are not pharmacologically responsive to obinutuzumab. Obinutuzumab binds human and cynomolgus monkey CD20 with similar affinity. Evaluation of the genotoxicity, carcinogenicity and dedicated safety pharmacology studies were not conducted and were not needed for this application.5 Repeat dose toxicology studies of 13-week or 26-week duration with extended recovery periods were conducted using IV administration of obinutuzumab. A separate 4-week study that evaluated subcutaneous (SC) administration was also completed. The IV route is recommended for administration of Gazyva. Toxicities observed from repeat dose studies were consistent with the intended pharmacology of obinutuzumab or were the apparent result of cross-species immunogenicity effects:

- *Near-100 per cent decreases in circulating B lymphocytes occurred after the 1st dose of ≥1 mg/kg or SC doses of 30 mg/kg. Corresponding B-cell depletion in lymphoid tissues at IV doses was also observed at these doses at necropsy. At the end of a 37-week recovery, circulating B-cell recovery was variable (individual peak values ranged from 7% to 152% of baseline), while lymphoid tissue B cells fully recovered when compared with controls. Transient decreases in NK cells were observed which can be explained by obinutuzumab-mediated ADCC activity.*

- *Hypersensitivity reactions were noted at all doses (≥5 mg/kg) in the 26-week study and were attributed to cross-species reactivity to a foreign protein. Clinical observations included acute anaphylactic/anaphylactoid reactions (clinical signs consisted of excessive salivation, facial erythema that progressed to the arms, with evident pruritus). Microscopic findings included an increased prevalence of systemic inflammation and infiltrates consistent with immune-complex mediated hypersensitivity reactions including glomerulonephritis, and arteritis/periarteritis and*

serosal/adventitial inflammation in multiple tissues. These reactions led to the unscheduled deaths of 6 (possibly 7) monkeys during the 26-week study. Although animals treated at all obinutuzumab dose levels were affected, the incidence and severity of inflammatory changes were greater in animals given 25 or 50 mg/kg than in animals given 5 mg/kg. Immune-complex deposition in glomeruli of some animals was confirmed by detection of electron dense deposits by immunohistochemistry or transmission electron microscopy.

- *Suspected opportunistic infections in an additional three unscheduled deaths from the shorter repeat-dose studies were considered a secondary result of obinutuzumab-mediated immunosuppression.*

No effects were noted for male and female reproductive organs in repeat dose toxicology studies. In males, no effects were noted on sperm morphology, concentration or motility. In females, no effects were noted on prolactin, estrus-related hormone levels or cycle duration.

An enhanced pre- and post-natal development (ePPND) toxicity study was conducted. Administration of obinutuzumab to pregnant cynomolgus monkeys resulted in a complete depletion of B lymphocytes in infants. Obinutuzumab did not affect embryofetal development, parturition, postnatal survival, or the growth and development of infants. The incidence of prenatal loss was higher in treatment groups when compared to controls but were within the range of historical data provided for the testing facility. Obinutuzumab crosses the blood-placental barrier and it is secreted in the milk of pregnant monkeys. A comparison of systemic exposure estimates between the high dose group in the ePPND study and clinical AUCs measured in patients with CLL showed that the exposure to obinutuzumab in monkeys were ~5 times the exposure in patients at the recommended clinical dose. Because of the depletion of B-cells and possible opportunistic infections, use of obinutuzumab during pregnancy is not recommended.

In vitro analysis of obinutuzumab using whole blood from healthy human donors indicated that obinutuzumab can cause first-infusion cytokine release in patients. Clinical study results demonstrated the frequent occurrence of infusion-related reactions IRRs) within 24 hours following the first infusion of obinutuzumab. The most common symptoms of the IRRs were nausea, chills, hypotension and pyrexia. Protocol amendments made during clinical investigation of obinutuzumab included reducing infusion rates, splitting the dose administered over two days or premedication with antipyretic, anti-histamine and corticosteroid prophylaxis. Prophylactic pretreatment with analgesics, and possibly steroids or antihistamines is recommended prior to dosing.

Unexpected tissue cross-reactivity staining using obinutuzumab was observed localized in the membrane of human and monkey liver epithelium, salivary glands and lung endothelium. The appearance of off-target effects from binding to these tissues was not readily apparent in the studies conducted in monkeys.

Toxicology studies were conducted solely using cynomolgus monkeys because other

species available for toxicity testing are not pharmacologically responsive to obinutuzumab. Obinutuzumab binds human and cynomolgus monkey CD20 with similar affinity. Evaluation of the genotoxicity, carcinogenicity and dedicated safety pharmacology studies were not conducted and were not needed for this application.

CDTL Comment: Toxicities observed in the clinical trial (lymphocyte depletion, opportunistic infections, and hypersensitivity infusion reactions) were predicted by the nonclinical studies. There are no outstanding Pharmacology Toxicology issues for this application.

5. Clinical Pharmacology/Biopharmaceutics

The primary Clinical Pharmacology review was conducted by Joseph Grillo, B.S. Pharm., Pharm.D. and Sarah Schrieber, Pharm.D. of DCP-5. The secondary review was conducted by the Clinical Pharmacology Team Leader, Julie Bullock, Pharm.D. The Pharmacometrics Review was conducted by Jeffry Florian, Ph.D., and supervised by Nitin Mehrotra, Ph.D. of DPM. The Primary review was co-signed by Julie Bullock.

The *italicized* text below is from the primary Clinical Pharmacology review.

The Office of Clinical Pharmacology has determined that there is sufficient clinical pharmacology and biopharmaceutics information provided in this BLA to support a recommendation of approval of Gazyva. The OCP requests no Post Marketing Commitments or Requirements. The OCP review does indicate that the following comments should be communicated to the Applicant:

- *Submit the results of your long-term 36 month frozen matrix stability testing for the ELISA developed by Roche and* (b) (4) *and used to detect obinutuzumab concentrations in your clinical trials submitted in support of this application when they are available.*
- *Submit the final study report and relevant data assessing the potential for obinutuzumab to prolong the QT interval in patients with previously untreated, low tumor-burden indolent NHL from a substudy of trial BO25454.*

Summary of Important Clinical Pharmacology Findings:

Gazyva (Obinutuzumab) is a recombinant monoclonal humanized and glycoengineered CD20 antibody of the IgG1 isotype. Obinutuzumab targets the extracellular loop of the CD20 transmembrane antigen on the surface of non-malignant and malignant preB and mature B lymphocytes.

The efficacy and safety of obinutuzumab in combination with chlorambucil (Clb) in previously untreated chronic lymphocytic leukemia (CLL) patients are based on a single pivotal phase 3 trial.

The applicant's proposed dosing regimen is based on a 28 day cycle and includes three components:

i) splitting of the initial dose over two days (100/900 mg on days 1 and 2 instead of 1000 mg on day 1) to reduce infusion related reaction risk;
ii) administration of 3000 mg (1000 mg every week for three weeks) in cycle 1 to overcome target-mediated drug disposition; and
iii) selection of a 1000 mg dose for cycles 2-6.

The PFS results from the phase 3 trial support that the proposed dosing regimen improved PFS across all exposure quartiles. Also, the dose intensification over cycle 1 results in obinutuzumab exposures closer to steady state by cycle 2. Further, the available evidence supports that splitting of the dose achieves its purpose of reducing infusion-related adverse events with the first dose.

An exposure-response relationship was identified for obinutuzumab and PFS, duration of response, and event-free survival in subjects with previously untreated lymphocytic leukemia. No relationship was identified between overall survival and obinutuzumab exposure; however, the sample size was small. There is also evidence of increased likelihood of certain adverse events with obinutuzumab treatment, including the percentage of subjects with grade 3 or higher cardiac events, tumor lysis syndrome, neutropenia, and thrombocytopenia. The available data did not support an exposure-response relationship between obinutuzumab exposure and adverse event rate.

Five clinical studies were submitted to characterize the PK/PD of obinutuzumab, however only the three trials that enrolled CLL patients were used to describe the PK/PD of obinutuzumab.

The PK of obinutuzumab were described using population PK analysis by a two-compartment pharmacokinetic model with two clearance mechanisms, one time-dependent clearance and the other linear and time independent. At the start of treatment, the time-dependent clearance is predominant but reduces over time. The model reports that at the start of treatment, the initial mean$_{geo}$ (CVgeo) obinutuzumab clearance (time-dependent clearance + time independent clearance; *CLinit) and half-life (t1/2init) were estimated at 0.44 (78) L/day and 6.2 (69) days, respectively. Obinutuzumab's time-dependent clearance was found to decline with a half-life of approximately 17 days. At steady-state (approximately 4 months), the linear time-independent clearance dominates. The model reports that at presumed steady state the terminal mean$_{geo}$ (CV$_{geo}$) obinutuzumab clearance (CL$_{term}$), volume of distribution (Vd$_{term}$) and half-life (t1/2$_{term}$) were estimated at 0.09 (46) L/day, 3.8 (23) L, and 28.4(43) days, respectively. Steady state exposure estimates were consistent with the NCA derived estimates. Body weight, gender, disease type (i.e., CLL, Non-Hodgkin's lymphoma (NHL), or mantle cell lymphoma (MCL)), and tumor size were identified as positive covariates in the population model, but their impact on obinutuzumab exposure did not warrant a dose modification. Mild or moderate renal impairment did not affect obinutuzumab exposure. There is insufficient data available to determine the effect of severe renal impairment or any degree of hepatic impairment on obinutuzumab exposure.*

A visual assessment of the mean dose normalized obinutuzumab Cmax and AUC7d in CLL patients from trial BO20999 shows a trend toward dose proportionality at doses studied in CLL patients (400 - 2000 mg). The calculated accumulation ratio following multiple dosing of

obinutuzumab ranged from 2.7 to 3.8 and 2.3 to 2.7 based on the AUC7d and Cmax, respectively.

In the phase 1 and 2 trials, circulating CD19+ B-cells were depleted (defined as CD19+ B-cell counts < 0.07 x 109/L) within the first three weeks of Gazyva therapy in the majority evaluable patients with CLL. In the phase 3 trial, 40 (91%) out of 44 evaluable CLL patients treated with Gazyva in combination with chlorambucil were B cell depleted at the end of treatment period. These patients remained depleted during the ensuing 6 months of follow up. Recovery of B cells was first observed within 9-18 months of follow up with a reported recovery in a total of 18 (46%) patients within 12-18 months.

Serum samples from CLL patients in the phase 3 trial were tested during and after treatment for antibodies to Gazyva. Approximately 13% (9/70) of Gazyva treated patients tested positive for anti-Gazyva antibodies at one or more time points during the 12 month follow-up period. The presence of Gazyva in patient serum at the time of anti-therapeutic antibody (ATA) sampling can interfere with the ability of this assay to detect anti-Gazyva antibodies. As a result, data may not accurately reflect the true incidence of anti-Gazyva antibody development. Neutralizing activity of anti-Gazyva antibodies has not been assessed.

QT Evaluation: There have been no specific assessments of QT/QTc interval in clinical studies conducted with obinutuzumab to date. ECG monitoring was included in early Phase I studies with obinutuzumab and no cardiac safety signal were identified from the ECG monitoring. The Agency agreed with the applicant's proposal to study the effect of obinutuzumab on the QT/QTc interval in a substudy of trial BO25454 which is planned to begin on or about July 15, 2013. The applicant anticipates completion in August, 2015. The protocol for this substudy was submitted to the Agency in April 2013 and no substantive issues were identified in either the IRT or OCP reviews in May 2013. The reviewer finds this plan acceptable and recommends a comment be sent to the applicant to submit the final study report and relevant data assessing the potential for obinutuzumab to prolong the QT interval in patients with previously untreated, low tumor-burden indolent NHL from a substudy of trial BO25454.

A mass balance trial was not conducted for obinutuzumab. Mass balance studies are generally not performed for protein drugs because they are degraded into amino acids that then recycled into other proteins.

Metabolism studies were not conducted for obinutuzumab. Metabolism studies are generally not performed for protein drugs because they are degraded into amino acids that are then recycled into other proteins.

The elimination of obinutuzumab can be described by two clearance mechanisms, one time dependent clearance and the other linear and time independent. At the start of treatment, the time-dependent clearance is predominant but reduces over time. At steady-state (approximately 4 months), the linear time-independent clearance dominates. The Pop-PK covariate analysis finds that the rate at which the time dependent clearance diminishes and the linear predominates is affected by tumor size.

Food effects and bioavailability are not an issue with intravenously administered medications.

Drug-Drug Interactions: No in vitro studies were conducted to evaluate drug-drug interactions. Since, monoclonal antibodies are generally catabolized by ubiquitous proteolytic enzymes the reviewer finds this acceptable. Additional studies are not recommended at this time. The proposed labeling specifies co-administration with chlorambucil. The interaction potential between these two agents is unknown at this time. The Agency agreed with the Applicant's proposal to not further evaluate the DDI potential between obinutuzumab and chlorambucil because the latter is "well-characterized" and its ADME properties (high clearance, short half -life) make any clinically significant drug-drug interaction with chlorambucil very unlikely. No additional investigation regarding this issue is recommended at this time.

Drug-Disease interactions: The covariate analysis indicated that CL_{Term} was 19% lower in NHL patients, and 68% higher in MCL patients compared to CLL patients. In addition, the decline of CL_{TD} was 87% faster in NHL compared to CLL patients. Based on these findings model-based simulations and simulations using conditional estimates of the individual PK parameters indicate that the steady-state AUCτ (C_{trough}) following the dosing regimen of study BO21004/CLL11 was approximately 27% (39%) higher in NHL patients and 39% (54%) lower in MCL patients compared to CLL patients. This covariate finding is somewhat limited by the inability to resolve the potential contribution of the different relative tumor size associated with the respective disease types. Despite this the reviewer finds this analysis acceptable. This issue should be considered when reviewing any future sNDA application for different diseases.

Extrinsic Factors:
There are no known extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) that are known to influence dose-exposure and/or –response.

Intrinsic Factors:
Body weight, gender, disease type (i.e., CLL, Non-Hodgkin's lymphoma (NHL), or mantle cell lymphoma (MCL)), and tumor size were identified as positive covariates in the population model, but their impact on obinutuzumab exposure did not warrant a dose modification.

<u>Age:</u> The covariate analysis indicated that the PK of obinutuzumab was independent of age. The PK of obinutuzumab was not evaluated in pediatric patients. The applicant is seeking a disease-specific waiver based on obinutuzumab's orphan drug designation.

<u>Gender:</u> The covariate analysis indicated the CL_{term} and Vd_c were 23% and 18% higher in males, and the time dependent clearance (CLTD) was 52% higher in males. Model-based simulations and simulations using conditional estimates of the individual PK parameters indicate that the steady state AUCτ (C_{trough}) for the dosing regimen evaluated in CLL11 was approximately 26% (29%) lower in males. The reviewer considers these results inconclusive because this covariate may have been potentially confounded with body weight, the impact of disease on exposure, and the sampling schedule. (b) (4)

Hepatic Insufficiency: There have been no formal trials undertaken to investigate the impact of hepatic impairment on obinutuzumab PK. There is insufficient data available to determine the effect of any degree of hepatic impairment on obinutuzumab exposure.

Renal Insufficiency: Mild or moderate renal impairment did not affect obinutuzumab exposure. There is insufficient data available to determine the effect of severe renal impairment on obinutuzumab exposure.

Race: The applicant attempted to explore the potential impact of Japanese ethnicity on the PK by conducting a post hoc descriptive analysis comparing AUC_{last} from trial JO21900 with trial BO20999 which employed a similar design. There were no CLL patients in trial JO21900. Following a request from the FDA the applicant stated, in a 6/3/13 response, that NCA dataset for trial JO21900 was not immediately available and could not be submitted. Therefore, these data could not be verified by the Agency. The Applicant does report that based on this analysis there was a marked overlap between the AUC_{last} distributions in the two studies and no clear difference was observed). Given the anecdotal nature of this analysis combined with the known disease effect and the Agencies inability to verify the JO21900 data, the reviewer finds these results inconclusive (b) (4)

Julie Bullock, Pharm.D. was the Team Leader for Clinical Pharmacology for this application. Her review concurs with the primary reviewers that there is sufficient information provided in this BLA to support approval of Gazyva for the treatment of patients with untreated CLL in combination with chlorambucil.

She provides an additional comment to be communicated to the Applicant as follows:

"We recommend exploring, as part of your future trials, weight-based dosing for obinutuzumab for the treatment of CLL as well as other indications that you are pursuing. While a fixed-dose of obinutuzumab was utilized in BO21004, an assessment of progression free survival based on obinutuzumab exposure quartiles indicated that higher obinutuzumab exposures were associated with longer progression free survival. These relationships remained even after accounting for confounding factors in the analysis such as baseline lymphocyte count, tumor burden, and ECOG score. In addition, the population PK analysis demonstrated that body weight was a covariate for obinutuzumab exposure, in addition to other factors such as overall tumor burden and type of disease. Altogether, these observations suggest that weight-based dosing of obinutuzumab may provide more consistent obinutuzumab exposures in patients, and in turn, a better anti-tumor response, particularly in subjects with heavier body weights."

CDTL Comment: There are no outstanding Clinical Pharmacology issues that would prevent the approval of Gazyva. Clinical Pharmacology has reviewed and provided input on the proposed Product Labeling. The Clinical Pharmacology comments above should be communicated to the Applicant in the approval letter.

6. Clinical Microbiology

N/A: only applicable to antimicrobial agents.

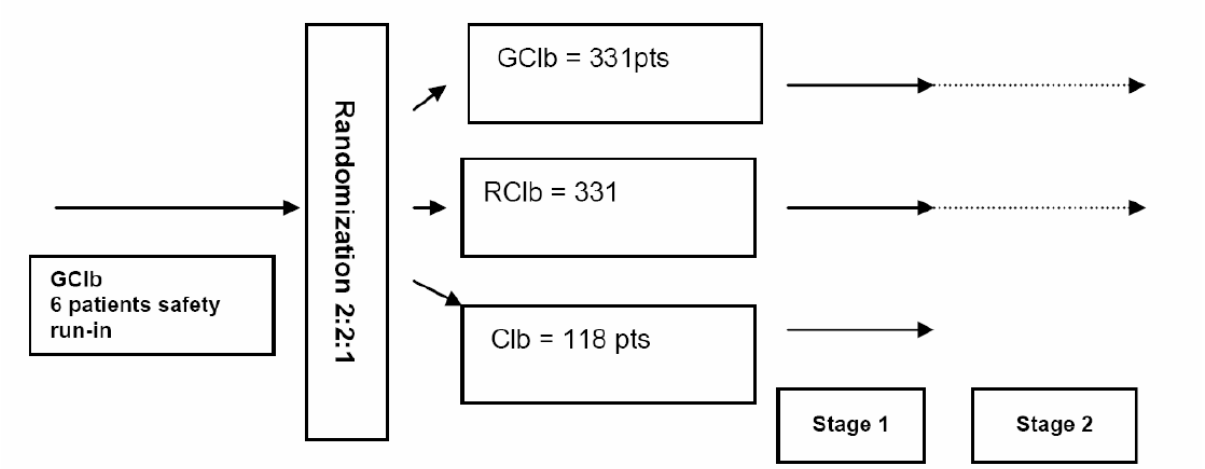
7. Clinical/Statistical- Efficacy

In support of the proposed indication, Genentech conducted trial 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.

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.

Trial Schema of BO21004/CL11



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.

<u>Treatment:</u>

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). This treatment plan was modified after Protocol Amendment G so that the first dose was divided up to provide 100 mg on Day 1 and 900 mg on day 2. Forty-five patients received this altered schedule of administration.

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/m2 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, chlorambucil: 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).

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, premedications were administered as follows:

- *Acetominophen/paracetamol 650-1000 mg by mouth 30 minutes prior to 1st infusion*
- *Antihistamine (i.e., diphenhydramine 50-100 mg) by mouth 30 minutes prior to 1st infusion*
- *Steroid (i.e., prednisolone or prednisone 100 mg IV at least one hour prior to the first obinutuzumab and rituximab infusion*

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.*

Tumor Lysis Syndrome Prevention: 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.

Trial Results:
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.

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.

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.

Trial B021004, 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. All patients fulfilled the criteria for initiating treatment including patients who were in Binet stages A and B. Known baseline negative prognostic factors for CLL were equally distributed between treatment arms. Baseline comorbidity was balanced between treatment arms. Details of these analyses can be found in Dr. Lee's review.

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).

Efficacy Results

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.

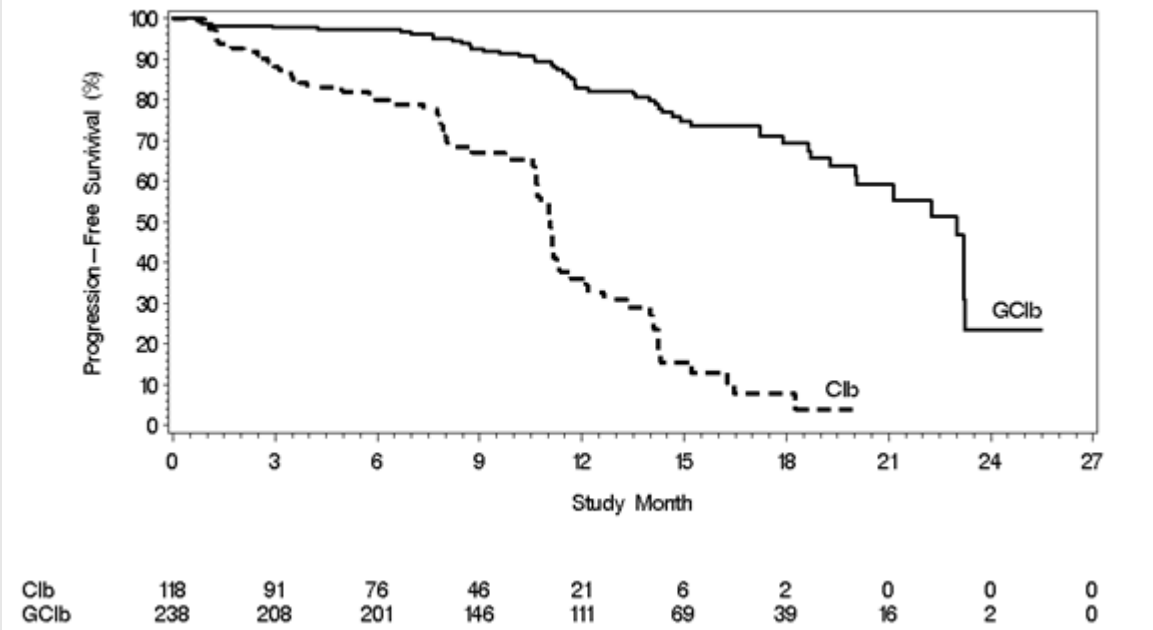
The IRC assessed hazard ratio (stratified) was 0.16 (95% CI: 0.11, 0.24), log-rank p-value <0.0001.

B021004, 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	

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%)].

B021004, Stage 1a: Kaplan Meier Estimates of IRC-Assessed PFS (ITT)



CDTL Comment: The PFS curves separate at around 2 months and remain separated throughout the observation time. The PFS advantage for obinutuzumab + chlorambucil is robust, statistically significant, and clinically meaningful. I concur with Dr. Lee's recommendation for regular approval of obinutuzumab in combination with chlorambucil for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL).

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.

B021004, 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.

CDTL Comment: Sensitivity analyses were conducted to evaluate the robustness of the primary analysis. The results of these analyses were supportive of the primary endpoint and can be found in Dr. Lee's review.

Key Secondary Analyses:

- 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].

- 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%)].

B021004, Stage 1a: Best Overall Response (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

CDTL Comment: The secondary endpoint of best overall response is supportive of the primary endpoint (PFS).

- 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.

- 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.

- Disease-free survival

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.

- 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.

- Overall survival

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.

- 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.

B021004, 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

Other Endpoints of Interest

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)

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.

B021004, Stage 1a: Hazard Ratio (GClb vs. Clb) for PFS by Subgroup (INV 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

Trial Conduct Issues:
Dr. Lee concluded that due to the small numbers of protocol violations and the equal distribution between arms, the violations are not likely to have affected the overall trial conclusions. I concur with that assessment.

(Source: Hyon-Zu Lee, Clinical Review)

The biostatistical primary reviewer was Chia-Wen Ko, Ph.D. Her team leader was Lei Nie, Ph.D. Concurrence was provided by Rajeshwari Sridhara, Ph.D., DB5 Division Director.

The Executive Summary from Dr. Ko's review states:

The pivotal trial supporting this application is an ongoing Phase III, open-label, three-arm randomized, parallel-group study of obinutuzumab + chlorambucil (GClb) vs. rituximab + chlorambucil (RClb) vs. chlorambucil (Clb) alone in previously untreated CLL patients. This trial includes two stages, with Stage 1 further divided into Stage 1a and Stage 1b. The primary objective for Stage 1a is to show that GClb is superior to Clb for an initial application. Then the primary objective for Stage 1b is to show that RClb is superior to Clb. As results from Stage 1were promising, the trial proceeded as planned to recruit more patients and continued onto Stage 2, where GClb will be compared to RClb for a possible labeling update application. To control for the Type I error, the study first performed a global closed testing for any difference in the primary endpoint among the three study arms before proceeding to the pairwise comparisons in Stage 1. The Type I error was allocated to one interim analysis and one final analysis in Stage 2 according to the Lan-DeMets alpha spending function for group sequential designs.

This BLA is based on data from 356 patients randomized in Stage 1a of the pivotal trial (GClb 238, Clb 118). Superiority of GClb over Clb was demonstrated for the addition of obinutuzumab to chlorambucil based on the primary endpoint progression-free survival as assessed by an independent radiology committee (IRC-assessed PFS): hazard ratio [95% confidence interval] 0.16 [0.11 – 0.24]; stratified log-rank test p-value < 0.0001; improvement in median 11.9 months (GClb 23.0 months, Clb 11.1 months). The PFS results by investigators were similar to the results by IRC. Subgroup analyses and additional sensitivity analyses for PFS did not reveal major issues to the interpretation of the primary analysis. Secondary response outcomes and event-free survival also supported the benefit of adding obinutuzumab to chlorambucil. Overall survival data at the time of data cut-off was not mature enough to obtain a reliable estimate with 13 deaths and 9 deaths reported for the GClb and Clb arm, respectively.

This reviewer recommends this application be approved for the proposed indication. (b) (4) the pivotal trial did not have a multiple testing plan for the secondary endpoints.

The Statistical team participated in editing the proposed label.

8. Safety

The Safety review was conducted by Barry Miller, MS, CRNP. The key findings of his review follow in italics. For details of the main safety analyses, the reader is referred to his review.

- *The safety of obinutuzumab was evaluated in a randomized trial [BO21004] of 356 patients with previously untreated chronic lymphocytic leukemia. MedDRA terminology, version 15.0, was used to categorize all adverse events. Adverse event grading was performed using the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.*

- *The safety evaluation consisted of data from Stage 1a of trial BO21004 [240 patients on the obinutuzumab plus chlorambucil arm (GClb) and 116 patients on the chlorambucil arm (Clb)]. In the experimental arm, obinutuzumab was given in 28 day cycles, with 1000 mg IV infusion weekly x3 in the first cycle followed by 1000 mg every cycle x5. In both arms, chlorambucil was given orally at 0.5 mg/kg on day 1 and 15 of each of 6 cycles.*

- *The most frequently reported Adverse Reactions with ≥5% incidence and ≥2% difference between the two treatment arms (with a higher rate in the obinutuzumab + chlorambucil arm were infusion related reactions (69% vs. 0%), neutropenia (40% vs. 17%), thrombocytopenia (15% vs. 7%), musculoskeletal pains (10% vs. 7%), pyrexia (10% vs. 7%), leukopenia (6% vs. 0%), and arthralgias (5% vs. 3%).*

- *There were notable differences between the investigator reported adverse events and treatment-emergent laboratory abnormalities derived from the LAB41ALL dataset. 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 organ dysfunction. However, to provide a more accurate picture of the laboratory abnormalities to expect with the use of Gazyva with chlorambucil, a separate laboratory abnormalities table was included in the labeling.*

- *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%).*

- *The most frequently occurring Serious Adverse Reaction in the Obinutuzumab arm was Infusion Related Reaction (11% for obinutuzumab + chlorambucil arm vs. 0% for chlorambucil-alone arm). 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. 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.*

- *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% in the chlorambucil alone arm.*

- *Tumor Lysis syndrome occurred in 4% of the patients in the obinutuzumab plus chlorambucil arm. There were no deaths from tumor lysis syndrome.*

- *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.*

- *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.

  Commonly Reported Adverse Reactions

Adverse Reactions Reported in ≥2% of Patients in Trial CLL11				
Adverse Reaction Preferred Term	**All Grades % GClb**	**Grades 3-4% GClb**	**All Grades % Clb**	**Grades 3-4 % Clb**
NEUTROPENIA	40.0	34.2	17.2	14.7
THROMBOCYTOPENIA	15.0	10.8	6.9	3.4
ANAEMIA	11.7	3.8	10.3	5.2
NAUSEA	10.0	0.0	25.0	0.0
COUGH	9.2	0.0	6.9	0.9
PYREXIA	8.8	0.4	6.0	0.0
DIARRHOEA	7.5	1.7	9.5	0.0
ASTHENIA	7.1	0.4	6.9	0.9

FATIGUE	7.1	1.3	8.6	0.0
CONSTIPATION	6.7	0.0	10.3	0.0
NASOPHARYNGITIS	6.7	0.4	6.0	0.0
LEUKOPENIA	6.3	5.0	0.0	0.0
HEADACHE	5.8	0.0	5.2	0.0
VOMITING	4.2	0.0	11.2	0.0
TUMOUR LYSIS SYNDROME	4.2	1.7	0.9	0.0
ARTHRALGIA	4.2	0.8	1.7	0.9
ABDOMINAL PAIN	3.8	0.0	5.2	0.0
BRONCHITIS	3.8	0.4	5.2	0.0
PRURITUS	3.8	0.0	3.4	0.0
ABDOMINAL PAIN UPPER	3.3	0.4	3.4	0.0
ORAL HERPES	3.3	0.0	0.9	0.0
URINARY TRACT INFECTION	3.3	0.8	1.7	0.9
BACK PAIN	3.3	0.4	0.9	0.0
INSOMNIA	3.3	0.0	4.3	0.0
RASH	3.3	0.0	2.6	0.0
PNEUMONIA	2.9	1.7	1.7	1.7
DECREASED APPETITE	2.9	0.0	7.8	0.0
HYPERURICAEMIA	2.9	0.4	0.0	0.0
PAIN IN EXTREMITY	2.9	0.0	1.7	0.0
OEDEMA PERIPHERAL	2.5	0.0	2.6	0.0
RESPIRATORY TRACT INFECTION	2.5	0.8	2.6	1.7
MUSCULOSKELETAL PAIN	2.5	0.0	1.7	0.0
DIZZINESS	2.5	0.0	3.4	0.0
DYSGEUSIA	2.5	0.0	2.6	0.0
EPISTAXIS	2.5	0.0	1.7	0.0
FEBRILE NEUTROPENIA	2.1	1.7	4.3	4.3
DYSPEPSIA	2.1	0.0	3.4	0.0
STOMATITIS	2.1	0.0	1.7	0.0
CHEST PAIN	2.1	0.0	1.7	0.9
NEUTROPHIL COUNT DECREASED	2.1	2.1	0.0	0.0
WHITE BLOOD CELL COUNT DECREASED	2.1	2.1	0.9	0.0
HYPERTENSION	2.1	0.8	1.7	1.7

CDTL Comment: The primary clinical review (combined efficacy and safety) states that regular approval is recommended for "obinutuzumab in combination with chlorambucil for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL)".

The primary safety review does not identify any recommended post-marketing requirements, post-marketing commitments, or REMS. I concur with Mr. Miller's conclusion that the data submitted to this BLA is adequate to perform the safety review.

9. Advisory Committee Meeting

No advisory committee was held for this application because the Division has experience with the product type, the trial design, and clinical endpoints used in the pivotal trial.

10. Pediatrics

Obinutuzumab is exempt from PREA requirements because it has been granted orphan drug designation for the CLL indication. The Applicant submitted a Request for Waiver of Pediatric Studies with this application (BLA Section 1.9.1). With clarification from PeRC, we have determined that the waiver is not necessary because the drug and indication are exempt from PREA. An acknowledgement letter will be issued stating that the Applicant is exempt from the PREA requirements because the biological product for this indication has orphan drug designation.

11. Other Relevant Regulatory Issues

Exclusivity Request: The Applicant states that under the PHS Act § 351(k)(7)(A) (42 U.S.C. § 262(k)(7)(A)), as amended by Title VII of the Patient Protection and Affordable Care Act, Pub. L. No. 111-148, obinutuzumab is a biological product that is not subject to the exclusions specified in § 351(k)(7)(C), and is therefore entitled to the 12-year period of exclusivity specified in § 351(k)(7)(A) and the 4-year deferral on filing of applications under § 351(k) specified in § 351(k)(7)(B).

Genentech conducted independent investigations for obinutuzumab, and is not relying on the clinical investigations conducted for its other licensed products to support approval of obinutuzumab.

Financial Disclosures: The Applicant submitted Form 3454 certifying that they did not enter into financial arrangements with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the trial.

From Section 3.3 of Hyon-Zu Lee's review:
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 investigator 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 positive financial disclosures for nine principal and sub-investigators that participated in the trial at nine different sites. The financial disclosures were reviewed with a conclusion that since so few patients were enrolled at the affected sites, it is not likely that these financial conflicts of interest affected the overall trial results.

Good Clinical Practice Issues: (from Hyon-Zu Lee's Review)
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 Harmonisation (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 and included in the request for Office of Scientific Investigations (OSI) inspections. These selections were two sites in the Russian Federation based upon higher accrual numbers than other sites. However, as there was a delay in issuing travel visas to Russia, so the sites for inspections were changed to one site in Austria and one site in France (Table below).

Requested OSI Clinical Site Audits for BO21004/CLL11

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 Franciso, 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 Sponsor 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 Sponsor 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.

Dr. Orencia posted his review on 10/21/13 and the recommendation from the results of the Sponsor inspection were No Action Indicated. He stated that the "study appears to have been conducted adequately, and the data generated appears acceptable in support of the respective indication."

CDTL Comment: No issues were identified in the Applicant Site audit that would call into question, the conduct of the trial or the reliability of the trial results to support the approval of Obinutuzumab. Trial site audits were not conducted because each site enrolled so few patients, the results could not discount the trial results.

Other Discipline Consults:

Division of Medication Error Prevention and Analysis (DMEPA):

- Proprietary Name Review: The Applicant submitted the proposed trade name of "GAZYVA". This name was reviewed by the Division of Medication Error Prevention and Analysis, and found to be 'conditionally acceptable'. The letter issued to the Applicant states that name would be re-reviewed 90 days prior to the approval of the BLA, and that if the name was found unacceptable at that time, they would be notified. As of the date of this review, no follow-up information has been received from DMEPA stating that the re-review came to a different conclusion.

- Label, Labeling, and Packaging Review: Kevin Wright, PharmD provided a review. Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with post marketing medication error data, the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the following:
  --Container Labels submitted April 22, 2013 (Appendix A)
  --Carton Labeling submitted April 22, 2013 (Appendix B)
  --Insert Labeling submitted April 22, 2013 (no image)

  Dr. Wright concluded that *the proposed container label and carton labeling can be improved to increase the readability and prominence of important information on the*

label to promote the safe use of the product. The following comments for consideration by the Review Division were issued:

A. Insert Labeling
1. Section 2: Dosage and Administration
a. Dangerous abbreviations, symbols, and dose designations that are included on the Institute of Safe Medication Practice's List of Error- Prone Abbreviations, Symbols, and Dose Designations appear throughout the package insert.[2] As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve such error prone abbreviations in the approved labeling of products. Thus, please revise the abbreviations, symbols, and dose designations as follows:
- Revise the '>' symbol appearing in the body of the text of Section 2.2 (Recommended Premedication), to read "greater than".

2. Revise Table 1 in the Section 2.1 (Recommended Dosage Regimen) to clearly delineate Cycle 1 from Cycles 2 to 6. Ensure all dosing information is displayed for Cycles 2 to 6 (i.e. day, dose, and rate of infusion).
3. We recommend incorporating the route of administrations for the premedications (e.g. Acetaminophen and anti-histamine) in Table 2: (Premedication to be Administered Before Gazyva Infusion to Reduce Infusion Reactions) of Section 2.2 Recommended Premedication.
4. We recommend using two bullet points in the sentence, "Administer as an intravenous infusion only. Do not administer as an intravenous push or bolus" of Section 2.5 Preparation and Administration under the subheading Administration. The addition of second bullet will help to differentiate the correct process versus the incorrect process (see example below):
- Administer as an intravenous infusion only.
- Do not administer as an intravenous push or bolus.

5. We recommend deleting the statement, (b) (4) appearing in Section 2.5 (Preparing and Administration) under the subheading Preparation.

Based on this review, DMEPA recommends the following be implemented prior to approval of this BLA:

A. Container Label
1. Ensure the proper name is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features. Additionally, the proper name should have a prominence commensurate with the prominence of the proprietary name in accordance with 21 CFR 201.10(g)(2).
2. Revise the proprietary name to appear in title case (i.e. Gazyva), this will help to optimize the readability of the proprietary name.
3. Revise the statement of strength to appear in a stacked format (see example below)

Gazyva
Obinutuzumab
Injection
1,000 mg/40 mL

(25 mg/mL)

4. Revise the statement, “Single Use Vial. Discard Unused Portion” to read, “Single Dose Vial. Discard Unused Portion”.

B. Carton Labeling
1. Ensure the carton labeling complies with recommendations A1 through A4.

CDTL: The DMEPA comments were sent to the Applicant on 09/13/13.

The Applicant responded on 09/20/13 as follows:
Regarding the container label comments they agreed with comment 1 and revised the label so that the proper name and proprietary name are the same size. They agreed with comment 2 and revised the container label and carton label so that Gazyva appears in title case. They agreed with comment 3 and revised the container label and carton label to provide the information in a stacked format as recommended. They acknowledged our comment #4, but requested to leave the language as “Single Use Vial. Discard Unused Portion” because “the text is accurate and consistent with the current draft USPI and recent Sponsor precedence”. They asked to further understand the Agency’s concerns and rational for the proposed change. The Division reviewed the Applicant’s request and concluded that “Single Use Vial” was the most accurate text since each vial contains 1000mg and the cycle 1 days 1 and 2 doses are 100 mg and 900 mg (less than the entire vial contents) . DMEPA agreed with the Division’s conclusion.

The Division issued the following Information Request on 09/23/13:
Thank you for your response to the information request regarding the carton and container labeling. Please find below the follow-up comment/additional request.

1. The Agency is in agreement with your rationale for keeping the statement “Single Use Vial. Discard Unused Portion”.

2. Delete (b) (4) from the carton labeling because it distracts the user's attention from more important information like the proprietary name, establish name, and statement of strength.

Please submit the revised carton labeling by 3 pm Wednesday, September 25, 2013.

Division of Risk Management (DRISK): Robert Pratt, M.D. provided a review of the need for a REMS or Risk Management Plan (RMP). The Applicant did not submit a proposed REMS or RMP. From Dr. Pratt’s review: *DRISK concurs with the Division of Hematology Products that, based on the available data and the potential benefits and risks of treatment, a REMS is not necessary for obinutuzumab and the risks associated with the product can be managed*

through labeling. If new safety information becomes available, this decision can be re-evaluated.

12. Labeling

- Proprietary name: Gazyva was deemed acceptable.

- OSE Division comments were communicated to the Applicant and addressed (see section 11).

- Physician labeling: Proposed edited labeling was sent to the Applicant on 10/10/13. The label was given a boxed warning for Hepatitis B reactivation and PML because of the class effects of anti-CD20 cytolytic antibodies (Arzerra and Rituxan). There were no cases of PML or hepatitis B reactivation in this CLL trial. There were cases of both in patients in non-CLL protocols using obinutuzumab. Because these are boxed warnings, they were placed prominently in the list of Warnings and Precautions, though they are not the most frequently occurring serious adverse reactions associated with obinutuzumab. The Adverse Reactions table included events that were reported at a frequency of ≥5% and at least 2% more than the control (chlorambucil) arm. The table in Section 8.0 of this review provides all events at a frequency of at least 2% without regard to the rate in the chlorambucil arm. Anemia was included because the difference between arms was 2% after rounding (per Applicant request). See final label. A table that contained treatment-emergent laboratory abnormalities was included in the labeling because of a large discrepancy between the frequency of lab abnormalities and reported laboratory Adverse Reactions.

- Carton and immediate container label issues were identified by DMEPA and comments were sent to the Applicants (per Section 11). Final carton and container labeling review is pending from DMEPA as of the date of this review.

- Patient labeling/Medication guide: N/A

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action: Regular Approval "For the treatment of patients with previously untreated chronic lymphocytic leukemia".

- Benefit Risk Assessment

The benefit to risk assessment of Gazyva for patients with previously untreated CLL is positive. CLL is a serious and life-threatening disease with a median survival time of 8-10 years. Though there are several approved drugs for CLL, few are appropriate for older, unfit patients. There is medical need for more effective, well-tolerated therapies for

elderly patients with CLL including those with significant co-morbidities who do not tolerate standard treatment regimens.

A statistically significant and clinically meaningful advantage was observed in median PFS for patients who were randomized to obinutuzumab + chlorambucil [GClb] as compared with patients who were randomized to receive chlorambucil alone [Clb]. The independent review committee assessed median PFS was 23.0 months in the GClb arm and 11.1 months in the Clb arm [hazard ratio 0.16 (95% CI: 0.11, 0.24), log-rank p-value <0.0001]. The secondary efficacy endpoint results were supportive of the primary endpoint.

The observed toxicities of Gazyva that occurred in ≥5% of patients and at a rate of at least 2% more than the control arm (Clb) included infusion related reactions (69% vs. 0%), neutropenia (40% vs. 17%), thrombocytopenia (15% vs. 7%), musculoskeletal pains (17% vs. 13%), pyrexia (10% vs. 7%), and leukopenia (6% vs. 0%). There were no grade 5 events reported with a difference between arms of ≥2%. The percentage of patients who withdrew from trial treatment due to adverse reactions was similar between arms {15% in Clb vs. 14% in GClb].

There were no differences in opinion between review team members regarding the benefit risk assessment for Gazyva.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies
  No REMS were required for this application.

- Recommendation for other Postmarketing Requirements and Commitments
  The Product Quality review team has requested the following PMCs:

1. Perform a formal verification study of the (b) (4) hold time for (b) (4). Submit the final study report to the Agency as a CBE-30 by February 28, 2014.

   The proposed PMC was sent to the Applicant for concurrence on 10/09/13. As of the date of this review, a response had not been received.

2. Submit a protocol for (b) (4). The protocol should include bioburden and endotoxin limits to demonstrate continued microbial control over (b) (4) The protocol should be submitted as a CBE-30 by 31 Dec 2013. Execute the protocol and provide the results in the annual report following the approval of the CE-30.

Comments to be conveyed to the applicant in the regulatory action letter:

Clinical Pharmacology Comments for the Applicant:

Submit the results of your long-term 36 month frozen matrix stability testing for the ELISA developed by Roche and (b) (4) *and used to detect obinutuzumab concentrations in your clinical trials submitted in support of this application when they are available.*

Submit the final study report and relevant data assessing the potential for obinutuzumab to prolong the QT interval in patients with previously untreated, low tumor-burden indolent NHL from a substudy of trial BO25454.

We recommend exploring, as part of your future trials, weight-based dosing for obinutuzumab for the treatment of CLL as well as other indications that you are pursuing. While a fixed-dose of obinutuzumab was utilized in BO21004, an assessment of progression free survival based on obinutuzumab exposure quartiles indicated that higher obinutuzumab exposures were associated with longer progression free survival. These relationships remained even after accounting for confounding factors in the analysis such as baseline lymphocyte count, tumor burden, and ECOG score. In addition, the population PK analysis demonstrated that body weight was a covariate for obinutuzumab exposure, in addition to other factors such as overall tumor burden and type of disease. Altogether, these observations suggest that weight-based dosing of obinutuzumab may provide more consistent obinutuzumab exposures in patients, and in turn, a better anti-tumor response, particularly in subjects with heavier body weights.

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/s/

VIRGINIA E KWITKOWSKI
10/22/2013