Summary Review for Regulatory Action

Date	Electronic stamp date
From	Richard Pazdur, MD
Subject	Office Director Decisional Memo
BLA #	125486
Applicant Name	Genentech
Date of Submission	April 22, 2013
PDUFA Goal Date	December 21, 2013
Proprietary Name / Established (USAN) Name	Gazyva Obinutuzumab
Dosage Forms / Strength	Liquid single-use vial; 1000 mg/40 mL (25 mg/mL)
Proposed Indication(s). See approved labeling for final approved indication.	For the treatment of patients with previously untreated chronic lymphocytic leukemia
Action:	Approval

Material Reviewed/Consulted: OND Action Package, including	Names of discipline reviewers
Division Director Review	Ann T. Farrell
Regulatory Project Manager Review	Beatrice Kallungal
Medical Officer Review	Hyon-Zu Lee, Barry W. Miller
Statistical Review	Chia-Wen Ko, Lei Nie
Pharmacology Toxicology Review	M. Stacy Ricci; Armaghan Emami; Pedro DelValle; Natalie Simpson; Haleh Saber
CMC ONDQA Reviews	Mate Tolnay, Laurie Graham, Marjorie A. Shapiro
BMAB Reviews	Donald Obenhuber, Kalavati Suvarna, Colleen Thomas
Biopharmaceutics Review	Jeffrey Florian
Clinical Pharmacology Review	Julie Bullock, Nam A Rahman
OPDP Reviews	Richard Lyght
OSI Review	Janice Pohlman
CDTL Review	Virginia Kwitkowski
OSE/DMEPA Consult	Kevin Wright, Yelena Maslov, Scott Dallas
OSE/DRISK Consult	Robert Pratt, Cynthia LaCivita, Claudi Manzo
Maternal Health Consult	NA

OND=Office of New Drugs BMAB = Biotech Manufacturing Assessment Branch
CMC= Chemistry, Manufacturing and Controls OSE= Office of Surveillance and Epidemiology
OPDP= Office of Prescription Drug Promotion DMPP=Division of Medical Policy Programs
OSI= Office of Scientific Investigations CDTL=Cross-Discipline Team Leader
OSE=Office of Surveillance and Epidemiology DRISK=Division of Risk Management
DMEPA= Division of Medication Error Prevention and Analysis

1 Regulatory Action

The Division of Hematology Products is recommending approval of obinutuzumab, 1000 mg/40mL (25mg/mL) single use vial for intravenous infusion for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL) in combination with chlorambucil. I concur with their recommendation for approval.

2 Introduction

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 on April 22, 2013. The application was complete upon submission and was filed as a priority review. Obinutuzumab received Breakthrough Therapy Designation concurrent, May 9, 2013, with the submission of their BLA.

Obinutuzumab is an anti-CD20 cytolytic antibody. Genentech proposed the indication of "the treatment of patients with previously untreated chronic lymphocytic leukemia". The application is supported by a single randomized, multi-center, controlled trial 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". Although the trial contained three arms, Genentech submitted the data for only two of the arms: obinutuzumab + chlorambucil and chlorambucil only. (b) (4)

Genentech informed the Agency that they were not prepared to launch (b) (4) if approved earlier than the scheduled PDUFA goal date in December 2013 but that they (b) (4). I concur with the conclusions reached by the Office of Biotechnology Products reviewers regarding the acceptability of the of the (b) (4).

3 Background

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. CLL is characterized by progressive accumulation of these leukemic cells in the peripheral blood, bone marrow, and lymphoid tissues.

Patients with CLL are generally asymptomatic and the median overall survival ranges from eight to ten years. Symptoms, when they do occur, include weight loss, fevers and night sweats. Presenting signs and symptoms include symptomatic anemia, thrombocytopenia, increasing hepatosplenomegaly and lymphadenopathy and have a predisposition to repeated infections. The median age at diagnosis of CLL is 72 years, with approximately 70% of patients diagnosed at age ≥65 years. 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.

Prior approvals of drugs/biologics for CLL have been granted based upon clinically relevant and statistically robust prolongation of progression-free survival (PFS) as the primary endpoint. A list of products that have been granted FDA approval for the treatment of CLL are shown in Table 1.

Table 1: FDA approved products for the treatment of Chronic Lymphocytic Leukemia (CLL).

Drug Name *Year 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

The Applicant's selected comparator of chlorambucil for this trial is acceptable, given the population selected. Chlorambucil is approved for the treatment of CLL at an oral dose of 0.2 mg/kg body weight daily. 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). In this study chlorambucil was initially dosed at 0.4 mg/kg with an increase to 0.8 mg/kg every 15 days. 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. Nevertheless, there was no advantage for fludarabine for PFS [19 vs. 18 mos.] or OS [46 mos. vs. 64 mos.]. 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 chlorambucil dose used in the current study was 0.5 mg/kg every 15 days.

4 CMC/Biopharmaceutics

There are no issues that preclude approval for CMC/biopharmaceutics. CMC reviewers have provided an overall acceptability for the manufacturing of drug product and drug substance.

Genentech stated early in the BLA review that (b) (4), the PDUFA goal date. Due to the Breakthrough status of this drug, the Agency planned to expedite the review of the BLA in order to take an action before the PDUFA goal date. Genentech informed the Agency that (b) (4) The Agency worked with Genentech to develop a plan for commercial launch (b) (4). The CMC review team confirmed that the (b) (4). Without this agreement, (b) (4).

Obinutuzumab is provided as a sterile liquid, and contains no preservatives. Each single-use 50 mL vial contains 1000 mg (nominal) obinutuzumab for intravenous (IV) infusion. The Drug Product is formulated as 25 mg/mL

obinutuzumab in 20 mM L-histidine/L-histidine hydrochloride (b) (4), 240 mM trehalose, and 0.02% (w/v) poloxamer 188 at pH 6.0. Obinutuzumab is supplied as a clear to slightly opalescent, colorless to pale brown, sterile liquid solution. The product is intended for IV administration.

A CMC PMC is requested to demonstrate that their (b) (4) remain clean and provide a protocol to demonstrate that.

5 Nonclinical Pharmacology/Toxicology

There are no issues that preclude approval for nonclinical pharmacology/toxicology. Pregnancy category C is recommended based on findings in the cynomolgus monkeys enhanced pre- and post-natal development study.

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 toxicology Post-Marketing Commitments or Requirements.

Obinutuzumab binds to CD20 expressed on B lymphocytes and mediates B-cell lysis through mechanisms that include antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and complement-dependent cytotoxicity (CDC). Pharmacology studies to demonstrate these activities were conducted using different types of lymphoma cells, e.g. diffuse large B-cell, mantle cell, and Burkitt's lymphomas. The manufacturing of obinutuzumab involves the manipulation of its pattern of glycosylation (termed glyco-engineering), 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.

Toxicology studies were conducted in the cynomolgus monkey, a pharmacologically relevant species, using the administration route and dosing regimens that adequately addressed safety concerns in humans. Obinutuzumab-related toxicities in animals included depletion of B lymphocytes and immunogenicity/hypersensitivity reactions. Infection seen in some animals may be secondary to lymphocyte depletion and inflammation in multiple organs may be secondary to the immunogenicity of the drug product. Anti-drug-antibody was formed in animals; however, this did not interfere with the study results as adequate exposure to obinutuzumab was obtained. There were no drug-related effects in male or female reproductive organs in general toxicology studies. An enhanced pre- and post-natal development (ePPND) study was conducted in cynomolgus monkeys. Obinutuzumab was not teratogenic in animals; however, B cells were depleted in the offspring. The B-cell counts returned to normal levels within 6 months of birth.

6 Site Inspections

Genentech maintained adequate oversight of the clinical trial. Monitoring of clinical investigator sites appeared to be adequate. Genentech took appropriate steps to bring noncompliant sites into compliance. At the conclusion of the inspection, no List of Inspectional Observations (Form FDA 483) was issued. The results of the clinical study are deemed reliable based on this inspection.

7 Clinical Pharmacology

There are no clinical pharmacology issues that preclude approval.

From the Clinical Pharmacology Review:

> *"The pharmacokinetics of obinutuzumab are complex due to the elimination of obinutuzumab by two clearance mechanisms; one time-dependent and the other linear (time-independent). Genentech's proposed dosing regimen as reviewed by Clinical Pharmacology, achieves its purpose of reducing infusion related adverse events with the first dose while the dose intensification over cycle 1 results in obinutuzumab*

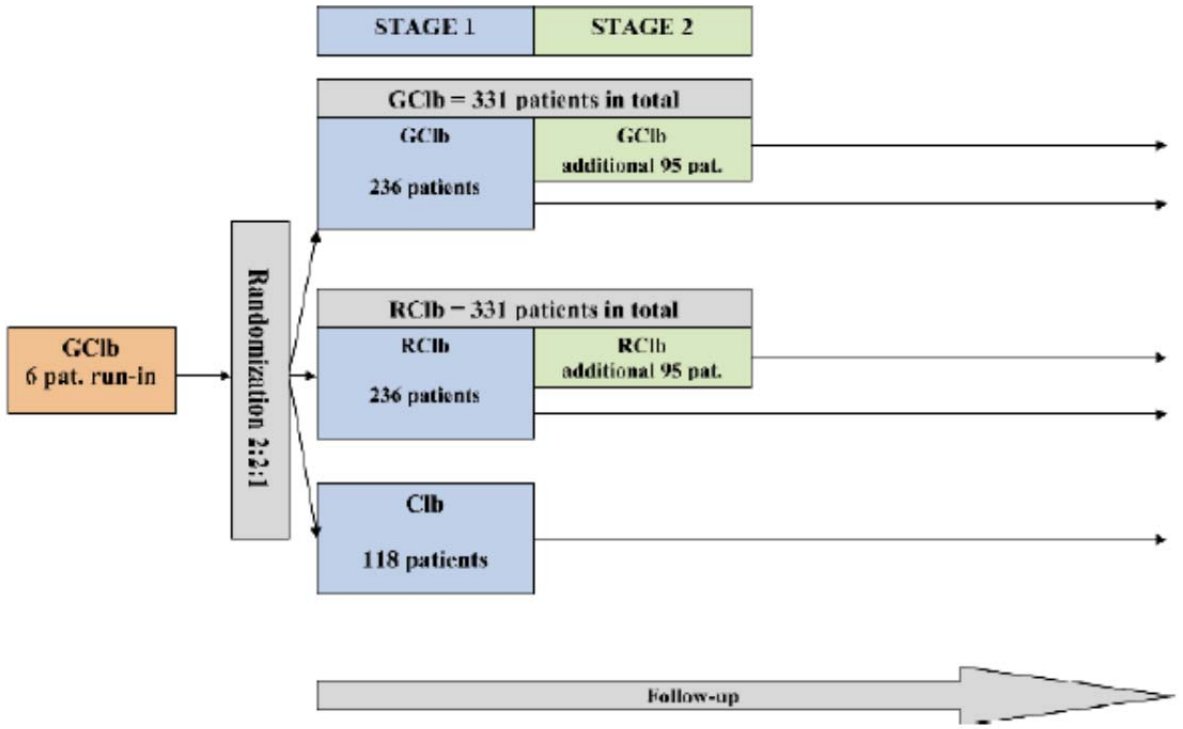
exposures closer to steady state by cycle 2. An exposure-response relationship was identified between obinutuzumab and PFS; however, no exposure-response relationships were identified between obinutuzumab and adverse event rate. There are no dose modifications or other instructions proposed for drug-drug interactions or special populations (e.g., renal impairment, hepatic impairment, age, race, gender, weight) at this time."

8 Clinical/Statistical-Efficacy

This application, supported by the registration trial BO21004/CL11, demonstrates substantial evidence of efficacy for the combination of obinutuzumab plus chlorambucil for patients with previously untreated chronic lymphocytic leukemia.

Genentech submitted the results of 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 to support this indication. 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. This trial was divided into two stages shown in Figure 1, and only the results for the chlorambucil alone and chlorambucil + obinutuzumab arms from Stage 1 were submitted with this application. The primary efficacy endpoint was progression-free survival (PFS) by an independent and blinded review committee (IRC) using the pre-specified NCI/International Workshop on CLL (IWCLL) criteria.

Figure 1: Trial design of BO21004/CLL11 submitted to support licensure of obinutuzumab.



Clb = chlorambucil; GClb = obinutuzumab + chlorambucil; pat. = patients; RClb = rituximab + chlorambucil

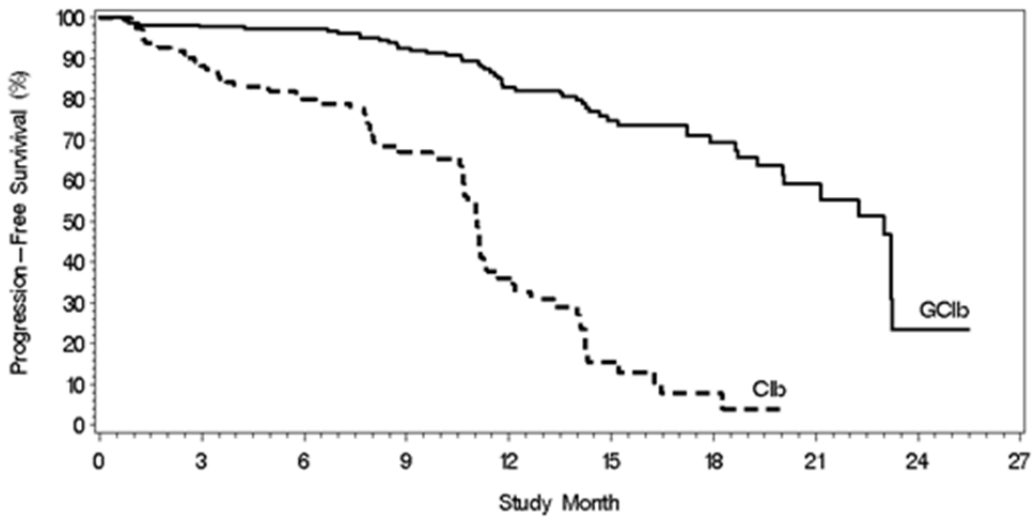
Based on the IRC data, 66/118 patients (55.9%) in the chlorambucil alone arm and 52/238 patients (21.8%) in the obinutuzumab + chlorambucil arm had a PFS event of death or disease progression at the time of stage 1 analysis (Table 2). The IRC assessed median PFS was 11.1 months in the chlorambucil arm (Clb) versus 23.0 months in the obinutuzumab + chlorambucil arm (GClb). The estimate for the median time to progression for the obinutuzumab arm may not yet be reliable because of the low percentage of patients at risk at this time point. The IRC assessed hazard ratio (stratified) was 0.16 (95% CI: 0.11, 0.24), log-rank p-value <0.0001.

Table 2: Primary Endpoint analysis of the ITT population.

Progression free survival	Clb (n=118)	GClb (n=238)
Patients with event	66 (55.9%)	52 (21.8%)
Patients without event [a]	52 (44.1%)	186 (78.2%)
Median PFS (months) [b]	11.1	23.0
Hazard ratio, 95% CI	0.16 (0.11, 0.24)	
P-value	< 0.0001	

The PFS curves shown in Figure 2 separate at around two months and remain separated. I concur with the primary reviewer that the PFS advantage of obinutuzumab + chlorambucil is robust and clinically meaningful for patients with previously untreated chronic lymphocytic leukemia (CLL).

Figure 2: Kaplan-Meier curves for IRC assessed progression-free survival for the ITT population.



Secondary measures of efficacy were aligned with the primary endpoint. The overall response rate for obinutuzumab-treated patients was 76% as compared to 32% for chlorambucil alone-treated patients. Moreover, a complete response was achieved in 25% of patients treated with obinutuzumab plus chlorambucil in contrast to none in the chlorambucil alone arm. The overall survival data were immature at the time of submission with only 22 events (6%) but the hazard ratio was favorable to obinutuzumab at 0.68 (95% CI: 0.29, 1.6).

9 Safety

The safety evaluation of obinutuzumab is based on the single randomized trial and is adequate to characterize the safety profile for the purpose of informing risk-benefit.

The safety of obinutuzumab was evaluated in a randomized trial of 356 patients with previously untreated chronic lymphocytic leukemia, 224 patients received the study drug. The demographics of the patients in this study are reflective of the population that will receive the drug once approved. Over 75% of the patients were ≥ 65 years of age with a mean of 71 years. Obinutuzumab was given in 28 day cycles, with 1000mg IV infusion weekly times three in the first cycle followed by 1000mg every cycle times five. In both arms, chlorambucil was given orally at 0.5 mg/kg on day 1 and 15 of each of 6 cycles.

As anticipated from the nonclinical studies, infusion reactions and lymphocyte depletion with infections were the predominant safety signals. The incidence of deaths within 30 days of the last treatment dose was lower in the obinutuzumab plus chlorambucil arm (1%) compared to the chlorambucil only arm (5%). Infusion related reactions were common with obinutuzumab occurring in 69% of patients. Grade 3 or 4 infusion reactions were experienced by 21% of patients. There were no infusion reaction related deaths. Symptoms of infusion related reactions (>20%) included nausea, chills, pyrexia, hypotension, and vomiting. Obinutuzumab pre-medication (instituted mid-trial) which included a corticosteroid, acetaminophen, and an antihistamine reduced the incidence of infusion reactions to 46%. Neutropenia occurred in 58% of patients in the obinutuzumab plus chlorambucil arm compared to 37% in the chlorambucil only. The incidence of infections was not higher in the obinutuzumab plus chlorambucil arm, though 23% of patients in the obinutuzumab plus chlorambucil arm received GCSF compared to 14% in chlorambucil alone-treated patients.

Tumor Lysis syndrome occurred in 4% of the patients in the obinutuzumab plus chlorambucil arm. There were no deaths from tumor lysis syndrome. Other common adverse events (>5%) were cough, fever, arthralgias, and musculoskeletal pains.

10 Advisory Committee Meeting

This application was not referred to ODAC because outside expertise was not necessary as there were no controversial issues that would benefit from advisory committee discussion. The clinical study design was acceptable and the application did not raise significant safety or efficacy issues in the intended population.

11 Pediatrics

Orphan designation was granted for obinutuzumab on February 17, 2012 for treatment of CLL, therefore obinutuzumab is exempt from the requirements of PREA for this indication.

12 Labeling

- Proprietary name: The proprietary name Gazyva submitted April 25, 2013 was determined to be acceptable.
- Premedication with glucocorticoid, acetaminophen, and an anti-histamine is recommended to mitigate the risk of infusion-related reactions.
- Boxed Warnings:
    - Hepatitis B virus reactivation and Progressive Multifocal Leukoencephalopathy (PML) are class labeling and both have been observed during the development of obinutuzumab.
- Warnings and Precautions
    - Infusion Reactions: Occur frequently despite mitigation with premedication.
    - Tumor Lysis syndrome: Acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, and/or hyperphosphatemia in patients with high tumor burden and/or high circulating lymphocyte count (> 25 x 10^9/L).

- Neutropenia and Thrombocytopenia: Grade 3-4 neutropenia and thrombocytopenia is observed in 34% and 12%, respectively in patients treated with obinutuzumab and chlorambucil.
- Immunization: class labeling – live virus vaccination can be fatal and vaccination is not likely to be effective until there is B-cell recovery.

13 Decision/Action/Risk Benefit Assessment

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

- Risk Benefit Assessment

  The benefit to risk assessment of Gazyva for patients with previously untreated CLL is positive with a substantial prolongation in progression-free survival (PFS) for treatment with the combination of obinutuzumab plus chlorambucil compared with chlorambucil alone. Patients receiving obinutuzumab in combination with chlorambucil demonstrated a significant improvement in median PFS of 23 months compared with 11.1 months with chlorambucil alone [hazard ratio 0.16 (95% CI: 0.11, 0.24), log-rank p-value <0.0001]. Although not reviewed, Genentech has publicly announced (July 23, 2013) that a pre-planned interim analysis of their Phase 3 CLL11 study showed that obinutuzumab plus chlorambucil was superior to rituximab plus chlorambucil in delaying disease progression in patients with previously untreated CLL. Final data will be forthcoming.

  Genentech stated early in the BLA review process that (b) (4) . Due to the Breakthrough designation of this drug, the Agency tried to expedite the review of this BLA and worked with Genentech to develop a plan for commercial launch (b) (4) The CMC review team confirmed (b) (4) . Without this agreement, (b) (4)

  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 this older population. More effective and well-tolerated therapies for elderly patients with CLL including those with significant co-morbidities who Gazyva do not tolerate standard treatment regimens are needed.

  Furthermore, the risk-benefit profile of Gazyva was discussed in the reviews of Dr. Farrell, Virginia Kwitkowski, Hyon-Zu Lee and Barry W. Miller, and I concur with their recommendation as well as the review team to approve this BLA.

- Recommendation for Postmarketing Risk Management Activities:
  No REMS were required for this application.

- Recommendation for other Postmarketing Study Commitments: See action letter.

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

/s/

TAMY E KIM
10/30/2013

RICHARD PAZDUR
10/30/2013