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APPLICATION NUMBER:

125326

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review Amendment

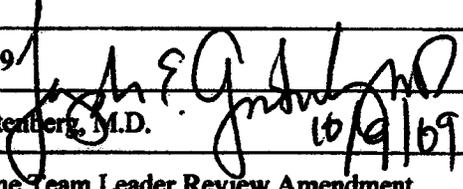
Date	October 9, 2009
From	Joseph E. Gootenberg, M.D.  10/9/09
Subject	Cross-Discipline Team Leader Review Amendment
NDA/BLA #	BLA 125326
Applicant	Glaxo Group limited d/b/a GlaxoSmithKline (GSK)
Date of Submission	January 30, 2009
PDUFA Goal Date	October 30, 2009
Proprietary Name / Established (USAN) names	Arzerra/ofatumumab
Dosage forms / Strength	20 mg/mL for IV infusion
Proposed Indication(s)	Treatment of patients with chronic lymphocytic leukemia who have received prior therapy
Recommended:	<i>Approval</i>

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1. Introduction to Amendment

GlaxoSmithKline (GSK) submitted Biologic License Application (BLA) 125326 for ofatumumab (proposed trade name Arzerra) for the treatment of patients with refractory chronic lymphocytic leukemia (CLL). The initial Cross Discipline Team Leader (CDTL) Review was dated September 21, 2009. Since the submission of that review two major potential approvability issues have been addressed by the review team. This review amendment is to update the CDTL Review to describe the resolution of those issues and to re-state this CDTL's recommendation to grant approval under the accelerated approval regulations for the use of ofatumumab in a population of patients with CLL who had an unmet medical need, i.e., previously treated patients whose disease is refractory to both fludarabine and alemtuzumab.

The two issues to be discussed are

- The inadequacy of the submitted immunogenicity data
- The clinical safety of the requirement to utilize 20 vials for each dose

2. Immunogenicity

During her review of the BLA action package, the Division of Biologic Oncology Products (DBOP) Division Director recognized that the number of patients contributing evaluable data from testing for immune responses to ofatumumab ("anti-drug antibodies" or ADA) was insufficient to provide adequate information regarding the immunogenicity of ofatumumab. GSK had reported no instances of positive human anti-human antibodies (HAHAs) during the conduct of study Hx-CD20-402, but provided little detail of the results. In study Hx-CD20-406, a validated Enzyme-Linked Immunosorbent Assay (ELISA) was used to test serum samples from 154 patients for anti ofatumumab antibodies during and after the 24 week treatment period. Results were negative in the 46 evaluable patients at the 8th infusion and in the 33 evaluable patients at the 12th infusion. Unfortunately, the particular assay utilized was not sufficiently sensitive to detect ADA in the presence of levels of ofatumumab present in many samples, and results from the remaining patients were inconclusive due to interference with the immunogenicity assay by circulating ofatumumab.

The ideal immunogenicity database for a therapeutic protein would include approximately 300 patients treated at the indicated dose and schedule. However, the results from all patients in study Hx-CD20-402 whose samples could be successfully tested were negative. The clinical and clinical pharmacology reviewers did not think that this was an issue that would preclude approval, and suggested that a more sensitive assay could be developed and additional samples tested in the post marketing period. GSK was notified of the situation and the need to provide Post Marketing Requirements (PMRs) to 1) develop a validated assay adequately sensitive to detect ADA in the presence of serum or plasma levels of ofatumumab expected to be present at the time of sampling and 2) utilize that assay to test an adequate number of samples from patients receiving ofatumumab, either through use of stored samples or by sampling of additional patients.

GSK provided PMRs to develop such an assay and conduct adequate testing on September 30, 2009. Review by the Quality, clinical and clinical pharmacology review

teams found the proposed methods, sampling plans and milestones to be acceptable to provide the necessary information in a timely manner. The proposed PMRs were incorporated into the approval letter and reviewed by the Safety Review Team (SRT). The wording of the PMRs in the proposed approval letter is as follows:

Assay development

To develop a validated, sensitive, and accurate assay for the detection of an immune response (binding antibodies) to Arzerra (ofatumumab) including procedures for accurate detection of antibodies to Arzerra (ofatumumab) in the presence of Arzerra (ofatumumab) levels that are expected to be present in the serum or plasma at the time of patient sampling.

The timetable submitted by GSK on October 6, 2009 states that this assay will be developed according to the following milestone:

Final Report Submission (Assay and Methodology): by March 31 2010

Assessment of anti-drug antibodies

To conduct an assessment of anti-drug antibody (ADA) response to Arzerra (ofatumumab) with a validated assay (required in PMR 2) capable of sensitively detecting ADA responses in the presence of Arzerra (ofatumumab) levels that are expected to be present at the time of patient sampling. ADA response will be evaluated in at least 300 patients, including Arzerra (ofatumumab)-treated patients enrolled in clinical trial OMB110911. The final report will include information on the level of Arzerra (ofatumumab) in each patient's test sample at each sampling time point.

The timetable submitted by GSK on October 6, 2009 states that this assessment will be conducted from clinical trial data according to the following milestones:

Patient Accrual Completed: by November 30, 2011
Final Report Submission: by December 31, 2013

The wording of the Immunogenicity section of the proposed physician package label is as follows:

6.2 Immunogenicity

There is a potential for immunogenicity with therapeutic proteins such as ofatumumab. Serum samples from patients with CLL in Study 1 were tested by enzyme-linked immunosorbent assay (ELISA) for anti ofatumumab antibodies during and after the 24 week treatment period. Results were negative in 46 patients after the 8th infusion and in 33 patients after the 12th infusion.

Immunogenicity assay results are highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to ARZERRA with the incidence of antibodies to other products may be misleading.

3. Requirement for 20 vials of ofatumumab per administration

As discussed in section 3.1 *General product quality considerations* of the September 21, 2009 CDTL review, the quality and clinical reviewers recognized that the requirement to utilize the contents of 20 vials of drug product to prepare the 2,000 mg dose of ofatumumab could potentially result in medication errors. However, administration of one vial (100 mg) too much or of one vial too little was strongly felt to be unlikely to have significant clinical consequences on either the anti-tumor activity or toxicity of ofatumumab, and this was not considered a safety issue. The total dose of ofatumumab delivered in the labeled treatment course is 22,300 mg, and, based on the prolonged pharmacokinetics and pharmacodynamic properties of ofatumumab, a course of 22,200 mg resulting from the omission of one vial or a course of 22,400 mg resulting from the use of one extra vial would represent an insignificant difference. In support of this theoretical assessment, the clinical reviewer provided information in his review regarding two patients enrolled in study Hx-CD20-406 who each received the contents of only 19 vials at one administration of ofatumumab. Both of these patients were responders. However, recognizing the inconvenience posed by this presentation, GSK has voluntarily committed to developing a ([redacted]) (20 mg/ml) single-use vial of ofatumumab and to submitting by December 31, 2010 a Prior Approval Supplement for its introduction into clinical use. b(4)

During the BLA 125326 review, DBOP consulted the Office of Surveillance and Epidemiology (OSE), Division of Medication Errors Prevention and Analysis (DMEPA) for safety expertise, particularly in the review of GSK's proposed Arzerra carton and container labels and package insert. DMEPA's consult review, received on July 31, 2009, noted a concern with the 20 vials/dose configuration that will be marketed for Arzerra prior to approval of the planned ([redacted]) single vial configuration. A teleconference was conducted with GSK on September 21, 2009. During this teleconference, GSK agreed to provide a protocol to address concerns associated with the 20 vial configuration. GSK subsequently communicated by email on September 22, 2009, that in lieu of a formal protocol, a detailed survey for pharmacists to complete would be submitted. DMEPA offered to review and provide recommendations on this GSK survey. GSK emailed this survey on September 28, 2009, which DMEPA evaluated with consultation from the OSE Division of Risk Management (DRISK). A final review was provided on October 6, 2009. The following is extracted from the "conclusions" section of that review. b(4)

"...GSK is attempting to mitigate the potential for medication errors using measures such as education, vial packaging configuration, a healthcare practitioner survey and a post-marketing commitment to develop a ([redacted]) vial by the end of 2010. Based on the above measures, DMEPA does not consider the necessity for 20 vials for the 2000mg dose an approvability issue from a medication error perspective. However, DMEPA defers to DBOP for assessment of the clinical consequences if less than 20 vials are used for a prescribed 2000 mg dose." b(4)

As discussed above DBOP, the primary clinical review Division, has concluded that no further pre-approval action from GSK is necessary because the 20 vial configuration represents a dosing convenience issue, not a safety issue. GSK's voluntary commitment to develop a ([redacted]) (20 mg/ml) single-use vial of ofatumumab and to submit a Prior b(4)

Approval Supplement for its introduction into clinical use by December 31, 2010 is adequate, and this issue presents no obstacle to approval.

The wording of the voluntary Post Marketing Commitment in the proposed approval letter is as follows:

Development of a () ofatumumab single-use vial

To submit a Prior Approval Supplement (PAS) for the introduction of a () mg ofatumumab single-use vial, 20 mg/mL, to reduce the number of vials needed for the 2000 mg dose. b(4)

The timetable submitted by GSK on August 20, 2009 states that this ofatumumab single-use vial will be developed according to the following milestone:)

Supplement Submission: by December 31, 2010

4. Recommended Regulatory Action

After consideration of the topics above, the recommendation of this Cross Discipline Team Leader (CDTL) is for approval of BLA 125326 contingent upon agreement between the Applicant and FDA on acceptable package labeling before the Action Date. The Clinical, Quality (CMC), Non-clinical Toxicology, and Clinical Pharmacology Review Teams have recommended Approval. The Office of Compliance Facilities Inspection Team and Division of Scientific Investigations have reported that these are no findings that would prevent approval. The Division of Risk Management considers the proposed risk management approach acceptable. DMEPA has determined that the proposed proprietary name, Arzerra, is acceptable. The Division of Biologic Oncology Products primary clinical reviewer, the Division of Biometrics V primary statistical reviewer and the Oncologic Drugs Advisory committee concluded that the results from the population of patients with CLL refractory to fludarabine and alemtuzumab in trial Hx-CD20-406 are reasonably likely to predict that ofatumumab may confer clinical benefit in CLL. The statistical team leader recommended non-approval due the level of uncertainty regarding the results. Section 7.2.5 *Discussion of notable efficacy issues* of the September 21, 2009 CDTL review provides this Cross Discipline Team Leader's argument to support concurrence with the efficacy findings of the primary clinical and statistical reviewers and the ODAC. Two PMRs have established commitments by GSK to provide adequate additional information regarding the incidence of anti-drug antibodies associate with the administration of ofatumumab. DBOP has concluded that the present requirement for the use of 20 vials to prepare the 2000 mg dose of ofatumumab is not a safety issue and can be addressed through a voluntary Post Marketing Commitment. This CDTL finds the risk/benefit assessment of the use of ofatumumab in patients with CLL refractory to fludarabine and alemtuzumab to be favorable, and therefore recommends approval.

Cross-Discipline Team Leader Review

Date	September 21, 2009
From	Joseph E. Gootenberg, M.D. <i>9/21/09</i>
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1. Introduction to Review

GlaxoSmithKline (GSK) submitted this Biologic License Application (BLA) for ofatumumab (proposed trade name Arzzeria) for the treatment of patients with refractory chronic lymphocytic leukemia (CLL). Ofatumumab is a recombinant, anti-CD20 IgG1κ human monoclonal antibody produced in a recombinant murine cell line, NSO. The Applicant designed their clinical development program to address the use of ofatumumab in the population of patients with CLL who had failed or who were intolerant to conventional therapies. For a subpopulation of these patients who had an unmet medical need, FDA agreed that it was acceptable to use as the primary endpoint the surrogate endpoint of durable objective response rate (ORR) for the purposes of accelerated approval under 21 CFR 601.40-46 (Subpart E). However, since the primary endpoint was a surrogate endpoint the Applicant is required to conduct additional adequate and well controlled clinical trials to confirm the clinical benefit of ofatumumab.

The Applicant conducted two single arm trials in patients with CLL whose disease was refractory to conventional treatments. The first, study Hx-CD20-402 was an open-label, international, multicenter, dose escalation study evaluating three dose levels of ofatumumab in 33 patients with elapsed or refractory CLL. Patients received up to four weekly doses of ofatumumab. This study was considered only supportive for the purposes of the joint clinical/statistical review because of differences in dose, dosing schedule, inclusion criteria, and monitoring compared to the primary study that provided data to demonstrate the safety and efficacy of ofatumumab, study Hx-CD20-406.

The second study, Hx-CD20-406, was an open-label, international, multicenter, single arm, non-comparative study evaluating ofatumumab in 154 patients with relapsed or refractory B-cell CLL who had an indication for treatment as defined by NCI Working Group (1996 NCIWG) guidelines. Patients were required to have disease refractory to an adequate course of fludarabine and to either be refractory to alemtuzumab, designated as “double refractory” (DR), or have bulky lymphadenopathy, designated as “bulky fludarabine refractory” (BFR). Twelve doses of ofatumumab were to be administered according to the following schedule:

- 300 mg during week 0
- 2,000 mg weekly from weeks 1 to 7, and on weeks 12, 16, 20, and 24

The primary endpoint was objective response occurring between the first dose of ofatumumab through week 24 as determined by an Independent Endpoints Review Committee (IRC) according to response criteria in the 1996 NCIWG guidelines. Duration of response was a secondary endpoint. Originally, the endpoint analyses were to be conducted separately for the DR and the BFR subgroups when data for 100 patients were available for each group. Subsequently, the trial analysis plan was revised to include an interim analysis when the primary endpoint data were available for 66 patients in the DR subgroup.

The efficacy data upon which accelerated approval will be considered is derived from the protocol-specified DR subgroup of 59 patients in study Hx-CD20-406. FDA considers this patient population, more than 90% of whom also received prior therapy that included an alkylating agent; to be a patient population with an unmet medical need. Data from the

BFR patient population and from "other" CLL patients enrolled in study Hx-CD20-406 and data from patients enrolled in study Hx-CD20-402 will be considered supportive in the regulatory decision making regarding approval of ofatumumab in the DR patient population. For drugs used to treat late stage malignancies, it is not uncommon for the efficacy results of one trial, with supportive data from other trials, to form the basis for granting accelerated approval. In addition, in heavily pre-treated cancer populations such as that investigated in study, Hx-CD20-406, spontaneous tumor responses are not expected, and a single arm trial may be acceptable as any tumor responses observed can be attributed solely to the anti-tumor activity of the investigational drug administered. As is required under the accelerated approval regulations, post-marketing studies are underway to confirm the clinical benefit(s) of ofatumumab.

The FDA safety database for ofatumumab consists of the 154 patients enrolled in Hx-CD20-406 who received the 2000 mg IV infusion dose proposed for approval.

Review of this application revealed important issues in several areas, as follows.

1) **Clinical/Statistical:** Although there are several issues concerning the reliability and accuracy of the efficacy determinations, including doubts regarding the results of the IRC review, the primary clinical and statistical reviewers recommended approval. Uncertainties regarding the reliability of the estimate of response rate, and the lack of evidence linking response rate to clinical benefit in CLL prompted the statistical Team Leader to recommend against approval. As will be discussed in greater detail in section 7.3 *Discussion of notable efficacy issues*, this CDTL does not concur with the statistical Team Leader's recommendation. Since this would be an accelerated approval, a trial to confirm clinical benefit of ofatumumab in CLL is underway.

2) **Safety:** Major safety concerns were limited to infusion reactions and the incidence of severe infections.

3) **Product:** The Quality reviewers had important concerns about the propensity of ofatumumab to form visible and sub-visible particulates. This was considered a serious finding as the processes involved in the formation of such particulates could theoretically affect the potency, purity and immunogenicity of the final product. Investigation into this phenomena indicated that the out-of-specification (OOS) results were not due to drug product degradation, but were due to an artifact created by shipping conditions from the sample storage site to the stability testing site. The Quality reviewers felt the information submitted by GSK's was sufficient to identify a root cause for the OOS results and that a corrective and preventative action (CAPA) plan implemented by GSK would ensure appropriate shipping and testing of future stability samples.

2. Background

Chronic lymphocytic leukemia (CLL) is a cancer characterized by the monoclonal expansion of relatively mature but immunologically incompetent malignant lymphocytes. In over 95% of patients with CLL, the malignant cells are B-lymphocytes (B-cells) which express the cell surface protein cluster of designation 20 (CD20). CD20 is expressed on normal B-cells during their differentiation and maturation, from the pre-B cell stage to the memory B-cell stage. It is expressed on a number of hematological malignancies, but

it is not expressed on plasma cells. The CD20 molecule is not shed from the cell surface and is not internalized following antibody binding.

Chronic lymphocytic leukemia (CLL) occurs at an age adjusted incidence rate of 4.1 per 100,000 per men and women each year, and as such is the most common of the chronic leukemia, comprising 30% of all adult leukemia. There are an estimated 15,000 new cases and 4,500 deaths annually in the United States. The median age of diagnosis is 72 years of age and the incidence of CLL in men is approximately twice that in women. Survival for patients with CLL can be variable with over half of patients living longer than 10 years; however, reported median survival is only two to three years for patients with high risk disease (Rai category III or IV or Binet stage 3). Survival is expected to be shorter for patients who have progressed following multiple lines of different chemotherapy. In a literature report based on single-center experience, the median survival of 54 patients refractory to alemtuzumab and fludarabine was 8 months.

Despite clinically relevant progress in the treatment of CLL, the disease still remains incurable by conventional therapy. Choice of therapy for CLL is influenced by age and co-morbid conditions. Patients who are younger than 70 and have limited co-morbidities are frequently treated with combination chemo-immunotherapy.

In the past decade, regular approval for the treatment of CLL has been based on demonstration of superior progression-free survival (PFS), while accelerated approval has been granted based on demonstration of durable objective tumor responses in patients with CLL that has progressed following available therapy (unmet medical need). The following drugs have been approved for the treatment of CLL in the modern era:

- Fludarabine received regular approval in 1991 (prior to the establishment of the accelerated approval regulations in 1992) based on durable response rates in two single-arm, open-label studies conducted in patients with CLL refractory to at least one prior standard alkylating-agent containing regimen. In these two studies, the ORR was 48% and 32%, with median durations of response of 1.75 and 1.25 years, respectively. Complete response rates were 13% in both studies.
- Alemtuzumab received accelerated approval in 2001 based on the results of three single-arm studies conducted in patients with CLL and progressive disease following alkylating agents and fludarabine. ORR in the three studies ranged from 21% to 33% with median durations of response of 7 to 11 months. Alemtuzumab was subsequently granted regular approval in 2007, on the basis of superior PFS [HR 0.58 (95% CI 0.43, 0.77), $p < 0.0001$ stratified log-rank test] in a randomized active-controlled study comparing alemtuzumab to chlorambucil in previously untreated patients with CLL. Alemtuzumab also demonstrated an improvement in ORR (83% vs. 55%) and complete response rates (24% vs. 2%) compared to chlorambucil.
- Bendamustine received regular approval in 2008 on the basis of superior PFS [HR 0.27 (95% CI 0.17, 0.43) $p < 0.0001$] in a randomized active-controlled study comparing bendamustine to chlorambucil in previously untreated patients with CLL. Bendamustine also demonstrated an improvement in ORR (59% vs. 26%) and complete response rates (8% vs. <1%) compared to chlorambucil.

Ofatumumab is a full length, human IgG1 kappa (κ) isotype antibody composed of identical heavy and light chains with a molecular weight of approximately 149,000 Dalton.

It is produced using standard mammalian cell cultivation technologies in a murine NS0 cell line transfected with expression constructs for the heavy and light chains of ofatumumab.

Ofatumumab binds human CD20 with high affinity and specificity. *In vitro*, and presumably *in vivo*, binding of ofatumumab causes death of CD20+ cells by inducing antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). The Fab domain of ofatumumab binds to the CD20 molecule and the Fc domain mediates immune effector functions to result in B cell lysis *in vitro*. As a proof-of-concept, ofatumumab was shown to exhibit anti-tumor activity in SCID mice bearing CD20+ human tumors.

The pharmacokinetics of ofatumumab reflect its molecular weight and its modes of elimination. Studies utilizing the proposed therapeutic dose showed mean volume of distribution at steady state values ranging from 1.7 to 5.1 L and calculated C_{max} and $AUC_{(0-\infty)}$ after an 8th infusion approximately 40% and 60% higher than after a 4th infusion. Ofatumumab is eliminated through both a target-independent proteolytic enzyme route and a major B-cell receptor-mediated route. Due to the depletion of B cells, the clearance of ofatumumab decreases substantially after subsequent infusions compared to the first infusion. The mean $t_{1/2}$ is approximately 14 days.

If approved, this will be the initial approval for Arzerra (ofatumumab), which will be granted as an accelerated approval for the treatment of patients with chronic lymphocytic leukemia (CLL) refractory to fludarabine and alemtuzumab. However, ofatumumab will not be the first anti-CD20 monoclonal antibody to be marketed. Another monoclonal antibody (Rituxan, Genentech, Inc.) that also binds specifically to the CD20 protein on the cell surface of certain malignant and non-malignant B-cells, has demonstrated efficacy in the treatment of a number of B-cell tumors and in rheumatoid arthritis. It received approval for treatment of patients with relapsed or refractory low-grade or follicular B-cell NHL as a single agent on November 26, 1997, for treatment of previously untreated diffuse large B-cell, CD20 positive NHL in combination with CHOP or other anthracycline-based chemotherapy regimens on February 10, 2006, for treatment in combination with methotrexate to reduce the signs and symptoms in adult patients with severely active rheumatoid arthritis who have had an inadequate response to one or more TNF antagonist therapies on February 28, 2006, for the treatment of non-progressing, low grade, CD20-positive B-cell NHL as a single agent after first-line CVP chemotherapy on September 29, 2006 and for treatment of previously untreated follicular, CD20-positive B-cell NHL in combination with CVP chemotherapy on September 29, 2006. Notably, Rituxan is not approved for the treatment of CLL, although clinical trials of Rituxan (not reviewed by FDA) in both previously untreated and previously treated patients with CLL have shown anti-tumor activity. Ofatumumab and Rituxan have not been compared against each other in clinical trials for any indication.

Ofatumumab was developed and carried into clinical trials by GenMab A/S, Copenhagen, Denmark (GenMab) and subsequently licensed to GSK. Major drug development milestones and agreements and communications between the Sponsor and FDA included the following:

On May 20, 2004, IND 11719 was submitted by GenMab.

On August 26, 2005 and November 30, 2005, meetings were held between GenMab and FDA to discuss the acceptability of a proposed trial to support accelerated approval (AA). At these meetings

- FDA recommended that Genmab conduct an additional phase 2 dose finding trial prior to studies designed to support accelerated or regular approval. Genmab stated that a second study could not be conducted prior to a "pivotal" trial.
- FDA identified durable ORR as an acceptable surrogate endpoint reasonably likely to predict clinical benefit in a patient population with an unmet medical need, i.e., no alternative therapy.
- Genmab proposed to conduct a study in 100 patients who "failed" both fludarabine and alemtuzumab to satisfy the requirement for demonstrating benefit in patients with an unmet medical need.
- FDA stated that a response rate of 15% would not be sufficient to predict clinical benefit; acceptability of a response rate of 20% would depend on data demonstrating that this result provides a significant advance over available therapy and is likely to predict benefit. FDA also stated that responses should be durable (at least 4-6 months) and associated with clear measures of clinical benefit.

In December 2005, Study Hx-CD20-406, "A single-arm, international, multi-center trial of HuMax-CD20, a fully human monoclonal anti-CD20 antibody, in patients with B-cell CLL who have failed fludarabine and alemtuzumab" was submitted to FDA (this trial population will be referred to as the "Double Refractory" or "DR" group).

In February 2006, Study Hx-CD20-406 Protocol Amendment 1 introduced a new patient group that was fludarabine refractory with bulky lymphadenopathy and was not required to receive prior alemtuzumab (this trial population will be referred to as the "Bulky Fludarabine-refractory" or "BFR" group)

In a letter to GenMab April 11, 2006, regarding Study HX-CD20-406 and amendment 1, FDA included the following advice from an expert consultant serving as a Special Government Employee (SGE) who reviewed the December 2005 protocol

- CLL patients who are refractory to both fludarabine and alemtuzumab (the DR population) have an unmet medical need.
- Patients with bulky, fludarabine-refractory CLL (the BFR population) should be analyzed separately from the DR population.
- ORRs of 10-20% were unlikely to predict clinical benefit.

In a letter to GenMab May 5, 2006, which considered SGE review and advice regarding the amended February 2006 protocol, FDA stated that

- In a population with unmet need, an ORR for which the lower bound of the 95% CI was at least 25% would be of interest.
- The median duration of response should be at least four months.

- Efficacy should be determined separately in the DR and BFR subgroups.

In June 2006, the first patient enrolled in study Hx-CD20-406.

In September 2006, Study Hx-CD20-406 Protocol amendment 2 specified a wholly fludarabine refractory population by excluding patients that were intolerant to or ineligible for treatment with fludarabine.

In April 2007, Study Hx-CD20-406 Protocol amendment 3 specified that the trial populations (DR and BFR) were to be analyzed separately and increased the sample size from 100 patients total to a sample size of 66 patients each in the DR and BFR subgroups.

In October 2007, Study Hx-CD20-406 Protocol amendment 4 increased the sample size in the DR and BFR subgroups from 66 to 100 patients and revised the trial analysis plan to include an interim analysis for efficacy when data from 66 DR patients were available.

In November 2007, the 154th patient, the last efficacy evaluable patient included in the interim analysis, was enrolled in Study Hx-CD20-406.

In April 2008, sponsorship of Study Hx-CD20-406 was transferred from Genmab to GSK.

May 19, 2008 was the data cut-off date for the planned interim analysis.

On September 29, 2008, a meeting was held between GSK, Genmab and FDA to discuss a possible BLA submission at which FDA raised the following issues

- The patient population included in the BFR subgroup did not meet the regulatory standard for having an unmet medical need as the protocol only required prior therapy with one drug.
- The 1996 NCIWG criteria did not require radiographic evaluation (unless to confirm CR) and the IRC was not provided with radiographs for most patients.
- The IRC "Independent Review", which relied on investigators' reported measurements of lymph nodes, liver, and spleen rather than review of radiographs was not "truly independent."

In December 2008, Protocol OMB110913 "A phase III, Open Label, Randomized Trial of Ofatumumab in Combination with Fludarabine-Cyclophosphamide versus Fludarabine-Cyclophosphamide Combination in Subjects with Relapsed B-Cell Chronic Lymphocytic Leukemia" was submitted to FDA as the proposed study for confirmation of clinical benefit.

On January 30, 2009, BLA 125326 was submitted by GSK seeking approval of ofatumumab for the treatment of patients with chronic lymphocytic leukemia who have received prior therapy. The submission was granted priority review by FDA with a PDUFA action date of July 30, 2009.

On March 10, 2009, ofatumumab was granted orphan-drug designation for the treatment of CLL.

In response to information request letters from FDA dated April 14, 2009 and May 11, 2009, on June 5, 2009 GSK submitted an amendment that was classified by FDA as a

major amendment, therefore extending the PDUFA action date by 3 months to October 30, 2009.

On June 23 2009, a teleconference was held between GSK and FDA to discuss the ofatumumab confirmatory trial at which the following issues were raised;

- Enrollment to Protocol OMB110913, the proposed study for confirmation of clinical benefit, was inadequate to meet accrual goals.
- GSK proposed that ongoing Protocol OMB110911, entitled, "A Phase III, Open-label, Randomized, Multicenter Trial of Ofatumumab Added to Chlorambucil versus Chlorambucil Monotherapy in Previously Untreated Patients with Chronic Lymphocytic Leukemia," which is intended to verify the clinical benefit of ofatumumab through demonstration of a clinically meaningful effect on progression-free survival, be designated as the proposed study for confirmation of clinical benefit.

On August 19, 2009, FDA agreed that Protocol OMB110911, as amended per FDA request, could serve as the proposed study for confirmation of clinical benefit.

3. CMC/Device

3.1. General product quality considerations

The Quality review team recommends that the BLA be approved provided that the Applicant and FDA reach a satisfactory agreement on specific revisions to the proposed label, which were provided during the labeling negotiations, and that the Applicant commits to specific PMCs addressing manufacturing and assay issues. These PMCs are enumerated in detail in the Recommendations/Risk Benefit Assessment section of this review. As discussed below, Quality reviewers' requests for additional data regarding a serious issue led to a "major amendment" that extended the PDUFA action date for BLA 125326 by 3 months.

The Quality Review specifically states that "The data submitted in this application support the conclusion that the manufacture of Ofatumumab is well controlled, and leads to a product that is pure and potent. The product is free from endogenous or adventitious infectious agents in a way that meets the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product is produced from the multiple production runs presented. It is recommended that this product be approved for human use (under conditions specified in the package insert)".

Ofatumumab is a full length, human IgG1 kappa (κ) isotype antibody composed of identical heavy and light chains with a molecular weight of approximately 149,000 Dalton. /

/ Ofatumumab specifically recognizes a combination epitope comprised of amino acids from both the large and small extracellular loops of human CD20. It is produced using standard mammalian cell cultivation technologies in a murine NS0 cell line transfected with expression constructs for the heavy and light chains of Ofatumumab.

b(4)

The Quality reviewers found the identity characterization testing, generation and maintenance of cell banks, cell culture and harvest, purification processes, process validation, viral inactivation steps, potency assay, stability testing and lot release specifications to be acceptable. Assays to assess the immunogenicity of ofatumumab in human studies were found to be sufficient and appropriately validated. It should be noted that ofatumumab will be administered using an approved infusion filter which will be packaged with the drug product.

One issue to be addressed in a Post Marketing Commitment is that the preparation of the 2,000 mg dose of ofatumumab requires the contents of 20 vials, which could potentially result in medication errors. However, administration of one vial (100 mg) too much or of one vial too little is unlikely to have significant clinical consequences on either the anti-tumor activity or toxicity of ofatumumab, and this is not considered a safety issue. GSK has committed to developing a (b)(4) (20 mg/ml) single-use vial of ofatumumab and to submitting by December 31, 2010 a Prior Approval Supplement for its introduction into clinical use.

b(4)

However, a most important issue, which ultimately resulted in the submission of a "major amendment", was the propensity of ofatumumab to form visible and sub-visible particulates. This was considered a serious finding as the processes involved in the formation of such particulates could theoretically affect the potency, purity and immunogenicity of the final product. Formation of particulates appears to be due to shear or shaking which may occur during manufacturing or shipping, and may also represent a pathway of product degradation. Shipping studies confirmed that a small number of particles form during transport and the Quality reviewers recommended that this should be considered if the release and stability specifications for this product are revised. During the review cycle, GSK submitted information to the BLA which suggested that several of the drug product lots produced at two commercial manufacturing sites failed sub-visible particulate testing (sub-visible particles greater than or equal to (b)(4) at 12 months (four lots at the Barnard Castle facility) or at 36 months (one lot at (b)(4))). This raised serious concerns in regard to the stability of commercial drug product lots. An Information Request letter containing multiple questions concerning these findings was issued to GSK on May 11, 2009. In addition, the Office of Compliance held an inspection of the drug product manufacturing facility at Barnard Castle, UK. Further investigation by GSK into this event indicated that the out-of-specification (OOS) results were not due to drug product degradation, but were due to an artifact created by new shipping conditions utilized to ship stability samples from the sample storage site to the testing site. Further testing of additional samples confirmed that the lots were not actually OOS and a corrective and preventative action (CAPA) plan was implemented by GSK to ensure appropriate shipping and testing of future stability samples. The Quality reviewers felt the information/data submitted on GSK's investigation into the OOS results was thorough and was sufficient to identify a root cause for the OOS results. The CAPA plan implemented was also felt to be adequate to ensure similar incidents do not occur in the future. As one component contributing to the resolution of this issue GSK submitted a response to the FDA May 11, 2009 letter on June 5, 2009. This response contained a large amount of data. To allow sufficient time for an adequate review of the submitted data, FDA classified this submission as a "major amendment" that extended the PDUFA action date for this BLA by 3 months.

b(4)

3.2. Facilities review/inspection

The Office of Compliance Facilities Review Team reported on inspections of 7 sites involved in the manufacturing and testing of ofatumumab and reported no pending or ongoing compliance actions to prevent approval of BLA 125326.

The sites inspected included:

Lonza Biologics plc
Slough
Berkshire UK

Lonza biologics, Inc
Portsmouth,
New Hampshire USA

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b(4)

Glaxo Operararions UK Limited
Barnard Castle
Co. Durham UK

Lonza Biologics plc
Wokingham
Berkshire UK

Non-major product quality items were identified and communicated verbally to the firm during closeout meetings. Firm management promised to implement the recommendations.

4. Nonclinical Pharmacology/Toxicology

The Nonclinical Pharmacology/Toxicology review team recommends that the BLA be approved pending agreement on specific revisions to the proposed label, which were provided during the labeling negotiations. There are no unresolved nonclinical issues and no additional postmarketing studies required to support this application.

4.1. General nonclinical pharmacology/toxicology considerations

Non-clinical data submitted in support of the application included tissue binding studies in human and cynomolgus monkey tissue panels, evaluation of in vitro pharmacologic activity (receptor binding, lysis of CD20-expressing cells) and in vivo pharmacologic activity (anti-tumor activity in SCID mice bearing human tumor xenografts, characterization of B-cell depletion in treated monkeys), pharmacokinetic studies in cynomolgus monkeys, and subacute (4 week) and chronic (7-month) toxicology studies in cynomolgus monkeys. In general, the major observed ofatumumab toxicities seen in nonclinical studies were extensions of its expected pharmacologic activity, i.e. the severe

and prolonged depletion of B-lymphocytes in both the circulation and in the major lymphoid organs (follicular germ centers of the spleen, cortical lymph nodes, and Peyer's patches in the gastrointestinal tract). B-cell depletion was reflected in the clinical studies, may be monitored and treated appropriately in the clinical setting and is considered a tolerable toxicity for the indicated patient population with chronic lymphocytic leukemia. Other toxicities noted in the 7-month repeat-dose cynomolgus monkey toxicity study included sporadic, non-severe infusion reactions, hematologic changes including lymphopenia, mild anemia and hemolysis, and changes in neo- and recall antigen responses.

4.2. Genotoxicity

Routine genotoxicity studies are not generally appropriate for biologics, and genotoxic potential is not experimentally assessed unless there is specific reason for concern about carcinogenic effects of a particular product. The Applicant did not conduct genotoxicity studies with ofatumumab, and the pharmacology/toxicology reviewer agreed that genotoxicity studies were not warranted. Ofatumumab is not expected to interact directly with DNA or other chromosomal components. In addition, ofatumumab is not pharmacologically active in the traditional models for short-term genetic toxicology testing (standard cell lines, standard rodent species), rendering such testing infeasible.

4.3. Carcinogenicity

Routine genotoxicity studies are not generally appropriate for biologics, and genotoxic potential is not experimentally assessed unless there is specific reason for concern about carcinogenic effects of a particular product. The Applicant did not conduct genotoxicity studies with ofatumumab, and the pharmacology/toxicology reviewer agreed that genotoxicity studies were not warranted. Ofatumumab is not expected to interact directly with DNA or other chromosomal components. In addition, ofatumumab is not pharmacologically active in the traditional models for short-term genetic toxicology testing (standard cell lines, standard rodent species), rendering such testing infeasible.

4.4. Reproductive toxicology

The Applicant assessed the effects of ofatumumab on embryo-fetal development in cynomolgus monkeys. Pregnant animals were treated weekly with ofatumumab at 0.7 and 3.5 times the recommended human dose from gestation day (GD) 20 through GD50. No maternal toxicity other than B-cell depletion was observed and there were no teratogenic effects noted in offspring delivered by Caesarean section on GD100. However, ofatumumab crossed the placental barrier and fetuses exhibited depletion of peripheral B cells and decreased spleen and placenta weights. These findings have been incorporated in proposed revisions to the product labeling, and Pregnancy Category C is recommended.

5. Clinical Pharmacology/Biopharmaceutics

The Clinical Pharmacology review team recommends that the BLA be approved provided that the Applicant and FDA reach a satisfactory agreement on specific revisions to the proposed label, which were provided during the labeling negotiations, and that the

Applicant commits to specific PMRs addressing safety issues related to the effect of ofatumumab on prolongation of QTc intervals. This review was the topic of an OCP Briefing was held on July 7, 2009.

5.1. General clinical pharmacology/biopharmaceutics considerations

Ofatumumab is a human IgG1κ monoclonal antibody that exerts its action by specific binding to the extracellular loops of the CD20 molecule. The CD20 molecule is expressed on normal B-lymphocytes (pre-B to mature B-lymphocytes) and on B-cell CLL. The CD20 molecule is not shed from the cell surface and is not internalized following antibody binding. The Fab domain of ofatumumab binds to the CD20 molecule and the Fc domain mediates immune effector functions that result in B-cell lysis *in vitro*. Data suggest that possible mechanisms of cell lysis include complement-dependent cytotoxicity and antibody-dependent, cell-mediated cytotoxicity. Because normal B-lymphocytes express CD20, treatment with ofatumumab results in prolonged depletion of normal B-cells. In patients with CLL refractory to fludarabine and alemtuzumab in study Hx-CD20-406, the median decrease in circulating B cells was 91% with the 8th infusion and 85% with the 12th infusion. The time to recovery of B cells to normal levels could not be determined due to insufficient patient follow-up.

Pharmacokinetic data were obtained from 146 patients with refractory CLL who received a 300 mg initial dose followed by 7 weekly and 4 monthly infusions of 2,000 mg. The C_{max} and $AUC_{(0-\infty)}$ after the 8th infusion in Study Hx-CD20-406 were approximately 40% and 60% higher than after the 4th infusion in Study Hx-CD20-402. The mean volume of distribution at steady state (V_{ss}) values ranged from 1.7 to 5.1 L. Ofatumumab is eliminated through both a target independent proteolytic enzyme route and a B cell receptor-mediated route. Ofatumumab exhibited dose dependent clearance in the dose range of 100 to 2,000 mg. Due to the depletion of B cells, the clearance of ofatumumab decreased substantially after subsequent infusions compared to the first infusion. The mean clearance between the 4th and 12th infusions was approximately 0.01 L/hr and exhibited large inter subject variability with CV% greater than 50%. The mean $t_{1/2}$ between the 4th and 12th infusions was approximately 14 days (range: 2.3 to 61.5 days).

5.2. Demographic interactions/special populations

Population PK studies were performed on data from patients with a wide variety of conditions, including 162 patients with CLL who received multiple infusions of single agent ofatumumab at doses ranging from 100 to 2,000mg. These studies did not identify weight, height, body surface area, gender, age or baseline serum creatinine clearance (range 33 to 287mL/min) to have a significant effect on the pharmacokinetics of ofatumumab. No dose adjustment is recommended based on these covariates. The effect of hepatic impairment on the PK of ofatumumab was not studied; however, variations in hepatic function are unlikely to influence the PK of ofatumumab. There are no adequate or well-controlled studies of ofatumumab in pregnant women, and it is not known whether it is secreted in human milk.

5.3. *Thorough QTc study or other QTc assessment*

QT evaluation is currently expected for all new molecular entity drugs and biologics during their clinical development. A thorough QT (TQT) study is not recommended for ofatumumab since current understanding is that monoclonal antibodies (mAbs) cannot access hERG pores via the intracellular side, the target site for most small-molecule QT-prolongation drugs. However, the potential of ofatumumab affecting QT interval through off-target mechanisms cannot be ruled out. QT studies were not conducted for ofatumumab. Two QTc studies will be performed as post marketing requirements (PMRs). The proposed studies have been reviewed by the QT interdisciplinary review team (IRT).

5.4. *Notable issues*

Adequate QTc studies must be performed as PMRs

6. **Clinical Microbiology**

This section is not applicable to this application.

7. **Clinical/Statistical-Efficacy**

7.1. *General Discussion*

The primary clinical reviewer (Office of Oncology Drug Products, Division of Biologic Oncology Products) and primary statistical reviewer (Office of Biostatistics, Division of Biometrics V) recommend that the BLA be approved provided that the Applicant and FDA reach a satisfactory agreement on specific revisions to the proposed label, and that the Applicant commits to a specific PMR required under accelerated approval regulations to conduct with due diligence clinical trial(s) to confirm the clinical benefit of ofatumumab in patients with CLL. As will be discussed further in section 7.2.5, *Discussion of notable efficacy issues*, the statistical team leader recommends against approval.

The Applicant conducted a clinical development program for ofatumumab in the treatment of patients with CLL who have received prior therapy. At a Pre-Phase 2 meeting held between GenMab and FDA to discuss the acceptability of a proposed trial to support accelerated approval, FDA identified durable ORR as an acceptable surrogate endpoint reasonably likely to predict clinical benefit in a patient population with an unmet medical need, i.e., no alternative therapy. GenMab proposed to conduct a single-arm clinical trial, study Hx-CD20-406, in 100 patients who had failed both fludarabine and alemtuzumab to satisfy the requirement for demonstrating benefit in patients with an unmet medical need. Subsequently, GenMab submitted the proposed study as a special protocol assessment (SPA). The Agency did not agree to the SPA. After a second round of SPA review, GenMab initiated study Hx-CD20-406 without an SPA agreement

Although the study Hx-CD20-406 enrolled a total of 154 patients, the efficacy data upon which accelerated approval will be considered are derived from the protocol-specified subgroup of 59 patients with disease refractory to fludarabine and alemtuzumab (the "double refractory" or DR population) who were considered by FDA to have an unmet

medical need. As the primary endpoint for the purpose of accelerated approval was the surrogate endpoint of durable objective response rate (ORR), the Applicant will be required to conduct additional adequate and well controlled clinical trials to confirm the clinical benefit of ofatumumab. Such trials have been initiated.

The results submitted to support approval of BLA 125326 were from a prespecified interim analysis conducted by a Data Monitoring Committee when 66 patients in the DR population were assessable for ORR. The results in the DR subgroup demonstrated positive results on the endpoint of ORR with an Investigator-determined response rate of 42% (99% CI: 26, 60) and a median duration of response (DOR) of 6.5 months (95% CI: 5.8, 8.3). There were no complete responses. Although these results were confounded by uncertainty introduced by the single arm trial design, erroneous classification of patients to the various subgroups, difficulties in applying the 1996 NCIWG response criteria and the conduct of the IRC review they were generally supported by the clinical and statistical reviewer's analysis.

7.2. *Efficacy*

7.2.1. *Dose identification/selection and limitations*

The doses of ofatumumab chosen for use in study Hx-CD20-406 to obtain data for approval were adapted from the highest dose (cohort C) investigated in the dose escalation study Hx-CD20-402 in which a trend was observed that the ORR increased with increasing ofatumumab exposure. There were no responses in either of the lower dose cohorts. All doses were administered by IV infusion. In study Hx-CD20-402 adverse reactions were primarily observed on the day of the first infusion. Therefore, in order to reduce the potential for infusion reactions, the first dose was reduced from 500 mg to 300 mg. All subsequent doses were 2000 mg. The dosing schedule of one 300 mg dose followed one week later by 2,000 mg once weekly for 7 infusions, followed 4 weeks later by 2,00 mg once every 4 weeks for 4 infusions was chosen based on the pattern of response and progression in relation to ofatumumab exposure in study Hx-CD20-402.

At a meeting held between GenMab and FDA on August 26, 2005 to discuss the acceptability of a proposed trial to support accelerated approval, FDA recommended that GenMab conduct an additional phase 2 dose finding trial prior to studies designed to support accelerated or regular approval. GenMab replied that a second study could not be conducted prior to a "pivotal" trial.

7.2.2. *Clinical studies essential to regulatory decision*

The primary data submitted by GSK in support of this BLA were from study Hx-CD20-406 entitled "A single-arm, international, multi-center trial of ofatumumab, a fully human monoclonal anti-CD20 antibody, in patients with B-cell chronic lymphocytic leukemia who have failed fludarabine and alemtuzumab". This study was an industry-sponsored, open-label, international, multicenter, single arm, non-comparative study evaluating ofatumumab in patients with elapsed or refractory B-cell CLL who had an indication for treatment as defined by NCI Working Group (1996 NCIWG) guidelines. Patients were required to have disease refractory to an adequate course of fludarabine and to either be refractory to alemtuzumab, designated as "double refractory" (DR), or have bulky

lymphadenopathy, designated as “bulky fludarabine refractory” (BFR). A group of patients not meeting the requirements of either of these categories was designated as “Other”. Patients were scheduled to receive a total of 12 doses of ofatumumab at the following doses and schedule:

- 300 mg during week 0
- 2,000 mg weekly from weeks 1 to 7, and on weeks 12, 16, 20, and 24

Prior to receiving ofatumumab, all patients were to receive premedication with an antihistamine, acetaminophen (1,000 mg or equivalent), and IV corticosteroids at doses according to a prespecified protocol. Protocol-specified treatment was to continue for a total of 12 doses until the patient experienced a critical adverse event, received prohibited therapy, withdrew consent, or was deemed by the investigator to have a medical reason to stop treatment. The protocol did not require that ofatumumab be discontinued for disease progression.

Physical exam and laboratory assessments for anti-tumor activity and adverse events were scheduled every four weeks until week 28 and then every three months until month 24. Disease status assessments included measurements of lymph nodes, liver and spleen by physical examination and a complete blood count including hemoglobin, platelets, lymphocytes and neutrophils. The primary endpoint was objective response occurring between the first dose of ofatumumab through week 24 as determined by an Independent Endpoints Review Committee (IRC) according to response criteria in the 1996 NCIWG guidelines. Duration of response was a secondary endpoint. Endpoint analyses were to be conducted separately for the DR and the BFR subgroups. In the original protocol, the analyses would occur when data for 100 patients were available for each group. The protocol was later amended to include an interim analysis when the primary endpoint data were available for 66 patients in the DR subgroup. To minimize the potential for bias in an open-label, single arm study, the IRC determination of disease response and disease progression rather than the Investigators’ evaluations would be used in the analyses.

Although the study Hx-CD20-406 enrolled a total of 154 patients, the efficacy data upon which accelerated approval will be considered is derived from the protocol-specified DR subgroup of 59 patients. FDA considers this patient population, more than 90% of whom also received prior therapy that included an alkylating agent, to be a patient population with an unmet medical need. Data from the BFR patient population and from “other” CLL patients enrolled in study Hx-CD20-406 and data from patients enrolled in study Hx-CD20-402 will be considered supportive in the regulatory decision making regarding approval of ofatumumab in the DR patient population. The FDA safety database for ofatumumab consists of the 154 patients enrolled in Hx-CD20-406 who received the 2000 mg IV infusion dose proposed for approval.

Table 1, adapted from Dr. Lemery’s clinical review, shows that most DR patients in study Hx-CD20-406 were white males with a median age of 64 years. A total of 54% were Rai stage III or IV at the time of screening.

Table 1: Demographics of Patients Enrolled in Study Hx-CD20-406

	DR (n=57)	BFR (n=79)	Other (n=16)	Total (n=154)
Sex [n (%)]				
Female	15 (25)	22 (28)	6 (37.5)	43 (28)
Male	44 (75)	57 (72)	10 (62.5)	111 (72)
Age (years)				
≥65 yr (%)	27 (46)	33 (42)	6 (37.5)	66 (43)
Median (%)	64	62	63	63
Race [n (%)]				
White	56 (95)	78 (99)	15 (94)	149 (97)
Asian	1 (2)	0	1 (6)	2 (1)
Black	0	1 (1)	0	1 (<1)
Other	2 (2)	0	0	2(<1)
Time from Original CLL Diagnosis (years)				
Mean (SD)	6.7 (4.1)	6.5 (3.8)	8.8 (3.5)	6.9 (3.9)
Median	6.0	5.9	7.5	6.3
Rai Stage at Screening [n, (%)]				
0	1 (2)	0	0	1 (1)
1	11 (19)	7 (9)	2 (13)	20 (13)
2	15 (25)	17 (22)	4 (25)	36 (23)
3	10 (17)	11 (14)	4 (25)	25 (16)
4	22 (37)	44 (56)	6 (38)	72 (47)
Time from Last CLL Treatment (years)				
Mean (SD)	0.52 (0.42)	0.68 (0.69)	0.92 (1.57)	0.65 (0.75)
Median	0.36	0.40	0.36	0.39
ECOG PS (n,%)				
0	27 (46)	25 (32)	3 (19)	55 (36)
1	19 (32)	41 (52)	9 (56)	69 (45)
2	12 (20)	13 (22)	4 (25)	29 (19)
3	1 (2)	0	0	1 (1)

The overall population in study Hx-CD20-406 was heavily pretreated. The median number of prior therapies in the DR group was 5 and in the BFR group was 4. Table 2, adapted from Dr. Lemery's clinical review, shows that in addition to receiving fludarabine and alemtuzumab, nearly all patients in the DR subgroup, as well as the in overall study population, had received an alkylating agent-containing regimen. Over 50% of the patients in study Hx-CD20-406 had received rituximab.

Table 1: Prior Therapies in Study Hx-CD20-406

Type of Prior Regimen	DR (N=59)	BFR (N=79)	Other (N=16)	Total (N=154)
Alkylating agent	93%	92%	100%	94%
Fludarabine	100%	100%	100%	100%
Alemtuzumab	100%	19%	63%	55%
Rituximab or rituximab-containing regimen	59%	54%	63%	57%

In the DR group, 88% of patients received at least 8 infusions of ofatumumab and 54% received 12 infusions.

The results submitted to support approval of BLA 125326 were from a prespecified interim analysis conducted by a Data Monitoring Committee when 66 patients in the DR population were assessable for ORR. For technical reasons, FDA has determined that the results from the investigators may be more reliable than those adjudicated by the IRC, and Investigator-determined results will be used in this review and in the product labeling. The results in the DR subgroup demonstrated positive results on the endpoint of ORR with an Investigator-determined response rate of 42% (99% CI: 26, 60) and a median duration of response (DOR) of 6.5 months (95% CI: 5.8, 8.3). All responses were partial responses or nodular partial responses; there were no complete responses. Although these results were confounded by uncertainty introduced by the single arm trial design, erroneous classification of patients to the various subgroups, difficulties in applying the 1996 NCIWG response criteria and the conduct of the IRC review, they were generally supported by the clinical and statistical reviewer's analysis.

7.2.3. Other efficacy studies

Study Hx-CD20-402 was an industry-sponsored, open-label, international, multicenter, dose escalation study evaluating three dose levels of ofatumumab in patients with elapsed or refractory CLL and a circulating lymphocyte count above 5,000/mcL. Patients received up to four weekly doses of ofatumumab according to the following schedules:

Cohort A (n=3)	first dose 100 mg, subsequent doses 500 mg
Cohort B (n=3)	first dose 300 mg, subsequent doses 1,000 mg
Cohort C (n=27)	first dose 500 mg, subsequent doses 2,000 mg

Dose escalation would proceed if three patients in the previous cohort were followed 5 weeks without protocol defined dose-limiting toxicity (DLT). An expansion cohort of 26 patients was planned for Group C if study-specific, safety-based stopping rules were not met. Assessments for anti-tumor responses included physical examination for lymph

nodes, liver, and spleen measurements. Responses occurring up to week 27 were determined for all patients. Adverse event reporting began with the first dose, was weekly during ofatumumab administration and monthly thereafter, and ended when the patient left the study. The last follow-up visit was scheduled to occur at 12 months (or approximately 11 months after the final dose of ofatumumab). Study Hx-CD20-402 was considered only supportive in the clinical review primarily due to differences in dose, dosing schedule, inclusion criteria, and monitoring compared to study Hx-CD20-406.

No responses were observed in the 3 subjects in cohort A, nor in the 3 subjects in cohort B. GSK's analysis of efficacy results for cohort C were an ORR of 48% (95% CI: 30, 70) with a median DOR of 4.4 months. The clinical reviewer's independent analysis of the data found these results to be acceptable.

7.2.4. Discussion of primary and secondary reviewers' comments and conclusions

Although both the primary clinical and primary statistical reviewers had reservations regarding the reliability of GSK's interpretation of the results of Hx-CD20-406, especially the IRC's response and progression assessments, after extensive re-evaluation of the data on an individual patient level, investigating the IRC internal procedures and conducting sensitivity analyses, they each concluded that although there may be uncertainty to the accuracy of the ORR and DOR estimates, they fall in a range that is reasonably likely to predict clinical benefit. As the clinical reviewer's point estimate for ORR in the DR population (41% with 99% CI: 25, 59) was similar to that determined by the investigators (42% with 99% CI: 26, 60), and in light of the issues regarding the IRC's review of response rates, he recommends the use of the Investigators' ORR determination for regulatory decision making and for labeling purposes. However he goes on to state:

"Because some deviation of the response criteria was necessary in the overall response assessment, there was substantial variability in the determination of dates of response, progression, or overall response. This variability created uncertainty in the determination of the ORR in study 406. This reviewer believes that the magnitude of this uncertainty will be inflated when clinicians try to compare the results of this study to other studies published in the literature. This reviewer believes that any comparisons of response rates across studies are thus not valid and should not be relied upon for marketing claims against any approved or unapproved drugs".

This CDTL concurs with the primary clinical and statistical reviewers' conclusions that the Hx-CD20-406 Investigators determinations of ORR and DOR appear to be more reliable than those of the IRC, fall in a range that is reasonably likely to predict clinical benefit, and should be used for labeling purposes.

The statistical Team Leader recommends against approval. This CDTL does not concur with this recommendation, which will be discussed further in section 7.2.5 *Discussion of notable efficacy issues.*

7.3. Discussion of notable efficacy issues

The statistical Team Leader recommends against approval. This CDTL does not concur with this recommendation.

The statistical Team Leader's "Conclusions and Recommendations" section reads as follows:

"Study Hx-CD20-406 is not an adequate and well controlled clinical trial. The estimation of response rate in study Hx-CD20-406 is not reliable due to both the difficulty in assessing response and the small sample size. In addition, response rate at a trial-level has not been linked to the demonstration of clinical benefit in CLL. There have been instances in CLL and other leukemias where comparisons on response have not corresponded to comparisons on overall survival or progression-free survival (PFS). The sponsor did not provide evidence linking response rate to clinical benefit in any setting of CLL. For further discussion see section 1.3 below. I believe this submission does not satisfy the requirements for approval (accelerated or regular approval) and recommend against approval."

First, this CDTL would consider Study Hx-CD20-406 to be a sufficiently or "well" controlled clinical trial. In a single arm trial in a heavily pre-treated population such as studied in this trial, the control is an implied historical control. Any anti-tumor effect observed must be attributed solely to the agent under investigation, as there is no precedent for any heavily pre-treated patient with CLL whose disease is refractory to fludarabine and alemtuzumab ever experiencing a spontaneous regression of their disease to the point of meeting the protocol criteria for "partial response".

The question of the adequacy of Study Hx-CD20-406 appears to be one of the accuracy and reliability in the estimation of the response rate. The primary clinical and statistical reviewers have gone to considerable lengths to reduce the uncertainty in the estimate of the treatment effect, and have concluded that due to inconsistencies and poor design in the IRC internal procedures, the Investigator-determined ORR is the more accurate and reliable value. Dr. Lemery, the primary clinical reviewer, performed a thorough and meticulous case-by case re-review of the response data on an individual patient level, and obtained results strikingly similar to those determined by the Investigators.(table 3)

Table 3: Summary of Point-Estimates of ORR with CIs for the DR Group

	Investigator-determined (N= 59)	FDA Clinical Reviewer (N=56)
ORR (N)	42% (25)	41% (23)
99% CI (%)	(26, 60)	(25,59)

Results such as these provide confidence that the estimates derived from the Investigators' determination of response are adequately accurate to be relied upon.

Given that there are no spontaneous responses in this setting, the final question hinges on the regulatory requirement that the magnitude of the effect on the surrogate endpoint (ORR) be reasonably likely to predict clinical benefit. The spirit of the accelerated approval regulations is to allow patients with serious or life threatening diseases with unmet medical needs early access to drugs that demonstrate anti-disease activity of a magnitude that is "reasonably likely" to predict that, upon further investigation, they will be found to confer clinical benefit. The threshold of anti-disease activity that is "reasonably likely to predict" clinical benefit is disease and prior therapy specific; an effect on a surrogate that may or may not predict benefit in first line NSCLC or second line metastatic colon cancer may bear no relationship to the effect on a surrogate that would predict benefit in heavily pretreated CLL. In a comparison to legal standards of proof, "reasonably likely to predict" would appear to be a category below "beyond a reasonable doubt" (almost 100% certainty) in criminal cases or "a preponderance of evidence" (51% or greater) in many civil cases. In the end, in the absence of rigorous data excluding the possibility of benefit, the decision rests on an informed speculation by clinical experts in the field, with the clear knowledge that not every "reasonably likely to predict" conclusion will in fact be confirmed with a demonstration of clinical benefit. In the final analysis, one might expect that a significant proportion would not.

In this case we have a number of independent opinions from clinical experts in the field. First, as noted in the regulatory history, during the IND stage of development a government SGE expert in the field of leukemia provided an opinion that in this setting an ORR of 10-20% was unlikely to predict clinical benefit, but that in a population with an unmet medical need an ORR where the lower bound of the 95% CI was at least 25% would be of interest. The investigator-determined ORR in study Hx-CD20-406 was 42% with a lower bound of the 99% (not 95%) CI of 26. Second, after a great deal of discussion regarding the reliability of the results and the possible flaws in the determination of tumor responses, on May 29, 2009 the Oncologic Drugs Advisory Committee comprising individuals possessing a wide range of expertise in cancer, voted 10 to 3 affirmative to the question, "Are the following results [of study Hx-CD20-406] reasonably likely to predict clinical benefit in patients with CLL that is refractory to fludarabine and alemtuzumab?" Additionally, expert FDA clinical and statistical reviewers, after exhaustive investigations into the reliability of the trial results, recommended approval of this BLA.

Finally, GSK has initiated and is conducting with due diligence study OMB110911, entitled, "A Phase III, Open-label, Randomized, Multicenter Trial of Ofatumumab Added to Chlorambucil versus Chlorambucil Monotherapy in Previously Untreated Patients with Chronic Lymphocytic Leukemia," a trial to investigate and confirm the clinical benefit of ofatumumab in CLL and has committed complete the trial by October 14, 2013 and to submit the final study report by June 30, 2014.

For these reasons, this CDTL disagrees with the recommendation of the statistics team leader and recommends that this BLA be approved.

8. Safety

8.1. General safety considerations

The safety database for this BLA consists of 181 patients with relapsed or refractory CLL in 2 open-label, single arm studies. The analysis will focus on 154 patients who received a uniform dose of ofatumumab on study Hx-CD20-406. These patients received 2,000 mg weekly from the second dose onward and then monthly according to the study Hx-CD20-406 schedule. Ninety percent of patients receive at least 8 infusions and 55% received all 12 infusions. The median age was 63 years (range 41 to 86 years, 72% were male and 97% were White). Given that the disease in question under consideration for accelerated approval in this application is a life threatening malignancy in an orphan population the size of the safety database for ofatumumab in refractory CLL is not unreasonable.

Clinical assessments were performed by investigators. Standard safety evaluations included assessment of AEs, laboratory evaluations (hematology and clinical biochemistry), human anti-human antibody (HAHA) testing, and vital signs during the treatment and follow-up phases. As per study protocol, deterioration of study disease was not to be reported as an AE unless it fulfilled the SAE criteria.

An independent external Data Monitoring Committee (DMC) was appointed to conduct ongoing regular safety surveillance of the study. The DMC's safety reviews included evaluations of all SAEs, all non-serious AEs of common terminology criteria for adverse events (CTCAE) Grade 3 and 4, and all other relevant safety data.

8.2. Safety findings from submitted clinical trials

There were several deaths of causes that are expected in this patient population, primarily disease progression and infections. GSK indicated that 24 out of 61 deaths occurred during treatment or follow-up and 37 were reported during extended follow-up. Thirty of the 37 deaths occurring during extended follow-up occurred after the initiation of new CLL therapy. The most common cause of death other than disease progression was infection; 19 of 154 patients (13%) had fatal infections. The percentage of patients who died of infections in the DR population was higher (17%) than the BFR population (6%). It is unclear if this difference was due to chance or was caused by more severe immunosuppression in the DR group from prior alemtuzumab therapy.

A total of 82 patients experienced a total of 152 SAEs. The most commonly reported SAEs were related to infections, occurring in 33% of patients. A total of 51 patients experienced 67 SAEs due to infections. Infections due to bacteria, viruses, and fungi were reported. The GSK study report described a 12% overall incidence rate of pneumonia using the MedDRA preferred term. If the high-level term "lower respiratory tract and lung infections" is used, then 16% (n=25) of patients had lower respiratory tract infections. One patient died of JC virus infection (manifested as progressive multifocal leukoencephalopathy). A total of 18 patients experienced SAEs in the blood SOC. Most cases involved cytopenias (neutropenia, thrombocytopenia, and anemia, including hemolytic anemia). Seven patients experienced 9 cardiac events; two cardiac events were reported during infusion days. Two experienced small intestinal obstruction; one had a

prior history of small bowel obstruction and CLL invasion of the celiac plexus and for the other no definitive cause of the intestinal obstruction could be identified.

A total of 106 (69%) out of 154 patients had an AE on day 0 or 1 after an infusion that was possibly attributable to an infusion related reaction. A total of 9 (6%) of 154 patients had a total of 14 \geq Grade 3 adverse reactions. These adverse reactions included myocardial infarction, pulmonary edema, myocardial ischemia, bronchospasm, dyspnea, hypersensitivity, macular rash, vasovagal syncope, back pain, cytokine release syndrome, throat irritation, and myocardial ischemia. The frequency of infusion reactions decreased after the third dose. Eighteen of 148 patients (12%) developed an infusion-related symptom after the third dose. There is no evidence that severe or serious TLS occurred during study Hx-CD20-406.

No clinically significant laboratory abnormalities were observed.

There were no reports of Hepatitis B reactivation with ofatumumab. However, on July 28, 2009, after the safety update, GSK submitted a safety report of a 54-year-old woman receiving ofatumumab in conjunction with methotrexate for rheumatoid arthritis who developed fatal newly acquired hepatitis B. Autopsy confirmed massive total liver necrosis.

8.3. *Safety update*

The submitted 90-day safety update showed no new safety signals.

8.4. *Immunogenicity*

Although there is a potential for immunogenicity with all therapeutic proteins, the incidence of immune responses to ofatumumab appears to be low. A validated ELISA assay was used to detect anti-ofatumumab antibodies. GSK reported no instances of positive human anti-human antibodies (HAHAs) during the conduct of study Hx-CD20-402. In study Hx-CD20-406, serum samples from 154 patients were tested for anti ofatumumab antibodies during and after the 24 week treatment period. Results were negative in the 46 evaluable patients at the 8th infusion and in the 33 evaluable patients at the 12th infusion. Results from the remaining patients were inconclusive due to interference with the immunogenicity assay by circulating ofatumumab.

The risk of immunogenicity with ofatumumab can be expected to be low for the following reasons:

- (1) In general, fully human IgG1 κ monoclonal antibodies such as ofatumumab have a low incidence of immunogenicity
- (2) The incidence of T cells that recognize epitopes on ofatumumab *in silico* was low;
- (3) In these trials, patients were immunosuppressed by premedication with corticosteroids
- (4) Ofatumumab-mediated lysis of B cells reduces the likelihood of an immune response

The package insert goes on to state: "Immunogenicity assay results are highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to ofatumumab with the incidence of antibodies to other products may be misleading."

8.5. Discussion of primary reviewer's comments and conclusions

The primary clinical reviewer, Dr. Steven Lemery, determined that the most concerning adverse events with ofatumumab were reactions associated with the infusion, common with therapeutic proteins and for the most part medically manageable, severe infection, which was in general of types and severity frequently seen with heavily treated patients with CLL and cardiac events, which may have been associated with infusion reactions. Treatment with ofatumumab was generally well tolerated in this study population with advanced, heavily pre-treated, highly refractory CLL with a high risk for rapid disease progression and infectious complications. He concluded that given the demonstrated benefits of ofatumumab that the benefit/risk ratio is favorable. This CDTL agrees that infusion reactions and severe and potentially fatal infections are the major safety concerns for this product.

8.6. Discussion of notable safety issues

Given the toxicity profile noted for ofatumumab, warnings regarding the following AEs should be included in the product label:

1. Infusion Reactions
2. Cytopenias
3. Progressive Multifocal Leukoencephalopathy
4. Hepatitis B
5. Intestinal Obstruction

9. Advisory Committee Meeting

A meeting of the Oncology Drugs Advisory Committee was held on May 29, 2009 to discuss ofatumumab for the treatment of patients with chronic lymphocytic leukemia who have received prior therapy. After discussion of the overall effect size, the unquantifiable uncertainties regarding the effect size due to sub-optimal Independent Review Committee assessment and lack of CT scans, and the safety profile, the committee voted 10 to 3 that the Investigator-reported ORR of 42% (99% CI 26, 60) with a median duration of response (DOR) of 6.5 months is an effect size that is reasonably likely to predict clinical benefit in patients with CLL refractory to fludarabine and alemtuzumab. Those voting "no" expressed the desire, based on the degree of uncertainty in the results, to wait for more definitive data from the ongoing randomized, controlled trials.

Additionally, the committee was asked to discuss considerations for optimal trial designs for studies intended to support marketing approval of drugs for the treatment of CLL. The major issue under consideration was whether to require CT (or other) imaging in all patients at regularly scheduled intervals.

Most members agreed that for regulatory decision making, CT scans should be used in the determination of objective response rates in patients with CLL (especially those with advanced disease).

10. Pediatrics

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new drugs are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

CLL is extraordinarily rare in children and it would not be possible to conduct studies in children due to the small number of patients available. Therefore, the Applicant originally requested a waiver from the requirements to conduct studies in children under the PREA. However, on March 10, 2009, ofatumumab was granted orphan drug designation for the treatment of CLL. Because this drug for this indication has orphan drug status, it is exempt from PREA requirements.

11. Other Relevant Regulatory Issues

11.1. Financial Disclosures

Based on the information submitted by the Applicant there were no financial conflicts of interest that would have the potential to bias the study Hx-CD20-406 or Hx-CD20-402 data.

11.2. DSI Audits

The Division of Scientific Investigations (DSI) inspected 5 clinical sites (3 in the United States and 2 in Europe) and found no regulatory violations which could bias the results of study Hx-CD20-406. In addition, audit of monitoring records at GenMab A/S offices in Copenhagen found no violations. Based on the results of these inspections, DSI reported the data are considered reliable in support of the specific indication.

12. Labeling

12.1. Proprietary name

The Office of Surveillance and Epidemiology (OSE) Division of Medication Error Prevention and Analysis (DMEPA) determined that the proposed proprietary name, Arzzeria, was acceptable.

12.2. Physician labeling

At the time of this review, labeling negotiations between GSK and FDA are ongoing. If agreement can be reached on a satisfactory package label, the recommendation of this reviewer will be for Approval. If agreement cannot be reached on a satisfactory package label, a Complete Response will need to be issued.

In general, the label was revised for brevity, clarity and to introduce direct and command language. This section of the review will focus on high-level labeling recommendations. Only notable and substantial content changes will be discussed in this section.

Specific revisions affecting the content of the label included:

1. Indications and Usage

This section was revised to reflect the specific population with an unmet medical need (patients refractory to alemtuzumab and fludarabine) from which the data on which the approval was based was obtained and to include wording indicating that the approval was on the basis of a surrogate endpoint under the provisions of the accelerated approval regulations, 21 CFR 601.40-46.

2. Dosage and Administration

This section was reformatted and the included dosing schedule revised for clarity. The Hx-CD20-406 protocol specified a complex dosing schedule, which was simplified to reduce the potential for dosing errors. Based on the PK/PD profile of ofatumumab, this change in scheduling of the 8th dose from 5 weeks to 4 weeks after the proceeding dose, should have no detrimental effects on either the safety or effectiveness of ofatumumab. Table of premedication dosing was replaced with short bulleted narratives conveying the same information.

3. Dosage Forms and Strengths

No change was made. Although DMEPA recommended that the word "injection" come after the word "vial" in this section of the label, DBOP precedent with the labels for alemtuzumab, bevacizumab, rituximab, cetuximab, and panitumumab is to omit this due to the safety concern that health practitioners could mistake the intent of the word "injection" and administer the product as a bolus.

5. Warnings and Precautions

"Infusion Reactions" was revised to conform to the FDA Clinical Reviewer's listing of the most severe or serious reactions occurring after ofatumumab administration. () was removed as it has not been observed. () was removed and relevant components moved to "Infusion Reactions". () was re-titled "Cytopenias" to reflect the underlying medical conditions and concerns. "Progressive Multifocal Leukoencephalopathy" was strengthened and "Hepatitis B Reactivation" was expanded to include the occurrence of fatal primary infection.

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6. Adverse Reactions

This section was revised to conform to PLR format and to incorporate the findings of the clinical reviewer's assessment of the data. In Table 2, Adverse Reactions were broken out into those found in the accelerated approval (DR) population, and those in the total population of study Hx-CD20-406. Immunogenicity was revised to clarify the large numbers of assays that were inconclusive due to interference by circulating ofatumumab, and to remove the speculative statement that the

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8. Use in Specific Populations

"Pregnancy" and "Nursing Mothers" were revised to conform to the findings of the Non-clinical toxicology, Clinical Pharmacology and Maternal Health Review Teams. Geriatric use was revised to state that insufficient numbers of patients older than 65 had been studied to draw conclusions.

11. Description

This section was revised to conform to the findings of the Quality (CMC) Review Team, and to provide the information necessary to inform a provider adequately to prescribe or decide to prescribe the drug.

12. Clinical Pharmacology

This section was revised to conform to the PLR format and to the findings of the Clinical Pharmacology Review Team, and to provide the information necessary to inform a provider adequately to prescribe or decide to prescribe the drug without introducing implied comparative or speculative clinical claims not backed by substantial evidence. Table 4 was omitted and the relevant information incorporated into text.

13. Nonclinical Toxicology

This section was revised to conform to the PLR format and to the findings of the Clinical Pharmacology Review Team, and to provide additional information on "Reproductive and Developmental Toxicology."

14. Clinical Studies

This section was revised for brevity, to emphasize the demographics and results of the specific population with an unmet medical need (patients refractory to alemtuzumab and fludarabine) from which the data on which the approval was based was obtained, to use the Investigators' reports of ORR and DOR, to omit the specific quantitative results of secondary endpoints and 1996 NCIWG criteria, and to remove unnecessarily complex tables.

15. References

Per PLR format, this section was removed.

17. Patient Counseling Information

This section was expanded to include important instructions for clinicians to convey to their patients. Because ofatumumab is an infusion administered by trained medical personnel under controlled conditions, the "Patient Information" to be given by the pharmacist to the patient with each prescription is not practical or necessary and was omitted.

12.3. Carton and container labels

The primary review division, the Division of Biologic Oncology Products (DBOP) consulted the Office of Biotechnology Products (OBP) and the Office of Surveillance and Epidemiology (OSE) to obtain CMC and safety expertise on GSK's proposed Arzerra carton and container labels. The two consult reviews for the Arzerra carton and container label, one from OBP and one from OSE, were received on June 19, 2009 and July 31, 2009, respectively. Each consult review contained recommendations for labeling revisions. On August 29, 2009, DBOP, OBP and OSE reviewers met to discuss label review proposals and agreed on recommendations to be sent to GSK. After DBOP Division Director concurrence on September 8, 2009, multiple, detailed FDA recommendations concerning both the carton and container labels were sent to GSK, who subsequently emailed requests for clarification on September 9, 2009 (see Project

Manager Ray Chiang's review for enumeration of recommendations). DBOP, OBP, and OSE concurred on responses to GSK's questions and FDA provided a response to GSK's questions on September 11, 2009. On September 15, 2009, GSK submitted revised carton and container labels. Upon evaluation, the review team concluded that GSK satisfactorily addressed FDA's requests and that the container and carton labels are acceptable.

12.4. Patient labeling/Medication guide

Ofatumumab is indicated for the treatment of patients with life-threatening cancer and is administered as an infusion by trained medical personnel under controlled conditions. As such, no additional clinical post-market risk management activities are to be instituted at this time. The proposed package insert contains patient counseling information for prescribing physicians (hematologists and oncologists).

13. Recommendations/Risk Benefit Assessment

13.1. Recommended Regulatory Action

As discussed in section 13.2, under the provisions of the accelerated approval regulations, this CDTL finds the risk/benefit assessment of the use of ofatumumab in patients with CLL refractory to fludarabine and alemtuzumab to be favorable. The Quality (CMC), Non-clinical toxicology, and Clinical Pharmacology Teams have recommended Approval. The Office of Compliance Facilities Inspection Team and Division of Scientific Investigations have reported that these are no findings that would prevent approval. The Division of Risk Management considers the proposed risk management approach acceptable. DMEPA has determined that the proposed proprietary name, Arzerra, is acceptable. The Division of Biologic Oncology Products primary clinical reviewer, the Division of Biometrics V primary statistical reviewer and the Oncologic Drugs Advisory committee concluded that the results from the population of patients with CLL refractory to fludarabine and alemtuzumab in trial Hx-CD20-406 are reasonably likely to predict that ofatumumab may confer clinical benefit in CLL. The recommendation of this Cross Discipline Team Leader is for approval of BLA 125326 contingent upon agreement between the Applicant and FDA on acceptable package labeling before the Action Date.

13.2. Risk Benefit Assessment

The primary clinical reviewer, the primary statistical reviewer and the Oncologic Drugs Advisory committee concluded that the data from the trial Hx-CD20-406 provide substantial evidence of an effect of sufficient magnitude on a surrogate endpoint, durable response, to reasonably predict that ofatumumab may confer clinical benefit in the indicated population of patients with CLL refractory to fludarabine and alemtuzumab. However, the statistical team leader recommended non-approval due the level of uncertainty regarding the results. Section 7.2.5 *Discussion of notable efficacy issues* of this review provides this Cross Discipline Team Leader's argument to support concurrence with the efficacy findings of the primary clinical and statistical reviewers and the ODAC

In light of the unmet medical need of this severely ill population, patients with CLL refractory to fludarabine and alemtuzumab, a relatively rapidly fatal condition, and the determination that it is reasonable to predict that ofatumumab may provide clinical benefit, a high level of toxicity would be necessary to result in an adverse Risk/Benefit Assessment. Toxicities in study Hx-CD20-406 were predominately reactions associated with the infusion, common with therapeutic proteins and for the most part medically manageable, and infection, which was in general of types and severity frequently seen with heavily treated patients with CLL. In the absence of a comparator arm it is difficult to judge whether severe or life-threatening infections are occurring at increased rates, and it is therefore difficult to assess the risk with complete accuracy and assurance. However, severe infections appear to occur at a rate that is within the range of the background rate for this population. The ongoing randomized, controlled confirmatory trial may do much to reduce the level of uncertainty associated with the results of the present single arm trial. The purpose of the accelerated approval regulations is to speed the availability of promising treatments to patients with severe illness who have unmet medical needs. In this situation, this reviewer agrees with the conclusions of the primary clinical reviewer and the primary statistical reviewer that the observed level of toxicity is tolerable when compared to the possibility of clinical benefit and finds the Risk/Benefit profile of ofatumumab in patients with CLL refractory to fludarabine and alemtuzumab to be favorable.

13.3. Recommendation for Postmarketing Risk Evaluation and Management (REMS) Strategies

The Division of Risk Management (DRISK) review team recommends that GSK be required to provide progress reports as described under 21 CFR 601.70, 21 CFR 601.44, and 21 CFR 600.80.

Ofatumumab is indicated for the treatment of patients with life-threatening cancer. As such, no additional clinical post-market risk management activities necessary at this time. The proposed USPI contains patient counseling information for prescribing physicians (hematologists and oncologists). DRISK finds the proposed risk management plan acceptable.

13.4. Safety concerns to be followed postmarketing

Cases of severe infusion reactions and infections should be followed postmarketing.

13.5. Postmarketing studies

13.5.1. Required studies (PMRs)

Accelerated Approval Confirmatory Trial:

1. To submit a final report for ongoing clinical trial OMB110911, entitled, "A Phase III, Open-label, Randomized, Multicenter Trial of Ofatumumab Added to Chlorambucil versus Chlorambucil Monotherapy in Previously Untreated Patients with Chronic Lymphocytic Leukemia" which is intended to verify the clinical benefit of Arzerra (ofatumumab) through demonstration of a clinically

meaningful effect on progression-free survival. The protocol for clinical trial OMB110911 was submitted to FDA on October 24, 2008 and as amended (Amendment 2) with submission to FDA on August 21, 2009; and began patient accrual on December 22, 2008.

The timetable submitted on August 20, 2009 states that this trial will be conducted according to the following milestones:

- Patient Accrual 50% Completed by August 30, 2010
- Patient Accrual 75% Completed by March 30, 2011
- Patient Accrual Completed by November 30, 2011
- Trial Completion Date: by October 14, 2013
- Final Report Submission: by June 30, 2014

QTc Interval Evaluation:

2. To conduct clinical trial OMB112855, a study of QTc intervals in patients who have been administered Arzerra (ofatumumab). QTc assessments will be performed in patients who have failed at least one fludarabine-containing regimen (at least two cycles) and failed at least one alemtuzumab-containing regimen (a minimum of at least 12 administrations) or who are considered inappropriate for treatment with alemtuzumab due to lymphadenopathy with at least one lymph node > 5 cm and requiring therapy and who receive the dose and schedule of Arzerra (ofatumumab) per the approved prescribing information. The number of patients evaluated for QTc interval changes will be at least 12. For the QTc assessments, ECGs will be collected in triplicate at baseline, at steady-state Arzerra (ofatumumab) concentrations, periodically on-therapy (e.g., every 3 months), and at the end of treatment. The final report will be a comprehensive combined report of the results (including primary data) of clinical trial OMB112855 and of the sub-trial assessing QTc intervals in OMB110911.

The timetable submitted on August 20, 2009, states that trial OMB112855 will be conducted according to the following milestones:

- Final Protocol Submission: by January 31, 2010
- Patient Accrual Completed: by June 30, 2011
- Trial Completion Date: by June 30, 2012
- Final Report Submission: by December 31, 2012

3. To conduct an assessment of QTc intervals as a sub-trial in clinical trial OMB110911. The total number of patients in OMB110911 with evaluable ECG measurements will be at least 50 (25 per treatment arm). For the QTc assessments, ECGs will be collected in triplicate at baseline, at steady-state Arzerra (ofatumumab) concentrations, periodically on-therapy (e.g., every 3 months), and at the end of treatment. The final report will be a comprehensive

combined report of the results (including primary data) of the sub-trial assessing QTc intervals in OMB110911 and of clinical trial OMB112855.

The timetable submitted on August 20, 2009, states that the QTc sub-trial in OMB110911 will be conducted according to the following milestones:

- Final Protocol Submission: by January 31, 2010
- Patient Accrual Completed: by June 30, 2011
- Trial Completion Date: by June 30, 2012
- Final Report Submission: by December 31, 2012

13.5.2. Commitments (PMCs)

Submission of Final Report for Study Hx-CD20-406

4. To submit the final report for clinical trial Hx-CD20-406 entitled "A single-arm international, multi-center trial of HuMax-CD20, a fully human monoclonal anti-CD20 antibody, in patients with B-cell Chronic Lymphocytic Leukemia who have failed fludarabine and alemtuzumab" to include objective response rates according to the IRC and objective response rates according to the clinical investigators. The final report will provide summary analyses and primary data. Accrual to this trial has been completed.

The timetable submitted on August 20, 2009, states that this trial will be conducted according to the following milestones:

- Trial Completion Date: by June 30, 2011
- Final Report Submission: by December 31, 2011

CMC/Quality

5. To reassess release and stability specifications for Arzerra (ofatumumab) drug substance and drug product through August 31, 2011. The assessment will be submitted in the 2011 annual report.
6. To develop and implement a quantitative specification for the icIEF assay used in the drug substance and drug product stability programs. The assessment will be submitted as a Changes Being Effected-30 (CBE-30) supplement by October 31, 2011.
7. To develop and validate a semi-quantitative assay for measurement of visible particulates. The test method and specification will be incorporated into drug substance and drug product lot release and stability programs and submitted as a CBE-30 supplement by October 31, 2011.
8. To submit by December 31, 2010 a Prior Approval Supplement (PAS) for the introduction of a ~~vial~~ ofatumumab single-use vial, 20 mg/mL, to reduce the number of vials needed for the 2000 mg dose.

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9. To revise the system suitability criteria for the robotic format of the complement-mediated antibody cytotoxicity potency assay so that the coefficient of variation (CV) (%) for duplicates is consistent with validation limits and is less than or equal to 25%. A final report including details of the system suitability criteria revisions will be submitted by March 31, 2010 and a revised potency assay SOP will be submitted in the 2010 annual report. Alternatively, the robot format of the potency assay will be removed from the BLA.
10. To perform leachables studies to characterize the potential presence of volatile leachables from the elastomeric stopper and the presence of / / / under accelerated conditions (25°C) for 6 months and at the recommended storage temperature for 24 months as outlined in the June 5, 2009 submission. The results of these studies will be submitted in the 2012 annual report. b(4)
11. To establish permanent control action limits for purification step yields and analyze 30 in-control points. The permanent control action limits and the results of the analysis of 30 in-control points will be submitted in the 2010 Annual Report.
12. To conduct a study or studies to identify the composition of visible particles observed in drug substance lots when particles are observed during ongoing stability studies of the drug substance conformance lots. The results of these studies will be submitted in the 2010 annual report.
13. To confirm the lack of a deleterious effect on the stability of drug substance of reprocessing at the / / step by monitoring the real-time stability of drug substance lot 09P01105 and performing accelerated stability studies on this lot at 25°C for 6 months and at 40°C for 3 months. The real time and accelerated studies will include the licensed drug substance stability program's tests and acceptance criteria. Real time stability data and results of the accelerated stability studies will be submitted in the annual report. b(4)
14. To update the bioburden test for cell culture, primary recovery, and purification samples from / / to filtration method. A study will be performed to establish the appropriate volume of each sample in the test. A final study report including the validation information and data for the updated bioburden test will be submitted by March 31, 2010. b(4)
15. To validate drug substance intermediate hold times for microbial control at commercial scale. A final report containing the validation data will be submitted by December 31, 2010.

13.5.3. Other agreements with Sponsor

None

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20579	SUPPL-26	BOEHRINGER INGELHEIM PHARMACEUTICA LS INC	FLOMAX (TAMSULOSIN HCL) 0.4MG CAPSULES

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

/s/

CHONGWOO YU
12/01/2009

JEE E LEE
12/02/2009

PRAVIN R JADHAV
12/02/2009

MYONG JIN KIM
12/03/2009