

**FDA Briefing Document**

**Oncologic Drugs Advisory Committee Meeting  
May 29, 2009**

**BLA STN 125326  
Arzerra® (ofatumumab)**

**Applicant: GlaxoSmithKline (GSK)**

**Division of Biologic Oncology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research  
U.S. Food and Drug Administration**

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## EXECUTIVE SUMMARY

The Applicant, GlaxoSmithKline, submitted Biologics License Application (BLA) BL STN 125326, requesting accelerated approval for Arzerra (ofatumumab) for the following proposed indication:

“Arzerra is indicated as a single agent for the treatment of patients with chronic lymphocytic leukemia (CLL). “

The application is based on the results of an interim analysis which demonstrated durable objective responses among patients enrolled in a single, multicenter, parallel-group, non-comparative study, titled 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 chronic lymphocytic leukemia who have failed fludarabine and alemtuzumab”. Although the study enrolled a total of 154 patients treated according to a uniform dose and schedule of ofatumumab, the primary efficacy data is derived from a protocol-specified subgroup of 59 patients with CLL whose disease is refractory to fludarabine and alemtuzumab (“Double Refractory” or DR) as discussed with the applicant (GSK) at the pre-BLA submission meeting and in accordance with the design of the study. 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. Objective tumor response rate and duration among 95 patients in two additional subgroups enrolled in Hx-CD20-406 and in 27 patients enrolled in a Phase 2 expansion cohort of a single arm study using a more abbreviated schedule of ofatumumab (Study Hx-CD20-402) are considered supportive efficacy information for this BLA.

As will be discussed, the magnitude of objective response rate (ORR) was dependent upon the assessor, with a higher response rate as determined by the independent review committee than by the investigators (58% vs. 42%) in the DR subgroup of study Hx-CD20-406. FDA’s review of the case report forms yielded an ORR which was similar to that of the investigators. Furthermore, because radiographs were not required for documentation of response, the independent review committee (IRC) did not conduct an independent assessment of tumor measurements in lymph nodes, spleen, or liver but instead relied on investigator-reported tumor measurements. The difference between the investigator-reported response rate and that of the IRC appears to arise from the consensus process which inflated the response rate. Therefore, FDA will rely on the investigator-reported ORR and response duration as the basis for approval and for labeling claims.

In study Hx-CD20-406, the most common AEs reported (>10% incidence) were pyrexia, cough, diarrhea, anemia, neutropenia, pneumonia, fatigue, dyspnea, rash, nausea, bronchitis, and upper respiratory tract infection. The most common infectious serious adverse events were lower respiratory tract infections and sepsis. Because Hx-CD20-406 was a single-arm study, the additive risk for infections that the administration of ofatumumab poses to heavily pre-treated and immunosuppressed patients with CLL cannot be ascertained.

The Committee will be asked to provide advice regarding whether the ORR observed in study Hx-CD20-406 is of sufficient magnitude to be reasonably likely to predict clinical benefit (the threshold of evidence to support accelerated approval). In addition, advice will be sought regarding the use of the 1996 or 2008 NCIWG criteria for determination of ORR in patients with CLL for regulatory decision-making.

## **INTRODUCTION**

This briefing document summarizes the pertinent contents of the application and FDA review to date, and most importantly identifies the key issues and questions for discussion at the meeting.

The information in this package represents the findings and opinions of FDA staff; this document contains statements of the FDA findings and conclusions that stem from their reviews and interpretations of the data presented. It must be emphasized that these documents do not represent FDA's final analyses, final decisions, or Office conclusions, and that no regulatory decision on the status of this application has been made. Indeed, an important piece of our thinking on these applications will be a full consideration of whatever advice the ODAC provides on these important issues.

### **The following are the key issues for this Advisory Committee:**

1. GlaxoSmithKline (GSK) is seeking accelerated approval for ofatumumab based on objective response rate (ORR) in one single arm study of patients with chronic lymphocytic leukemia (Hx-CD20-406) supported by data from a second dose-escalation study with a single-arm expansion cohort (Hx-CD20-402). FDA considers ORR a measure of antitumor activity, and except for limited circumstances (i.e., durable responses for refractory acute myelogenous leukemia), not a direct measure of clinical benefit as required for regular approval.

FDA has, on occasion, accepted ORR and response duration observed in single-arm studies in settings where there is no available therapy as substantial evidence to support accelerated approval. A key issue in the review of this BLA is whether the ORR observed in study Hx-CD20-406 is of sufficient magnitude to be reasonably likely to predict clinical benefit (the threshold of evidence to support accelerated approval). In patients with CLL, FDA considers a meaningful improvement in either overall survival (OS) or progression free survival (PFS) as direct evidence of clinical benefit.

2. ORR in this application is based on the 1996 NCIWG criteria. FDA requests the committee's advice regarding the use of these criteria or the 2008 NCIWG criteria to determine ORR in patients with CLL for regulatory decision-making. The evidentiary standard required for regulatory decision-making is generally higher than those employed for clinical decision-making or for informing the overall practice of medicine. Issues identified during the course of the review of the information in this application with regard to implementation of these criteria include: 1) the role of

imaging (ultrasound or CT) in evaluation and documentation of an objective response, and 2) patient selection (including the application of the response criteria in patients with no measurable disease at baseline).

## REGULATORY BACKGROUND

Chronic lymphocytic leukemia (CLL) occurs at an age adjusted incidence rate of 4.1 per 100,000 per men and women each year.<sup>1</sup> The median age of diagnosis is 72 years of age and the incidence of CLL in men is approximately twice that in women.<sup>1</sup> 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).<sup>1,2</sup> 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.<sup>3</sup>

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.<sup>4</sup>

### FDA Approvals for Chronic Lymphocytic Leukemia (CLL)

Table 1 shows FDA approved therapies for the treatment of patients with CLL.

**Table 1: FDA approved therapies for CLL**

Drug	Approval Date	Class	Specific Indication(s)
bendamustine	March 20, 2008	Alkylating agent	CLL
alemtuzumab	Sept. 17, 2007 (regular)	Anti-CD52 monoclonal antibody	B-cell CLL
alemtuzumab	May 7, 2001 (accelerated)	Anti-CD52 monoclonal antibody	B-cell chronic lymphocytic leukemia (B-CLL) in patients who have been treated with alkylating agents and who have failed fludarabine therapy.
fludarabine	April 18, 1991	Fluorinated nucleotide analog	Patients with CLL whose disease has not responded to or has progressed following treatment with at least one standard alkylating agent regimen
cyclophosphamide	Nov. 16, 1959	Alkylating agent	CLL (unspecified); most frequently administered as part of a combination chemotherapy regimen
chlorambucil	March 18, 1957	Alkylating agent	CLL

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.

Fludarabine received regular approval in 1991 based on demonstration of durable response rates in two single-arm, open-label studies conducted in 48 and 31 patients, respectively with CLL refractory to at least one prior standard alkylating-agent containing regimen. In these studies, the ORRs were 48% and 32%, with median durations of response of 1.75 and 1.25 years, respectively, and complete response rates were 13% in both studies. Approval of fludarabine occurred prior to the establishment of the accelerated approval regulations in April, 1992.

Alemtuzumab received accelerated approval in 2001 based on the results of three single-arm studies enrolling 149 patients with CLL and progressive disease following alkylating agents and fludarabine. The overall response rate (ORR) in the three studies ranged from 21% to 33% with median durations of response of 7 to 11 months.<sup>5</sup>

Alemtuzumab was 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% and 55%) and complete response rates (24% vs. 2%) compared to chlorambucil.

Bendamustine was granted 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.

The ODAC did not recommend approval for Genasense, which was presented to the ODAC in September 2006. Genasense was studied in a randomized trial of fludarabine and cyclophosphamide (FC) versus FC plus Genasense in 230 patients with relapsed or refractory CLL. The addition of Genasense to FC resulted in a higher CR plus nodular partial response rate (17% vs. 7%,  $p = 0.025$ ). However, the addition of Genasense did not improve the overall response rate (41% vs. 45%), time-to-progression, or survival.

## Pre-submission Regulatory Background BLA 125326

- December 2004      Ofatumumab received Fast Track designation for the investigation of ofatumumab in combination with fludarabine for treatment of patients with previously untreated CLL to show an improvement in progression free survival as compared with fludarabine therapy.
- November 2005      Pre-phase 2 meeting
- FDA identified durable objective response rate as an acceptable surrogate endpoint reasonable 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 patients who “failed” both fludarabine and alemtuzumab to satisfy the requirement for demonstrating benefit in patients with an unmet medical need.
  - Genmab proposed a sample size of 100 patients.
- 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 chronic lymphocytic leukemia who have failed fludarabine and alemtuzumab” submitted to FDA.
- February 2006      Protocol Amendment 1 introduced a bulky fludarabine refractory patient group that was not required to receive prior alemtuzumab
- April 2006          FDA letter re: 12/2005 protocol and amendment 1; included advice from FDA’s expert consultant serving as a Special Government Employee (SGE) who reviewed the 12/2005 protocol:
- CLL patients who are “double refractory” (DR) to both fludarabine and alemtuzumab have an unmet medical need.
  - Patients with bulky, fludarabine-refractory CLL (BFR) should be analyzed separately from the DR population.
  - Overall response rates of 10-20% were unlikely to predict clinical benefit.
- May 2006          FDA letter re: amended protocol Feb 2006, which considered SGE review and advice:
- In a population with unmet need, an observed response rate where the lower bound of the 95% CI for the ORR was at least 25% would be of interest.
  - Median duration of response should be at least four months.
  - Efficacy should be determined separately in the DR and BFR subgroups.
- June 2006          First patient enrolled (informed consent signed) in study Hx-CD20-406.

September 2006	Protocol amendment 2 removed the inclusion criterion specifying that patients may be intolerant to or ineligible for treatment with fludarabine (i.e., specified a fludarabine refractory population).
April 2007	<p>Protocol amendment 3</p> <ul style="list-style-type: none"> <li>• Specified that the trial populations (DR and BFR) were to be analyzed separately.</li> <li>• Increased sample size from 100 patients total to a sample size of 66 patients each in the DR and BFR subgroups.</li> <li>• Removed the inclusion criteria specifying that patients may be ineligible for alemtuzumab for reasons other than being BFR.</li> </ul>
October 2007	<p>Hx-CD20-406 (Amendment 4)</p> <ul style="list-style-type: none"> <li>• Increased the sample size in the DR and BFR subgroups from 66 to 100 patients.</li> <li>• Revised analysis plan to include an interim analysis for efficacy when data from 66 DR patients were available.</li> </ul>
November 2007	The 154 <sup>th</sup> patient was enrolled and received their first dose of ofatumumab (the last efficacy evaluable patient included in the interim analysis).
April 2008	Sponsorship of study Hx-CD20-406 was transferred from Genmab A/S to GSK.
May 2008	Data cut-off date for interim analysis (May 19, 2008).
September 2008	<p>Pre-BLA meeting with GSK, Genmab and FDA. Issues raised by FDA included</p> <ul style="list-style-type: none"> <li>• The patient population studied in the BFR subgroup did not meet the regulatory standard for having an unmet medical need; the protocol only required prior therapy with one drug (fludarabine).</li> <li>• 1996 NCIWG criteria did not require radiographic evaluation (unless to confirm CR) and the IRC were not provided with radiographs for most patients.</li> <li>• Independent review, which relied on investigators' measurements of lymph nodes, liver, and spleen rather than review of radiographs was not "truly independent."</li> </ul>
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" submitted to FDA as the proposed study for confirmation of clinical benefit.
January 2009	BLA 125326 submitted

## STUDY HX-CD-20-406 STUDY DESIGN

Study Hx-CD20-406 is an open-label, multicenter, international, non-comparative trial to investigate the ORR and safety of ofatumumab in patients with CLL. Twenty-six percent of patients were enrolled in the United States. Most of the remaining patients were enrolled at European sites.

### Treatment Plan

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 as shown in Table 2.

**Table 2: Required Glucocorticoid Premedication (Study Hx-CD20-406)**

<b>Ofatumumab Infusion Number</b>	<b>IV glucocorticoid dose (prednisolone or equivalent [mg])</b>
1	100 mg
2	100 mg
3-8	0-100 mg*
9	100 mg
10-12	50-100 mg*

\* Dose may be reduced in a stepwise fashion if no  $\geq$  Grade 3 AEs occur (note that the dose can only be reduced to 50 mg for the 10<sup>th</sup> through the 12<sup>th</sup> doses).

Protocol-specified treatment was to continue for a total of 12 doses until the patient experienced a critical adverse event, became pregnant, 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.

### Study Population

Eligibility was limited to adult patients ( $\geq$ 18 years of age) with B-cell CLL who had an indication for treatment as defined by NCI Working Group (1996 NCIWG) guidelines.<sup>6</sup> Patients were required to be refractory to an adequate course of fludarabine (minimum of two cycles) as defined by one of the following: failure to achieve at least PR to a fludarabine-containing regimen; disease progression during fludarabine treatment; or disease progression in responders within 6 months of the last dose of a fludarabine containing regimen. Patients were also required to either be refractory to alemtuzumab (a

minimum of 12 administrations), designated as “double refractory” (DR), or have bulky lymphadenopathy with at least one lymph node > 5 cm, designated as “bulky fludarabine refractory” (BFR). ECOG performance status was to be  $\leq 2$ .

Study Hx-CD20-406 contained a third patient group deemed “other.” This patient group consisted of patients enrolled in earlier versions of the protocol whose disease characteristics did not meet the final definitions of fludarabine- or alemtuzumab-refractory CLL.

### **CLL Disease Status Assessments**

Disease status assessments were to occur at baseline and every four weeks until week 28. Thereafter, disease status assessments were to occur every three months until month 24. CLL disease status assessments included measurements of lymph nodes by physical examination, measurements of the liver and spleen by physical examination, peripheral blood lymphocyte counts, and a complete blood count including hemoglobin, platelets, and neutrophils. At each visit, patients were asked whether they had experienced constitutional symptoms. Bone marrow aspiration and biopsy and CT scan of the neck, chest, abdomen, and pelvis were required at baseline. A repeat bone marrow and CT scan was only required to confirm a possible complete response.

### **Safety monitoring**

Adverse events were monitored during the ofatumumab treatment period (until week 28) and at three month intervals during the follow-up period (until 24 months). Serious adverse events, deaths, new CLL treatment, and B-cell recovery were monitored until month 48 (extended follow-up period). Follow-up for B-cell recovery stopped if new CLL treatment was initiated.

### **Efficacy Endpoint**

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.<sup>6</sup> Duration of response was a secondary endpoint. Details of the criteria for complete response (CR) can be found in 1996 NCIWG guidelines. FDA’s review determined that there were no CT-scan confirmed CRs in study Hx-CD20-406.

Determination of a partial response required the following:

- $\geq 50\%$  decrease in the peripheral blood lymphocyte count from the pretreatment baseline value;
- $\geq 50\%$  reduction in lymphadenopathy (defined as the sum of the products [SUP] of the lymph nodes);
- $\geq 50\%$  reduction in the size of the liver or spleen.
- At least one of the following:

- polymorphonuclear leukocytes  $\geq 1,500/\text{mcL}$  or 50% improvement over baseline;
- platelets  $> 100,000/\text{mcL}$  or 50% improvement over baseline;
- or hemoglobin  $> 11 \text{ gm/dL}$  or 50% improvement over baseline without transfusions.

Complete and partial responses were required to be maintained for at least two months (per NCIWG guidelines). Duration of response was measured from onset of response until evidence of progressive disease.

Determination of progression (per 1996 NCIWG guidelines) required at least one of the following:

- $\geq 50\%$  increase in the sum of the products of at least two lymph nodes on two consecutive occasions at least two weeks apart (at least one node must be  $\geq 2 \text{ cm}$ ) or the appearance of new palpable lymph nodes (NCIWG guidelines do not specify a threshold size for new nodes)
- $\geq 50\%$  increase in the size of the liver or spleen as determined by measurement below the respective coastal margin or appearance of new palpable hepatomegaly or splenomegaly, which was not previously present
- $\geq 50\%$  increase in the absolute number of circulating lymphocytes to at least  $5,000/\text{mcL}$
- Transformation to a more aggressive histology

## **Analysis Plan**

The sample size assumptions for the final version of the protocol were based on a predicted overall response rate (complete plus partial response rates) of 30%. If the true overall response rate was 30%, the probability that the exact 2-sided 99% confidence interval would exclude a response rate of 15% was 63% based on data from 66 patients and 92% based on data from 100 patients (at a 4.7% significance level). The final efficacy analyses were to be conducted separately for the DR and the BFR subgroups when data for 100 patients were available for each group.

The protocol was amended on October 31, 2007 (Amendment 4) to include an interim analysis when the primary endpoint data were available for 66 patients in the DR subgroup. The data monitoring committee (DMC) conducting the interim analysis would notify Genmab if the lower limit of the 99% CI excluded a response rate of 15% or less. Over 96% of the patients were enrolled when the protocol was amended to include the interim analysis. The IRC charter specified that Genmab would have access to the results of the IRC assessments on an ongoing basis. IRC assessments were to be conducted after 4, 30, 60, 90, 120, 150, 180, 210, and 225 patients had reached the primary endpoint. The interim analysis for potential early study termination was added after approximately 60% of patients' response assessments were completed.

The protocol-specified primary analysis of ORR was based on the IRC-determined response assessment. Additional analyses included ORR based on investigator

assessments and duration of response. Duration of response (DOR) was defined as the time from the initial response to progression as assessed by the IRC, or to death. For the analysis of DOR, the following scenarios were censored: no progression at the end of the trial; treatment discontinued for undocumented progression, toxicity, or other reasons; new anti-cancer therapy started; and death or progression after two or more consecutive missed visits.

### **IRC Procedures**

The IRC consisted of 5 members, at least two of whom would independently evaluate each patient's response. For every patient visit, each reviewing IRC member was to independently determine a response by reviewing the investigator's clinical assessments and lab components of the primary efficacy data from electronic CRFs. The IRC was blinded to the investigators' response determinations. CT scans were not included in the IRC assessment.

If the initial two IRC reviewers' overall objective response assessments were not in agreement, the response was to be independently adjudicated by a third IRC member. If the adjudicator's assessment did not agree with either of the two initial reviewers, then a panel of at least 2 of the 5 members was to convene and re-review the data to provide a consensus read.

### **EFFICACY RESULTS**

The DMC conducted an interim analysis when 66 patients in the DR population were assessable for overall response rate with a data cut-off of May 19, 2008.

During May and June of 2008, Genmab conducted an internal review and questioned the IRC's grouping classification (DR, BFR, or other) for 19 patients. Genmab requested that the IRC assess, and if appropriate, re-assign the classification of these 19 patients and conducted the re-assessment in a face-to-face meeting with two IRC members. As a result of this review, 10 patients were re-classified into a different population group; thus, the final DR population consisted of 59 patients.

In the following sections describing efficacy results, the DR patient population will be emphasized or highlighted as the efficacy results in this population form the primary basis for accelerated approval.

### **Concomitant Glucocorticoids and Protocol Violations during Study Hx-CD20-406**

According to the Hx-CD20-406 clinical study report, there were 21 patients who had a tumor response and received concomitant glucocorticoids during the first 24 weeks on study. Of these 21 patients, 7 patients received systemic corticosteroids at doses greater than 25 mg of prednisolone (per protocol, single doses less than 30 mg of prednisolone were allowed for the treatment of respiratory tract disorders). One patient in the BFR group received methylprednisolone 60 mg on days 38 to 42 and on days 57 to 72 for a

diagnosis of rheumatism. The other 6 patients received systemic corticosteroids at doses of more than 25 mg prednisolone for one or two days.

In the opinion of the FDA clinical reviewer, most other protocol violations were unlikely to affect the overall study results.

### **Exclusion of Patients from FDA Analyses**

FDA excluded data from the following three patients from the efficacy dataset and all analyses; therefore, in FDA efficacy analyses, the total number of DR patients evaluated was 56 rather than the 59 reported by the Applicant.

Although the protocol eligibility specified that patients should have an indication for treatment as defined by NCI Working Group (1996 NCIWG) guidelines, FDA noted that two patients in the DR group had no measurable disease by physical examination, no lymphocytosis, and platelet counts of  $\geq 100,000/\text{mcL}$  at baseline. Because these two patients (406118 and 406222) could be designated as partial responders by 1996 NCIWG criteria even if they had stable disease, they were removed from the FDA efficacy analysis dataset.

A third patient included in the GSK analysis of the DR population was excluded in the FDA efficacy analysis dataset. Patient 406116 was deemed a partial responder by the IRC. However, at baseline, the patient's lymphocyte count was less than  $1,000/\text{mcL}$ , the patient had no peripheral lymphadenopathy, and the patient had less than 25% lymphocytes in the bone marrow. The patient was eligible for the study because of progressive disease in the liver measured by CT scan. The patient was designated a responder because the liver became non-palpable after treatment with ofatumumab. After the baseline visit, the patient underwent biopsy of a liver lesion that revealed mantle cell lymphoma and the patient was determined to have two lymphoproliferative disorders. Thus, FDA could not determine whether the patient's physical exam changes represented a mantle cell lymphoma response or a CLL response.

## Demographics of Study Hx-CD20-406

Table 3 shows that most patients enrolled in study Hx-CD20-406 were white males. Median age was 63 years. A total of 63% of patients were Rai stage III or IV at the time of screening.

**Table 3: Demographics of Patients Enrolled in Study Hx-CD20-406**

	<b>DR (n=59)</b>	<b>BFR (n=79)</b>	<b>Other (n=16)</b>	<b>Total (n=154)</b>
<b>Sex [n (%)]</b>				
Female	<b>15 (25)</b>	22 (28)	6 (37.5)	43 (28)
Male	<b>44 (75)</b>	57 (72)	10 (62.5)	111 (72)
<b>Age (years)</b>				
≥65 yr (%)	<b>27 (46)</b>	33 (42)	6 (37.5)	66 (43)
Median (%)	<b>64</b>	62	63	63
<b>Race [n (%)]</b>				
White	<b>56 (95)</b>	78 (99)	15 (94)	149 (97)
Asian	<b>1 (2)</b>	0	1 (6)	2 (1)
Black	<b>0</b>	1 (1)	0	1 (<1)
Hispanic/Latino	<b>1 (2)</b>	0	0	1(<1)
Other (Arab)	<b>1 (2)</b>	0	0	1(<1)
<b>Time from Original CLL Diagnosis (years)</b>				
Mean (SD)	<b>6.7 (4.1)</b>	6.5 (3.8)	8.8 (3.5)	6.9 (3.9)
Median	<b>6.0</b>	5.9	7.5	6.3
<b>Rai Stage at Screening [n, (%)]</b>				
0	<b>1 (2)</b>	0	0	1 (1)
1	<b>11 (19)</b>	7 (9)	2 (13)	20 (13)
2	<b>15 (25)</b>	17 (22)	4 (25)	36 (23)
3	<b>10 (17)</b>	11 (14)	4 (25)	25 (16)
4	<b>22 (37)</b>	44 (56)	6 (38)	72 (47)
<b>Time from Last CLL Treatment (years)</b>				
Mean (SD)	<b>0.52 (0.42)</b>	0.68 (0.69)	0.92 (1.57)	0.65 (0.75)
Median	<b>0.36</b>	0.40	0.36	0.39
<b>No. of patients with prognostic factors [n (%)]</b>				
CD38+ > 20%				
CD5,CD19+ cells (n=152)	<b>34 (58)</b>	34 (44)	5 (31)	73 (48)
FISH 13 q- alone (+/-) (n=151)	<b>5 (9)</b>	13 (17)	1 (6)	19 (13)
FISH 17p- (+/-) (n=148)	<b>17 (30)</b>	14 (18)	2 (13)	33 (22)
<b>ECOG PS (n,%)</b>				
0	<b>27 (46)</b>	25 (32)	3 (19)	55 (36)
1	<b>19 (32)</b>	41 (52)	9 (56)	69 (45)
2	<b>12 (20)</b>	13 (22)	4 (13)	29 (19)
3	<b>1 (2)</b>	0	0	1 (1)

## Prior Therapies

The overall population in study Hx-CD20-406 was heavily pretreated. In the DR population (n=59), the number of prior therapies ranged from 1 to 14. Two patients in the DR group received one prior therapy; both of these patients received fludarabine combined with alemtuzumab. The median number of prior therapies in the DR group was 5 and in the BFR group (n=79) was 4. The median number of therapies in the “other” group (n=16) was 6.5.

Table 4 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. A total of 88% of patients received an alkylating agent regimen that did not include chlorambucil. A total of 81% of patients received a combination therapy that included fludarabine plus one other drug. Over 50% of the patients in study Hx-CD20-406 received rituximab.

**Table 4: 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	<b>93%</b>	92%	100%	94%
Alkylating agent other than chlorambucil alone or combination regimen	<b>88%</b>	85%	100%	88%
Bendamustine alone or bendamustine-containing regimen	<b>3%</b>	6%	13%	6%
Fludarabine	<b>100%</b>	100%	100%	100%
Combination therapy that includes fludarabine plus at least one other drug*	<b>85%</b>	82%	63%	81%
Alemtuzumab	<b>100%</b>	19%	63%	55%
Rituximab or rituximab-containing regimen	<b>59%</b>	54%	63%	57%

\*the other drug could include a monoclonal antibody, steroid, or chemotherapy (or a combination of different therapies)

## Summary of Efficacy Results

The FDA efficacy results will focus on the DR subgroup patient population.

Table 5 summarizes the efficacy results submitted by GSK. As discussed in the next section of this briefing document, the IRC determination was dependent on the investigators' measurements of lymph nodes, spleen, and liver on physical examination and review of laboratory data, and effectively represented an audit of the investigator assessments. The finding of a higher ORR by the IRC than by that based on the investigators' response status was an unexpected result. The IRC identified 9 and 10 additional patients with an objective response in the DR and BFR subgroups, respectively, than did the investigators.

**Table 5: Applicant's Summary of ORR**

	<b>DR (N=59)</b>	<b>BFR (N=79)</b>
<b>IRC</b>		
ORR (N)	<b>58% (34)</b>	47% (37)
CR	<b>0</b>	1% (1)
nPR*/PR	<b>58% (34)</b>	46% (36)
99% CI	<b>(40%, 74%)</b>	(32%, 62%)
<b>Investigator</b>		
ORR (N)	<b>42% (25)</b>	34% (27)
99% CI	<b>(26%, 60%)</b>	(21%, 49%)

## GSK Algorithm-Based Analysis of IRC Response Assessments

To investigate the robustness of the IRC results, the applicant performed a computer algorithm-based analysis of the IRC response assessments (Table 6). The algorithm should be considered as a strict application of the NCIWG 1996 guidelines, excluding any clinical judgments (for example, transient changes in lymphocyte counts). The algorithm, copied directly from the applicant's summary of clinical efficacy, is as follows:

### Sponsor Sensitivity Analysis

The Sponsor performed a sensitivity analysis of the IRC response assessment using an algorithm based on the response criteria in the NCIWG 1996 guidelines to programmatically calculate the primary endpoint of response rate from the efficacy data as recorded in the eCRF. Since it is not possible to duplicate the clinical expertise of the IRC members in a computer program, the following assumptions were made for certain clinical situations that impact the assessment of response by the algorithm (Data Source: Hx-CD20-406 Study Report [Appendix 1.14](#)).

- The algorithm defined non-response in cases where transient changes occurred in lymphocyte counts, lymph node size, organomegaly, hematologic values or components of constitutional symptoms that lasted for 1 or more evaluations, but were not sustained. The IRC may have determined that these transient changes were clinically insignificant and compatible with continued response instead of progressive disease.
- The algorithm compared all response data with baseline values for the purposes of determining response and progressive disease, as per NCIWG 1996 guidelines.
- The algorithm defined response duration of 2 months to be a minimum of 56 days based on the actual date of evaluation visit and not on the planned or scheduled visit date. This is compatible with the every 4 week scheduled evaluation visit during the 24 week treatment period.
- The algorithm required that at least 2 consecutive visits at least 56 days apart with confirmed response be present to confirm response duration of at least 2 months. The IRC may have determined that a visit confirming response and a visit confirming progressive disease at least 56 days apart constituted a response. The IRC may also have determined response for subjects who responded and remained in response for less than 56 days by the time of the data cut-off 19 May 2008.
- The algorithm interpreted the adverse event of Richter’s transformation as proof of disease progression regardless of other response criteria.
- The algorithm defined “non-response” when response was not evaluable because subjects began treatment with normal baseline components of response such as normal lymphocyte count or normal lymph nodes and therefore an improvement from baseline could not be demonstrated.

**Table 6: Applicant’s Summary of ORR by IRC and by Computer-based Algorithm**

	<b>DR (N=59)</b>	<b>BFR (N=79)</b>
<b>IRC</b>		
ORR (N)	<b>58% (34)</b>	47% (37)
CR	<b>0</b>	1% (1)
nPR*/PR	<b>58% (34)</b>	46% (36)
99% CI	<b>(40%, 74%)</b>	(32%, 62%)
<b>Computer-algorithm</b>		
ORR (N)	<b>37% (22)</b>	30% (24)
99% CI	<b>(22%, 55%)</b>	(18%, 45%)

## **FDA Review of IRC Assessment**

In order to minimize bias in the assessment of ORR or PFS in open-label trials, FDA generally recommends a blinded independent review of the primary efficacy endpoint (ORR or PFS) using objective records (radiographs, laboratory, and pathologic reports) as available. Generally, independent review is performed by radiologists, masked to the investigator's response assessment and to the treatment administered. The IRC in study Hx-CD20-406 was blinded only to investigator response assessments and did not evaluate radiographs. The IRC determination of response for involved disease sites was based solely on investigator-determined lymph node, spleen, and liver measurements. Because there was not an independent radiological confirmation of disease sites, possible investigator bias in the measurements of lymph nodes or hepatosplenomegaly could not be adequately controlled.

Genmab twice requested that the IRC reconvene to consider whether some of the responses should be down-graded. Genmab first identified 18 patients with a reported duration of response of less than 56 days (the duration required to determine a partial response). Two IRC members re-convened and downgraded responses for three patients. A second re-consensus panel was requested by Genmab after the application of a programmed response algorithm to the IRC response assessment for 17 patients, which resulted in the downgrading of responses in 2 patients.

### **Discrepancies between the FDA Statistical Reviewer's Derived IRC Response Determination (Based on Individual Reader's Response Determination) versus Reported Final IRC Response Determination**

The IRC response rates were 58% and 47% in the DR and BFR groups, respectively, notably higher than the 42% and 34% rates determined by the investigators. This finding is different than that generally found when an IRC is utilized in an open-label study. FDA also noted the requests by Genmab for re-assessments by the IRC as described in the paragraph above. For both these reasons, FDA closely evaluated the IRC dataset containing response assessments for readers 1 and 2, the adjudicator, and the final IRC determination. In that review, the clinical and statistical reviewers noted differences between the individual readers, the adjudicator, and the final IRC determination that did not appear to conform to the IRC charter. Utilizing the procedure for final IRC overall response determination described in the IRC charter and Hx-CD20-406 protocol, the FDA statistical reviewer derived a final IRC response determination for each patient using the individual (Table 7) determinations for IRC reader 1, reader 2, and an adjudicator (if required by the charter). According to the IRC charter, if the two readers were in agreement, their assessments should have been the final IRC overall response (shaded rows). A case was to go to an adjudicator only if the two initial readers were in disagreement. If the adjudicator's read agreed with one of the initial reader's, then the final IRC assessment should have been the adjudicator's reading. Table 7 shows 15 cases in which combinations of assessments occurred that should have resulted in the patient

being designated a non-responder; however, the final IRC determination in each case was partial response.

**Table 7: IRC Final Response Assessments that Differed from Agreements between IRC Readers**

Group	Patient	Reader 1	Reader 2	Adjudicator	IRC Final (sponsor)
<b>DR</b>	406118	PR	SD	SD	PR
	406147	SD	SD	PD	PR
	406158	PD	PD	PR	PR
	406195	PR	SD	SD	PR
	406199	SD	SD	NA	PR
	406203	PD	PD	PD	PR
	406210	PR	SD	SD	PR
	406218	SD	SD	PR	PR
<b>BFR</b>	406108	SD	SD	PD	PR
	406144	SD	SD	NA	PR
	406162	SD	PD	PD	PR
	406204	SD	PD	SD	PR
	406223	PD	PD	NA	PR
	406225	SD	SD	PD	PR
	406243	SD	SD	SD	PR

SD = stable disease; PR = partial response; PD = progressive disease  
 Shaded rows: reader 1 and reader 2 in agreement

### Variability in IRC Response Assessments

In order to have consistent application, tumor response criteria should, ideally, be unambiguous such that given the same data, similar conclusions will be drawn by all response assessors.

The FDA statistical reviewer conducted an analysis of the IRC response assessments using the per-visit response data generated by each IRC reader. Table 8 shows the frequency of response disagreement between IRC readers and the number of cases that went to adjudication. Note that in no cases were there disagreements related to radiographic findings. Each reader assessed identical lymphocyte measurements, hematology laboratory values, and investigator liver, spleen, and lymph node measurements. Even with identical information, there was frequent disagreement regarding whether to consider a patient a responder.

**Table 8: Variability in Response Assessments of IRC Members**

	<b>Percentage of cases in which IRC readers 1 and 2 disagreed on individual patient's response. [%, (N)]</b>	<b>Percentage of cases that went to adjudication* [%, (N)]</b>
<b>DR (N=59)</b>	<b>36 % (21)</b>	<b>58 % (34)</b>
BFR (N=79)	46 % (36)	58 % (46)

\*Note that some cases went to adjudication even though the initial two IRC readers' response assessments were in agreement

The following case (406147) illustrates the challenge of consistent application of the 1996 NCIWG criteria for response assessment in patients with CLL. The investigator designated this patient as a non-responder; however, after consensus IRC adjudication, the patient was designated a responder. FDA statistical reviewer's re-analysis of the IRC and adjudicator per-visit response records (Table 7) determined that this patient was not a responder. The details of this case are as follows:

Patient 406147 had a baseline ALC of 4,300/mcL; LN SUP (sum of products of the diameters) of 20.25 cm<sup>2</sup>, a liver edge of 11 cm below the costal margin, and a spleen that was 4 cm below the costal margin. At the week 4 visit, the patient was determined to have responded with a LN SUP of 2 cm<sup>2</sup>, liver edge 6 cm below the costal margin, and spleen that was 2 cm below the costal margin. At the week 12 visit, a new 1 x 1 cm breast lymph node was present and the liver edge was now 4 cm below the left costal margin (it was not palpable at the week 8 visit). The overall LN SUP more than doubled each visit during the next two visits approximately four weeks apart and at the 20 week visit, the breast lymph node increased in size to 6 x 5 cm.

If the date of progression for this patient was considered at the week 12 visit, this patient should be considered a non-responder (response duration not  $\geq$  2 months). At this visit, the patient had an increased liver size compared to the previous visit (non-palpable) and a new lymph node. This new lymph node was still present at the 16 week visit and was greatly enlarged at the 20 week visit, indicating that the new lymph node at visit 11 was more than just a transient non-pathological lymph node. Thus depending on whether progression was considered to occur at week 12 or week 20, this patient could be considered a non-responder or a responder.

### Statistical Reviewer’s Analysis of ORR

The FDA statistical reviewer performed an additional analysis of ORR (Table 9) following the IRC charter-specified procedures for the determination of the final IRC response using per-visit IRC response assessments for Reader 1, Reader 2, and the Adjudicator (“FDA Algorithm for IRC Final Assessment”). The purpose of the analysis was to investigate whether the IRC response determination and adjudication were performed in accordance with the IRC charter and procedures. In this analysis, to define a patient as a responder, the IRC reader must have considered that the response was at least 56 days in duration. Furthermore, if the overall response determination of the initial two IRC readers were in agreement, then the adjudicator’s assessment (if adjudicated) would be ignored. The FDA statistical reviewer found that the number of responses obtained through this strict adherence to the IRC charter and procedures was notably fewer than the number of patients with objective responses determined by the IRC final assessment.

**Table 9: Comparison of ORR Analyses per IRC Final Assessment and per FDA-Algorithm for IRC Final Assessment**

Analysis	DR		BFR	
	IRC Final Assessment (N=59)	FDA Algorithm for IRC Final Assessment (N=56)	IRC Final Assessment (N=79)	FDA Algorithm for IRC Final Assessment (N=79)
ORR (N)	<b>58% (34)</b>	<b>32% (18)</b>	47% (37)	27% (21)
99% CI	<b>(40, 74)</b>	<b>(17, 50)</b>	(32, 62)	(15, 41)

### FDA Clinical Reviewer’s Assessment of Response

The FDA clinical reviewer performed a case-by-case review of laboratory data, CRFs, and electronic case report forms for all patients in the DR patient group and one patient listed as a complete responder in the BFR group. Table 10 below shows four selected cases where the FDA’s response determination differed from the IRC. Note that the patient who was designated as having a CR did not undergo confirmatory imaging, and the other three patients appeared to have disease progression prior to the 2 month period of response duration necessary for being designated a responder.

**Table 10: Selected Cases in which the FDA Clinical Reviewer’s Response Determination differed from the IRC’s Response Determination**

Patient	Case Description
406157 (BFR)	This patient was determined to be a complete responder by the IRC. At baseline this patient had no peripheral lymphadenopathy, no hepatomegaly, no splenomegaly, and a baseline lymphocyte count of 7,700/mcL. At baseline, this patient had a mesenteric lymph node measuring 82.55 cm <sup>2</sup> . This patient was designated a complete responder even though the patient had no follow-up CT scan to confirm resolution of the massive mesenteric lymph node. Repeat bone marrow examination was also not performed.
406261 (DR)	In the efficacy narrative contained in the BLA, the Applicant stated that this patient’s (partial) remission lasted 49 days. FDA agreed that on the 49 <sup>th</sup> day after the initial designation of response, this patient’s CLL progressed by lymphocyte criteria (lymphocyte count more than doubled and was ≥ 5,000/mcL), a new lymph node was palpable, and the liver became palpable. Despite the clear evidence of progression prior to 60 days, the IRC designated this patient as a partial responder.
406199 (DR)	In the efficacy narrative contained in the BLA submission, the Applicant stated that this patient’s (partial) remission lasted from July 18, 2007 to July 24, 2007. Less than 10 days following the first visit qualifying the patient as a responder by the lymph node criterion, the patient had increasing lymphadenopathy and a newly palpable liver edge. Despite the clear evidence of progression prior to 60 days, the IRC designated this patient as a partial responder.
406203 (DR)	The first documented date of response for this patient occurred on visit 10 as the LN SUP (lymph node sum of the products of the diameters) decreased from 244.25 to 27 cm <sup>2</sup> . At the following visit (less than 30 days later), the LN SUP was 94 cm <sup>2</sup> and a new submandibular left node was reported by the investigator. Thus, this patient appeared to have evidence of progression prior to 60 days; however, the IRC designated this patient as having a PR. The investigator assigned this patient as having progression during this visit, due to the LN SUP more than tripling from the nadir.

**FDA Clinical Reviewer’s Analysis of ORR**

As discussed in the section describing the FDA Clinical Reviewer’s Assessment of Response, the FDA clinical reviewer conducted a case-by-case review of all patients in the DR group evaluating all laboratory data, CRFs, and electronic case report forms submitted in the BLA. Note that the FDA clinical reviewer did not use the most strict interpretation of the 1996 NCIWG criteria under which the detection of *any* new node (for example, a 1x1 cm lymph node that regressed at the next visit) would designate a progression event.

Table 11 summarizes the point estimates for ORRs based on investigators' assessments, final IRC assessments, and FDA clinical reviewer's assessment of the efficacy narratives. To be consistent with the IRC's methods, the FDA clinical reviewer's case-by-case analysis did not consider additional data obtained from CT scan reports, which were available for a limited number of patients. The point estimate for the FDA clinical review was similar to that of the investigators (41% versus 42%). However, as will be described subsequently in this document (in the FDA Special Considerations Section), five responding patients may have been re-classified as non-responders if follow-up CT scan results were included in the FDA clinical reviewer's response determinations. Removing these five patients from the FDA clinical reviewer's responder group would yield a 32% ORR

**Table 11: Summary of Point-Estimates of ORR with CIs for the DR Group**

	<b>Investigator-determined (N= 59)</b>	<b>FDA Clinical Reviewer (N=56)</b>	<b>IRC (N=59)</b>
ORR (N)	42% (25)	41% (23)	58% (34)
99% CI (%)	(26, 60)	(25,59)	(40, 74)

### Summary of Applicant's Results for Secondary Efficacy Endpoints

Table 12 shows the GSK summary results for duration of response (DOR) and the results of a GSK sensitivity analysis of DOR in which only those patients with no progression at the end of study were censored, and all other scenarios were considered as observed events.

**Table 12: GSK Results for DOR**

<b>Duration of Response (mos.)</b>	<b>DR (N=59)</b>	<b>BFR (N=79)</b>
Median (95% CI) – primary analysis	<b>7.1, (3.7, 7.6)</b>	5.6, (3.6, 7.0)
Median (95% CI) – sensitivity analysis	<b>5.3, (3.7, 7.4)</b>	5.5, (3.6, 6.4)

### Study Hx-CD20-402

Supportive study Hx-CD20-402 was a multicenter, non-comparative, dose escalation study with a dose expansion cohort. Eligible patients had CLL that was relapsed or refractory after one treatment and had circulating lymphocytes greater than 5,000/mcL. Patients were allocated to one of three groups and received ofatumumab according to the following doses and schedules:

- Group A (n=3): 100 mg for one dose followed by three weekly infusions of 500 mg
- Group B (n=3): 300 mg for one dose followed by three weekly infusions of 1,000 mg
- Group C (n=27) 500 mg for one dose followed by three weekly infusions of 2,000 mg.

Patients were permitted to receive a maximum of four doses of ofatumumab as compared to a maximum of 12 doses in study Hx-CD20-406.

The patients in cohort C were less heavily pretreated than patients in the Hx-CD20-406 study. Patients in cohort C received a median of 2 prior therapies. GSK's summary of efficacy results for cohort C are as follows (these results have yet to be verified by FDA): ORR 48% (95% CI: 30, 70) with a median DOR of 4.4 months.

## **SAFETY RESULTS**

The review of safety is ongoing. The analysis of patient withdrawals, patient deaths, and serious and common adverse events are based on 154 patients enrolled in Study Hx-CD20-406, who were treated at the dose and schedule for which GSK seeks approval.

Analysis of adverse events resulting from drug infusion (infusional toxicity) was conducted in 648 patients enrolled in completed or ongoing studies in CLL (N=215), follicular lymphoma (N=147), diffuse large-B-cell lymphoma (N=4), rheumatoid arthritis (N=277 [N = 66 ofatumumab or placebo]), and chronic obstructive pulmonary disease (N=5).

### **Exposure and Patient Withdrawals**

Most patients (90%) enrolled in study Hx-CD20-406 received  $\geq 8$  doses of ofatumumab. Eighty-five patients (55%) of the 154 patients completed the planned treatment course of 12 doses of ofatumumab. According to the [WITHDRAW] dataset provided by GSK, the reasons for withdrawal among the 69 patients were progressive disease (n=40), followed by death (n=10), "other (n=9)," adverse events (n=5), and patient refusal (n=5). The majority of withdrawals due to death or adverse events were due to infections. FDA notes that the reasons for withdrawal provided in the dataset differed from those contained in the GSK clinical study report in which progression of disease (n=35) and adverse events (n=21) were the most common reasons for withdrawal from treatment.

### **Common and Severe Adverse Events**

Table 13 shows the most common adverse events (AEs) and the most common severe AEs ( $\geq$  Grade 3) reported during treatment and follow-up periods in study Hx-CD20-406 for the DR subgroup and the pooled study population. The most common AEs ( $>10\%$  incidence in the full study population) were pyrexia, cough, diarrhea, anemia,

neutropenia, pneumonia, fatigue, dyspnea, rash, nausea, bronchitis, and upper respiratory tract infection.

**Table 13: Per-Patient Incidence of Adverse Reactions in Study Hx-CD20-406 by MedDRA Preferred Term**

Adverse Event Preferred Term	DR All Grades n=59	DR ≥ Grade 3 n=59	Pooled All Grades n=154	Pooled ≥ Grade 3 n=154
	%	%	%	%
PYREXIA	25	5	20	%
COUGH	19	0	19	3
DIARRHOEA	19	0	18	0
ANAEMIA	17	8	16	0
NEUTROPENIA	15	10	16	5
PNEUMONIA	17	10	16	12
FATIGUE	15	0	15	10
DYSPNOEA	19	5	14	0
RASH	14	0	12	2
NAUSEA	12	0	11	0
BRONCHITIS	19	2	11	0
UPPER RESPIRATORY TRACT INFECT	3	0	11	1
OEDEMA PERIPHERAL	8	2	9	0
CHILLS	10	0	8	1
NASOPHARYNGITIS	8	0	8	0
BACK PAIN	12	2	8	0
URTICARIA	5	0	8	1
INSOMNIA	10	0	7	0
HEADACHE	7	0	6	0
DISEASE PROGRESSION	2	2	6	0
HERPES ZOSTER	7	2	6	4
TACHYCARDIA	7	2	5	1
SINUSITIS	3	2	5	1
MUSCLE SPASMS	3	0	5	2
HYPERHIDROSIS	5	0	5	0
HYPERTENSION	8	0	5	0
HYPOTENSION	3	0	5	0
ABDOMINAL PAIN	5	0	5	0
LOWER RESPIRATORY TRACT INFECT	2	0	5	0
RHINITIS	7	0	5	0
SEPSIS	5	5	5	0
PARAESTHESIA	5	0	5	5
PRURITUS	5	0	5	0

In an analysis performed using MedDRA high level terms, the per-patient incidence of “lower respiratory tract and lung infections” in the overall (n=154) study population was 32%; (14% ≥ Grade 3). This is in contrast to the findings of analyses using MedDRA preferred terms which yielded values of 16% for the preferred term pneumonia with 10% being ≥ Grade 3 in severity.

## Deaths

A total of 24/154 (16%) patients died during the treatment or follow-up study periods in study Hx-CD20-406. A total of 37 patients died during extended follow-up (30 patients died following new anti-CLL therapy). The most common cause of death due to an AE was infection. Based on the data in the BLA, the FDA clinical reviewer determined that infections may have contributed to patient deaths in 12% of patients.

One infectious death was caused by progressive multifocal leukoencephalopathy. This patient's pre-study medical history was notable for "multiple" pneumonias and suspected aspergillus pneumonia, indicating severe immunosuppression prior to receiving ofatumumab.

The second most common cause of death was CLL progression. One patient died due to myocardial infarction two days after their last dose of ofatumumab.

## Serious Adverse Events

Table 14 shows the per-patient incidence of serious adverse events according to MedDRA system organ class (SOC) term in Study Hx-CD20-406 as a whole and by patient subgroup. The highest incidence of serious adverse events was in the infections SOC.

Table 15 provides the per-patient incidence of serious infectious events by MedDRA preferred term for the entire study Hx-CD20-406 study population. Respiratory infections and sepsis were the most common serious infectious events among patients in Study Hx-CD20-406.

**Table 14: Percentage of Patients in Study Hx-CD20-406 who had a Serious Adverse Event by MedDRA SOC (System Organ Class) Term**

MedDRA SOC	DR (N=59) %	BFR (N=79) %	Other (N=16) %	Total (N=154) %
INFECTIONS AND INFESTATIONS	37	29	38	33
BLOOD AND LYMPHATIC SYSTEM DISORDERS	10	8	38	12
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	8	9	19	10
CARDIAC DISORDERS	3	5	6	5
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	3	3	6	3
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	3	3	6	3
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	3	3	0	3
NERVOUS SYSTEM DISORDERS	7	0	0	3

**Table 15: Infections SAEs by MedDRA Preferred Term (Study Hx-CD20-406 [N=154])**

Preferred Term Infections SAEs	%
PNEUMONIA	12%
SEPSIS	5%
BRONCHOPNEUMONIA	2%
HERPES ZOSTER	2%
NEUTROPENIC SEPSIS	2%
SINUSITIS	2%
URINARY TRACT INFECTION	2%

### **SAEs temporally related to Immunological Infusion Reactions**

To evaluate infusion reactions, FDA evaluated SAEs in the immune system SOC and combined these with certain other symptoms related to infusion reactions or cytokine release (bronchospasm, rash, laryngeal edema). In study Hx-CD20-406, two out of 154 (1%) patients experienced SAEs due to infusion reactions. In the FDA review of 648 patients who received ofatumumab in all studies, 13 (2%) patients were reported to have experienced SAEs due to ofatumumab related infusion reactions. A pilot study of ofatumumab in patients with chronic obstructive pulmonary disease was stopped because two out of five patients experienced Grade 3 bronchospasm during or following drug infusions.

FDA analysis of immunological reactions differed from the GSK analysis of all potential SAEs related to infusions (in study Hx-CD20-406). SAEs reported on any infusion day in study Hx-CD20-406 included neutropenia (n=4), myocardial ischemia (n=2), myocardial infarction (n=1), pneumonia (n=1), sinusitis (n=1), urinary tract infection (n=1), cytokine release syndrome (n=-1), hypersensitivity (n=1), and deep vein thrombosis (n=1).

In the FDA analysis, four (3%) out of 154 patients in the Hx-CD20-406 study experienced angina or myocardial infarction within two days of a dose of ofatumumab.

### **Neutropenia**

New onset and increase in the severity of baseline neutropenia occurred during treatment with Hx-CD20-406. Table 16 is a shift table that compares each patient's baseline neutrophil count (by CTCAE grade) with their nadir neutrophil count. Note that 45 out of 108 (42%) patients with Grade 0 neutrophil counts at baseline experienced Grade 3 or 4 neutropenia.

FDA's preliminary analysis of safety identified five patients with prolonged Grade 4 neutropenia lasting greater than 14 days among the 108 patients with Grade 0 neutropenia at baseline.

**Table 16: Shift Table of Neutrophil Counts during Study Hx-CD20-406 (N=154)**

Baseline CTCAE Grade	Highest Post-Baseline CTCAE Grade				
	0	1	2	3	4
0	28	8	27	26	19
1	1	1	1	2	0
2	0	0	2	11	2
3	0	1	1	4	6
4	0	0	0	2	11

### **Safety Summary**

Study Hx-CD20-406 was the only study to evaluate ofatumumab at the doses and schedule for which the applicant is seeking approval. Infections (including infectious deaths) occurred frequently in this study. The applicant's analysis of deaths demonstrated a higher percentage of infectious deaths (17%) in the DR population than in the BFR population (6%).

In the BLA submission, GSK stated that the incidence of fatal infections was lower (10%) than that quoted in the literature (48%).<sup>7</sup> FDA does not agree with this statement because the cited literature report was a retrospective literature review that followed the clinical course of 27 patients over a median of two treatment regimens (versus one for the ofatumumab study).<sup>7</sup> Nevertheless, FDA agrees that based on literature reports, the background rate of severe and fatal infections in heavily treated CLL patients is high. Patients in the Hx-CD20-406 trial frequently had a history of severe infections. Because of the high background rate of infections in this patient population and the absence of an internal control, it is not possible to determine the additional risk of infection posed by the administration of ofatumumab. However, FDA notes that neutropenia may increase the risk of life-threatening infections in this patient population.

Infusional toxicity was common, manifesting as fever, dyspnea, and rash despite premedication with intravenous corticosteroids (50-100 mg methylprednisolone or equivalent), an antihistamine, and acetaminophen (1,000 mg or equivalent) prior to each dose.

Myocardial infarction or angina was noted in four patients within two days of a dose of ofatumumab. The population of patients with CLL (older age) may be at higher risk for myocardial events. It is not possible in a single arm study to determine whether ofatumumab may increase the risk for myocardial event in susceptible patients.

### **SPECIAL FDA CONSIDERATIONS**

During review of this application, certain issues were discovered and were subject to additional analyses. These included a review of the 1996 NCIWG criteria used to determine ORR in CLL for regulatory decision making and concerns related to the IRC's adjudication of responses in study Hx-CD20-406 (discussed in the IRC Review section of this document).

## 1996 NCIWG Criteria

The 1996 NCIWG response guidelines were used as the criteria for response assessment in study Hx-CD20-406. The standards required for regulatory decision-making are often higher than those employed for clinical decision-making or for informing the overall practice of medicine. FDA regards the following issues as problematic in the determination of ORR for regulatory decision making.

- Confirmatory radiologic imaging (e.g., CT scans) was not required except to confirm a CR, affecting the ability to conduct a fully independent assessment of response.
- Assessment of patients who have baseline lymphocyte counts below normal
- Variability in the determination of patient responses observed for study Hx-CD20-406 (discussed in the IRC Review section of this document).

## Lack of Follow up Imaging

The 1996 NCIWG criteria did not require that patients undergo follow-up CT scans to confirm a partial response or disease progression. Follow-up CT scans were required only to confirm a complete response. The 1996 guidelines did not provide a rationale regarding why CT scans were not required for confirmation of a partial response.

Since the criteria for a partial response require a reduction in lymphadenopathy and of either hepatomegaly or splenomegaly of  $\geq 50\%$ , an accurate assessment of lymph node, liver, and spleen size is important. Table 17 shows partial results of studies evaluating the reliability of physical examination for detecting lymph nodes and measuring lymph nodes and spleen size. These studies show that lymph nodes are frequently missed by physical examination. Furthermore, small errors in investigator measurements by physical examination may result in misclassification in response assessments.

**Table 17: Studies that Evaluated the Reliability of Physical Examination for Lymph Node Size or Splenomegaly**

Study	Results
Gobbi <sup>8</sup> , 2002	$R^2 = 0.53$ and $0.37$ for supraclavicular and axillary areas, respectively (physical examination [PE] vs. ultrasound [US])
Gerrits <sup>9</sup> , 1994	6/47 (13%) lymphoma patients: cervical LNs not detected by PE
Bruneton <sup>10</sup> , 1987	8 of 29 (28%) of lymphoma relapses not detectable by PE
Tamayo <sup>11</sup> , 1993	Sensitivity for detecting splenomegaly by PE $\leq 64\%$ for palpation and $\leq 75\%$ for percussion
Herrada <sup>12</sup> , 1997	In breast cancer, PE did not correlate well with pathological findings regarding axillary LN size ( $r = 0.318$ )

The studies cited in Table 17 showed that physical examination (PE) of supraclavicular and axillary lymphadenopathy were not consistently reliable compared to ultrasound. In general, the performance characteristics of physical examination were better for the cervical and inguinal lymph nodes compared to ultrasound ( $R^2$  was 0.90 and .80, respectively in the Gobbi study). Furthermore, in the Gobbi study, up to 75% of lymph nodes in the supraclavicular region, 46% in the axillary region, 32% in the cervical region, and 19% in the inguinal region had measurement errors greater than 50% comparing physical examination to ultrasound.

One additional study was published evaluating CT scans versus physical examination for progression in 82 CLL patients.<sup>13</sup> The authors concluded that in the study, CT scans did not provide additional benefit compared to the NCIWG CLL response criteria.<sup>13</sup> This retrospective study was not included in the above table because it was unclear if physical examination results were influenced by prior knowledge of radiographic results. Furthermore, the number of non-assessable patients was much higher in the CT scan group.

FDA noted that even when confirmatory CT scans were obtained during the conduct of study Hx-CD20-406, they were not used by the IRC for response determination. The IRC charter contained the following statement:

For the evaluation of CRs, the IRC will also be provided with imaging data. CT-scanning is not a standard requirement for response evaluation in CLL and has not been a part of the response evaluation for other approved drugs for treatment of CLL (alemtuzumab and fludarabine). In order to compare results from the Hx-CD20-406 with historical data, CT scans will not be included in the response evaluation, but made available to the IRC for additional information.

According to GSK data, a total of 21 of 154 patients (14%) in study Hx-CD20-406 (11/59 in the DR population) underwent repeat CT scans. Not all of the repeat scans were obtained to confirm a CR. A total of 19 of these 21 patients were designated as responders by the IRC.

FDA conducted a review of the 19 responding patients (per IRC) who underwent repeat CT scanning. Of these 19 patients, 10 underwent a CT scan on a week that the investigator deemed the patient as having either a PR or CR based on physical examination and lymphocyte counts. Utilizing CT scan findings, only three of these 10 patients would be designated as responders by lymph node criteria (a decrease of > 50% of the SUP of the lymph nodes).

Furthermore in the DR group, 9 out of 11 patients who were considered responders by the IRC underwent repeat CT scans assessment. If CT scans were used instead of physical examination for response determination, five of the patients may have been re-classified as non-responders.

During the FDA review, the following examples from the DR group show how follow-up radiography may have either

- Reclassified the response category of patients (when repeat CT scans were obtained), or
- Assisted in the response classification of patients (who did not have repeat CT scans)

Patient	Case Description
406118	At baseline, this patient had no measurable disease by physical examination (peripheral lymphadenopathy, splenomegaly, or hepatomegaly) and no lymphocytosis. Furthermore, the platelet count remained above 100,000/mcLmcL at baseline ensuring that, if stable, this patient would have been considered a responder (whether or not there was any actually anti-CLL activity). This patient had a lymph node in the peritoneum measuring 15.27 cm <sup>2</sup> on baseline CT. Although this patient was designated as PR, there were no objective findings to support this designation and this patient was removed from the FDA analysis. Radiographic follow-up may have provided evidence of objective anti-tumor activity for this patient.
406140	By physical examination, this patient had a baseline lymph node sum of products of the diameters (LN SUP) of 21 cm <sup>2</sup> and a LN SUP of 0 cm <sup>2</sup> on study visit 16. Yet by CT scan, the baseline nodal SUP was 28.96 cm <sup>2</sup> versus 19.73 cm <sup>2</sup> on the day of visit 16. This patient had a reported complete nodal response by PE and was designated having a partial response; however, if only CT scan was used for LN response assessment, this patient would have not been deemed a responder.
406153	This patient had modest peripheral lymphadenopathy by PE at baseline with an LN SUP of 7.25 cm <sup>2</sup> . On visit 11, the LN SUP was 0 cm <sup>2</sup> by physical examination. However, the baseline and visit 11 LN SUPs by CT scan were 22.11 and 21.92 cm <sup>2</sup> , respectively. Furthermore, the patient had spleen enlargement on CT scans at baseline and follow-up. Using the 1996 NCI WG criteria this patient is considered a responder; however, this patient may have been classified as having stable disease if repeat CT scans were required.
406195	This patient had a LN SUP (by PE) of 1.5, 0.5, 1, and 0 cm <sup>2</sup> at baseline, visit 6, visit 10, and visit 11. The patient was deemed a partial responder based on lymphocyte counts. This patient did not exhibit a 50% decrease in the SUP of the LNs for two months; however, this patient's LNs always were less than 1 cm <sup>2</sup> after baseline until progression. A more valid assessment of this patient's lymphadenopathy would have been a follow-up scan of a right (arterial) iliac node that measured 24.56 cm <sup>2</sup> at the time of the baseline CT scan.

Patient	Case Description
406205	This patient, deemed a responder, had no lymph nodes at baseline, but had a spleen that was 14 cm under the coastal margin. The spleen subsequently became undetectable by physical examination and was not palpable on visit 11. A confirmatory CT scan at this time revealed stable organ (spleen) enlargement. Thus, by CT scan, this patient might have been designated a non-responder.
406219	This patient had minimal peripheral lymphadenopathy at baseline (SUP 2 cm <sup>2</sup> ) and had a (peripheral) nodal SUP between 0 and 2 cm <sup>2</sup> from baseline until visit 15. A porta-caval node measured 13.95 cm <sup>2</sup> at the baseline CT scan. A confirmatory CT scan prior to visit 11 revealed a stable porta-caval node measuring 8.49 cm <sup>2</sup> and five new non-measurable lymph nodes. The patient continued to have splenic enlargement by CT despite having no palpable splenomegaly. This patient was designated a responder but would be considered to have stable disease or progression using the CT scan results.

These cases illustrate the potential differences in response assessments that include radiographic imaging compared to physical examination alone. FDA notes that the revised NCIWG guidelines published in 2008 recommend CT scans to evaluate response to therapy in clinical trials.<sup>14</sup>

### Assessments of Patients with Lymphocyte Counts below Baseline

A total of 7 of 23 (30%) responders identified by FDA and 13 of 34 (38%) responders identified by the IRC in the DR patient group had baseline lymphocyte counts less than 5,000/mcL. Presumably, this represents persistent effects of prior (pre-study) treatment. The 1996 NCIWG criteria do not provide guidance on response criteria for such patients. The FDA clinical reviewer's determination of ORR did not require a  $\geq 50\%$  reduction in lymphocyte count if the baseline lymphocyte count was less than 5,000/mcL.

## DISCUSSION

GSK seeks accelerated approval for Arzerra (ofatumumab), as a single agent for the treatment of patients with CLL. For this application, FDA considers the alemtuzumab- and fludarabine- refractory patient population (double-refractory or DR group) as having unmet medical need; over 90% of the DR patients in study Hx-CD20-406 had progressed following treatment with an alkylating agent. In contrast, FDA does not consider the patient population studied in the BFR group as meeting the regulatory standard for having an unmet medical need; the protocol only required prior therapy with one drug (fludarabine). FDA has determined that GSK will need to conduct a comparative study in order to support approval in a patient population (BFR) who were only required to be refractory to one drug. 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 decision making regarding approval of ofatumumab in the DR patient population.

The following regulations regarding the standards for licensing a biological drug under accelerated approval are contained in Subpart E of 21 CFR Part 601:

FDA may grant marketing approval for a biological product on the basis of adequate and well-controlled clinical trials establishing that the biological product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity.

The major issue regarding this application is whether the effect sizes of the surrogate endpoints, ORR and DOR, observed in the DR population in study Hx-CD20-406 are reasonably likely to predict clinical benefit.

FDA acknowledges that administration of ofatumumab as a single agent yields anti-tumor activity in patients with CLL. For labeling claims, FDA will rely on the investigator-reported ORR and response duration as the basis for approval. However, FDA notes that the magnitude of the anti-CLL activity in study Hx-CD20-406 is difficult to quantify due to the following factors:

- Lack of objective radiographic confirmation of lymph node responses
- Lack of reduction in lymphocyte counts for a notable subset of the patient population who had normal lymphocyte counts at baseline ( $\geq 30\%$  in the DR patient group)
- Variability in response assessments between IRC readers, IRC adjudicators, investigators, and FDA using the 1996 NCIWG criteria
- Requirement for premedication with corticosteroids

FDA requests ODAC discussion on whether the magnitude of the activity (ORR and DOR) observed in study Hx-CD20-406 is sufficient to be reasonably likely to predict clinical benefit. FDA notes that the existence of anti-tumor activity alone does not satisfy the standards for accelerated approval; for example, there must be a threshold for which an observed ORR would or would not predict clinical benefit.

Furthermore, FDA requests ODAC advice regarding the measurement of ORR in clinical trials for patients with CLL as an endpoint for regulatory decision-making. Specific topics for discussion may include the following:

- For regulatory decision-making, is imaging (either ultrasound or CT scan) necessary to accurately and objectively measure lymph node size? FDA notes that the revised NCIWG guidelines for CLL published in 2008 recommend CT scans to evaluate response to therapy in clinical trials.<sup>14</sup> Should imaging be required for trials in CLL intended to provide data for regulatory decision-

making? FDA reminds the committee that heavily pretreated CLL patients with normal lymphocyte counts may have measurable disease only in their lymph nodes.

- Should patients with no measurable disease be eligible for clinical trials designed to measure ORR for regulatory decision making? Should patients without lymphocytosis be eligible for clinical trials designed to measure ORR for regulatory decision making (FDA acknowledges that frequently, such patients should receive treatment in clinical practice due to cytopenias or constitutional symptoms).

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