

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**125326**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

## CLINICAL PHARMACOLOGY REVIEW

### Team Leader's Secondary Review

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BLA: 125326/0	Submission Date: 01/30/09
Brand Name (Generic Name)	Arzerra ®(Ofatumumab)
Sponsor	GlaxoSmithKline (GSK)
Submission Type; Code	NME, Priority
Relevant IND(s)	BB-IND 11719
PDUFA Date	7/30/09, extended to 10/30/09 (due to a major amendment submission)
Formulation Strength(s)	100 mg/5 mL single-use vial
Proposed Indication	Treatment of patients with chronic lymphocytic leukemia (CLL) who have received prior therapy
FDA's consideration of Indication	Accelerated approval for the treatment of patients with chronic lymphocytic leukemia (CLL) who have disease refractory to alemtuzumab and fludarabine, based on studies that have investigated response rate, a surrogate endpoint for clinical benefit. Studies to determine whether Arzerra confers clinical benefit are ongoing.
Proposed Dosing Regimen	<ul style="list-style-type: none"><li>• Arzerra is administered at an initial dose of 300 mg, followed 1 week later by 2,000 mg once weekly for 7 infusions, followed 4 / weeks later by 2,000 mg once every 4 weeks for 4 infusions.</li><li>• Premedicate with an intravenous infusion of a corticosteroid (as appropriate), an oral analgesic, and an oral or intravenous antihistamine.</li></ul>
Clinical Division	DBOP
Review Division	Clinical Pharmacology Division 5/OCP
Primary Reviewer	Jun Yang, Ph.D.
Pharmacometrics Reviewer/TL	Justin Earp, Ph.D. / Christopher Tornoe, Ph.D.
Pharmacogenomics Reviewer/TL	Mike Pacanowski, Pharm.D., M.P.H./ Issam Zineh, Pharm.D., M.P.H.
Secondary Reviewer (Team Leader)	Hong Zhao, Ph.D.
Division Director	Nam Atiqur Rahman, Ph.D.

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## **1. Recommendation**

The application is acceptable from a clinical pharmacology perspective provided that the sponsor and the Agency come to a mutually satisfactory agreement regarding the language in the package insert and the sponsor commits to the postmarketing study addressing safety issues related to the effect of Arzerra on QT prolongation.

## **2. Postmarketing Requirement (PMR) Study**

Clinical pharmacology review team recommends that the sponsor should conduct a QT study as a postmarketing requirement. The sponsor should perform ECG measurements in patients receiving ofatumumab treatment to evaluate the potential effect of ofatumumab treatment on QT interval. See attached PMR request for QT evaluation.

## **3. Summary of Clinical Pharmacology Review**

**Introduction:** GlaxoSmithKline submitted this Biologics License Application (BLA) for a new molecular entity (NME), Ofatumumab (Arzerra<sup>®</sup>). The sponsor seeks FDA approval for Arzerra to indicate for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received prior therapy. In support of the proposed indication, the sponsor provided results from an interim analysis of an ongoing registration study Hx-CD20-406 and a completed supportive study Hx-CD20-402. Clinical pharmacology data in patients with CLL were obtained from these two clinical studies as well as from studies in other studied patient populations.

The demonstration of safety and efficacy of ofatumumab is based primarily upon the results of an interim analysis of Study Hx-CD20-406. This study was a single-arm trial which included three CLL patient populations: patients who were refractory to both fludarabine and alemtuzumab - double-refractory (DR, n=59), patients who were refractory to fludarabine and considered not suitable for treatment with alemtuzumab due to bulky lymphadenopathy - bulky fludarabine-refractory (BFR; n=79), and patients who did not meet the criteria of DR or BFR (Other; n=16). FDA considers an accelerated approval of ofatumumab for the treatment of DR patients with CLL, based on the studies that have investigated response rate, a surrogate for clinical benefit. Studies to determine whether ofatumumab confers clinical benefit are ongoing.

**Mechanism of Action:** Ofatumumab is a human IgG1κ monoclonal antibody (mAb) that specifically binds to CD20 expressed on human B-cells. The binding of ofatumumab to CD20 induces cell death through complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC).

**Efficacy Results:** The primary surrogate endpoint for clinical benefit for the registration study Hx-CD20-406 is objective response rate (ORR) according to the 1996 NCI-WG guidelines over the period from screening to week 24. The efficacy results of this trial showed that the ORR [99% confidence interval (CI)] in DR patient population were 41%

(99% CI: 25; 59) based on FDA analysis, 42% (99% CI: 26; 60) by GSK investigator and 58% (99% CI: 40; 74) by the Independent Review Charter (IRC). The ORR in the DR patient population was better than the protocol pre-specified response rate of greater than 15% at the lower limit of the 99% CI. See Clinical Review. With the limited number of patients studied in this clinical trial, it is found that chromosomal abnormalities (i.e., 17p deletion) and elevated  $\beta$ 2-microglobulin were associated with lower ORR and poorer overall survival. DR patients with chromosome 17p deletion (n=15) had a 33% ORR (99% CI: 8; 68), whereas patients with no chromosomal abnormalities (n=7) had a 71% ORR (99% CI: 20; 98). See Attached Pharmacogenomics Review.

**Safety Profile:** The safety data from the Hx-CD20-406 and Hx-CD20-402 studies suggested that treatment with ofatumumab was generally tolerated in the study population with advanced, heavily pre-treated, highly refractory CLL and a high risk for rapid disease progression and infectious complications. Among 181 patients who received the 2000 mg ofatumumab in Studies Hx-CD20-402 and Hx-CD20-406, 167 patients had 1401 adverse events (AEs), with 160 of 1401 AEs were serious AEs (SAEs). SAEs in 29 out of 89 patients were considered to be treatment related. Sixty-four (64) patients died as of the cut off date for the safety analysis (61 in study Hx-CD20-406 and 3 in study Hx-CD20-402). In study Hx-CD20-406, 24/61 deaths were due to infections. The most common AEs were pyrexia (20%), cough (18%), diarrhea (17%), fatigue (15%), rash (15%), neutropenia (15%), anemia (14%), dyspnea (14%) and pneumonia (14%). The most common reason for withdrawal from the studies was disease progression followed by infection. See Clinical Review.

**Dose-Response Relationship and Rationale for Clinical Dose Selection:** The exposure-response relationship for the effectiveness (complete & partial remission) is evidenced in both the supportive dose ranging study Hx-CD20-402 (500mg, n=3; 1000mg, n=3; 2000mg, n=27) and the registration study Hx-CD20-406 (2000mg, n=59). Based on the limited number of patients studied in both studies, the trend was observed that the therapeutic response increased with increasing ofatumumab exposure (AUC). Therefore, the overall benefit risk of the highest dose of 2000 mg studied in the clinical trials is acceptable from clinical pharmacology point of view. See Attached Pharmacometrics review.

**Pharmacodynamics (PD):** In DR patients with CLL, the median decrease in circulating CD19-positive B cells was 91% (n=51) after the 8<sup>th</sup> infusion and 85% (n=32) after the 12<sup>th</sup> infusion. The B-cell recovery period could not be evaluated due to insufficient patient follow-up.

**Pharmacokinetics (PK):** Pharmacokinetic data were obtained from 146 patients with refractory CLL who received a 300 mg/kg initial dose followed by seven weekly and four monthly infusions of 2000 mg/kg dose. The  $C_{max}$  were 40% higher and  $AUC_{(0-\infty)}$  were 60% higher after the 8<sup>th</sup> infusion than those after the 4<sup>th</sup> infusion. The mean  $V_{ss}$  values ranged from 1.7 to 5.1 L. Ofatumumab is eliminated through a target-independent route and a B cell-mediated route. Due to the depletion of B cells with subsequent infusions, the clearance of ofatumumab was significantly decreased compared to that after the first

infusion. Clearance exhibited large inter-subject variability with CV% greater than 50%. The mean  $t_{1/2}$  between 4<sup>th</sup> and 12<sup>th</sup> infusions was approximately 14 days (range 2.3-61.5 days). In a separate single dose study, ofatumumab exhibited dose-dependent clearance in the dose range of 100 to 2000 mg.

**Specific Populations:** No PK data are available in patients with hepatic or renal impairment. However, patients with hepatic or renal impairment are unlikely to require dose modification because ofatumumab is eliminated through a target-mediated route and is also catabolized by ubiquitous proteolytic enzymes that spread all over the body. Cross-study analyses were performed on the combined data from patients with a variety of conditions, including 162 patients with CLL, who received multiple infusions of Arzerra as a single agent at doses ranging from 100 to 2,000 mg. The effects of various covariates, e.g., body size (weight, height, body surface area), age, gender, baseline creatinine clearance, on ofatumumab PK were assessed in a population PK analysis. Volume of distribution and clearance increased with body weight. Gender (41% male and 59% female) had a modest effect (14% to 25%) on ofatumumab PK. These effects are not considered clinically important, and no dosage adjustment is recommended based on either body weight or gender. Age did not significantly influence ofatumumab PK in patients ranging from 21 to 86 years of age. Creatinine clearance (CrCL) at baseline was not a clinically significant factor on ofatumumab PK in patients with calculated CrCL values ranging from 33 to 287 mL/min.

In animal studies, ofatumumab crossed the placental barrier and fetuses and exhibited depletion of peripheral B cells and decreased spleen and placenta weights. Ofatumumab should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus. It is not known whether ofatumumab is secreted in human milk; however human IgG is excreted in human milk. Published data suggest that neonatal and infant consumption of breast milk does not result in substantial absorption of these maternal antibodies into circulation. Caution should be exercised when ofatumumab is administered to a nursing woman. The safety and effectiveness of ofatumumab in pediatric patients (< age 18) have not been established. The sponsor requested for granting a full waiver to conduct studies with ofatumumab in pediatric patient population and the justification is that CLL is rare in patients younger than 40 years of age.

**Drug Interactions:** No formal drug-drug interaction (DDI) studies have been conducted with Ofatumumab. Ofatumumab is used as monotherapy for the proposed indication. Patients treated with ofatumumab are pre-medicated with corticosteroids. The DDI between ofatumumab and corticosteroids was not evaluated; however the potential for DDI between ofatumumab and corticosteroids is expected to be low.

**Immunogenicity:** There is a potential for immunogenicity with therapeutic proteins such as ofatumumab. An ELISA assay was used to detect the anti-ofatumumab antibodies. Serum samples from 154 patients with CLL treated with ofatumumab were tested for anti-ofatumumab antibodies during the 24-week treatment period. Results were negative in 46/139 patients after 8<sup>th</sup> infusion and 33/85 patients after 12<sup>th</sup> infusion. Results from the remaining patients were classified as inclusive due to interference with the

immunogenicity assay by circulating concentrations of ofatumumab. The risk of immunogenicity with ofatumumab is expected to be low because the following reasons: (1) as rituximab, a chimeric anti-CD20 mAb has low incidence of immunogenicity, ofatumumab is a fully human IgG1κ mAb; (2) low incidence of T cells that recognize epitopes on ofatumumab *in silico*; (3) patients are highly immunosuppressed with premedication of corticosteroids; and (4) lysis of B cells reduces the likelihood of an immune response to ofatumumab.

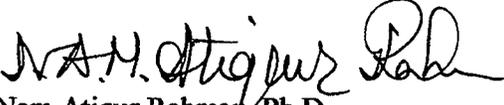
**QT Evaluation:** The potential of ofatumumab treatment on QT interval has not been studied during the product development. Thorough QT (TQT) study is not recommended for ofatumumab since mAbs cannot access hERG pore via intracellular side, the target site for most small-molecule QT-prolongation drugs. However, the potential of ofatumumab affecting QT interval through off-target mechanisms cannot be ruled out. The sponsor should assess the potential of ofatumumab treatment on QT interval through an ECG monitoring in their ongoing trials. The sponsor has proposed to address the QT issue in Study OMB112855 (2000 mg ofatumumab as monotherapy in refractory CLL patients). The proposed QT study protocol has been reviewed by the QT interdisciplinary review team (IRT). See attached PMR request for QT evaluation.

**Risk-Benefit Assessment:** This application was discussed at the Oncology Drug Advisory Committee (ODAC) meeting held on May 29, 2009 and the consensus among the committee members was that the ofatumumab clinical data demonstrate a favorable risk-benefit profile for DR patients with CLL. Postmarketing studies with improved study design and study quality should be conducted to confirm clinical benefit and address the safety concerns of treatment with ofatumumab.

#### 4. Labeling Recommendation

Please see Clinical Pharmacology recommended labeling modifications in the Clinical Pharmacology primary review by Dr. Jun Yang.

 7/10/09  
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 7/13/09  
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**Clinical Pharmacology Review**

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<b>BLA: 125326</b>	Submission Date(s): 01/30/09
<b>Brand Name</b>	Arzerra®
<b>Generic Name</b>	Ofatumumab
<b>Submission Type; Code</b>	NME, Priority Review
<b>Formulation; Strength(s)</b>	100 mg/5 mL single-use vial
<b>Proposed Indication</b>	Patients with chronic lymphocytic leukemia (CLL) who have received prior therapy
<b>Relevant IND(s)</b>	BB-IND 11719
<b>PDUFA Date</b>	7/30/09
<b>Sponsor</b>	GlaxoSmithKline
<b>Clinical Division</b>	Biologic Oncology Product
<b>OCP Division</b>	Clinical Pharmacology V
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OCP Briefing was held on July 7, 2009 attended by:

Shiew-Mei Huang, Gil Burckart, Steven Lemery, Padmaja Mummaneni, Hae-Young Ahn, Jeanne Fourie, Shashi Amur, Ting Eng C Ong, Bahru Habtemariam, Bei Yu, Seong Jang, Lei Zhang, Jian Wang, Yoriko Harigaya, Jang-IK Lee, Issam Zineh, Hong Zhao, Atiqur Rahman, Brian Booth.

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## EXECUTIVE SUMMARY

### 1.1 Recommendation

The application is acceptable from a Clinical Pharmacology perspective. The proposed labeling is under revision at the time of completion of this review (see 3. Detailed labeling recommendations).

### 1.2 Post Market Requirement /Commitment (PMR/PMC)

The sponsor is requested to assess the effect of Ofatumumab on QTc as a PMR. The sponsor agreed to conduct this QT assessment in their future clinical trials. No additional PMR or PMC studies are recommended in the area of clinical pharmacology.

### 1.3 Summary of Clinical Pharmacology Findings

**Introduction:** Ofatumumab is a human IgG1 $\kappa$  monoclonal antibody (mAb) that specifically binds to CD20 expressed on human B- cells. The binding of Ofatumumab to CD20 induces cell death through complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC).

Ofatumumab is being developed for treatment of patients with chronic lymphocytic leukemia (CLL). The current BLA was submitted under the provisions of accelerated approval based on the surrogate endpoint of objective response rate (ORR) that is reasonably likely to predict clinical benefit in patients with chronic CLL who have received prior therapy.

Clinical pharmacology data in patients with CLL are provided from two clinical studies, a completed supportive study, Hx-CD20-402 and an ongoing pivotal study Hx-CD20-406. The demonstration of safety and efficacy of Ofatumumab is based primarily upon the results of an interim analysis of Study Hx-CD20-406. This study included 3 CLL patient populations, patients who were refractory to both fludarabine and alemtuzumab (double-refractory (DR); n=59), patients who were refractory to fludarabine and considered not suitable for treatment with alemtuzumab due to bulky lymphadenopathy (bulky fludarabine-refractory (BFR); n=79) and patients who did not meet the criteria of DR or BFR (Other; n=16). Only the treatment in DR patient population meets the criteria of accelerated approval.

**Pharmacokinetic Characteristics:** Ofatumumab exhibits dose-dependent pharmacokinetics (PK) over the dose range of 100-2000 mg. The major elimination routes of Ofatumumab include target-independent clearance (CL) and CD20-positive B cell-mediated disposition.

The PK of Ofatumumab was characterized in patients with relapsed and refractory CLL in two studies, Study Hx-CD20-402 (four weekly infusions) and Study Hx-CD20-406 (eight weekly infusions followed by four infusions at four-week intervals). PK of Ofatumumab after 1<sup>st</sup> and 4<sup>th</sup> infusion were evaluated in the supportive study Hx-CD20-402. Exposure of Ofatumumab (AUC and C<sub>max</sub>) increased more than proportionally with dose. The geometric mean values for CL were 63.7 mL/h after the first infusion and 8.5 mL/h after the fourth infusion. This large change in CL after subsequent infusions occurred with the

depletion of B cells. The  $C_{max}$  and  $AUC_{(0-\infty)}$  after the 8<sup>th</sup> infusion were approximately 40% and 60% higher than after the 4<sup>th</sup> infusion. The mean  $V_{ss}$  values ranged from 1.7 to 5.1 L. CL exhibited large intersubject variability with CV% greater than 50%. The geometric mean  $t_{1/2}$  was 1.3 days after the 1<sup>st</sup> infusion and approximately 14 days (range 2.3-61.5 days) between 4<sup>th</sup> and 12<sup>th</sup> infusions.

**Pharmacokinetics in Specific Populations:** No formal PK studies have been conducted in patients with hepatic or renal impairment, or patients in geriatric and pediatric populations. Renal and hepatic functions are unlikely to influence the PK of Ofatumumab. Results of a population PK analysis indicate that no dose adjustment is necessary for age, gender and renal function. Although clearance (CL) increases with body weight, this increase is not clinically significant and therefore, no dosage adjustment is recommended based on body weight.

**Drug Metabolism and In vivo Drug-Drug Interaction:** No studies on the metabolism of Ofatumumab have been performed in humans. Metabolism studies are not generally performed for biologic products. No formal drug-drug interaction studies have been performed since Ofatumumab is used as monotherapy in the proposed indication.

**Pharmacodynamic Findings:** In the pivotal study, median decrease in circulating CD19-positive B cells was 91% (n=50) after the 8<sup>th</sup> infusion and 85% (n=32) after the 12<sup>th</sup> infusion in DR patients. In BFR patients, the median decrease in circulating CD19-positive B cells was 93% (n=70) after the 8<sup>th</sup> infusion and 91% (n=41) after the 12<sup>th</sup> infusion. The B-cell recovery period could not be evaluated due to insufficient patient follow-up.

**Rationale of Dose Selection:** The exposure-response relationship for effectiveness (complete & partial remission) is evidenced in both the supportive dose ranging study (Hx-CD20-402) and pivotal study (Hx-CD20-406). In both studies, the effectiveness increases with increasing ofatumumab exposure (AUC). Therefore, dosing the highest studied dose would yield the greatest therapeutic benefit. There were no critical safety concerns at the highest studied dose in the phase III trial, making the 2000 mg dose acceptable.

**Immunogenicity:** As with all therapeutic proteins, Ofatumumab has the potential to induce an immune response. An ELISA assay was used to detect the anti-product antibodies in the pivotal study. Serum samples from 154 patients with CLL treated with Ofatumumab were tested for anti-Ofatumumab antibodies during the 24-week treatment period and follow-up. Results were negative in 46/139 patients after 8<sup>th</sup> infusion and 33/85 patients after 12<sup>th</sup> infusion. Results from the remaining patients were categorized as inconclusive due to interference with the immunogenicity assay by high level of circulating Ofatumumab.

**QT/QTc Evaluation:** The potential of Ofatumumab treatment on QT interval has not been assessed in patients with chronic CLL. The sponsor proposed to address the QT issue in their future Study OMB110913 (1000 mg Ofatumumab in combination with fludarabine and cyclophosphamide (OFC) in relapsed CLL patients) and in Study OMB112855 (2000 mg Ofatumumab as monotherapy in refractory CLL patients). The proposed QT study protocol has been reviewed by the QT interdisciplinary review team

(See attachment 3).

**Efficacy Profiles:** The primary endpoint of efficacy for pivotal study Hx-CD20-406 is objective response rate (ORR) according to the 1996 NCI-WG guidelines over the period from screening to week 24. The ORR value (99% confidence interval (CI)) in DR population was determined as 41% (99% CI: 25-59) according to FDA analysis, 42% (99% CI: 26-60) by GSK investigator and 58% (99% CI: 40-74) by IRC. The ORR in BFR population was 34% (99% CI: 21-49) and 47% (99% CI: 32-62) as determined by the investigator and IRC, respectively. The ORR in the DR patient population exceeded the pre-specified response rate (excluding 15% at the lower limit of the 99% CI). Chromosomal abnormalities (i.e., 17p deletion) and elevated  $\beta$ 2-microglobulin were associated with lower ORR and poorer overall survival. DR patients with chromosome 17p deletion (n=15) had a 33% ORR (99% CI: 8-68), whereas patients with no chromosomal abnormalities (n=7) had a 71% ORR (99% CI: 20-98).

**Safety Profiles:** The safety data from the Hx-CD20-406 and Hx-CD20-402 studies suggested that treatment with Ofatumumab was generally tolerated in the study population with advanced, heavily pre-treated, highly refractory CLL and a high risk for rapid disease progression and infectious complications. Among 181 patients who received the 2000 mg Ofatumumab in Studies Hx-CD20-402 and Hx-CD20-406, 167 patients had 1401 adverse events (AEs), 89 had SAEs (160 of 1401 AEs were SAEs), where 29 patients considered to be drug related. Sixty-four patients died as of the cut off date for the safety analysis (61 in Study Hx-CD20-406 and 3 in Study Hx-CD20-402). In Study Hx-CD20-406, 24/61 deaths were due to infections. The most common AEs were pyrexia (20%), cough (18%), diarrhea (17%), fatigue (15%), rash (15%), neutropenia (15%), anemia (14%), dyspnea (14%) and pneumonia (14%). The most common reason for withdrawal from the studies was disease progression followed by infection.

**Conclusion:** Overall, acceptable Clinical Pharmacology information is presented in this BLA. The single-arm, pivotal clinical trial demonstrated clinical benefit of Ofatumumab in chronic CLL patients who have received prior therapy. The risk-benefit of Ofatumumab treatment for patients with chronic CLL was discussed at the Oncology Advisory Committee meeting (ODAC) in ASCO on May 29, 2009.

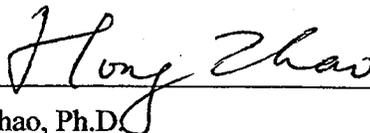
**Signatures:**

 7/2/09

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## 2 QUESTION BASED REVIEW

### 2.1 GENERAL ATTRIBUTES

#### 2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

**Chemistry and Physical-Chemical Properties:** Ofatumumab is a human monoclonal antibody (IgG1 $\kappa$  antibody) with an isoelectric point at approximately [redacted]. The molecular weight (MW) of Ofatumumab is approximately 149 kDa. The EC50 value of Ofatumumab in human peripheral blood mononuclear cells (PBMCs) was determined to be approximately [redacted] ng/mL. The dissociation rate constant (kd) of Ofatumumab has been calculated to be approximately [redacted].

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**Formulation:** The solution for intravenous (IV) infusion is a clear, colorless, aqueous solution containing 20 mg/mL of Ofatumumab in a [redacted] mM citrate buffer, pH 6.5, containing [redacted] mM sodium chloride. It is supplied in Type 1 glass vials sealed with a [redacted] coated [redacted] rubber stopper which is secured with a [redacted] mm aluminum overseal and a [redacted] flip-off cap. Each vial contains 5 mL of a solution intended for intravenous infusion following dilution in saline. Prior to administration, the product is diluted into an infusion bag containing isotonic pyrogen-free saline. During administration of the IV infusion, the product solution is filtered through an in-line sterile [redacted]  $\mu$ m pore size filter.

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#### 2.1.2 What are the proposed mechanisms of action and therapeutic indications?

**Mechanism of Action:** The binding of Ofatumumab to the membrane-proximal, small loop epitope on the CD20 molecule induces recruitment and activation of the complement pathway at the cell surface, leading to complement-dependent cytotoxicity (CDC) and resultant lysis of tumor cells. In addition, the binding of Ofatumumab induces cell death through antibody-dependent cell-mediated cytotoxicity (ADCC).

**Proposed Indication:** The sponsor proposed indication of Ofatumumab is for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received prior therapy.

#### 2.1.3 What are the proposed dosage and route of administration?

**Proposed Dose and Route of Administration:** The recommended dosage is an initial dose of 300 mg followed 1 week later by ARZERRA 2,000 mg once weekly for 7 infusions, followed 4 [redacted] weeks later by ARZERRA 2,000 mg once every 4 weeks for 4 infusions, for a total of 12 infusions. Patients should be premedicated 30 minutes to 2 hours prior to infusion of ARZERRA with an intravenous (IV) corticosteroid (as

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appropriate), an oral analgesic, and an oral or IV antihistamine.

## 2.2 GENERAL CLINICAL PHARMACOLOGY

### 2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The sponsor conducted a phase 1/2 supportive study (Hx-CD20-402) and an ongoing pivotal study (Hx-CD20-406) in patients with CLL to support this BLA submission. The sampling time schedules for pharmacokinetics (PK), B cell count as well as response assessment are listed in Table 1.

**Table 1. Clinical Studies of Ofatumumab**

Study	Phase	Regimen	Population	N	Sampling
Hx-CD20-001	I	IV infusion of 300, 500, 700, or 1000 mg at weeks 0, 1, 2, and 3	relapsed / refractory Grade I-II FL	40 (10/dose level)	<u>PK</u> : weeks 0, 1, 2, 3, 4, 7, and 26, Months 9 and 12 <u>B cells</u> : predose, weeks 1, 4, 11, 19, and 26, Months 9 and 12 <u>Response</u> : weeks 11, 19, 26
Hx-CD20-402	I	IV infusion of: 100/500/500/500 mg 300/1000/1000/1000mg 500/2000/2000/2000mg at Weeks 0/1/2/3	relapsed / refractory CLL	33 (3, 3, and 27 in 3 dose groups)	<u>PK</u> : weeks 0, 1, 2, 3, 4, 7, and 27, Months 9 and 12 <u>B cells</u> : predose, Weeks 1, 4, 7, 11, 15, 19, 23, and 27, months 9 and 12 <u>Response</u> : week 19
Hx-CD20-403	I/II	Part A: Two IV infusions of 0, 300, 700, or 1000 mg at Weeks 0 and 2	RA	Part A: n=39 (32 active)	<u>PK</u> : weeks 0, 1, 2, 3, 4, 8, 16, and 24 <u>B cells</u> : weeks 0, 1, 2, 4, 8, 12, 16, 20, and 24 plus every 12 weeks until return to baseline <u>Response</u> : weeks 12, 16, 20, and 24
		Part B: Two IV infusions of 0, 300, 700, or 1000 mg at Weeks 0 and 2	RA	Part B: n=225 (169 active)	<u>PK and B cells</u> : same as Part A. <u>Response</u> : weeks 12, 16, 20, 24, 36, and 48
Hx-CD20-406	III	IV infusion of 300 mg (Week 0), 2000 mg weekly for 7 weeks, then every 4 weeks for 4 doses (i.e., Weeks 1, 2, 3, 4, 5, 6, 7, 12, 16, 20, and 24)	refractory CLL	n=154 at interim analysis;	<u>PK</u> : weeks 0, 7, 24, and 28, Months 9, 12, and 24 <u>B cells</u> : predose, weeks 1, 7, 12, and 24, months 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, and 48 <u>Response</u> : weeks 4, 8, 12, 16, 20, 24, 28, months 9, 12, 15, 18, 21, and 24

Pivotal Study (Hx-CD20-406): Hx-CD20-406 is a single-arm, international, multi-center

trial of Ofatumumab in patients with B-cell CLL who have received prior treatment. In this study, Ofatumumab was administered as eight weekly infusions (initial infusion 300 mg, then seven infusions of 2000 mg), followed five weeks later by four infusions of 2000 mg given at four-week intervals. This study evaluated the safety, efficacy, and pharmacokinetics (PK) profile of Ofatumumab in CLL patients who were refractory to both fludarabine and alemtuzumab (double-refractory (DR); n=59) or refractory to fludarabine and considered not suitable for treatment with alemtuzumab due to bulky lymphadenopathy (bulky fludarabine-refractory (BFR); n=79); patients with CLL who did not meet the criteria of DR or BFR were also enrolled prior to a protocol amendment (Other; n=16).

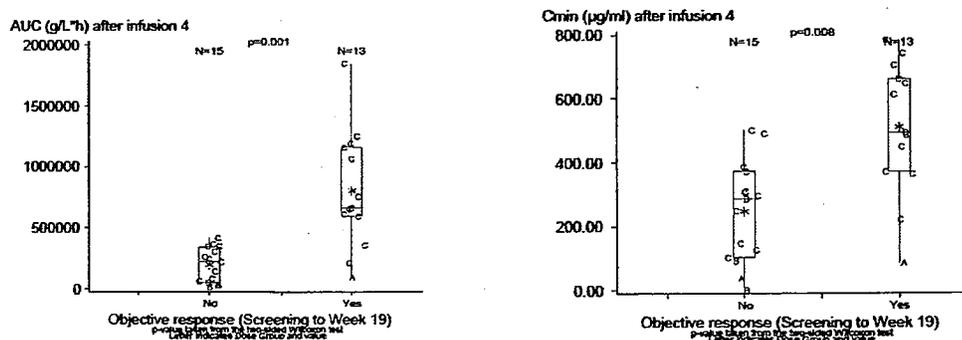
**Supportive study (Hx-CD20-402):** Study Hx-CD20-402 evaluated the safety, efficacy, and pharmacokinetic (PK) profile of Ofatumumab in patients with relapsed or refractory chronic lymphocytic leukemia (CLL) using four weekly infusions at three dose levels (Group A = 100/500/500/500 mg, n=3; Group B = 300/1000/1000/1000 mg, n=3; Group C = 500/2000/2000/2000 mg, n=27). The findings from this study served as the rationale for the ongoing pivotal study (Hx-CD20-406).

**Other Clinical Pharmacology Studies:** Clinical pharmacology data are also available in patients with other diseases (Hx-CD20-001, Hx-CD20-403, Table 1). Further supportive safety data on Ofatumumab in this application include studies for other indications such as follicular lymphoma (FL), diffuse large B cell lymphoma (DLBCL), rheumatoid arthritis (RA), and chronic obstructive pulmonary disease (COPD).

### 2.2.2 What is the basis of the dose selection?

The dose in pivotal study was primarily selected based on supportive study Hx-CD20-402, where patients with relapsed or refractory CLL received four weekly infusions at three dose levels (Group A = 100/500/500/500 mg, n=3; Group B = 300/1000/1000/1000 mg, n=3; Group C = 500/2000/2000/2000 mg, n=27). The response rate (RR) is determined over the period from screening to week 19 (confirmation for 2 months). The pooled data analysis on AUC and Cmin as estimated after 4<sup>th</sup> infusion indicated that the RR increases with increasing Ofatumumab exposure (Figure 1).

**Figure 1: Objective Response versus AUC and Cmin After 4<sup>th</sup> Infusion in Hx-CD20-402 Study (Responders= "yes" and Non-responders="no")**



A relationship between efficacy endpoints and PK parameters (after 4<sup>th</sup> infusion) were further analyzed by polynomial logistic regression analysis. In Table 2a, a statistically significant correlation between RR and PK parameters (all p values were less than 0.01) suggested that RR is conditional on systemic exposure to Ofatumumab. Other efficacy endpoints such as duration of response (DOR), time to progression and time to next anti-CLL therapy, were also correlated with exposure as determined by AUC (positive correlation) and CL (negative correlation) ( $p \leq 0.002$ ) (Table 2b).

**Table 2a. Correlation Between Objective Response and PK Parameters (Study Hx-CD20-402).**

PK parameter after 4 <sup>th</sup> infusion	No Adjustment p=	Adjusted for	
		Body weight p=	Body surface area p=
CL	<0.001	0.005	0.001
AUC	0.001	0.002	0.001
C <sub>max</sub>	0.006	0.005	0.003
C <sub>min</sub>	0.008	0.003	0.004
T <sub>1/2</sub>	0.001	<0.001	<0.001

**Table 2b: Relation Between Survival Endpoints and AUC and CL After 4<sup>th</sup> Infusion.**

	Duration of response			Time to progression			Time to next anti-CLL therapy		
	Spearman coefficient	p-value	n <sup>a)</sup>	Spearman coefficient	p-value	n <sup>a)</sup>	Spearman coefficient	p-value	n <sup>a)</sup>
AUC	0.655	0.002	20	0.836	<0.001	29	0.729	<0.001	29
CL	-0.713	<0.001	20	-0.850	<0.001	29	-0.755	<0.001	29

It was noted that between 4 and 11 weeks, a subgroup of patients in Study Hx-CD20-402 responded with a slower decrease in sum of product diameters (SPD) on lymph node size. However, a small portion of patients experienced an increase in SPD toward the end of the trial or lost clinical response at week 15 or 19. Therefore, increasing the number of weekly infusions to eight might be beneficial to patients. Adverse events (AEs) were primarily observed on the day of the first infusion. The initial dose of 300 mg was thus selected to minimize infusion reactions.

In summary, the use of 2000 mg Ofatumumab in pivotal study appeared acceptable from a clinical pharmacology perspective.

### 2.2.3 What are the clinical endpoints used to assess efficacy in the pivotal clinical efficacy study? What is the clinical outcome in terms of efficacy and safety?

**Primary Efficacy Endpoint:** The demonstration of safety and efficacy of Ofatumumab is based primarily upon the results of an interim analysis of the ongoing pivotal study (Study Hx-CD20-406). A summary of demographics of patient population in the pivotal study is included in Table 3. The primary endpoint of efficacy is objective response rate (ORR) over the period from screening to week 24 according to the 1996 NCI-WG guidelines. Patients with complete remission (CR), nodular partial remission (nPR), or partial remission (PR) were classified as responders, while patients with stable disease (SD) or progressive disease (PD) were classified as non-responders. Responses were required to be maintained for at least 2 months.

**Table 3. Summary of Demographics of Patient Populations in Study Hx-CD20-406**

	DR (n=59)	BFR (n=79)	Other (n=16)	Total (n=154)
Female	25 %	28 %	37.5 %	28 %
Male	75 %	72 %	62.5 %	72 %
≥65 yr	46 %	42 %	37.5 %	43 %
Median age (years)	64	62	63	63
Race (white)	95 %	99 %	94 %	97 %

The ORR values analyzed by FDA, GSK investigator and IRC are summarized in Table 4. The ORR in DR group exceeded the pre-specified response rate (excluding 15% at the lower limit of the 99% CI).

**Table 4. Summary of Primary and Secondary Efficacy Endpoints for Study Hx-CD20-406**

	DR (N=59)	BFR (N=79)
<b>Primary Endpoint</b>		
ORR (FDA)	41% (99% CI: 25-59)	NA
ORR (Investigator)	42% (99% CI: 26-60)	34% (99% CI: 21-49)
ORR (IRC)	58% (99% CI: 40-74)	47% (99% CI: 32-62)
<b>Secondary Endpoints (IRC)</b>		
DOR (month)	7.1 (95% CI: 3.7-7.6)	5.6 (95% CI: 3.6-7.0)
PFS (month)	5.7 (95% CI: 4.5-8.0)	5.9 (95% CI: 4.9-6.4)
TNCLL (month)	9.0 (95% CI: 7.3-10.7)	7.9 (95% CI: 7.1-9.3)
OS (month)	13.7 (95% CI: 9.4-NA)	15.4 (95% CI: 10.2-22.2)

NA: not available.

**Subgroup analysis:** No statistically significant differences in ORR across subgroups were observed with regard to age, prior therapy or palpable lymph nodes at baseline. Lymph node size at baseline did not appear to significantly affect the response to Ofatumumab in either the DR or BFR groups, although the RR in patients with lymph nodes >5 cm were numerically lower compared to patients with smaller lymph node enlargements.

**Secondary Efficacy Endpoints:** The major secondary endpoints included duration of response (DOR) (time from the initial response to progression), progression free survival (PFS) (time from baseline until progression), time to next CLL therapy (TNCLL) and overall survival (OS) (time from Week 0 to death). A summary of secondary efficacy endpoints for the pivotal study was assessed by IRC as shown in Table 4.

**B-cell counts:** The peripheral blood CD5+CD19+ B cells were monitored using a flow cytometry assay during the periods of treatment and follow-up. The CD5+CD19+ B cells provided a reliable surrogate measure for B-CLL cell population because; 1) B-CLL is a monoclonal proliferation of lymphocyte expressing CD5 antigen (CD5+ CLL). 2) CD19 and CD20 have similar expression profiles on B-cell subpopulation. 3) Detection of

CD20+ cells could be impaired as the administered ofatumumab would occupy most CD20 molecules.

As such, an assay for assessment of CD5+CD19+ cells was utilized to measure the count of malignant B cell in the pivotal study. The median decrease in circulating B cells was 91% (n=50) after the 8<sup>th</sup> infusion and 85% (n=32) after the 12<sup>th</sup> infusion in DR patients. The median decrease in circulating B cells in BFR patients was 93% (n=70) after the 8<sup>th</sup> infusion and 91% (n=41) after the 12<sup>th</sup> infusion. The B-cell recovery period could not be evaluated due to insufficient patient follow-up.

**Safety:** The safety data from the Hx-CD20-406 and Hx-CD20-402 studies suggested that treatment with Ofatumumab was generally tolerated in the study population with advanced, heavily pre-treated, highly refractory CLL and a high risk for rapid disease progression and infectious complications.

Among 181 patients who received the 2000 mg dose in Studies Hx-CD20-402 and Hx-CD20-406, 167 patients had 1401 adverse events (AEs), 89 had severe adverse events (SAEs) (160 of 1401 AEs were SAEs), where 29 patients considered to be drug related (Table 5).

**Table 5. A Summary of AEs in CLL Patients.**

Number of patients	Hx-CD20-406 (2000mg) (N=154)	Hx-CD20-402+ Hx-CD20-406 (2000 mg) (N=181)
Any AE, n (%)	146 (95)	167 (92)
Drug-related AEs, n (%)	98 (64)	119 (66)
All SAEs, n (%)	82 (53)	89 (49)
Drug-related SAEs, n (%)	25 (16)	29 (16)
Fatal (Grade 5) SAEs, n (%)	24 (16)	25 (14)
All AEs leading to withdrawal from treatment, n (%)	22 (14) <sup>a</sup>	23 (13) <sup>a</sup>

The most common AEs were pyrexia (20%), cough (18%), diarrhea (17%), fatigue (15%), rash (15%), neutropenia (15%), anemia (14%), dyspnea (14%) and pneumonia (14%). The most common reason for withdrawal from the studies was disease progression followed by infection AE. Infusion reactions were commonly reported AEs. Infusion reactions were most common with the first two infusions and diminished in frequency with subsequent infusions.

Sixty-four patients died as of the cut off date for the safety analysis (61 in Study Hx-CD20-406 and 3 in Study Hx-CD20-402). Of the 61 deaths in Study Hx-CD20-406, 6 occurred within 8 weeks of starting therapy (early deaths), 40 patients died >60 days after the last dose of Ofatumumab. Eight patients died within 1 to 30 days after last dose of Ofatumumab, and 7 patients within >30-60 days after the last Ofatumumab dose. The most common cause of death besides disease progression (17 patients) was septic complications (15 patients), followed by pneumonia (11 patients).

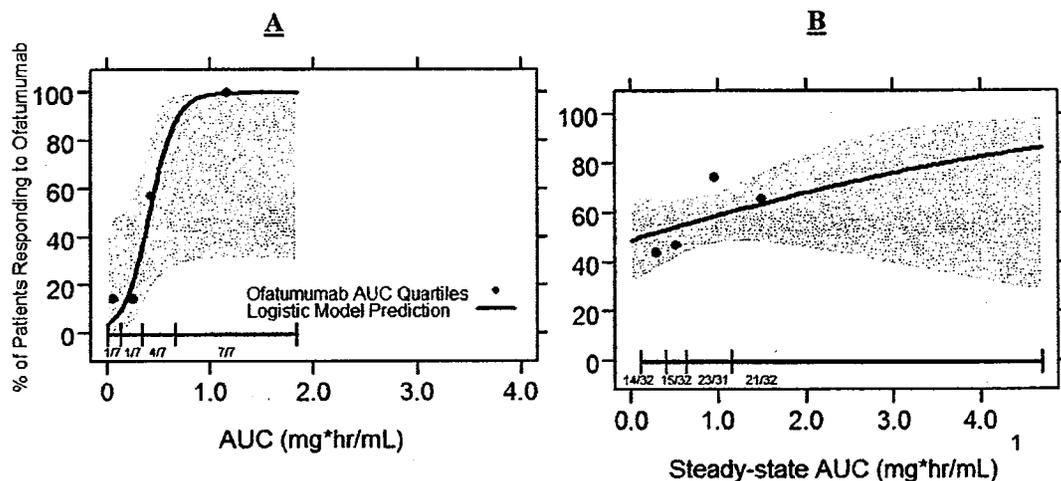
**2.2.4 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationship? (if yes, refer to 2.6 Analytical Section; if no, describe the reasons)**

Yes. Ofatumumab concentrations in serum samples were measured by an ELISA method to assess PK parameters.

**2.2.5 What are the characteristics of the exposure-response relationships for effectiveness?**

The exposure-response relationship for effectiveness (complete & partial remission) is evidenced in studies 402 (dose ranging study) and 406 (pivotal efficacy trial) in Figure 2. It is clear in study 402 following 100-2000 mg (Figure 2, panel A) that with increasing ofatumumab exposure (AUC) there is increasing effectiveness. The relationship that effectiveness increases with exposure is not as steep in study 406 (Figure 2, panel B) for patients receiving 2000 mg.

**Figure 2. Increasing Ofatumumab Exposure Increases Effectiveness.** Solid circles represent the observed percentage of patients responding to ofatumumab treatment in each AUC quartile. The solid line and shaded area represent the mean (95%) logistic regression predictions. The exposure range in each AUC quartile is denoted by the horizontal black line at the bottom of the graph. Numbers indicate responders/total patients per quartile.



**2.2.6 Does this drug prolong the QT or QTc interval?**

The potential of Ofatumumab treatment on QT interval has not been studied in patients with chronic CLL. The QT study will be requested as post market requirement (PMR). The sponsor proposed QT studies to address the QT issue in Study OMB110913 (1000 mg Ofatumumab in combination with fludarabine and cyclophosphamide (OFC) in

relapsed CLL patients) and in Study OMB112855 (2000 mg Ofatumumab as monotherapy in refractory CLL patients). The proposed QT study plan has been reviewed by FDA QT interdisciplinary review team (IRT) (See Appendix III: QT IRT Review).

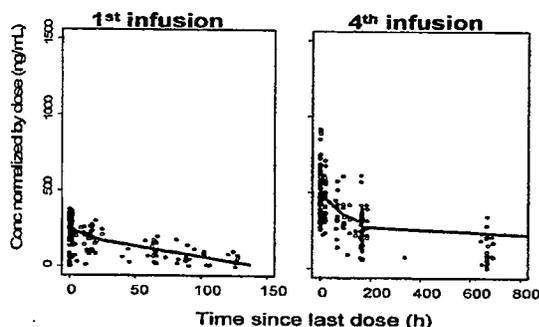
**2.2.7 Pharmacokinetic characteristics of the drug and its major metabolites.**

**2.2.7.1 What are the pharmacokinetic characteristics of the drug?**

Ofatumumab exhibited dose-dependent clearance in the dose range of 100 to 2000 mg. Ofatumumab is eliminated through a target-independent route and a B cell-mediated route. The PK of Ofatumumab was characterized in patients with relapsed and refractory CLL in two studies, Study Hx-CD20-402 (four weekly infusions) and Study Hx-CD20-406 (eight weekly infusions followed by four infusions at four-week intervals).

PK of Ofatumumab after 1<sup>st</sup> and 4<sup>th</sup> infusion were evaluated in supportive Study Hx-CD20-402. Exposure of Ofatumumab (AUC and C<sub>max</sub>) increased more than proportionally with dose (Figure 3). The geometric mean values for CL and t<sub>1/2</sub> were 63.7 mL/h and 1.3 days after the first infusion, 8.5 mL/h and 11.5 days after the fourth infusion (Table 6).

**Figure 3. Dose-Normalized Serum Concentration vs. Time Profile of Ofatumumab in Study Hx-CD20-402.**



**Table 6. Summary of Ofatumumab PK Parameter Values in CLL Patients.**

Infusion Number	Patient number	CL (mL/hr)		t <sub>1/2</sub> (days)	
		Mean	Range	Mean	Range
1 <sup>a</sup>	27	64	/	1.3	/
4 <sup>a</sup>	24	8.5	/	11.5	/
8 <sup>b</sup>	127	9.5	/	15.8	/
12 <sup>b</sup>	77	10.1	/	13.9	/

a= Study Hx-CD20-402; b= Study Hx-CD20-406

b(4)

In pivotal study, PK data were only collected after 8<sup>th</sup> and 12<sup>th</sup> infusion in refractory CLL patients. The geometric mean values for CL and t<sub>1/2</sub> were 9.5 mL/h and 15.8 days after the eighth infusion, and 10.1 mL/h and 13.9 days after the twelfth infusion (Table 6). The mean V<sub>ss</sub> values ranged from 1.7 to 5.1 L. Due to the depletion of B cells with subsequent infusions, the CL of Ofatumumab was significantly decreased compared to that after the first infusion (PK parameters after 1<sup>st</sup> and 4<sup>th</sup> infusion were obtained from Study Hx-

CD20-402). CL exhibited large intersubject variability with CV% greater than 50%. The mean  $t_{1/2}$  between 4<sup>th</sup> and 12<sup>th</sup> infusions was approximately 14 days (range 2.3-61.5 days).

**2.2.7.2 Is this a high extraction ratio or a low extraction ratio drug?**

Not applicable to biologic products.

**2.2.7.3 Does mass balance study suggest renal or hepatic the major route of elimination?**

No mass balance study has been conducted for Ofatumumab. Mass balance studies are not generally performed for protein drugs because they are degraded into amino acids that then recycled into other proteins.

**2.2.7.4 What are the characteristics of drug metabolism?**

Metabolism studies are not generally performed for biologic products because they are degraded into amino acids that are then recycled into other proteins.

## **2.3 INTRINSIC FACTORS**

***2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure and/or response and what is the impact of any differences in exposure on the pharmacodynamics?***

***Pharmacokinetics in Special Populations:*** No formal PK studies have been conducted in patients with hepatic or renal impairment, or patients in geriatric and pediatric populations. Renal and hepatic functions are unlikely to influence the PK of ofatumumab. Results of population PK analysis indicated that no dose adjustment is necessary for age, gender and renal function. Although volume of distribution and clearance (CL) increased with body weight, this increase was not clinically significant and therefore, no dosage adjustment is recommended based on body weight.

***2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dosage regimen adjustments, if any, are recommended for each of these groups? If dosage regimen adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.***

***a) Elderly***

No formal PK study of ofatumumab was conducted in elderly patients ( $\geq 65$  years). In pivotal Study Hx-CD20-406, 27/59 DR patients and 46/79 BFR patients were over 65 years old. Population PK analysis indicated that age did not significantly influence ofatumumab PK in patients with age ranged from 21 to 86 years old. No substantial differences were seen in safety and efficacy related to age.

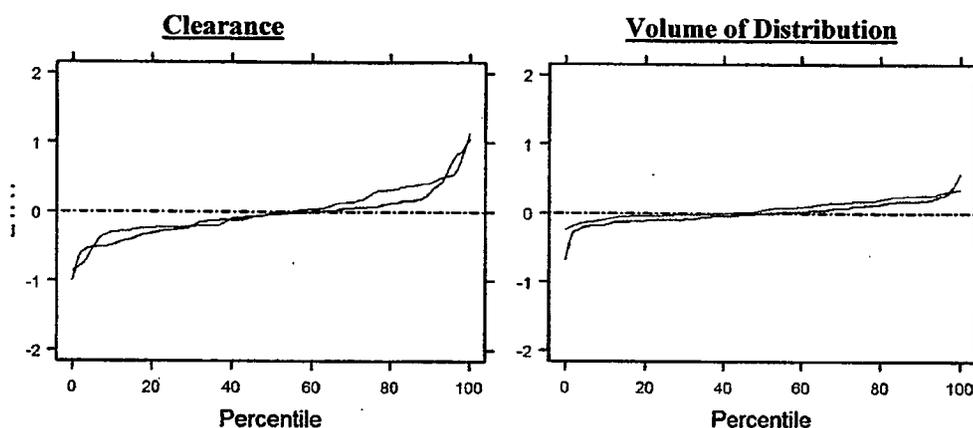
***b) Pediatrics***

The sponsor requested that FDA grant a full waiver to conduct study in pediatric patients as CLL is rare in patients younger than 40 years old.

### c) Gender

Gender has modest effect (14-25%) on CL with male having higher CL than female, however, this effect is not clinically important. After correcting for body weight differences, male and female have similar PK profiles regarding CL and volume of distribution (Figure 4). Therefore, no dosage adjustment is recommended.

**Figure 1. Gender Does Not Influence Ofatumumab PK After Correcting For Body Weight Differences.** The solid red and blue lines indicate male and female CL and  $V_d$  percentiles for intersubject variation from the final population PK model. The dashed black line is a reference line at zero.



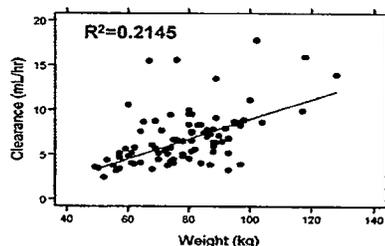
### d) Race

Only a few non-white patients (97% are Caucasian) were enrolled in the clinical studies. No meaningful analysis has been conducted to evaluate the effect of race on Ofatumumab PK.

### e) Body Weight

CL appeared to increase with body weight ( $R^2=0.2145$ , see Figure 5). However, this increase was not clinically important due to large intersubject variabilities. No dosage adjustment is recommended based on body weight.

**Figure 5. Clearance After 8<sup>th</sup> Infusion vs. Body Weight For Patients In Study Hx-CD20-406**



**f) Renal impairment**

Creatinine clearance calculated at baseline was not a clinically significant factor on Ofatumumab PK in patients with creatinine CL values ranging from 33 to 287 mL/min. No dose adjustment for patients with mild to moderate renal impairment. No PK study has been conducted in patients with severe renal impairment. However, renal impairment is less likely to be a major factor as IgG is catabolized by ubiquitous proteolytic enzymes.

**g) Hepatic impairment**

No formal PK studies were conducted in patients with hepatic impairment. However, hepatic impairment is not expected to be a major factor as IgG is catabolized by ubiquitous proteolytic enzymes.

**h) Genomics**

Subjects in study Hx-CD20-406 were evaluated for the following prognostic and pharmacogenetic biomarkers: FISH-detected chromosomal abnormalities (13q deletion, 11q deletion, 12q trisomy, 17p deletion, 6q deletion), immunoglobulin heavy chain variable region (IgVH) mutational status, CD38+, Fcγ receptor polymorphism (*FCGR3A* V158F, *FCGR2A* H131R), β2-microglobulin, thymidine kinase, and circulating CD20.

Chromosome 17p deletion and elevated serum β2-microglobulin were associated with lower (but not absent) response rates and poorer overall survival in the overall population and in the DR and BFR subgroups, which is consistent with prior studies in CLL patients (See Appendix II: Genomics Group Review).

In the overall population, the odds ratio for non-response among patients with chromosome 17p deletion (detected in 22%), relative to patients without any chromosomal abnormalities, was 3.05 (95% CI: 1.07-8.70). Higher baseline β2-microglobulin decreased responsiveness in the overall population (odds ratio 5.67, 95% CI: 2.31-13.95). Overall survival followed similar trends.

ORRs and the respective 95% CI for the DR subgroup are shown in the Table 7. The heterogeneity in ORR was not statistically significant in the DR subgroup due to the small sample size, as the magnitude of the point estimate in the DR subgroup was similar to that of the overall population. The lower limit of the 99% CI for ORR exceeded the 15% threshold only in the DR subgroup with no chromosomal abnormalities.

**Table 7. Objective Response Rate for the DR Subgroup In Pivotal Study.**

Double Refractory					ORR – FDA Adjudication		
					N OR / N total	% (95%CI)	Odds Ratio (95%CI)
<b>Total</b>					22 / 54	41 (26-55)	—
<b>Chromosomal aberrations</b>							
17p-	11q-	12q+	13q-	6q-			
-	-	-	-	-	5 / 7	71 (31-100)	1.00 (reference)
+	+/-	+/-	+/-	+/-	5 / 15	33 (6-61)	5.00 (0.70-35.5)
-	+	+/-	+/-	+/-	10 / 24	42 (20-63)	3.50 (0.56-21.8)
-	-	+	+/-	+/-	0 / 3	0 (0-17)	...
-	-	-	+	-	2 / 5	40 (0-93)	3.75 (0.33-42.5)

$\beta$ 2-microglobulin concentrations were variable and substantial overlap was evident between responders and non-responders. CD38+ was associated with ORR only in DR patients, and was not associated with overall survival. ORR or survival did not differ as a function of the other prognostic biomarkers.

Ofatumumab affinity for its target may vary according to *FCGR3A* genotype. Genotype determination for *FCGR2A* and *FCGR3A* was incomplete in Study Hx-CD20-406 and the analyses are inconclusive.

### 2.3.2.1 What pregnancy and lactation use information is there in the application?

**Pregnancy Category C:** There are no adequate or well-controlled studies of Ofatumumab in pregnant women. A reproductive study using doses up to 3.5 times the recommended dose of Ofatumumab in pregnant cynomolgus monkeys did not demonstrate maternal toxicity or teratogenicity. Fetuses exhibited depletion of peripheral B cells and decreased spleen and placenta weights. The kinetics of B-lymphocyte recovery and the potential long-term effects of peri-natal B-cell depletion in offspring from Ofatumumab-treated dams are unknown.

Ofatumumab does not bind normal human tissues other than B lymphocytes; it is not known if binding occurs to unique embryonic or fetal tissue targets. Because animal reproduction studies are not always predictive of human response, Ofatumumab should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus. The results of the study in pregnant monkeys showed that Ofatumumab can cross the placental barrier. Women of childbearing potential should use adequate contraception during treatment with Ofatumumab and for at least 6 months after the final

**Nursing Mothers:** It is not known whether Ofatumumab is secreted in human milk, however human IgG is excreted in human milk. Published data suggest that neonatal and infant consumption of breast milk does not result in substantial amounts of antibody in circulation. Because many drugs are secreted in human milk, a decision should be made whether to discontinue nursing or discontinue drug, taking into account the terminal half-life of the Ofatumumab (approximately 14 days [range 2.3-61.5 days]) and the importance of the drug to the mother.

### 2.3.2.2 Other factors that are important to understand the drug's efficacy and safety

**Immunogenicity:** As with all therapeutic proteins, there is a potential for immunogenicity with therapeutic proteins such as Ofatumumab. The presence of anti-product antibodies (APA) may alter the PK of a biologic product by potentially enhancing or decreasing the clearance of the biologic product. The clinical significance of antibodies to ofatumumab is unknown.

The immunogenicity of Ofatumumab has been evaluated using two different enzyme linked immunosorbent assays (ELISA), a (F(ab')<sub>2</sub>) binding antibody assay and a whole Ofatumumab binding antibody assay. The (F(ab')<sub>2</sub>) binding antibody assay was used to test samples from Study Hx-CD20-001 (FL), Study Hx-CD20-402 (CLL), and Study Hx-CD20-403 (RA). Out of the 274 patients who received Ofatumumab in these studies, two samples were identified as positive (Table 8). However, conclusions regarding these results are limited in that the (F(ab')<sub>2</sub>) binding antibody assay was restricted to detection of antibodies of just one isotype (IgG1) and was not capable of detecting antibodies to CH2 and CH3 domains.

**Table 8. Summary of Anti-Product Antibody Results in Clinical Studies**

Study type (disease)	Study number	Number of Patients	Dose schedule	Doses (mg)	Route of administration	Incidence of immunogenicity
Phase I/II (FL)	Hx-CD20-001	40	4 weekly doses	300, 500, 700 or 1000	i.v.	1/40
Phase I/II (CLL)	Hx-CD20-402	33	4 weekly doses (1 low + 3 high)	100+500, 300+1000 or 500+2000	i.v.	0/33
Phase I/II (RA)	Hx-CD20-403 Part A+B	201	2 infusions 2 weeks apart	300, 700 or 1000	i.v.	1/201
Pivotal trial in (CLL)	Hx-CD20-406	154 (interim data)	300 mg + 7 weekly + 4 monthly 2000 mg	300 (initial infusion) + 2000	i.v.	0/154*

\*, Results were negative in 46/139 patients after 8<sup>th</sup> infusion and 33/85 patients after 12<sup>th</sup> infusion. Results from the remaining patients were classified as inconclusive due to interference with the immunogenicity assay by circulating Ofatumumab.

The (F(ab')<sub>2</sub>) binding antibody assay was subsequently superseded by the whole Ofatumumab binding antibody assay in that the latter assay can detect antibodies of most major isotypes (exception: monovalent IgG4) that bind to any Ofatumumab epitope (i.e., not restricted to the Fab portion). The whole Ofatumumab binding assay was used to test samples from pivotal study Hx-CD20-406 (Table 8). Serum samples from 154 patients treated with Ofatumumab were tested for anti-product antibodies (APA) at baseline, at week 12 (4 weeks after 8<sup>th</sup> infusion), and at 3, 6 and 12 months after 12<sup>th</sup> infusion (the last dose administration). No positive results were reported (Table 8), however, results from over 60% of samples are inconclusive due to on board drug interference.

The incidence of antibody positivity is highly dependent on the specific assay and its sensitivity. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, timing of sample collection, concomitant medications and underlying disease. For these reasons, comparison of the incidence of antibodies to ofatumumab with the incidence of antibodies to other products may be misleading.

## **2.4 EXTRINSIC FACTORS**

**2.4.1 *What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence exposure and/or response and what is the impact of any differences in exposure on pharmacodynamics?***

None of the extrinsic factors including drugs, herbal products, diet, smoking, and alcohol use were studied for their influence on Ofatumumab exposure and/or response.

**2.4.2 *Based upon what is known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors? If dosage regimen adjustments across factors are not based on the exposure-response relationships, describe the basis for the recommendation.***

None.

### **2.4.3 *Drug-Drug interactions***

**2.4.3.1 *Is there an *in vitro* basis to suspect *in vivo* drug-drug interaction?***

Unknown.

**2.4.3.2 *Is the drug a substrate of CYP enzymes?***

Unknown.

**2.4.3.3 *Is the drug an inhibitor and/or an inducer of CYP enzymes?***

Unknown.

**2.4.3.4 *Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?***

Unknown.

**2.4.3.5 *Are there other metabolic/transporter pathways that may be important?***

No. Metabolism studies are not generally performed for biological products because they are degraded into amino acids that then recycled into other proteins. Therefore, classical biotransformation studies as performed for pharmaceuticals are not needed.

**2.4.3.6 Does the label specify co-administration of another drug (e.g., combination therapy in oncology) and if so, has the interaction potential between these drugs been evaluated?**

Patients treated with Ofatumumab are pre-medicated with corticosteroids. The potential drug-drug interaction (DDI) between Ofatumuamb and corticosteroids was not evaluated. The chance of DDI between Ofatumuamb and corticosteroids is expected to be low.

**2.4.3.7 What other co-medications are likely to be administered to the target patient population?**

Granulocyte colony-stimulating factor (GCSF) might be used in CLL patients during the treatment with Ofatumumab. However, the use of GCSF in CLL patients was not indicated in this BLA submission. The potential DDI between ofatumuamb and GCSF was not evaluated.

**2.4.3.8 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?**

Ofatumumab is proposed for monotherapy use in CLL patients. No formal DDI studies have been conducted for Ofatumumab and concomitant medications.

**2.4.3.9 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions, if any?**

Unknown.

**2.4.3.10 Are there any unresolved questions related to metabolism, active metabolites, metabolic drug interactions or protein binding?**

Unknown.

## **2.5 GENERAL BIOPHARMACEUTICS**

**2.5.1 *What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?***

Not applicable because Ofatumumab is given via IV infusion.

**2.5.2 When would a fed BE study be appropriate and was one conducted?**

Not applicable for biological products given via IV infusion.

**2.6 ANALYTICAL SECTION**

**2.6.1 How are the active moiety identified and measured in the serum in the clinical pharmacology and biopharmaceutics studies?**

An enzyme-linked immunosorbent assay (ELISA) was utilized to quantify Ofatumumab in human serum. For determination of anti-ofatumuamb antibodies, two different ELISAs, a F(ab')<sub>2</sub> binding antibody assay and a whole binding antibody assay, were employed over the course at the development program. The whole binding antibody assay is superior to the F(ab')<sub>2</sub> binding assay.

**2.6.2 For all moiety measured, is free, bound or total measured? What is the basis for that decision, if any, and is it appropriate?**

Not applicable.

**2.6.3 What bioanalytical methods are used to assess concentrations?**

**Assay for Ofatumumab concentration determination:** Serum ofatumuamb concentrations were determined by an ELISA assay. The assay used a mouse monoclonal anti-idiotypic antibody to capture Ofatumumab and an Fc-specific anti-human IgG1 antibody coupled to horseradish peroxidase (HRP) to detect Ofatumumab. The substrate azino benzothiazoline sulfonic acid (ABTS) was used to generate a colorimetric endpoint.

The analytical method for the determination of human serum Ofatumumab has an analytical range of 0.1 to 10.0 µg/mL. Precision of the assay, as determined by coefficients of variation, was <13.1% and accuracy, as determined by %bias, was within ± 14.8% at all concentrations within the analytical range. Sample linearity was validated up to 1:51,200 dilution, providing an effective analytical range of 0.1 to 5120 µg/mL. Ofatumumab has been shown to be stable in human serum for at least two freeze-thaw cycles, for up to two weeks at 4°C and at -20°C, and for up to one year at -70°C. A summary of the validation data is presented in Table 9.

**Table 9: Summary of Ofatumumab Analytical Method and Validation Results (ELISA).**

Validation Report	Clinical Study No	Summary of Method and Validation Parameters
Quantification of HuMax-CD20 Antibodies in Human Serum – Validation Report (September 2008)	Hx-CD20-001 Hx-CD20-402 Hx-CD20-403 Hx-CD20-406 Hx-CD20-408	Methodology: Antibody capture sandwich ELISA with detection using an Fc-specific anti-human IgG <sub>1</sub> coupled to HRP. Range: 0.1 to 10 µg/mL Precision and Accuracy: Within run: 3.4 to 13.1% and -9.9 to 14.8% Between run: 6.8 to 9.4% and -0.7 to 9.7% Freeze Thaw stability: 2 cycles from -20°C Short Term Stability: up to 2 weeks at 4°C and -20°C Long term Stability: up to 1 year at -70°C Linearity of Dilution: up to 1/51,200 dilution

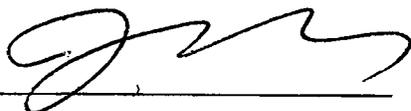
Quality Control (QC) samples were analyzed with each batch of study samples against separately prepared calibration standards. The QC validation of this analytical method appeared acceptable (Table 10).

**Table 10: Between-Run Accuracy and Precision of Quality Control Samples**

STUDY	Nominal Concentrations (ng/mL)			
	QC 80	QC 20	QC 2.5	
Study Hx-CD20-001	Overall Mean (ng/mL)	80.4	19.2	2.6
	S.D. (within-run means)	7.62	1.13	0.30
	Precision (%CV)	9.5	5.9	11.5
	Average Bias (%)	0.5	-4.0	5.5
	n	178	178	178
		QC 80	QC 20	QC 2.5
Study Hx-CD20-402	Overall Mean (ng/mL)	82.8	19.2	2.6
	S.D. (within-run means)	8.90	1.40	0.24
	Precision (%CV)	10.7	7.3	9.2
	Average Bias (%)	3.6	-4.0	2.4
	n	136	136	136
		QC 80	QC 20	QC 2.5
Study Hx-CD20-403	Overall Mean (ng/mL)	81.5	19.6	2.8
	S.D. (within-run means)	9.67	1.52	0.28
	Precision (%CV)	11.7	7.7	10.0
	Average Bias (%)	1.9	-1.9	10.6
	n	560	560	549
		QC 80	QC 20	QC 2.5
Study Hx-CD20-406	Overall Mean (ng/mL)	81.1	18.9	2.5
	S.D. (within-run means)	8.05	1.21	0.90
	Precision (%CV)	9.9	6.4	35.3
	Average Bias (%)	1.4	-5.6	1.8
	n	429	429	429
		QC 80	QC 20	QC 2.5
Study Hx-CD20-408	Overall Mean (ng/mL)	85.4	18.7	2.6
	S.D. (within-run means)	17.84	1.17	0.21
	Precision (%CV)	20.9	6.3	8.0
	Average Bias (%)	6.8	-5.5	5.9
	n	16	16	16
		QC 80	QC 20	QC 2.5

**Assay for immunogenicity testing:** Serum samples from early clinical studies were tested using the (F(ab')<sub>2</sub>) binding antibody assay. For each patient sample, a dilution series was made and the titre (i.e. the dilution that yields the O.D. closest to 0.100) was determined. A patient is regarded to be positive if there is at least an eight-fold increase in titre versus their pre-infusion value. However, the (F(ab')<sub>2</sub>) binding antibody assay was restricted to detection of antibodies of just one isotype (IgG<sub>1</sub>) and was not capable of detecting antibodies to CH2 and CH3 domains.

The whole binding antibody assay was designed to detect anti-Ofatumumab antibodies of all isotypes (with the exception of monovalent IgG4). This assay was used in ongoing pivotal study Hx-CD20-406. The assay consisted of a screening assay (with a negative cut-off (NCO) setting) and a confirmatory assay, in which samples with O.D. greater than the NCO during screening were re-analysed under immunodepletion conditions. A NCO for the screening assay was established using 20 naïve cynomolgus serum samples. The nominal assay sensitivity (established using a mouse-anti-Ofatumumab mAb) was 0.98 ng/mL in assay buffer. Coefficient of variation (CV) in intra-assay and inter-assay were less than 20%. Interference from Ofatumumab is expected in any immunogenicity assay; thus, negative results are only conclusive when they are measured in samples with Ofatumumab concentrations <500 ng/mL.



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Jun Yang, Ph.D.

Clinical Pharmacology Reviewer, Biologic Product Team

Division of Clinical Pharmacology V

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Hong Zhao, Ph.D.

Team Leader, Biologic Product Team

Division of Clinical Pharmacology V

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       § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

4.2 APPENDIX 2 - OCP FILING REVIEW FORM

## Office of Clinical Pharmacology

### *New Drug Application Filing and Review Form*

General Information About the Submission

	Information		Information
DA/BLA Number	125326/000	Brand Name	ARZERRA
CP Division (I, II, III, IV, V)	V	Generic Name	Ofatumumab
Medical Division		Drug Class	Biologics/Oncology
CP Reviewer	Jun Yang	Indication(s)	CLL who received prior therapy
CP Team Leader	Hong Zhao	Dosage Form	100 mg/5mL vial
Pharmacometrics Reviewer	Justin C. Earp	Dosing Regimen	Initially 300mg/2000mg weeklyx7/2000mg weeklyx4(4/week after 8 <sup>th</sup> infusion)
Date of Submission	1/30/2009	Route of Administration	IV infusion
Estimated Due Date of OCP Review		Sponsor	GSK
Medical Division Due Date		Priority Classification	Priority
PDUFA Due Date	8/1/2009		

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### *Clin. Pharm. and Biopharm. Information*

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
PK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:	x			
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				

#### 4 APPENDICES

##### 4.1 APPENDIX 1 – PM REQUEST FORM

##### **Pharmacometrics Consult Request Form**

Request for Pharmacometrics Review

Enter your e-mail address (REQUIRED):

Application Type (REQUIRED):	<input type="radio"/> IND <input type="radio"/> NDA <input checked="" type="radio"/> BLA	Application # (REQUIRED):	125326
Application Subtype (REQUIRED):	<input type="radio"/> NME <input type="radio"/> Pediatric <input checked="" type="radio"/> Other	Submission # (REQUIRED):	0
Sponsor (REQUIRED):	GSK	Brand Name (REQUIRED):	ARZERRA
Priority Classification (REQUIRED):	6 month	Generic Name (REQUIRED):	Ofatumumab
Indication(s) (REQUIRED):	CLL with prior treatment	Submission Date (m/d/yy) (REQUIRED):	1/30/09
OCP Review Due Date (m/d/yy) (REQUIRED):		Medical Division (REQUIRED):	DBOP
OCP Reviewer (REQUIRED):	Jun Yang	OND Reviewer (REQUIRED):	Steve Lemery
OCP Team Leader (REQUIRED):	Hong Zhao	OND Team Leader (REQUIRED):	Steve Lemery
Advisory Committee Meeting Date (if any, m/d/yy):	End of May	PDUFA / Action Date (m/d/yy):	7/31/09
Purpose of Pharmacometrics Request:	review of the population PK PD model, perform data analysis and evaluate results based on population PK PD model.		
Pharmacometrics Review Process:			
<ul style="list-style-type: none"> <li>A 'scoping' meeting will be scheduled by Pharmacometrics Staff to discuss the key review questions, review plan and timelines. The following will be invited to the scoping meeting: PM TL/secondary reviewer, PM Director, OCP reviewer, OCP TL, OCP Division Director, Medical and Statistical reviewers. A secondary PM reviewer will be assigned by the PM TL before/after the scoping meeting.</li> </ul>			

# OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

## 1 SUMMARY OF FINDINGS

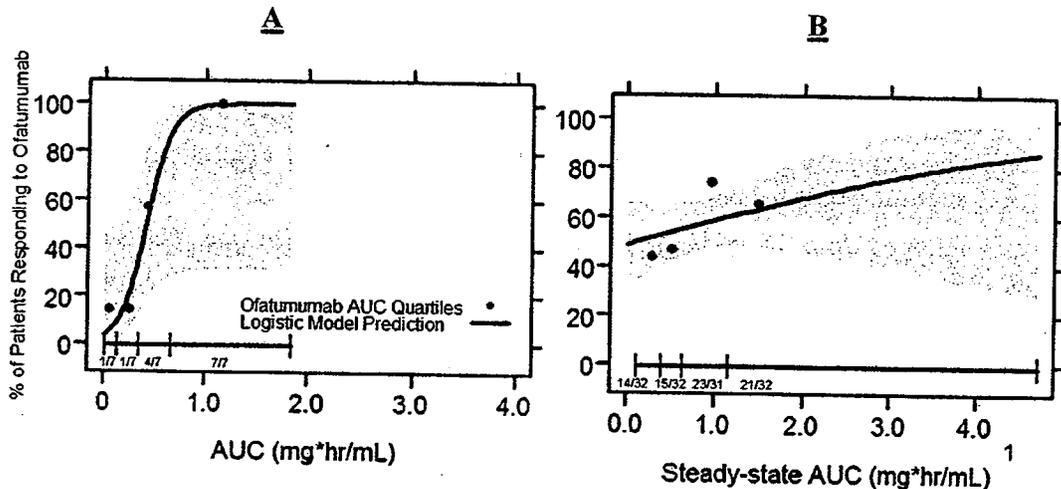
### 1.1 Key Review Questions

The purpose of this review is to address the following key questions.

#### 1.1.1 Is there evidence of exposure-response for effectiveness?

Yes, the exposure-response relationship for effectiveness (complete & partial remission) is evidenced in studies 402 (dose ranging study) and 406 (pivotal efficacy trial) in Figure 1. It is clear in study 402 following 100-2000 mg (Figure 1, panel A) that with increasing ofatumumab exposure (AUC) there is increasing effectiveness. The relationship that effectiveness increases with exposure is not as steep in study 406 (Figure 1, panel B) for patients receiving 2000 mg.

**Figure 1. Increasing Ofatumumab Exposure Increases Effectiveness.** Solid circles represent the observed percentage of patients responding to ofatumumab treatment in each AUC quartile. The solid line and shaded area represent the mean (95%) logistic regression predictions. The exposure range in each AUC quartile is denoted by the horizontal black line at the bottom of the graph. Numbers indicate responders/total patients per quartile.



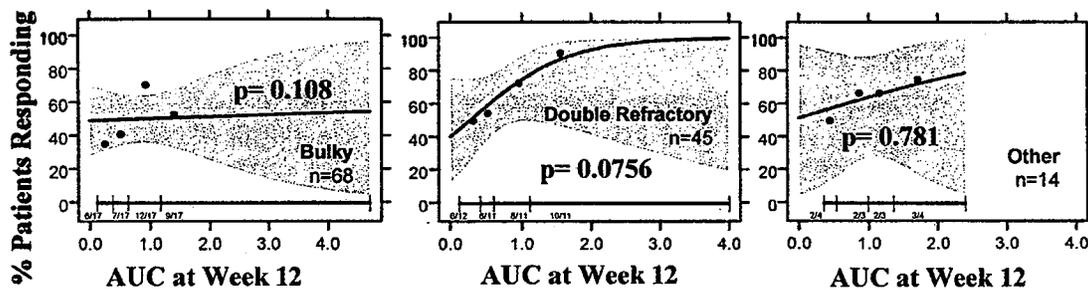
#### 1.1.2 Does the exposure-response relationship for effectiveness support the proposed 2000-mg dose?

Yes, the response rate increases with higher dose and exposure (see Figure 1 for exposure-response). Therefore, dosing the highest studied dose would yield the greatest therapeutic benefit. There were no critical safety concerns at the highest studied dose in the phase III trial (study 406), making the 2000 mg dose acceptable. Higher doses were not feasible to study.

### 1.1.3 Does the disease state determine the observed response rate?

Yes, the type of chronic lymphocyte leukemia (bulky, double refractory, or other) determines the response rate to ofatumumab. Figure 2 shows that each of these populations responded differently to ofatumumab. The bulky group showed the least response to ofatumumab. On the other hand, the double refractory and 'other' groups showed consistent and increasing effectiveness with higher exposures to ofatumumab. In the later two disease types (DR and other) higher exposure resulted in higher probability of response. This observation supports the 2000 mg dose for treatment of the DR and other forms of CLL.

**Figure 2. Patients with double refractory disease respond to ofatumumab faster than other disease types. Solid circles represent the observed percentage of patients responding to ofatumumab treatment in each AUC quartile. The solid line and shaded area represent the mean (95%) logistic regression predictions. The exposure range in each AUC quartile is denoted by the horizontal black line at the bottom of the graph. Numbers indicate responders/total patients per quartile.**



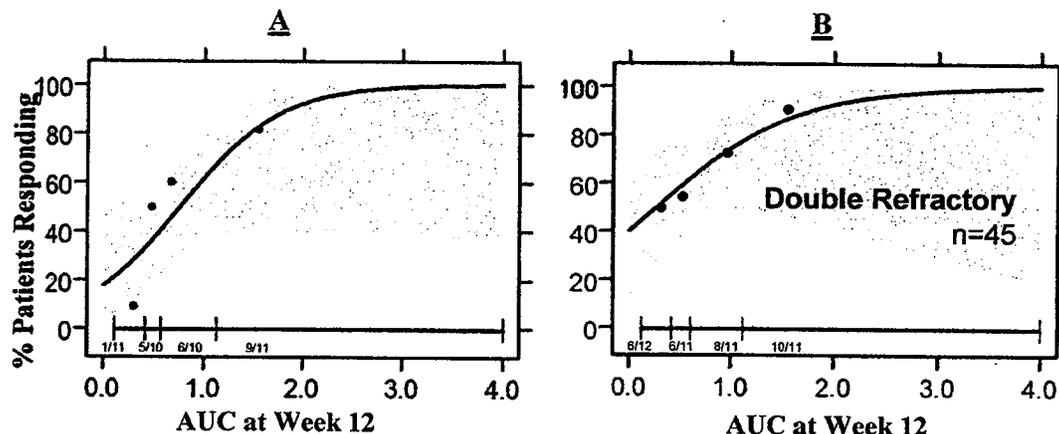
### 1.1.4 Is the exposure-response analysis for the FDA-adjudicated data consistent with the analysis for the sponsor-adjudicated data (section 1.1.3)?

Yes, the exposure-response relationship for the FDA-adjudicated data is similar to the that of the sponsor's data for the DR population in section 1.1.3.

Data was obtained from the clinical reviewer who individually reviewed each subject in the DR population of study 406. A logistic regression relating objective response to exposure (AUC at week 12) was performed in the same manner as for section 1.1.3 with the exception that the CLL disease factor was not included because FDA-adjudicated data for patients with 'bulky' or 'other' disease were not available.

Figure 3 shows a side-by-side comparison of the results for the analyses on the FDA and sponsor's adjudicated data. Both cases show a clear exposure-response relationship for the double refractory CLL population with an odds ratio of 4.3 for the FDA adjudicated data. This means a 4-fold increase in probability of response when doubling the mean exposure for 2000 mg ofatumumab.

**Figure 3. Analysis with FDA Adjudicated data (Panel A) on Patients in the DR Population is Comparable to the Analysis on the Sponsor's Data (Panel B). Solid circles represent the observed percentage of patients responding to ofatumumab treatment in each AUC quartile. The solid line and shaded area represent the mean (95%) logistic regression predictions. The exposure range in each AUC quartile is denoted by the horizontal black line at the bottom of the graph. Numbers indicate responders/total patients per quartile.**



#### 1.1.5 Does anti-ofatumumab antibody titer affect the PK & PD of ofatumumab?

The data are insufficient to determine the effects of immunogenicity. As per the clinical pharmacology reviewer's document, the assay did not detect immunogenicity in a sufficient population to determine the impact of anti-drug antibodies on ofatumumab PK or B-cell depletion:

#### 1.1.6 Do the results of the sponsor's population PK analysis agree with the parameter values and conclusions presented in the label?

The sponsor's population pharmacokinetic model is acceptable. The values in the label are consistent with the population model predictions. The sponsor also claims that no dosage adjustment is necessary based on body weight, age, gender, or renal impairment. No data was available to assess the effects of hepatic impairment.

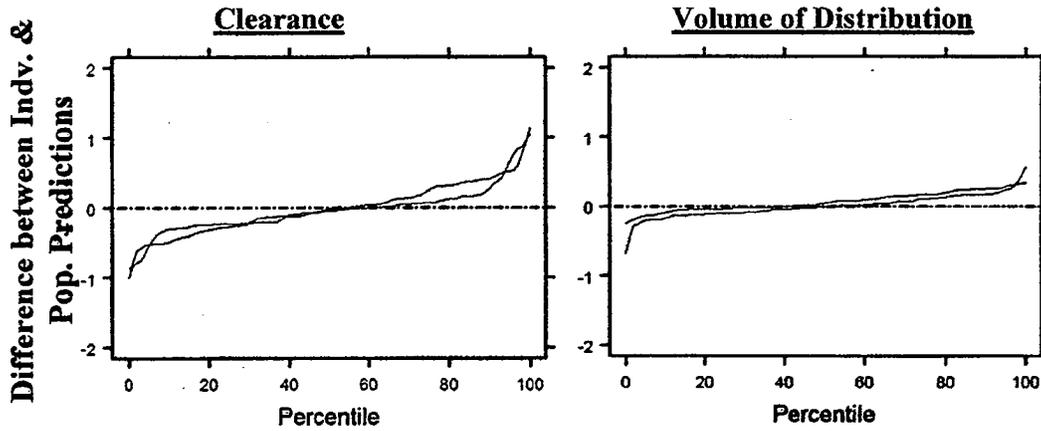
A dosing regimen based on body weight was not necessary. Although, body weight was found to be an important descriptor of between-subject variation for pharmacokinetics, it did not explain intersubject variation for the clinical endpoint. The lack of change in response rate with weight combined with the large variation in the data (sections 1.1.2 & 1.1.3) as indicated from the confidence intervals suggests that dosing by body weight will not improve the response weight.

The sponsor's labeling conclusions were consistent with the results of the population PK analysis. The population pharmacokinetic analysis indicates that age did not affect the pharmacokinetics of ofatumumab. There was no effect of gender on clearance and volume of distribution evidenced similar values in males compared to females (see

Figure 4). No dose adjustment by gender is necessary. These findings are consistent with the sponsor's conclusions.

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On Original*

**Figure 4. Gender does not influence Ofatumumab PK after correcting for Body Weight Differences. The solid red and blue lines indicate male and female CL and  $V_d$  percentiles for intersubject variation from the final population PK model. The dashed black line is a reference line at zero.**

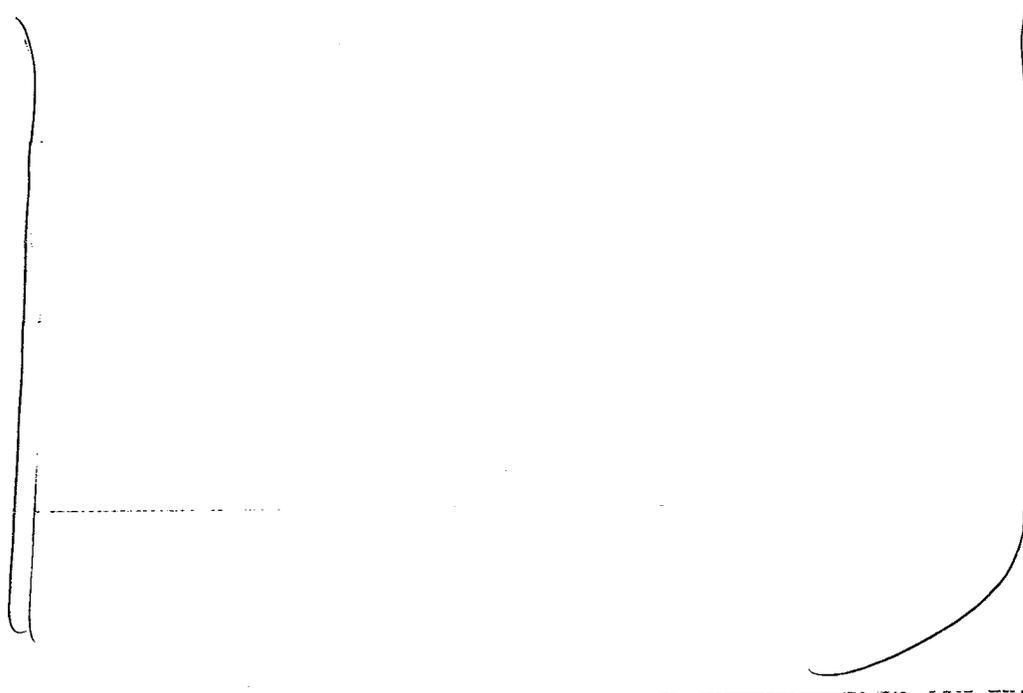


**1.2 Recommendations**

The Office of Clinical Pharmacology has reviewed the BLA for ofatumumab and found it to be acceptable.

**1.3 Label Statements**

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.



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\_\_\_\_\_ § 552(b)(4) Trade Secret / Confidential

X § 552(b)(4) Draft Labeling

\_\_\_\_\_ § 552(b)(5) Deliberative Process

Withheld Track Number: Clin Pharm/Bio- 2



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Justin C. Earp, PhD

Pharmacometrics Reviewer

Office of Clinical Pharmacology

7/7/09

Date



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Christoffer W. Tornoe, PhD

Pharmacometrics Team Leader

Office of Clinical Pharmacology

7/13/09

Date

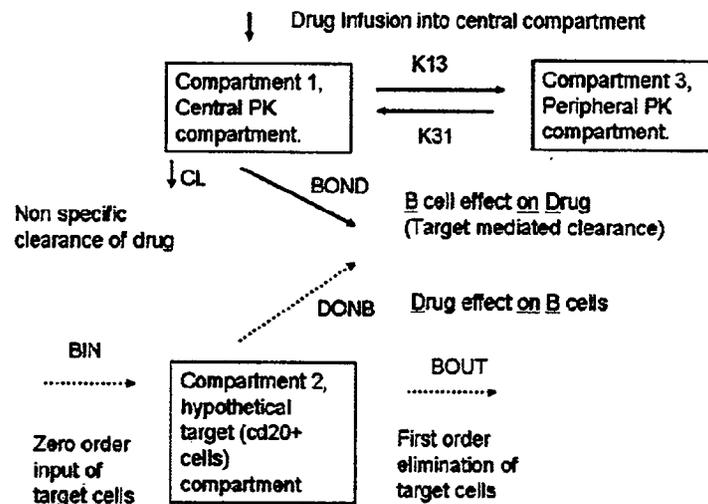
## 2 RESULTS OF SPONSOR'S ANALYSIS

The sponsor conducted both a population PK analysis as well as examination of exposure-response models for both pharmacodynamic measure such as immune cell counts and also for clinical response. The results are summarized in brief below. Further details may be found in Appendix A.

### 2.1 Population Pharmacokinetic Analysis

The sponsor used a non-linear semi-mechanistic pharmacokinetic model owing to the fact that clearance of ofatumumab appeared to changed over time with repeated administration of ofatumumab (Figure 5).

**Figure 5. Diagram of pharmacokinetic model with B-cell-dependence clearance. Compartment 2 represents total body mass of target. Solid arrow represent drug mass transfer/elimination, dotted arrow represents target elimination.**



The model incorporates target-mediated clearance, where the drug binds linearly to a hypothetical target mass (proportional to concentration and target mass), and both are eliminated.

#### Methods:

Data from a total of 320 patients from 123 sites were used for this analysis. Thirty-eight patients were from Study Hx-CD20-001 (follicular lymphoma, FL), 33 from Study Hx-CD20-402 (chronic lymphocytic leukemia, CLL), 196 from Study Hx-CD20-403 (rheumatoid arthritis, RA), and 53 from Study Hx-CD20-406 (CLL).

**Table 1. Studies used in Analysis and Treatment Description**

Study Hx-CD20-001	4 weekly doses of either 300, 500, 700 or 1000 mg
Study Hx-CD20-402	4 weekly doses. The first dose was 100, 300 or 500 mg (groups A, B and C). The second to fourth dose was 500, 1000 or 2000 mg.
Study Hx-CD20-403	2 doses, on days 0 and 14 of 0, 300, 700 or 1000 mg Only data from patients who received active treatment were included.
Study Hx-CD20-406	8 weekly infusions followed by 4 monthly infusions. The first dose was 300 mg, subsequent doses were 2000 mg.

**Conclusions:**

- Ofatumumab follows two-compartment pharmacokinetics with a long half-life consistent with other IgG1 monoclonal antibodies and a typical volume of distribution equal to plasma volume.
- The non-target-mediated clearance was 6.65 mL/hr (2.02 mL/kg/day) for a patient with an average weight of 79.2 kg.
- The volume of distribution of the central compartment was 3.05 L (39 mL/kg) for a patient with an average weight of 79.2 kg.
- Height and weight were predictors of volume of distribution of the central compartment and weight was a predictor of non-target-mediated ofatumumab clearance.

**2.2 Pharmacodynamic Model for Exposure – Response Relationship**

The relationship between clinical response (complete or partial remission) and pharmacokinetic exposure ( $C_{max}$ ,  $C_{min}$ , and AUC on the first and final dose) and BOND (a measure of target-mediated clearance) was examined. A simple logistic regression model between the quantities and clinical response is shown in Table 2 for Study Hx-CD20-402. Most of the measures of ofatumumab exposure showed a relationship to clinical response at Week 19 or Week 27.

**Table 2. Simple logistic regression of ofatumumab exposure vs. clinical response in Study Hx-CD20-402**

PK parameter	Disease/Study/week	Intercept	Coefficient	P value (coefficient not equal 0)
AUC, first dose	CLL/Hx-CD20-402/19	-1.8890	0.2589	0.0239
Cmin, first dose	CLL/Hx-CD20-402/19	-1.260	0.05185	0.0687
Cmax, first dose	CLL/Hx-CD20-402/19	-3.079	0.02229	0.0308
AUC, fourth dose	CLL/Hx-CD20-402/19	-3.782	0.01030	0.0104
Cmin, fourth dose	CLL/Hx-CD20-402/19	-0.6641	0.00298	0.3178
Cmax, fourth dose	CLL/Hx-CD20-402/19	-4.176	0.004206	0.0119
AUC, first dose	CLL/Hx-CD20-402/27	-1.8890	0.2589	0.0239
Cmin, first dose	CLL/Hx-CD20-402/27	-1.260	0.05185	0.0687
Cmax, first dose	CLL/Hx-CD20-402/27	-3.079	0.02229	0.0308
AUC, fourth dose	CLL/Hx-CD20-402/27	-3.782	0.01030	0.0104
Cmin, fourth dose	CLL/Hx-CD20-402/27	-0.6641	0.00298	0.3178
Cmax, fourth dose	CLL/Hx-CD20-402/27	-4.176	0.004206	0.0119

**Conclusions:**

- CD19+ B cells in the peripheral blood in FL and RA were related to the estimates of the pharmacokinetic-derived target cell mass, with a lag time describing the return of cells.
- For CLL in Study Hx-CD20-402, drug exposure was predictive of clinical response at weeks 19 and 27. A similar pattern was seen for other survival endpoint measures.

**3 REVIEWER'S COMMENTS**

- The sponsor's population pharmacokinetic analysis was sufficient to describe the data and identify the major covariates (weight, height, and disease type) that affect clearance and volume of distribution.
- The sponsor's logistic regression for patients with CLL was done only for study 402 (4 week dosing trial). This trial was smaller than study 406 (33 vs 154 patients) with a much shorter duration of therapy (4 weeks vs 8 weeks, once monthly thereafter). This analysis also does not examine the effects of body weight or disease type on the response to ofatumumab (These issues will be addressed in the reviewer's analysis.).

## 4 REVIEWER'S ANALYSIS

### 4.1 Objectives

Analysis objectives are:

1. To determine the exposure-response relationship for effectiveness of ofatumumab and whether body weight or disease type influence this relationship.
2. To use the results of objective (1) to establish whether the proposed dose is adequate.
3. To determine if the presence of anti-ofatumumab antibodies significantly impact the PK and/or PD of Ofatumumab

### 4.2 Methods

#### 4.2.1 Data Sets

Data sets used are summarized in Table 3.

**Table 3. Analysis Data Sets**

Study Number	Name	Link to EDR
402	pkpd.xpt	<a href="\\cbsap58\M\leCTD_Submissions\STN125326\0000\m5\datasets\hx-cd20-402\analysis">\\cbsap58\M\leCTD_Submissions\STN125326\0000\m5\datasets\hx-cd20-402\analysis</a>
406	pkpar.xpt	<a href="\\cbsap58\M\leCTD_Submissions\STN125326\0000\m5\datasets\hx-cd20-406\analysis">\\cbsap58\M\leCTD_Submissions\STN125326\0000\m5\datasets\hx-cd20-406\analysis</a>
406	effprim.xpt	<a href="\\cbsap58\M\leCTD_Submissions\STN125326\0000\m5\datasets\hx-cd20-406\analysis">\\cbsap58\M\leCTD_Submissions\STN125326\0000\m5\datasets\hx-cd20-406\analysis</a>

#### 4.2.2 Software

The population pharmacokinetic analysis was conducted using NONMEM software (Double Precision, Version VI). Models were compiled and run using the G77 Fortran Compiler. S-PLUS (ver. 7.1) was utilized for compiling data and generating diagnostic plots.

#### 4.2.3 Models

An exposure-response model for effectiveness was developed correlating the individual's AUC with their complete response status for both the sponsor- and FDA-adjudicated data. A multiple linear logistic regression was used to correlate objective response (complete remission and partial remission) with AUC. AUC appeared to be the best predictor of exposure from the sponsor's Table 2. Disease type and body weight were also tested as covariates that may affect the response. Modeling results are presented in Table 4.

#### *Sponsor-Adjudicated Data:*

The model was tested for differences in intercept and slope between each disease type (i.e. bulky, double refractory, other). The magnitude of parameter estimate, odds-ratio, p-value, and reduction in residual error, were used to determine whether a parameter should be included in the model. The AUC value was corrected by (AUC-

mean(AUC))/mean(AUC) and the corrected value was used in the logistic regression. This permitted a more accessible interpretation of the odds ratio as the increase in response rate when doubling the mean therapeutic exposure.

When considering each disease population independently, corrected AUC did not significantly affect the probability of response in the double-refractory, ( $p=0.0756$ ) bulky ( $p=0.108$ ), or 'other' groups ( $p=0.781$ ). There were too few subjects in the group 'other' to test different from the bulky or double-refractory groups. When the data were pooled and interaction terms were included to explain differences between disease states, all parameters lost their significance as the model was over-parameterized. In essence the data contained too much variation to discern the contribution of both drug and disease effect.

The clinical division's final assessment of ofatumumab efficacy was made with the FDA-adjudicated data in only the double-refractory population. Without data from the bulky or 'other' groups, there is no need for disease effects in the model, reducing over-parameterization.

**Table 4. Exposure-Response Models & Logistic Regression Parameters.**

	Disease State	Odds-Ratio, (95% CI)	Slope	P-Value	N
<b>Sponsor-Adjudicated Data</b>	Double Refractory	1.63 (0.95, 2.8)	0.490	0.0756	45
	Bulky, Fludarabine Refractory	1.36 (0.94, 2.0)	0.305	0.108	68
	Other	1.27 (0.24, 6.8)	0.238	0.781	14
<b>FDA-Adjudicated Data</b>	Double Refractory	4.33 (1.6, 12)	1.47	0.0049	42

***FDA-Adjudicated Data:***

The logistic model for the data adjudicated by the clinical division was developed in the same manner as for the sponsor-adjudicated data (Table 4). However, only drug exposure and body weight were considered as factors to correlate with response. The effect of AUC on the response was very significant. Body weight did not have a significant effect on the response rate ( $p=0.624$ ).

**4.3 Results**

**4.3.1 Is there evidence of exposure-response for effectiveness?**

Yes, the exposure-response relationship for effectiveness (complete & partial remission) is evidenced in studies 402 (dose ranging study) and 406 (pivotal efficacy trial) in Figure 1. It is clear in study 402 following 100-2000 mg (Figure 1, panel A) that with increasing ofatumumab exposure (AUC) there is increasing effectiveness. The relationship that effectiveness increases with exposure is not as steep in study 406 (Figure 1, panel B) for patients receiving 2000 mg.

There are differences between study 402 and 406 that should be noted. Data from 28 patients were used for 402 where as study 406 had AUC data for 127 subjects. Dosing was stopped at 4 weeks in study 402 and after 24 weeks in study 406. Study 402 had 3 dose arms (500, 1000, and 2000 mg) whereas study 406 only had one 2000 mg dose arm. Complete response was evaluated at weeks 27 for study 402 and up to 108 weeks in study 406.

#### **4.3.2 Does the exposure-response relationship for effectiveness support the proposed 2000-mg dose?**

Yes, the response rate increases with higher dose and exposure (see Figure 1 for exposure-response). Therefore, dosing the highest studied dose would yield the greatest therapeutic benefit. There were no critical safety concerns at the highest studied dose in the phase III trial (study 406), making the 2000 mg dose acceptable. Higher doses were not feasible to study.

#### **4.3.3 Does the disease state determine the observed response rate?**

Yes, the type of chronic lymphocyte leukemia determines the response rate to ofatumumab. Study 406 had 127 patients with available AUC values and with three different disease classifications (bulky, double refractory, or other). Logistic regression was performed to show the overall trend of each group (see Section 4.2.3 Models). The observed data are shown as quartiles to reduce the visual noise.

The bulky group showed the least response to ofatumumab. On the other hand, the double refractory and 'other' groups showed consistent and increasing effectiveness with higher exposures to ofatumumab. In the later two disease types (DR and other) higher exposure resulted in higher probability of response. This observation supports the 2000 mg dose for treatment of the DR and other forms of CLL.

**Figure 2** shows that each of these populations responded differently to ofatumumab. The bulky group showed the least response to the drug. On the other hand, the double refractory and 'other' groups showed consistent and increasing effectiveness with higher exposures to ofatumumab. In the later two disease types (DR and other) higher exposure resulted in higher probability of response. This observation supports the 2000 mg dose for treatment of the DR and other forms of CLL.

#### **4.3.4 Is the exposure-response analysis for the FDA-adjudicated data consistent with the analysis for the sponsor-adjuticated data (section 1.1.3)?**

Yes, the exposure-response relationship for the FDA-adjudicated data is similar to the that of the sponsor's data for the DR population in section 1.1.3.

Data was obtained from the clinical reviewer who individually reviewed each subject in the double refractory population of study 406. A logistic regression relating objective response to exposure (AUC at week 12) was performed in the same manner as for section 1.1.3 with the exception that the CLL disease factor was not included because FDA-adjuticated data for patients with 'bulky' or 'other' disease were not available.

Figure 3 shows a side-by-side comparison of the results for the analyses on the FDA and sponsor's adjudicated data. Both cases show a clear exposure-response relationship for the double refractory CLL population.

#### **4.3.5 Does anti-ofatumumab antibody titer affect the PK & PD of ofatumumab?**

The data are insufficient to determine the effects of immunogenicity. As per the clinical pharmacology reviewer's document, the assay did not detect immunogenicity in a sufficient population to determine the impact of anti-drug antibodies on ofatumumab PK or B-cell depletion:

“Serum samples from 154 patients with CLL treated with ARZERRA were tested for anti-ofatumumab antibodies during the 24-week treatment period. Results were negative in 46/139 patients after 8<sup>th</sup> infusion and 33/85 patients after 12<sup>th</sup> infusion. Results from the remaining patients were classified as inclusive due to interference with the immunogenicity assay by circulating concentrations of Ofatumumab.”

#### **4.3.6 Do the results of the sponsor's population PK analysis agree with the parameter values and conclusions presented in the label?**

The sponsor's population pharmacokinetic model is acceptable. The values in the label are consistent with the population model predictions. The sponsor also claims that no dosage adjustment is necessary based on body weight, age, gender, or renal impairment. No data was available to assess the effects of hepatic impairment.

A dosing regimen based on body weight was not necessary. Although, body weight was found to be an important descriptor of between-subject variation for pharmacokinetics, it did not explain intersubject variation for the clinical endpoint. The inclusion of bodyweight in the pharmacokinetics of ofatumumab decreased between subject variation from 27.6 to 24.0% for volume of distribution while it did not change the intersubject variation for clearance. However, a change from 60 kg to 120 kg body weight results in a doubling in clearance from 5 to 10 mL/hr. Despite, this change in exposure no change in response rate was observed for individuals with less than median body weight compared to those above median body weight. The lack of change in response rate with weight combined with the large variation in the data (sections 1.1.2 & 1.1.3) as indicated from the confidence intervals suggests that dosing by body weight will not improve the response weight.

The sponsor's labeling conclusions were consistent with the results of the population PK analysis. The population pharmacokinetic analysis indicates that age did not affect the pharmacokinetics of ofatumumab. There was no effect of gender on clearance and volume of distribution evidenced similar values in males compared to females (

Figure 4). No dose adjustment by gender is necessary. These findings are consistent with the sponsor's conclusions.

#### 5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\
LogOfat2.ssc	File used to plot and run logistic regression for study 402	\\cdsnas\pharmacometrics\Ofatumumab\er\efficacy
LogOfat3d.ssc	File used to plot and run logistic regression for study 406	\\cdsnas\pharmacometrics\Ofatumumab\er\efficacy

## **6 APPENDIX A: SPONSOR'S PHARMACOKINETIC/DYNAMIC REPORT SYNOPSIS**

**Title:** Ofatumumab Combined Study Population Pharmacokinetic/Pharmacodynamic Analysis

**Studies:**

Study Hx-CD20-001:

- 14 investigators in Denmark, Germany, Netherlands, Poland, United Kingdom, and United States
- Study period: 12 April 2004 – 8 November 2005

Study Hx-CD20-402:

- 12 investigators in Denmark, France, Netherlands, Poland, and United States
- Study period: 2 September 2004 – 5 April 2006

Study Hx-CD20-403 Part A:

- 17 investigators in Denmark, Poland, United Kingdom, and United States
- Study period: 28 February 2005 – 4 January 2006

Study Hx-CD20-403 Part B:

- 39 investigators in Denmark, France, Hungary, Poland, United Kingdom, and United States
- Study period: 8 August 2005 – ongoing (data available through Week 24)

Study Hx-CD20-406:

- 41 investigators in the Czech Republic, Denmark, France, Germany, Italy, Poland, Spain, Sweden, United Kingdom, and United States
- Study period: 13 June 2006 – ongoing (pharmacokinetic data through 9 April 2008)

### **Phase of development: III**

**Objectives:**

- To characterize the pharmacokinetics of ofatumumab in patients with chronic lymphocytic leukemia (CLL), including analysis of supportive data from patients with follicular lymphoma (FL) and rheumatoid arthritis (RA).
- To identify influential covariates on ofatumumab pharmacokinetics in patients with CLL, FL, and RA.
- To develop a pharmacokinetic/pharmacodynamic (PK/PD) model for the relationship between ofatumumab concentrations or pharmacokinetic parameter values and:
  - B-cell counts after ofatumumab administration

- clinical outcome in patients with CLL (limited to Study Hx-CD20-402) and/or FL in the ofatumumab monotherapy setting.

**Methodology:**

Data from four studies (Study Hx-CD20-001, Study Hx-CD20-402, Study Hx-CD20-403, and Study Hx-CD20-406) were used in this analysis.

**Number of subjects:**

Data from a total of 320 patients from 123 sites were used for this analysis. Thirty-eight patients were from Study Hx-CD20-001 (follicular lymphoma, FL), 33 from Study Hx-CD20-402 (chronic lymphocytic leukemia, CLL), 196 from Study Hx-CD20-403 (rheumatoid arthritis, RA), and 53 from Study Hx-CD20-406 (CLL).

**Diagnosis and main criteria for inclusion:**

- Study Hx-CD20-401 – Relapsed or refractory follicular lymphoma
- Study Hx-CD20-402 – Relapsed or refractory chronic lymphocytic leukemia
- Study Hx-CD20-403 – Rheumatoid arthritis with treatment failure on one or more disease modifying antirheumatic drugs
- Study Hx-CD20-406 – B-cell chronic lymphocytic leukemia who have failed fludarabine and alemtuzumab or have failed fludarabine and are not candidates for alemtuzumab due to bulky disease

**Treatment administration:**

- Study Hx-CD20-001 4 weekly doses of either 300, 500, 700 or 1000 mg
- Study Hx-CD20-402 4 weekly doses. The first dose was 100, 300 or 500 mg (groups A, B and C). The second to fourth dose was 500, 1000 or 2000 mg.
- Study Hx-CD20-403 2 doses, on days 0 and 14 of 0, 300, 700 or 1000 mg Only data from patients who received active treatment were included.
- Study Hx-CD20-406 8 weekly infusions followed by 4 monthly infusions. The first dose was 300 mg, subsequent doses were 2000 mg.

**Criteria for evaluation:**

All available ofatumumab serum concentration data that were within the lower and upper limits of quantification were used in the pharmacokinetic analysis. A total of thirty-five observations from ten patients were above the quantification limit after the last weekly infusion in Study Hx-CD20-406 and were not included. All available data from the flow cytometry were used in the pharmacokinetic/pharmacodynamic (PK/PD) analysis. All available clinical response and duration of response data (which for CLL was limited to Study Hx-CD20-402) were used in the clinical response analysis and the duration of response analysis. Response data were not available from Study Hx-CD20-406 at the time of the analysis.

**Statistical methods:** Nonlinear mixed effects modeling (NONMEM®) was used to describe the pharmacokinetics of ofatumumab. Logistic regression in R® (lrm function from the design package) was used for analysis of response data.

## Summary:

### Pharmacokinetics:

The population pharmacokinetics (PK) of ofatumumab were best described by a two-compartment model with a long half-life. This is typical for monoclonal antibodies. While any monoclonal antibody for which a specific target is present will exhibit some degree of target-mediated clearance, an important difference between ofatumumab and other monoclonal antibodies was the magnitude of the target-mediated clearance. The large mass of CD20+ B cells in these diseases (the oncology diseases in particular) make the target-mediated clearance large relative to other monoclonal antibodies. A previous description of a monoclonal antibody with significant target-mediated clearance included a saturable model [Gibiansky, 2007].

Variation in pharmacokinetics of ofatumumab with time was noted early in the development of ofatumumab but was not well quantified. This analysis models that time dependency explicitly as change in target-mediated clearance. This suggests that the changes in clearance are not truly time-dependent but occur as a result of a complex relationship between dosing and time. While target-mediated distribution [Mager, 2001] and clearance [Gibiansky, 2007] have been previously described, the data from the present studies suggested a different form for the model. In addition to the saturable model [Gibiansky, 2007], a simple linear model has been used to describe rituximab in RA [Ng, 2005]. Both the saturable model and linear models were examined in this analysis. It was found that the model explicitly including target-mediated clearance better described the data, and it was more consistent with the understanding of the biology.

In addition to the target-mediated pharmacokinetic effects, this analysis examined whether the target cells (CD20+ B cells) in the peripheral blood relate to the target-mediated pharmacokinetic changes. The total body CD20+ B-cell mass was not measured. Rather, an (unscaled) quantity that is intended to represent this mass was incorporated into the pharmacokinetic model. This hypothetical total body CD20+ B-cell mass (henceforth referred to as the pharmacokinetic-derived target mass) may be related to the peripheral blood CD20+ B cells by way of trafficking into and out of the lymph nodes and other sites.

The pharmacokinetic analysis found that the non-target-mediated clearance was 6.65 mL/hr (2.02 mL/kg/day), with a central volume of distribution of 3.05 L (39 mL/kg) for a patient with an average body mass of 79.2 kg. This body mass (79.2 kg) was used as the typical patient because it was the mean body mass in the four studies. The peripheral compartment rate constants were: 0.016 hr<sup>-1</sup> (Central to Peripheral, k<sub>13</sub>) and 0.0187 hr<sup>-1</sup> (Peripheral to Central, k<sub>31</sub>), respectively.

This yielded a non-target-mediated half-life on the order of 606 hours (25 days), consistent with other monoclonal antibodies, including 31 days for siplizumab [Gibiansky, 2007]. The target-mediated clearance depended on the target mass, with elimination of drug proportional to both drug concentration and target mass; therefore, there was no simple expression for target-mediated clearance. Relevant covariate relationships for the pharmacokinetic model included increases in clearance with increases in weight and increases in volume of distribution of the central compartment with increases in weight and height.

The target-mediated clearance depended on disease, with both the effect of drug on CD20+ B cells and the CD20+ B-cell effect on drug clearance being unique for each disease. In practice, the effect of B cells on drug (BOND) quantifies the magnitude of the target-mediated clearance, and the effect of drug on B cells (DONB) quantifies how rapidly and at what concentration that clearance declines. One important addition to the population pharmacokinetic model was that there appeared to be a subpopulation of patients (~15%) that had a much larger effect of B cells on drug and therefore a much larger target-mediated clearance. No biological explanation was available for this finding, and no covariates (including disease, age, weight, study, gender, and race) were found to be predictive.

The central volume of distribution was found to show an interindividual variance of 0.0575 (log normal, CV~6%). A value this small is typical for intravenous high molecular weight proteins with small volumes of distribution. Volume of distribution of the central compartment was also found to show a modest degree of interoccasion variability (variance = 0.0641, log normal, CV~7%).

Non-target-mediated clearance also demonstrated only a modest degree of interindividual variance (0.307, log normal, CV~31%), typical for such molecules.

#### **Pharmacodynamics:**

A total of three pharmacodynamic models were attempted, one for CD19+ B cells in FL and RA, one for CD5+CD19+ B cells in CLL, and one for total lymphocytes. CD19 staining is used as a surrogate marker for CD20+ cells. The use of CD20 as a marker is precluded by the interference of ofatumumab with the flow cytometry assay. CD19 and CD20 have been shown to have similar expression profiles on B-cell subpopulations [Breedveld, 2007]. The primary goal of this model was to describe the time course of return of CD19+ B cells and total lymphocytes after drug administration was stopped.

A relationship was found between estimated pharmacokinetic-derived target mass and peripheral blood CD19+ B cells. The structural model for this PK/PD relationship was different for the different diseases. FL and RA were found to be described by a model with a lag time between the pharmacokinetic-derived target mass and the peripheral blood CD19+ cells. This lag was modeled as a sequential series of compartments. The relationship between pharmacokinetic-derived target mass and peripheral blood CD5+CD19+ B cells in CLL did not seem to have a lag time. However, the between-subject variability in the peripheral blood CD5+CD19+ model for CLL was very large (coefficient of variance between approximately 193% and 446%<sup>1</sup>). This large between-subject variability in the parameters is likely outside the range where the first order conditional method provides a reasonable approximation to the distribution. This violation of assumptions may have resulted in the algorithm having difficulty appropriately separating between-subject from within-subject variability and may have resulted in significant bias in the model.

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<sup>1</sup> The calculation of CV% is approximate as the model specified an exponential interindividual error model, and at large values, this model deviates from a constant coefficient of variation model (CCV), although the two models (CCV and exponential) are treated identically in NONMEM.

In contrast to the model for CD19+ B cells, the model for total lymphocytes did not suggest a relationship between the pharmacokinetic-derived target mass and peripheral total lymphocytes. This relationship was explored in a very limited way due to numerical difficulties with the solution.

**Outcomes:**

Exploratory analysis was performed on the relationship between the modeled ofatumumab pharmacokinetics and clinical response in the oncology indications based on available data from Study Hx-CD20-001 and Study Hx-CD20-402. This analysis suggested an exposure-response relationship (AUC, C<sub>min</sub>, and C<sub>max</sub>) for CLL (Study Hx-CD20-402 only) but not for FL. At least two explanations are available for this relationship. First, a higher exposure may cause a greater depletion of target cells, and therefore a longer period before disease is clinically detectable. Second, a greater response, for reasons unrelated to pharmacokinetics (e.g., CD20+ expression), may lead to decreased target-mediated clearance and therefore higher exposure. Therefore, it cannot be determined whether the pharmacokinetic exposure had a causal relationship with response or whether the magnitude of the change in B-cell mass affected the pharmacokinetics.

Exploratory analysis was also performed between drug exposure and survival endpoints. Similar to the relationship between exposure and measures of clinical response, a relationship was seen for CLL patients in Study Hx-CD20-402<sup>2</sup> but not for FL. A similar caveat about interpreting the presence of a correlation as being causation applies.

**Conclusions:**

- Ofatumumab follows two-compartment pharmacokinetics with a long half-life consistent with other IgG1 monoclonal antibodies and a typical volume of distribution equal to plasma volume.
- The non-target-mediated clearance was 6.65 mL/hr (2.02 mL/kg/day) for a patient with an average weight of 79.2 kg.
- The volume of distribution of the central compartment was 3.05 L (39 mL/kg) for a patient with an average weight of 79.2 kg.
- Height and weight were predictors of volume of distribution of the central compartment and weight was a predictor of non-target-mediated ofatumumab clearance.
- CD19+ B cells in the peripheral blood in FL and RA were related to the estimates of the pharmacokinetic-derived target cell mass, with a lag time describing the return of cells.
- For CLL in Study Hx-CD20-402, drug exposure was predictive of clinical response at weeks 19 and 27. A similar pattern was seen for other survival endpoint measures.

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<sup>2</sup> Clinical response data were not available for Study Hx-CD20-406 at the time of the analysis.

(Source: Sponsor's Population PK and PK/PD Report  
\\cbsap58\M\CTD Submissions\STN125326\0000\m5\53-clin-stud-rep\535-rep-effic-  
safety-stud\cl\5353-rep-analys-data-more-one-stud\rm2008-00710.)

## 7 APPENDIX B: REFERENCES

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## CLINICAL PHARMACOLOGY GENOMICS GROUP REVIEW

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<b>BLA Number</b>	125326
<b>Submission Type; Code</b>	Priority
<b>Applicant Name</b>	GlaxoSmithKline
<b>Submission Date</b>	01/30/09
<b>Brand Name</b>	Arzzeria
<b>Generic Name</b>	Ofatumumab
<b>Proposed Indication</b>	Double refractory or bulky fludarabine refractory CLL
<b>Dosing</b>	300 mg x 1 > 2,000 mg IV QW x 7 > followed 4 ~ weeks later by 2,000 mg Q4W x 4
<b>Genomics Reviewer</b>	Mike Pacanowski, Pharm.D., M.P.H.
<b>Team Leader</b>	Issam Zineh, Pharm.D., M.P.H.

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## 1. BACKGROUND

Ofatumumab is a human anti-CD20 antibody (IgG1/k). The applicant is seeking approval of ofatumumab for the treatment of chronic lymphocytic leukemia (CLL) in subjects who have received prior therapy (bulky fludarabine refractory [BFR] or fludarabine/ alemtuzumab refractory [DR]).

CLL follows a heterogeneous disease course. Various staging systems and biomarkers have been developed to guide decision-making with regard to initiating therapy. Numerous biomarkers have demonstrated prognostic value in CLL, namely chromosomal aberrations detected by fluorescence in situ hybridization (FISH),  $\beta$ 2-microglobulin, thymidine kinase, circulating CD20 cells, and CD38+. (Krober 12149225, Dohner 11136261) The utility of these biomarkers in treatment decisions and prognosis has yet to be sufficiently demonstrated to support routine clinical use (Binet 16223776, NCI Guidelines 2009), although testing for chromosomal abnormalities is regarded as "desirable" and gaining broader acceptance in the clinical workup of CLL (Hallek 18216293) and as a stratification factor in clinical trials (e.g., UK CAM-PRED, German CLL20; Zenz 18452094).

The applicant evaluated the prognostic value of several biomarkers in the clinical development of ofatumumab, and those data were submitted in the current BLA. No labeling claims have been proposed based on these biomarkers, and it is noted that the labels for rituximab and alemtuzumab also do not contain such biomarker information.

*The purpose of this review is to evaluate whether chromosomal abnormalities and other CLL biomarkers predict response in the setting of ofatumumab treatment for refractory CLL.*

## 2. BLA CONTENT RELATED TO GENOMICS

The sponsor conducted 2 clinical studies to support the efficacy of ofatumumab in CLL: Hx-CD20-406 (DR/BFR CLL; n=154) and Hx-CD20-402 (relapsed/refractory CLL; n=33). An additional study in previously untreated CLL, Hx-CD20-407, is ongoing. As prespecified in the protocol for each clinical study, subjects were evaluated for the following prognostic and pharmacogenetic biomarkers:

- Prognostic factors: FISH-detected chromosomal biomarkers (13q deletion, 11q deletion, 12q trisomy, 17p deletion, 6q deletion; p53 deletion), immunoglobulin heavy chain variable region (IgVH) mutational status (unmutated/mutated), CD38+ (defined as >20% among CD5+CD19+ cells compared to isotype controls)
- Other markers of relevance for the efficacy of ofatumumab: Fc $\gamma$  receptor polymorphism (FCGR3A V158F, FCGR2A H131R),  $\beta$ 2-microglobulin, thymidine kinase, circulating CD20, antigen density

The lattermost 4 were added as protocol amendments, while C  $\rightarrow$  mutations were removed, partly for reasons related to the assay.

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Nonclinical studies relevant to pharmacogenomics included an evaluation of antibody binding in primates (GMB3001-002), reflecting affinity differences due to genetic variation in the Fc $\gamma$  receptors.

### 3. Key Questions and Summary of Genomics Findings

#### 3.1. Do chromosomal abnormalities and other CLL biomarkers identify non-responders to ofatumumab?

*Yes, the presence of 17p del and elevated  $\beta$ 2-microglobulin were consistently associated with lower response rates and survival in CLL subjects treated with ofatumumab. These findings were not significant in the DR subgroup likely due to the reduction in sample size. However, the magnitude of the point estimate in the DR subgroup was similar to that of the overall population. Variability in response assessment and the use of objective response as a surrogate limit interpretability of these findings.*

Chromosomal abnormalities were tested in almost all patients enrolled in study 406. IgVH mutational status was evaluated 53%. Subjects were categorized by the sponsor using a hierarchical model as follows: 17p del positive; 11q del positive but 17p del negative; 12q trisomy positive but 17p del negative and 11q del negative; no abnormalities; and 13q del positive alone. This parameterization is consistent with previous reports in the literature (Dohner 11136261) demonstrating that 17p del is associated with a poor prognosis and 13q del is associated with a favorable prognosis.

Neither modified Rai nor Binet stage were predictive of response or survival following ofatumumab treatment (not shown). Responders had a more favorable overall survival profile (not shown). In the DR population, objective response (OR) rates varied according to the presence of chromosomal abnormalities in a manner that is consistent with published studies, as shown in the following table. Among DR patients, all responses were PR. While not significant in the DR population alone, chromosomal status was a strong predictor of response in the overall population (n=148) – the odds ratio for non-response was 3.05 (95% confidence interval [CI] 1.07-8.70, p=0.008) for chromosome 17p del. It is notable that the magnitude of the point estimate was similar or greater in the DR subgroup and the impact of chromosomal abnormalities on response rates was not heterogeneous across the DR and BFR subgroups. No differences in PFS as a function of chromosomal abnormalities were noted in the DR population. OS tended to be shorter in subjects with 17p del, although this was not statistically significant. Strong trends toward poorer outcomes among subjects with 17p del was noted in the overall population – the hazard ratio was 1.81 (95%CI 0.99-3.31, p=0.056) for PFS and 1.88 (95%CI 0.88-4.00, p=0.1) for OS.

17p-	Double Refractory				N resp / N tot	OR – FDA		PFS – IRC Hazard Ratio (95%CI)	OS – IRC Hazard Ratio (95%CI)
	11q-	12q+	13q-	6q-		% (95%CI)	Odds Ratio (95%CI)		
-	-	-	-	-	5 / 7	71 (31-100)	1.00 (reference)	1.00 (reference)	1.00 (reference)
+	+/-	+/-	+/-	+/-	5 / 15	33 (6-61)	5.00 (0.70-35.5)	0.96 (0.29-3.16)	4.01 (0.86-18.6)
-	+	+/-	+/-	+/-	10 / 24	42 (20-63)	3.50 (0.56-21.8)	0.54 (0.19-1.52)	1.55 (0.34-7.12)
-	-	+	+/-	+/-	0 / 3	0 (0-17)	...	1.33 (0.41-4.34)	2.65 (0.37-18.9)
-	-	-	+	-	2 / 5	40 (0-93)	3.75 (0.33-42.5)	0.85 (0.29-2.55)	3.23 (0.44-23.8)
Total					22 / 54	41 (26-55)			

Data regarding IgVH mutation status were incomplete (66% missing) and thus the analyses are inconclusive. Elevated CD38+ and  $\beta$ 2-microglobulin were associated with responses as shown in the following table. Only  $\beta$ 2-microglobulin showed an effect on both OS and PFS. Elevated thymidine kinase was associated with survival, but an effect of thymidine kinase was not evident for any of the other outcomes. Similar findings for OR were apparent in the BFR subgroup and the overall population (see Appendix I).

Double Refractory	OR – FDA Odds Ratio (95%CI)	PFS – IRC Hazard Ratio (95%CI)	OS – IRC Hazard Ratio (95%CI)
IgVH, vs. no mut	0.58 (0.08-4.56)	0.74 (0.19-2.89)	0.39 (0.05-2.77)
CD38+	1.56 (1.03-2.37)	0.95 (0.73-1.25)	1.06 (0.53-2.10)
↳CD38+ > 20%†	5.00 (1.58-15.8)	0.85 (0.41-1.79)	1.05 (0.48-2.26)
cCD20	0.69 (0.11-4.21)	0.99 (0.34-2.86)	3.06 (0.78-12.0)
↳cCD20 > 35.2†	1.56 (0.53-4.56)	1.22 (0.64-2.33)	2.07 (0.94-4.52)
$\beta$ 2-MG	5.16 (1.07-24.8)	2.20 (0.98-4.94)	5.46 (1.93-15.4)
↳ $\beta$ 2-MG > 6960†	1.99 (0.66-5.96)	1.36 (0.70-2.61)	2.75 (1.27-5.96)
TK	1.27 (0.63-2.55)	1.25 (0.81-1.92)	1.85 (1.13-3.02)
↳TK > 47.3†	1.56 (0.52-4.69)	1.39 (0.72-2.67)	2.19 (1.02-4.72)
CD38, cCD20, $\beta$ 2-microglobulin, and TK log-transformed prior to analysis to normalize			
*based on Wald test for global association			
†dichotomized based on median			

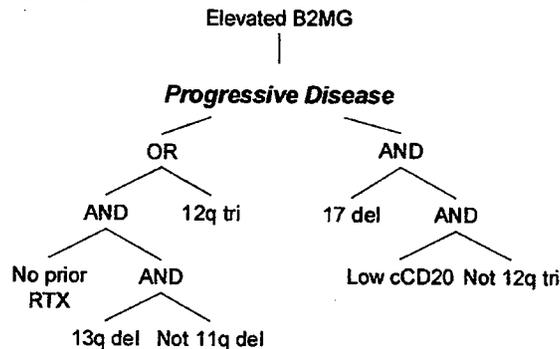
Results for the overall population and DR subgroup using IRC-adjudicated responses are detailed in Appendix I. The point estimates were comparable when using the IRC-adjudicated data.

### Progressive Disease

A descriptive review of all 11 subjects with PD (based on the IRC adjudication; 10 of which had chromosomal biomarker data) was performed to identify trends. All of the subjects with PD progressed in the first 2 months, all had received >2 CLL treatments (range: 3-8), 8 were Rai stage III-IV or Binet stage C, and 8 were enrolled based on BFR. The only chromosomal aberration that distinguished PD subjects was 12q trisomy in BFR, with a 38% vs. 4.6% progression rate between 12q trisomy positive and negative subjects, respectively.  $\beta$ 2-microglobulin was elevated with respect to the overall median in 9 of the subjects with PD (median 9853, IQR 7180-9650).

To identify the best biomarker profile to capture subjects at risk for PD in the overall population, logic regression using logistic model was performed. Logic regression is a method of identifying significant combinations among a set of predictors using Boolean combinations and an adaptive algorithm that selects a combination that minimizes the residual sum of squares or the

deviance.(Koooperberg 11793751) All of the biomarkers detailed above were eligible for entry, in addition to prior rituximab therapy. Model selection was optimized using cross validation. The best fitting model had 8 leaves across 3 trees. As shown in the figure below, PD was predicted by  $\beta$ 2-microglobulin concentration; among subjects who had not received rituximab, 13q alone was predictive if the subject was not also 11q del; and 17 del was predictive in subjects with low cCD20 without 12q trisomy. Similar modeling was performed to allow entry of age, sex, ECOG status, DR vs. BFR subgroup, Rai or Binet stage; none of the aforementioned variables entered the model save for BFR, since all almost all PD patients were BFR. Thus, a core set of predictors related to the likelihood of response/non-response to ofatumumab include prior experience with rituximab,  $\beta$ 2-microglobulin concentrations, cCD20 levels, and chromosomal status for 13q, 12q, and 17p.



### 3.2. What prior evidence supports the use of chromosomal, cytometric, or protein biomarkers in the setting of anti-CD20 therapy for CLL?

IgVH mutations have been the most widely studied genomic biomarker and are considered a reference standard for prognostic biomarker performance (NCI Guidelines 2009), but the technically intensive nature of the assay prevents routine use. FISH-detected chromosomal abnormalities (13q deletion, 11q deletion, 12q trisomy, 17p deletion, 6q deletion, and p53 deletion) and CD38+ have repeatedly demonstrated prognostic value in CLL (disease progression and survival), as have other serum biomarkers such  $\beta$ 2-microglobulin and thymidine kinase (Hallek 18519404).

The biological role for many of these markers is not fully understood. Subjects with unmutated IgVH have the potential to exhibit clonal evolution due to karyotypic instability, which is more likely to result in chromosomal abnormalities. Thus these biomarkers are often correlated.(Kharfan-Dabaja 18618518) Deletion of 17p and 11q may affect regulation of key tumor suppressor genes, TP53 and ATM, respectively.

IgVH mutations have been shown to increase apoptotic responses to rituximab (Tinhofer 16956841) and correlated with response to anti-CD20 therapy in several studies.(Tinhofer 16956841, Byrd 16344317, Kay 17008537, Keating 15767648, Lin abstract Blood 2007). The clinical studies that have evaluated the prognostic value of chromosomal abnormalities in the setting of rituximab therapy are summarized in the table below. Most studies included subjects with untreated CLL. In these studies, 17p del and 11q del were consistently associated with poorer prognosis and lower response rates to anti-CD20 monoclonal antibody therapy relative to

subjects without chromosomal abnormalities or subjects with the 13q del, which has been associated with a favorable prognosis.

Reference	Subjects	Regimen	Endpoint	Biomarker Association
Byrd 2006 16344317	Untreated, symptomatic CLL (n=88)	Rituximab concurrent or sequential with fludarabine	OR, PFS, OS	17p- (n=3), 0 CR 11q- (n=15) ↓ PFS
Kay 2007 17008537	Untreated, progressive CLL (n=65)	Rituximab + pentostatin + cyclophosphamide	OR, PFS	17p- (n=3) associated with PD, otherwise no biomarker effects noted
Woyach 2008 19225537	Relapsed CLL/SLL [alemtuzumab naïve] (n=34)	Rituximab + etanercept	OR	17p- (n=8), 8 SD 11q- (n=5), 1 PR, 3 SD, 1 PD 12q+ (n=4), 2 PR/ 1 SD
Tam 2009 19414856	Untreated high-risk (17p-) CLL (n=49 on rituximab regimens)	FCR-like, CFAR, rituximab monotherapy, R-CHOP, R-CVP, etc.	OR	17p- (n=49) 15 CR, 5 nPR, 15 PR
Tam 2008 18324964	Untreated CLL (n=59)	Rituximab + GM-CSF	OR	12q+ (n=14), 13 CR/PR 11q- (n=4), 2 CR/PR 17p-/13q-/normal (n=41), 30 CR 17p- (n=2), 1 CR/PR
Tam 2008 18411418	Untreated CLL (n=300)	FCR	OR, OS, FFS, TTP	17p- (n=8), ↓ CR, OS
Tsimberidou 2009 19117034	Untreated high risk (11q-) CLL (n=39)	FCR-like, CFAR, rituximab monotherapy, R-CHOP, R-CVP, etc.	OR	11q-, 38 OR
Bowen 2007 18067017	CLL treated with steroids and rituximab (n=37)	High-dose methylprednisolone + rituximab	OR	13q- (n=6), 4 CR/PR 12q+ (n=2), 2 CR/PR 11q (n=6), 4 CR/PR 17p- (n=9), 5 CR/PR
Zent 2008 18759253	Untreated high-risk (17p-, 11q-, or IgVH unmutated w/ CD38+ and/ or ZAP70+) CLL (n=30)	Alemtuzumab + rituximab	OR	11 CR, 10 nPR, 6 PR

Source: Genomics Reviewer

### 3.3. What is the impact of Fcγ receptor gene polymorphisms on ofatumumab treatment response in CLL?

*Primates with the V158 allele of FCGR3A demonstrate higher ofatumumab affinity. Despite the functional consequences of FCGR3A V158F and FCGR2A H131R, ofatumumab treatment response/ outcomes do not appear to vary significantly across these genotype groups, which is consistent with the pharmacogenetic observations for rituximab in CLL. The findings of this study are inconclusive due to incomplete data for the study population.*

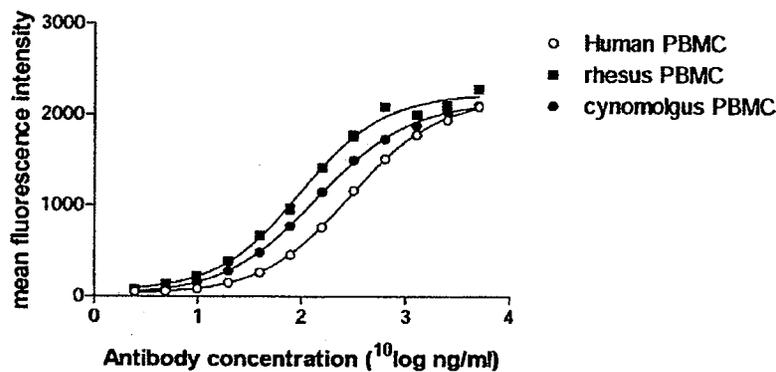
*FCGR3A and FCGR2A encode Fcγ receptors IIIa and IIa, respectively, and are involved in the clearance of antibody-antigen complexes from circulation. These receptors are expressed on macrophages, natural killer cells, dendritic cells, and mast cells. FCG2RA and FCG3RA are polymorphic in humans. The most commonly studied polymorphism in FCGR3A is V158F and in FCGR2A is H131R. The F158 and R131 alleles have lower affinity for human IgG (Shields 11986321, 11096108) and reduced ADCC (Weng 12975461). Both polymorphisms have been associated with poorer rituximab treatment response/ outcomes in subjects with follicular and diffuse large B-cell lymphomas (Weng 12975461, Cartron 11806974, Paiva 18474295), but other studies have not supported this observation (Carlotti 17650444, Mitrovic 17606457). The predictive nature of these alleles have not been substantiated in leukemias.(Farag 14563637, Lin 15217834)*

The sponsor evaluated cross-reactivity between primates and humans in study gmb3001-002 (*Examination of non-human primate cross-reactivity of HuMax-CD20*). The objective of the study was to demonstrate binding of ofatumumab in human lymphoid tissue (tonsil, PBMCs) and cross-reactivity in lymphoid tissue and PBMCs from rhesus and cynomolgus monkeys. IHC and flow cytometry was performed to evaluate binding and EC50. From a pharmacogenomic standpoint, primates generally carry the V158 form of the receptor, thus differences in binding characteristics across species may be reflective of the polymorphic form in humans.

Sequencing of cynomolgus and human CD20 revealed that the human had an alanine at position 158, whereas the monkey had the high-affinity valine. It is unclear why alanine was identified at this locus in the sponsor's sequencing, as valine or phenylalanine are the two alleles found at this locus in humans.

	145	150	155	160	165	170	175	180	
Human	KIS	HFLKM	ESLNF	IRAHT	PYINT	YNCEP	ANPSE	KNSPS	TQCY
Cyno	KIS	HFLKM	ESLNF	IRVHT	PYINT	YNCEP	ANPSE	KNSPS	TQCY

The sponsor reported that the EC<sub>50</sub> for ofatumumab was highest in humans (287 vs. 97 in rhesus vs. 139 in cynomolgus). The results of the flow cytometry study are shown in the following figure.



The reduced affinity associated with the F158 allele in humans has been attributed to diminished ADCC (Weng 12975461). Thus, to the extent that ofatumumab exerts its efficacy via ADCC in CLL, variable responses to treatment might be expected across genotype groups. However, ofatumumab is believed to be active in CLL due to potent complement dependent cytotoxicity (CDC). No effect of *FCGR2/3A* polymorphisms on treatment outcome in CLL has been described for rituximab (Farg 14563637) or alemtuzumab (Lin 15217834).

Genotyping for *FCGR2/3A* polymorphisms were evaluated in 52%-67% of subjects enrolled in Study 0406. Genotypes were obtained using allelic discrimination (TaqMan) with standard operating procedures. The genotype distributions are shown in the following table (each in Hardy-Weinberg equilibrium).

Biomarker	Status	DR (n=59)	BFR (n=79)
FCGR2A	V/V	5	12
	V/F	11	15
	F/F	3	6
	missing	40	46
FCGR3A	H/H	8	10

H/R	14	23
R/R	6	9
missing	31	37

*FCGR2A* and *FCGR3A* genotype was not significantly associated with the clinical outcome of ofatumumab treatment in terms of objective response, PFS or OS in the DR subgroup, as shown in the following table. Trends were evident for *FCG3RA*, although data were not available for a sizable proportion of the population which could limit the power. Thus, the analysis is indeterminate and should be considered exploratory.

Double Refractory		OR – FDA	PFS – IRC	OS – IRC
		Odds Ratio (95%CI)	Hazard Ratio (95%CI)	Hazard Ratio (95%CI)
FCGR2A, vs. H/H	H/R	0.82 (0.26-2.59)	1.01 (0.52-1.97)	3.03 (0.61-15.0)
	R/R	1.71 (0.48-6.16)	1.06 (0.50-2.23)	1.67 (0.35-7.85)
FCG3RA, vs. V/V	V/F	0.69 (0.15-3.19)	1.52 (0.59-3.89)	0.98 (0.53-1.80)
	F/F	1.72 (0.35-8.51)	2.23 (0.84-5.91)	...

#### 4. COMMENTS

Chromosome 17p del and serum  $\beta$ 2-microglobulin are associated with lower (but not absent) response rates and overall survival in subjects with refractory CLL treated with ofatumumab. These findings are consistent with the literature, although the marginal significance due to the small DR sample size, use of objective response as a surrogate, and the variability in response assessment limit interpretation of these findings. Any additional studies conducted by the sponsor in the setting of CLL should include analysis of chromosomal aberrations.

Ofatumumab affinity for its target may vary according to *FCGR3A* genotype. Genotype determination for *FCGR2A* and *FCGR3A* was incomplete and the analysis is inconclusive.

#### 5. RECOMMENDATIONS

No action indicated pending additional clinical trial data.

## 6. INDIVIDUAL STUDY REVIEW

### Study 0406

Study Hx-CD20-406 was an open-label single arm study. The primary objective was to evaluate the efficacy of ofatumumab (response rate – i.e. CR+nPR+PR), and secondarily the safety, immunogenicity, and pharmacokinetic profile of ofatumumab. CLL subjects enrolled in the study either had received 2 cycles of fludarabine and 12 doses of alemtuzumab (DR; n=59) or 2 cycles of fludarabine but had bulky disease and were not eligible for alemtuzumab (BFR; n=79). Subjects were given ofatumumab 300 mg × 1, followed by 2000 mg QW × 7, then 2000 mg Q4W × 4. Rituximab was used by 57% of subjects prior to entry. Outcomes were as follows: primary – response rate (CR, nPR, PR vs. PD, SD); secondary – duration of response, PFS, time to next CLL treatment, and OS. Subjects were followed for 24 months. The overall response rate was approximately 50%. The main findings of the study are shown in the following table:

Efficacy Endpoint	Double Refractory N=59	Bulky Fludarabine Refractory N=79	Combined Double Refractory + Bulky Fludarabine Refractory N=138
<b>Primary Endpoint</b>			
RR, % (99% CI)	58 (40, 74)	47 (32, 62)	51 (40, 63)
<b>Secondary Endpoints</b>			
	<b>Median, months</b>		
Duration of Response	7.1	5.6	5.6
Progression Free Survival	5.7	5.9	5.7
Time to Next CLL Treatment	9.0	7.9	8.2
Overall Survival	13.7	15.4	15.4

Data Source: ISE Table 103.1.1, ISE Table 104.1.1, ISE Table 104.3.1.1, ISE Table 104.5.1, ISE Table 104.6.1  
RR = response rate by Week 24

Source: Hx-CD20-406 report body, table 3

Among the DR subjects, 2% and 31% had PD and SD, respectively, while 8% and 41% of BFR subjects had PD and SD, respectively. The overall response rate (CR + nPR + PR) was 58% for DR, and 47% for BFR. Three “non-evaluable” DR subjects had PD and withdrew.

Following FDA review, several subjects were reclassified from the IRC adjudicated outcome as nonresponders or not evaluable as follows. Both analyses are presented.

### *Biomarker ascertainment*

Biomarker ascertainment and categorical distribution (or mean values) for DR and BFR subjects in study 0406 are shown in the following table. Chromosomal abnormalities were common except for the 6q del. Antigen density (CD19, CD55, CD59, and CD20) was measured in only 13 DR and 10 BFR subjects and were not reviewed.

Biomarker	Status	DR (n=59)	BFR (n=79)	All (n=154)
IgVH	- / +	5 / 15	7 / 30	14 / 51
	missing	39	42	73
13q-	- / +	31 / 26	39 / 39	80 / 71
	missing	2	1	3
11q-	- / +	32 / 25	52 / 26	55 / 96
	missing	2	1	3
12q+	- / +	49 / 8	65 / 13	124 / 27

	missing	2	1	3
17p-	- / +	40 / 17	62 / 14	115 / 33
	missing	2	3	6
6q-	- / +	56 / 1	73 / 5	144 / 6
	missing	2	1	4
CD38+	Mean, SD	39, 35 /	27, 25	32, 20
	missing	0	2	2
cCD20	Mean, SD	37, 12	36, 15	37, 35
	missing	5	11	22
β2 microglobulin	Mean, SD	7069, 2939	7843, 3449	7457, 6950
	missing	1	1	2
Thymidine kinase	Mean, SD	54, 45	61, 51	61, 47
	missing	1	4	5

Source: abstracted from Hx-CD20-406 report body, table 4.12.1

### ***Biomarker status and baseline characteristics***

17p del tended to be more common in DR subjects than BFR subjects, although none of the biomarkers differed significantly in frequency between DR and BFR subjects. Comparing subjects with each chromosomal aberration alone with all other subjects, no statistically significant differences were noted for sex, race, ECOG performance status, Rai or Binet stage, number of prior therapies. Among DR subjects, individuals with 17p del and 11q del were less likely to have received prior rituximab.

### ***Chromosomal, cytometric and protein biomarkers as predictors of ofatumumab efficacy***

#### **Objective Response (OR)**

The sponsor conducted *exploratory* analyses for the CLL biomarkers using logistic or Cox proportional hazards regression. OR rates following ofatumumab treatment are depicted in the following table. BFR tended to be associated with lower OR rates. Based on IRC-reported OR rates, in DR subjects, 12q trisomy was associated with the lowest response rate (33%); 17p del and 11q del subjects also had lower response rates compared to subjects without abnormalities, while 13q del was favorable. These findings are consistent with previous reports (Dohner 11136261). Similar findings were observed in the overall population. In BFR subjects, response rates in 11q del and 12q trisomy subjects were similar or better than subjects with no abnormalities. The 6q del was rare.

OR		DR - Investigator					DR - FDA		DR - IRC		BFR - IRC		All - IRC	
17p del	11q del	12q tri	13q del	6q del	OR/ Total (N)	OR % (95%CI)								
-	-	-	-	-	5/8	63 (24-91)	5/7	71 (31-100)	6/8	75 (39-100)	8/19	42 (17-67)	16/30	53 (34-73)
+	+/-	+/-	+/-	+/-	6/14	43 (18-71)	5/15	33 (6-61)	7/17	41 (15-67)	2/14	14 (0-36)	9/33	27 (11-44)
-	+	+/-	+/-	+/-	10/23	43 (23-66)	10/24	42 (20-63)	15/24	63 (41-84)	14/22	64 (41-86)	32/50	64 (50-78)
-	-	+	+/-	+/-	0/3	0 (0-71)	0/3	0 (0-17)	1/3	33 (0-100)	3/8	38 (0-77)	7/16	44 (16-71)
-	-	-	+	-	3/5	60 (50-95)	2/5	40 (0-93)	4/5	80 (35-100)	9/13	69 (40-98)	14/19	74 (51-96)
Tot*					24/53	45 (31-60)	22/54	41 (26-55)	33/57	58 (44-72)	36/76	47 (36-59)	78/148	53 (44-61)

\*for subjects with FISH biomarker data

Source: abstracted from Hx-CD20-406 report body tables 10.14.1-5; Genomics reviewer

All responses were PR except one sponsor-reported CR in a BFR subject with 13q del and one nPR in subject who was neither DR or BFR.

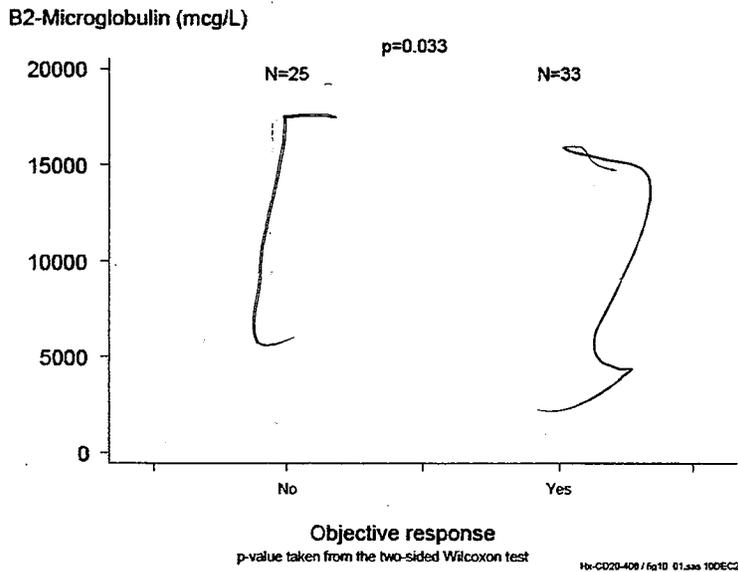
Odds ratios for non-response were estimated using logistic regression as shown in the following table. IgVH mutational status was missing for the majority of patients, thus the findings for IgVH are inconclusive. In the overall population, subjects with the 17p del had a 3-fold higher risk for not responding.  $\beta$ 2-microglobulin was also significantly associated with responsiveness to ofatumumab treatment. Similar trends were noted when analyzing DR and BFR subjects separately but the associations were not statistically significant. The Breslow-Day test for heterogeneity of odds ratios across the DR, BFR, and other subgroups was not significant for any of the chromosomal markers. The findings were similar for FDA and IRC-adjudicated responses. No significant biomarker effects were noted when using investigator-reported responses. It is notable that the clinical staging systems did not appear to predict the likelihood of achieving an OR.

Objective Response		DR - FDA				DR - IRC				All - IRC			
		Odds Ratio	95% Confidence Interval	P*	Odds Ratio	95% Confidence Interval	P*	Odds Ratio	95% Confidence Interval	P*			
<b>Biomarkers</b>													
Chromosomal Aberrations – hierarchical model, vs. none	17p-	5.000	0.704	35.495	0.6180	4.286	0.661	27.785	0.3328	3.048	1.067	8.704	0.0076
	11q-	3.500	0.562	21.811		1.800	0.297	10.901		0.643	0.256	1.614	
	12q+	...	...	...		6.000	0.335	107.420		1.469	0.434	4.981	
	13q-	3.750	0.331	42.467		0.750	0.050	11.311		0.408	0.117	1.422	
IgVH, vs. no mut		0.583	0.075	4.562	0.6075	0.545	0.065	4.561	0.5758	1.260	0.369	4.299	0.7121
CD38+		1.559	1.027	2.365	0.0369	1.519	0.996	2.318	0.0525	1.162	0.919	1.470	0.21
CD38+†	>20%	5.000	1.583	15.796	0.0061	5.714	1.731	18.868	0.0042	1.690	0.889	3.211	0.1094
cCD20		0.694	0.114	4.211	0.6915	1.344	0.245	7.357	0.7335	1.154	0.461	2.885	0.76
cCD20†	>35.2	1.560	0.534	4.557	0.4162	1.818	0.640	5.165	0.2617	1.275	0.673	2.417	0.4566
$\beta$ 2-MG		5.158	1.074	24.779	0.0405	5.576	1.215	25.583	0.0270	5.677	2.310	13.950	0.0002
$\beta$ 2-MG†	>6960	1.992	0.665	5.964	0.2180	2.661	0.915	7.739	0.0724	3.233	1.671	6.252	0.0005
TK		1.270	0.632	2.552	0.5018	0.982	0.506	1.907	0.9581	1.278	0.842	1.940	0.25
TK†	>47.3	1.562	0.521	4.685	0.4257	0.952	0.333	2.727	0.9276	1.433	0.759	2.704	0.2672
<b>Clinical Staging</b>													
Modified Rai, vs. I	II	1.371	0.288	6.535	0.5700	1.531	0.311	7.533	0.9848	2.088	0.655	6.652	0.41
	III	3.600	0.491	26.398		1.167	0.200	6.805		3.500	1.006	12.179	
	IV	2.100	0.482	9.140		1.458	0.329	6.456		2.333	0.807	6.749	
Binet, vs. A	B	0.917	0.110	7.666	0.2914	0.643	0.106	3.913	0.8816	0.993	0.270	3.659	0.85
	C	2.222	0.269	18.363		0.765	0.132	4.426		1.200	0.342	4.217	
CD38, cCD20, $\beta$ 2-microglobulin, and TK log-transformed prior to analysis to normalize													
*based on Wald test for global association													
†based on median													

Source: Genomics reviewer; FAS

$\beta$ 2-microglobulin was one of the strongest predictors of response in the overall population, but was marginally associated with responses in the DR subgroups (both investigator-, FDA- and IRC-adjudicated). The distribution of individual values are in responders vs. nonresponders among DR subjects is shown in the following figure. Higher  $\beta$ 2-microglobulin concentrations were associated with poorer responses, although substantial overlap exists between the two groups.

Figure 10.01.03.1 Objective response and B2-microglobulin at baseline, DR, FAS



Source: Hx-CD20-406 report body figure 10.1.3.4

Progression-Free and Overall Survival

PFS followed similar trends as OR, as shown in the following table (sponsor’s analysis based on IRC-adjudicated progression). Subjects with no abnormalities had a response duration of 10.1 months (2.8-10.1) and 6.7 months (2.0-7.7) for DR and BFR, respectively. Subjects with no chromosomal abnormalities had the most favorable outcomes, while subjects with 17p del, 11q del, and 12q trisomy had lower response rates. Whereas response rates were relatively higher in subjects with the 13q del, PFS did not differ (3.7 months and 5.6 months for DR and BFR, respectively). Additionally, responses were most durable among those without any abnormalities, and not greater among those with 13q del. Subjects with 12q trisomy had the shortest response duration.

	17p-	11q-	12q+	13q-	6q-	DR Median duration (months)	95%CI	BFR Median duration (months)	95%CI	All Median duration (months)	95%CI
<b>PFS – IRC</b>	-	-	-	-	-	9.3	3.7-12.0	7.1	3.8-9.0	7.9	4.0-8.9
	+	+/-	+/-	+/-	+/-	5.0	2.6-10.7	2.9	1.6-6.4	4.1	2.6-6.4
	-	+	+/-	+/-	+/-	6.4	4.8-8.3	6.0	3.7-8.0	6.4	4.9-8.0
	-	-	+	+/-	+/-	3.7	2.3-4.4	5.1	0.6-5.9	5.5	2.3-11.1
	-	-	-	+	-	5.7	-	7.1	4.6-7.4	7.1	5.5-13.3
<b>Response Duration – IRC</b>	-	-	-	-	-	10.1	2.8-10.1	6.7	2.0-7.7	6.4	3.0-7.7
	+	+/-	+/-	+/-	+/-	7.7	0.7-9.8	5.5	-	7.7	0.7-9.8
	-	+	+/-	+/-	+/-	7.1	3.7-7.6	4.6	2.7-8.7	6.0	3.7-7.4
	-	-	+	+/-	+/-	0.2	-	2.1	1.8-2.8	2.4	0.2-
	-	-	-	+	-	3.7	1.3-	5.6	1.8-16.8	5.6	2.5-12.4

Source: abstracted from Hx-CD20-406 report body tables 10.19.1-5, 10.5.1-5; based on K-M estimates

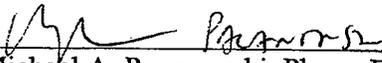
Cox proportional hazards regression was conducted to evaluate differences in survival according to the presence of chromosomal abnormalities and other CLL biomarkers in the DR population. The results of unadjusted analysis are shown in the following table (reviewer's analysis). Subjects with the 17p del tended to have worse OS, but chromosomal abnormalities were not significantly associated either PFS or OS. Circulating CD20,  $\beta$ 2-microglobulin, and thymidine kinase were marginally associated with OS, with higher baseline levels portending poorer OS.

DR		PFS – IRC			OS – IRC				
		HR	95% Confidence Interval		P*	HR	95% Confidence Interval		P*
<b>Biomarkers</b>	<b>Parameterization</b>								
Chromosomal Aberrations – hierarchical model, vs. none	17p-	0.963	0.293	3.160	0.6823	4.009	0.864	18.603	0.2022
	11q-	0.540	0.192	1.520		1.554	0.339	7.120	
	12q+	1.332	0.408	4.341		2.649	0.372	18.853	
	13q-	0.854	0.286	2.553		3.233	0.438	23.851	
IgVH, vs. non-mutated	mutated	0.740	0.190	2.889	0.6652	0.388	0.054	2.771	0.3454
CD38+		0.957	0.730	1.254	0.0583	1.061	0.535	2.103	0.7514
↳ CD38+	>20%	0.856	0.410	1.788	0.6792	1.046	0.484	2.258	0.9096
cCD20		0.993	0.345	2.856	0.9895	3.059	0.780	11.998	0.1089
↳ cCD20	>35.2	1.225	0.643	2.332	0.5368	2.066	0.945	4.517	0.0690
$\beta$ 2-microglobulin		2.196	0.976	4.938	0.0572	5.459	1.931	15.437	0.0014
↳ $\beta$ 2-microglobulin	>6960	1.355	0.705	2.606	0.3620	2.752	1.272	5.957	0.0102
TK		1.245	0.807	1.921	0.3213	1.850	1.130	3.02	0.0145
↳ TK	>47.3	1.394	0.726	2.675	0.3180	2.195	1.021	4.719	0.0441
<b>Clinical Staging</b>									
Modified Rai, vs. I	II	1.568	0.573	4.295	0.3486	0.972	0.296	3.194	0.3817
	III	1.602	0.539	4.762		0.773	0.184	3.240	
	IV	2.172	0.802	5.880		2.045	0.721	5.802	
Binet, vs. A	B	0.573	0.185	1.779	0.3821	0.774	0.205	2.92	0.2322
	C	0.914	0.311	2.690		1.600	0.464	5.521	
CD38, cCD20, $\beta$ 2-micro, and TK log-transformed prior to analysis to normalize									
*based on Wald test for global association									

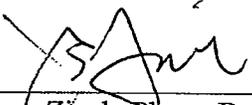
Source: Genomics reviewer; FAS

In the overall population, consistent with the findings for OR, 17p del carriers were at higher risk for progression as compared to subjects with no chromosomal abnormalities, but again this was not statistically significant. Additionally, increasing  $\beta$ 2-microglobulin was also associated with poorer PFS, as was CD38+. None of the FISH biomarkers were significant predictors for OS, although a trend toward higher risk was noted among subjects with the 17p-. TK,  $\beta$ 2-microglobulin and cCD20 were associated with OS in the overall population.

Using the stepwise selection algorithm,  $\beta$ 2-microglobulin and 17p del consistently entered as significant predictors of OR, PFS, and OS in the overall population and the DR and BFR subgroups. CD38+, 12q del, and 11q del also entered into the model, albeit less consistently.

  
\_\_\_\_\_  
Michael A. Pacanowski, Pharm.D., M.P.H.  
Primary Reviewer, Genomics Group  
Office of Clinical Pharmacology

7/13/09  
\_\_\_\_\_  
Date

  
\_\_\_\_\_  
Issam Zineh, Pharm.D., M.P.H.  
Associate Director for Genomics, Genomics Group  
Office of Clinical Pharmacology

7/13/09  
\_\_\_\_\_  
Date



# Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
DIVISION OF CARDIOVASCULAR AND RENAL  
PRODUCTS

Date: April 21, 2009

From: Suchitra Balakrishnan, M.D., Ph.D.  
Christine Garnett, Pharm.D.

Through: Norman Stockbridge, M.D., Ph.D.  
Division Director  
Division of Cardiovascular and Renal Products /CDER

To: Raymond S. Chiang, M.S.  
Regulatory Project Manager  
Division of Biologic Oncology Products

Subject: QT-IRT Consult to BLA 125,326

*Suchitra Balakrishnan* 4/21/09  
*Christine Garnett* 4/21/09  
*Norman Stockbridge* 4/21/09

**Interdisciplinary Review Team for QT Studies Consultation:  
Protocol Review**

<b>BLA</b>	STN 125326
<b>Generic Name</b>	Ofatumumab (ARZERRA)
<b>Sponsor</b>	GlaxoSmithKline
<b>Indication</b>	Treatment of patients with CLL who have received prior therapy
<b>Dosage Form</b>	IV infusion
<b>Drug Class</b>	Monoclonal antibody
<b>Therapeutic Dose</b>	proposed monotherapy dosing regimen in subjects with refractory chronic lymphocytic leukemia (CLL): 300 mg initial infusion, followed one week later by 2000 mg infusions once weekly for seven infusions, followed four / / weeks later by 2000 mg infusions once every four weeks for four infusions, for a total of twelve infusions.
<b>Duration of Therapeutic Use</b>	Sub-Acute
<b>Maximum Tolerated Dose</b>	Not defined
<b>Application Submission Date</b>	30 Jan 2009
<b>Review Classification</b>	Standard
<b>Date Consult Received</b>	26 Feb 2009
<b>Clinical Division</b>	OODP/DBOP/HFD 150

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**1 SUMMARY**

**1.1 Comments to be Sent to Sponsor**

1. We recommend you incorporate the following elements into your assessment of the ECGs recorded during this study:
  - a. Review of all ECGs from a particular subject by a single reader, preferably on one day,
  - b. Pre-specify the lead for interval measurements.
  - c. Baseline and on-treatment ECGs should be based on the same lead.
2. We are also interested in the effects of Ofatumumab on other ECG intervals. Please submit PR and QRS interval data with the study report and descriptive waveform morphology changes. This data would be reviewed but we do not have any regulatory thresholds for evaluation of other ECG intervals

3. When you submit your 'QT study' report, please include the following items:
  - a. Copies of the study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed
  - b. Electronic copy of the study report
  - c. Electronic or hard copy of the clinical protocol
  - d. Electronic or hard copy of the Investigator's Brochure
  - e. Annotated CRF
  - f. A Define file which describes the contents of the electronic data sets
  - g. Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes for the primary statistical analyses
  - h. Please make sure that the ECG raw data set includes at least the followings: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate HR, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g. QTcB, QTcF, QTcI, etc., if there is a specifically calculated adjusting/slope factor, please also include the adjusting/slope factor for QTcI, QTcN, etc.). Lead, ECG ID (link to waveform files if applicable).
  - i. Data set whose QT/QTc values are the average of the above replicates at each nominal time point.
  - j. Statistical programs with analysis datasets that were used to analyze the study endpoints as well as to perform exposure-response analysis
  - k. Narrative summaries and case report forms for any
    - i. Deaths
    - ii. Serious adverse events
    - iii. Episodes of ventricular tachycardia or fibrillation
    - iv. Episodes of syncope
    - v. Episodes of seizure
    - vi. Adverse events resulting in the subject discontinuing from the study
  - l. ECG waveforms to the ECG warehouse ([www.ecgwarehouse.com](http://www.ecgwarehouse.com))
  - m. A completed Highlights of Clinical Pharmacology Table

## **1.2 QT Interdisciplinary Review Team Comments to DBOP**

The sponsor's proposed ECG sub-studies are adequate to characterize large effects on the QT interval due to ofatumumab. We recommend performing screening ECGs and repeat ECGs as clinically indicated in the main studies for safety assessments.

For nonclinical evaluation, we recommend that standard in vivo toxicology studies in dogs or monkeys incorporate CV and ECG assessments into the design.

## **2 BACKGROUND**

### **2.1 Product Information**

Ofatumumab (GSK1841157) is a fully human monoclonal antibody (mAb), Immunoglobulin G1 kappa (IgG1κ), targeting an epitope on the CD20 molecule. Ofatumumab is being developed by GlaxoSmithKline (GSK) and Genmab for oncology indications, autoimmune indications (rheumatoid arthritis), and neurological indications (multiple sclerosis).

### **2.2 Preclinical Information**

Source: IB dated 11 February 2009

“In the 4 week and 7 month studies, ECG assessments were performed using a Nihon Kohden electrocardiogram and leads I, II, III, aVL and VF, once pre-study and at a target 30 minutes and 24 hours after dosing on pre-specified days. There were no drug-related adverse effects on heart rate or QT interval in the monkeys at doses up to and including 100 mg/kg.

“Specific in vitro electrophysiology studies to assess the potential for delayed ventricular repolarization (e.g. hERG assay) are inappropriate for proteins, such as monoclonal antibodies, as their presence interferes with these assays. In addition, it is considered unlikely that a large protein such as ofatumumab would block the hERG pore, or any other cardiac channel, which is the main mechanism by which hERG is inhibited [Sanguinetti, 2004; Vargass, 2008]. For these reasons, in vitro electrophysiology studies were not conducted with ofatumumab.”

### **2.3 Clinical Experience**

Source: IB dated 11 February 2009 and Sponsor’s QT proposal

“Ofatumumab is currently being investigated in the treatment of follicular lymphoma (FL), chronic lymphocytic leukemia (CLL), diffuse large B-cell lymphoma (DLBCL), rheumatoid arthritis (RA), and multiple sclerosis (MS). The data cut-off for this Investigator’s Brochure is 14 November 2008. As of the time of data cut-off, more than 1000 subjects have been enrolled in ofatumumab studies since the first study was initiated, including approximately 850 subjects who have been exposed to Ofatumumab.

“As of 04 August 2008, there have been no serious adverse events of syncope, heart block, sustained or non-sustained ventricular arrhythmias, or sudden death. There have been two reports of serious cardiac atrial arrhythmias (atrial fibrillation), both involving the same 46 year old female patient who had received ofatumumab once for RA in April 2006 (Study Hx-CD20-403) and was withdrawn from treatment due to an allergic reaction: pruritus, dysphagia, and rhinitis.

“There has also been one report of QTc prolongation associated with tumor lysis syndrome in CLL trial Hx-CD20-406. The 55 year-old male subject with no history of cardiac disease experienced grade 2 palpitation, sinus tachycardia (heart rate 105-126 bpm, up from 88 bpm pre-infusion), increase in SBP (from 119 mm Hg pre-infusion to a maximum of 168 mm Hg during or post-infusion), and QTc prolongation (details regarding QTc measurements and whether the ECG was manually adjudicated were not reported). Chest X-ray was normal. Ofatumumab administration was interrupted and the subject was treated with IV hydration and allopurinol. Ofatumumab administration was resumed at a lower dose without complications.

“One serious case of bradycardia (heart rate of 29 bpm), temporally related to Ofatumumab administration, has been reported in a 71 year-old male subject in FL trial Hx-CD20-405. ECGs obtained every fifteen minutes for 2 hours revealed no QTc prolongation (intervals between 404 and 425 milliseconds). Bradycardia resolved upon administration of IV corticosteroids and the ofatumumab infusion was restarted without incident.”

*Reviewer’s Comments: Subjects in the RA and MS trials are administered lower doses of ofatumumab.*

*The sponsor has the following statement for investigator guidance, “Patients with a history of cardiac disease should be monitored closely. Ofatumumab should be discontinued in patients who experience serious or life-threatening cardiac “arrhythmias.” Arrhythmias have been reported as infusion reactions and include palpitations, tachycardia, palpitations and bradycardia.*

## **2.4 Clinical Pharmacology**

Appendix 5.1 summarizes the key features of ofatumumab’s clinical pharmacology.

## **3 QT STUDY DESIGN**

ECG and QT evaluation will occur in two settings:

- in a subset of patients in the OMB110913, and
- in a study of patients with refractory CLL receiving monotherapy (Study OMB112855).

### **3.1 Study Description**

#### **3.1.1 Design**

OMB110913:

Study OMB110913 is an open-label, two-arm, randomized, Phase III study of ofatumumab in combination with fludarabine and cyclophosphamide (OFC) vs. fludarabine and cyclophosphamide (FC) combination therapy in subjects with relapsed CLL.

OMB112855:

Single arm study of patients with refractory CLL receiving monotherapy

### 3.1.2 Treatment Regimens

#### 3.1.2.1 Treatment Arms

OMB110913:

The ofatumumab regimen in this study is 300 mg on Day 1 and 1000 mg on Day 8, followed by 1000 mg every 28 days for 6 cycles in combination with fludarabine and cyclophosphamide.

OMB112855:

Subjects will be treated with 300 mg Ofatumumab on Day 1, followed by seven 2000-mg infusions at weekly intervals, followed five weeks later by four 2000-mg infusions at four-week intervals.

#### 3.1.2.2 Sponsor's Justification for Dose and Design

For a number of reasons, thorough QT studies performed in strict accordance with the E14 guidance are not commonly carried out in either oncology drugs or monoclonal antibodies, unless there is a particular concern (e.g., a class effect for QT prolongation or cardiomyopathy, cardiac tissue binding, underlying disease having significant effect on the heart, etc.). GSK believes the following components of the E14 guidance are not practical and/or feasible as part of a QT interval assessment for ofatumumab.

*Section 2.2: The "thorough QT/QTc study" ...is typically carried out in **healthy volunteers** and is used to determine whether or not the effect of a drug on the QT/QTc interval in target patient population should be studied intensively during later stages of drug development.*

Because of the potential toxicity associated with prolonged B cell depletion, i.e., increased risk for infection, cytokine release syndrome, and other adverse reactions associated with ofatumumab infusions (see AE section above), the exposure of healthy volunteers to ofatumumab is not suitable. For these reasons, ofatumumab has not been administered to healthy volunteers. The E14 Guidance clearly points out some drugs might not be suitable for study in healthy volunteers because of issues related to tolerability. With respect to ofatumumab, a QT/QTc assessment can only be attempted in the intended treatment patient population.

*Section 2.2.1: The "thorough QT/QTc study" should be adequate and well-controlled, with mechanisms to deal with potential bias, including randomization, **appropriate blinding, and concurrent placebo control group**. The confidence in the ability of the study to detect QT/QTc prolongation can be greatly enhanced by the use of **a concurrent positive control group** to establish assay sensitivity.*

Ofatumumab is given by IV administration in doses ranging from 300 mg (day 1) to 2000 mg (day 8 and thereafter). The ofatumumab infusions are prepared in 1000 ml sterile, pyrogen free 0.9% NaCl to yield a 0.3 mg/ml and 1 mg/ml ofatumumab concentration for the first (300 mg) and subsequent infusions (1000 mg, 2000 mg), respectively. The first infusion is administered over 4.5 hours, gradually increasing the infusion rate with the

absence of infusion reactions. Subsequent infusions are administered over 4 hours, again with an increase in the infusion rate as tolerated. Premedication before each ofatumumab infusion must be given within 30 minutes to 2 hours prior to the treatment. The incorporation of a concurrent positive control in OMB112855 poses significant recruitment issues due to the increased duration of a study visit, as well as logistical issues at the outpatient site level.

Section 2.2.2: *.....ensure that the dose-response and generally the concentration response relationship for QT/QTc prolongation have been characterized, including exploration of concentrations that are higher than those achieved following the anticipated therapeutic doses.*

Exposure of the intended population to multiples of the anticipated therapeutic dose is not suitable in this patient population as it would induce undue risk of prolonged B-cell depletion in the patients, especially for patients that are non-responders. Putting patients at a higher risk than is necessary for the development of infections secondary to exaggerated prolonged B-cell depletion is not appropriate from a clinical safety or ethical standpoint.

*Reviewer's Comments: Acceptable*

### **3.2 Study Subjects**

OMB110913: Subjects with relapsed CLL

OMB112855: Subjects 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 considered inappropriate for treatment with alemtuzumab due to lymphadenopathy with at least one lymph node > 5 cm and requiring therapy.

### **3.3 Study Assessments**

#### **3.3.1 ECG and PK Assessments**

OMB110913:

Twelve (12)-lead ECGs will be collected in triplicate (within 5 minutes of each other) on Day 1 (predose and end of infusion) and at the end of infusions on Cycle 1 Day 8 (OFC arm only) and Cycle 6 Day 1 (planned study Day 141) within the substudy patients in both treatment arms. ECGs will be sent to a centralized ECG laboratory, where the readers will be blinded to time, treatment, and subject identifier. Ofatumumab or F-ara-A and cyclophosphamide concentrations will be determined at the end of the Ofatumumab or cyclophosphamide infusions, respectively.

**Table 1 ECG and blood sample collection schedule in OMB110913**

Study Day	Dosing <sup>1</sup>	ECG <sup>1</sup>	PK Sampling for sub-study relative to infusions <sup>2</sup>
<b>OFC</b>			
Cycle 1 Day 1	OFC	Predose EOI-O EOI-C	Predose EOI-O 0.5 h after EOI-O EOI-C 2-16 h after EOI-C Prior to next FC (at least 2 h apart)
Cycle 1 Day 8	O	EOI-O	Predose EOI-O 0.5 hr after EOI-O
Cycle 6 Day 1 (planned study day 141)	OFC	EOI-O EOI-C	Predose EOI-O EOI-C 2-16 h after EOI-C Prior to next FC (at least 2 h apart)
<b>FC</b>			
Cycle 1 Day 1	FC	Predose EOI-C	Predose EOI-C 2-16 h after EOI-C Prior to next FC (at least 2 h apart)
Cycle 6 Day 1 (planned study day 141)	FC	EOI-C	Predose EOI-C 2-16 h after end of C Prior to next FC (at least 2 h apart)

1. O=Ofatumumab, F=Fludarabine, C=Cyclophosphamide, FC=Fludarabine-Cyclophosphamide, EOI=End of infusion

2. n=hour

**OMB112855:**

Twelve (12)-lead ECGs will be collected in triplicate (within 5 minutes of each other) during day 1 (predose and end of the first infusion) and at the end of the infusions on Day 8, planned study Day 50 (eighth weekly infusion), and planned study Day 169 (twelfth infusion; fourth monthly infusion). Ofatumumab concentrations will be determined at the end of the ofatumumab infusions on Days 1 and 8 of Cycle 1, Day 1 of Cycle 8 (planned study Day 50), and Day 1 of Cycle 12 (planned study Day 169).

**Table 2 ECG and blood sample collection schedule in OMB112855**

Study Day	Dosing	ECG collection relative to infusions	Pharmacokinetic sampling relative to infusions
1	300 mg	Predose, End of Infusion (EOI)	Predose, EOI
8	2000 mg	EOI	EOI
50	2000 mg	EOI	EOI
169	2000 mg	EOI	EOI

**3.3.2 Safety Assessments**

*Reviewer's Comment: Main protocols were not available for review by the IRT.*

## 4 DATA ANALYSIS PLAN

### 4.1 Statistics

#### 4.1.1 Sample Size

OMB110913: ECG data will be collected in a substudy of 50 patients (25 patients per treatment arm), allowing assessment of both ofatumumab-fludarabine-cyclophosphamide effects on QTc and fludarabine-cyclophosphamide effects on QTc.

OMB112855: ECG data will be collected in a study of 12 subjects.

*Reviewer's Comments: Acceptable according to the table below.*

**Sample sizes for constant mean effect over time  
(4 time points, independent,  $\alpha = 0.05$ ,  $\beta = 0.15$ )**

<i>SD, ms</i>	<i>Distance (non-inferiority margin, true mean difference to be detected)</i>		
	<i>5 (20, 15)</i>	<i>10 (20, 10)</i>	<i>15 (20, 5)</i>
<i>9</i>	<i>75</i>	<i>19</i>	<i>9</i>
<i>11</i>	<i>112</i>	<i>28</i>	<i>13</i>
<i>13</i>	<i>157</i>	<i>40</i>	<i>18</i>
<i>15</i>	<i>208</i>	<i>52</i>	<i>24</i>
<i>17</i>	<i>267</i>	<i>67</i>	<i>30</i>
<i>19</i>	<i>334</i>	<i>84</i>	<i>38</i>

#### 4.1.2 ECG evaluations

ECG data from study OMB110913 and study OMB112855 will not be pooled before data analyses are performed. Data will be presented by each time point for each study.

Triplicate ECG measurements at each time point for each subject will be averaged prior to statistical analyses.

#### 4.1.3 Analysis of QTcF

Change from baseline in QTcF will be analyzed by a mixed effects analysis of variance. The treatment group will be considered as a fixed effect term in the model. The preinfusion QTcF value will be included as a covariate. Subject will be considered a random effect.

A point estimate, two-sided 90% confidence interval (95<sup>th</sup> percentile) will be generated for the difference of treatment at post-infusion Days 1 and 8 of Cycle 1 and Day 1 of Cycle 6 for study OMB110913.

Since there is only one treatment group in study OMB112855, the statistical analysis will not be conducted. The summary statistics for change from baseline in QTcF will be

provided at post-infusion Days 1 and 8 of Cycle 1, Day 1 of Cycle 8 and Day 1 of Cycle 12 for study OMB112855.

#### **4.1.4 Categorical Analysis**

An outlier analysis will be performed to determine the number and percentage of subjects in which an increase from baseline in QTc greater than 30 ms and 60 ms occur for each time point for each treatment. Individual subjects who have a QTc value greater than 450, 480, and 500 ms will be summarized by post-infusion on Days 1 and 8 (only subjects randomized to the ofatumumab combination arm) of Cycle 1, and Day 1 of Cycle 6 for each treatment for study OMB110913, and by post-infusion on Days 1 and 8 of Cycle 1, Day 1 of Cycle 8, and Day 1 of Cycle 12 for study OMB112855.

#### **4.1.5 Morphological Analyses**

Additional analyses may include tables and listings of the number and percentage of subjects with significant ST, T wave, and U wave abnormalities. Summary statistics for raw QT, HR, and RR data also will be provided by study.

#### **4.2 Clinical Pharmacology**

Exploratory PK/PD analyses to investigate whether plasma ofatumumab concentrations affect QT interval may be undertaken, data permitting, using mixed effects modeling.

## 5 APPENDICES

### 5.1 Highlights of Clinical Pharmacology

#### Highlights of Clinical Pharmacology - Ofatumumab

Therapeutic dose	The maximum proposed clinical dosing regimen for ofatumumab is the proposed monotherapy dosing regimen in subjects with refractory chronic lymphocytic leukemia (CLL): 300 mg initial infusion, followed one week later by 2000 mg infusions once weekly for seven infusions, followed four weeks later by 2000 mg infusions once every four weeks for four infusions, for a total of twelve infusions.	
Maximum tolerated dose	Maximum tolerated dose was not defined.	
Principal adverse events	Infections, infusion reactions (most common with the first two infusions), and hematologic abnormalities (neutropenia, anemia, thrombocytopenia)	
Maximum dose tested	Single Dose	No single-dose studies were conducted.
	Multiple Dose	The highest individual ofatumumab dose studied in a multiple-dose regimen was 2000 mg. The maximum clinical dosing regimen was 300 mg initial infusion, followed one week later by 2000 mg infusions once weekly for seven infusions, followed four to five weeks later by 2000 mg infusions once every four weeks for four infusions, for a total of twelve infusions.
Exposures Achieved at Maximum Tested Dose	Single Dose	No single-dose studies were conducted.
	Multiple Dose Geometric mean (%CV)	Maximum ofatumumab exposures were observed at the eighth weekly infusion (seventh weekly infusion of 2000 mg) in subjects with refractory CLL using the twelve-infusion regimen:  C <sub>max</sub> = 1482 µg/mL (50%)  AUC(0-∞) = 674,463 µg.h/mL (85%)
Range of linear PK	The pharmacokinetics of ofatumumab is nonlinear, likely related to target-mediated elimination (see below). Ofatumumab C <sub>max</sub> and AUC values appeared to increase more than proportionally with dose over a dose range of 100 to 500 mg at first infusion in CLL, 500 to 2000 mg at fourth infusion in CLL, and 300 to 1000 mg at first infusion and at fourth infusion in subjects with follicular lymphoma (FL). Clearance decreased with repeated administration due to reduction in target CD20 <sup>+</sup> B-cells; clearance values were similar at fourth, eighth, and twelfth infusion in subjects with CLL.	
Accumulation at steady state Geometric mean (%CV)	Maximum ofatumumab exposures were observed at the eighth weekly infusion (seventh weekly infusion of 2000 mg) in subjects with refractory CLL using the twelve-infusion regimen: C <sub>max</sub> = 1482 µg/mL (50%); AUC(0-∞) = 674,463 µg.h/mL (85%). At twelfth infusion (fourth monthly infusion), C <sub>max</sub> was 881 µg/mL (42%), and AUC(0-∞) was 265,707 µg.h/mL (79%). The dosing regimen was 300 mg initial infusion, followed one week later by 2000 mg infusions once weekly for seven infusions, followed four to five weeks later by 2000 mg infusions once every four weeks for four infusions, for a total of twelve infusions.	
Metabolites	Ofatumumab is a protein for which the expected metabolic pathway is degradation to small peptides and individual amino acids by ubiquitous	

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	proteolytic enzymes. Metabolites have not been identified.	
<b>Absorption</b>	<b>Absolute/Relative Bioavailability</b>	Ofatumumab is administered by intravenous infusion; thus, absolute bioavailability is 100%.
	<b>Tmax</b> Median (minimum-maximum)	Tmax occurred at or shortly after the end of infusion; initial infusions were at lower rates to reduce infusion reactions. In the pivotal trial: <ul style="list-style-type: none"> <li>• First infusion: 7.4 h (0.3 – 34.0 h)</li> <li>• Eighth infusion: 4.5 h (3.9 – 7.3 h)</li> <li>• Twelfth infusion: 4.5 h (3.9 – 100.2 h)</li> </ul>
<b>Distribution</b>	<b>Vd/F or Vd</b> Geometric mean (%CV)	Vss values in subjects with CLL (two studies): <ul style="list-style-type: none"> <li>• First infusion (n=27): 3.2 L (44%)</li> <li>• Fourth infusion (n=24): 1.7 L (44%)</li> <li>• Eighth infusion (n=127): 5.1 L (42%)</li> <li>• Twelfth infusion (n=77): 4.7 L (30%)</li> </ul>
	<b>% bound</b>	Protein binding was not determined for this monoclonal antibody.
<b>Elimination</b>	<b>Route</b>	Ofatumumab is eliminated in two ways: a target-independent pathway as with other IgG molecules and a target-mediated pathway related to binding to B cells; B cells are depleted with ofatumumab therapy. From the population PK model, target-independent clearance is estimated as 6.7 mL/h, which is ~10% of first infusion clearance in CLL and ~70% of clearance at later infusions in CLL (see below).
	<b>Terminal t½</b> Geometric mean (%CV)	Ofatumumab t½ values in subjects with CLL (two studies): <ul style="list-style-type: none"> <li>• First infusion (n=27): 1.3 days (109%)</li> <li>• Fourth infusion (n=24): 11.5 days (77%)</li> <li>• Eighth infusion (n=127): 15.8 days (40%)</li> <li>• Twelfth infusion (n=77): 13.9 days (26%)</li> </ul>
	<b>CL/F or CL</b> Geometric mean (%CV)	Ofatumumab CL values in subjects with CLL (two studies): <ul style="list-style-type: none"> <li>• First infusion (n=27): 63.7 mL/h (140%)</li> <li>• Fourth infusion (n=24): 8.5 mL/h (98%)</li> <li>• Eighth infusion (n=127): 9.5 mL/h (50%)</li> <li>• Twelfth infusion (n=77): 10.1 mL/h (47%)</li> </ul>

<b>Intrinsic Factors</b>	<b>Age</b>	Age was not found to be a significant factor accounting for interindividual variability in ofatumumab pharmacokinetics (21-86 years of age). At the maximum exposure (eighth weekly infusion in maximum proposed clinical dosing regimen), mean Cmax and AUC values were 15% and 15% higher in subjects ≥65 years of age.
	<b>Sex</b>	Gender accounted for 14-25% of interindividual variability in ofatumumab pharmacokinetics after accounting for differences in body size. At maximum exposure (eighth weekly infusion), mean Cmax and AUC values were 51% and 61% higher in female subjects.
	<b>Race</b>	Almost all subjects (96%) were Caucasian.
	<b>Hepatic &amp; Renal Impairment</b>	<p>There are no data in hepatically impaired subjects. IgG1 molecules such as ofatumumab are catabolized by ubiquitous proteolytic enzyme, which are not restricted to hepatic tissue. Therefore, changes in hepatic function are unlikely to have any effect on the elimination of ofatumumab.</p> <p>Renal impairment (indicated by baseline calculated creatinine clearance) was not a clinically significant factor for ofatumumab pharmacokinetics. At maximum exposure (eighth weekly infusion), mean Cmax and AUC values were 7% higher and 0.4% lower at CLcr 50-80 mL/min and 14% higher and 17% higher at CLcr 30-50 mL/min compared to values at CLcr &gt;80 mL/min.</p>
<b>Extrinsic Factors</b>	<b>Drug interactions</b>	Co-administration with CYP isoenzyme substrates, inducers, or inhibitors is not expected to result in clinically relevant pharmacokinetic drug-drug interactions; therefore, no formal drug-drug interaction studies have been performed.
	<b>Food Effects</b>	No food effect assessment has been made; ofatumumab is administered by intravenous infusion.
<b>Expected High Clinical Exposure Scenario</b>	The expected high clinical exposure scenario is the highest observed clinical exposure at the proposed maximum clinical dosing regimen. At the maximum exposure (eighth weekly infusion in subjects with refractory CLL), the maximum observed Cmax and AUC(0-∞) values were 3672 µg/mL and 4,701,101 µg.h/mL.	

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

<b>Office of Clinical Pharmacology</b>				
<i>New Drug Application Filing and Review Form</i>				
<u>General Information About the Submission</u>				
	Information		Information	
NDA/BLA Number	125326/000	Brand Name	ARZERRA	
OCP Division (I, II, III, IV, V)	V	Generic Name	Ofatumumab	
Medical Division		Drug Class	Biologics/Oncology	
OCP Reviewer	Jun Yang	Indication(s)	CLL who received prior therapy	
OCP Team Leader	Hong Zhao	Dosage Form	100 mg/5mL vial	
Pharmacometrics Reviewer	Justin C. Earp	Dosing Regimen	Initially 300mg/2000mg weeklyx7/2000mg weeklyx4(4 \ week after 8 <sup>th</sup> infusion)	
Date of Submission	1/30/2009	Route of Administration	IV infusion	
Estimated Due Date of OCP Review		Sponsor	GSK	
Medical Division Due Date		Priority Classification	Priority	
PDUFA Due Date	8/1/2009			
<b>Clin. Pharm. and Biopharm. Information</b>				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
<b>STUDY TYPE</b>				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x			
<b>I. Clinical Pharmacology</b>				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
<b>Healthy Volunteers-</b>				
single dose:				
multiple dose:				
<b>Patients-</b>				
single dose:				
multiple dose:	x			
<b>Dose proportionality -</b>				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
<b>Drug-drug interaction studies -</b>				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
<b>Subpopulation studies -</b>				

b(4)

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
<b>PD -</b>				
Phase 2:	x	1		
Phase 3:	x	1		
<b>PK/PD -</b>				
Phase 1 and/or 2, proof of concept:	x	1		
Phase 3 clinical trial:	x	1		
<b>Population Analyses -</b>				
Data rich:	x	1		
Data sparse:	x	1		
<b>II. Biopharmaceutics</b>				
<b>Absolute bioavailability</b>				
<b>Relative bioavailability -</b>				
solution as reference:				
alternate formulation as reference:				
<b>Bioequivalence studies -</b>				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
<b>Food-drug interaction studies</b>				
<b>Bio-waiver request based on BCS</b>				
<b>BCS class</b>				
<b>Dissolution study to evaluate alcohol induced dose-dumping</b>				
<b>III. Other CPB Studies</b>				
<b>Genotype/phenotype studies</b>				
<b>Chronopharmacokinetics</b>				
<b>Pediatric development plan</b>				
<b>Literature References</b>				
<b>Total Number of Studies</b>		8		

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

	Content Parameter	Yes	No	N/A	Comment
<b>Criteria for Refusal to File (RTF)</b>					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?		x		
2	Has the applicant provided metabolism and drug-drug interaction information?		x		
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?		x		
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	x			
5	Has a rationale for dose selection been submitted?	x			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	x			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	x			
8	Is the electronic submission searchable, does it have appropriate	x			

File name: 5\_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA\_BLA or Supplement 090808

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	hyperlinks and do the hyperlinks work?			
<b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b>				
<b>Data</b>				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x		
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?		x	
<b>Studies and Analyses</b>				
11	Is the appropriate pharmacokinetic information submitted?	x		
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?		x	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?		x	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?		x	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?		x	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?		x	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x		
<b>General</b>				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x		
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		x	

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?**  
 \_\_\_ Yes \_\_\_

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.  
*None*

<i>[Signature]</i>	2/27/09
Reviewing Clinical Pharmacologist	Date
<i>[Signature]</i>	2/27/09
Team Leader/Supervisor	Date

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