

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125326**

**MEDICAL REVIEW(S)**



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Oncology Drug Products  
Division of Biologic Oncology Products

## CLINICAL REVIEW AND EVALUATION

### CLINICAL STUDIES

**BLA/Serial Number:** 125326/0  
**Drug Name:** Ofatumumab  
**Indication(s):** Alemtuzumab and Fludarabine refractory CLL  
**Applicant:** Glaxo Group Limited d/b/a GlaxoSmithKline  
**Date(s):** Submission Date: 01/30/09, PDUFA Date: 10/30/09, extended 3 months due to a major amendment submission  
**Review Priority:** Priority  
**Medical Division:** Division of Biological Oncology Products  
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**Statistical Reviewer:** Jenny Zhang, Ph.D.  
**Concurring Reviewers:** Mark Rothmann, Ph.D., Statistical Team Leader  
Aloka Chakaravarty, Ph.D., Division Director, DBV

## STATISTICS SIGNATURES/DISTRIBUTION LIST

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HFD-711/Dr. Zhang, Dr. Rothmann, Dr. Chakravarty  
HFD-700/Ms. Patrician

## JOINT CLINICAL AND STATISTICAL REVIEW

Application Type	BLA
Application Number(s)	125326/0
Priority or Standard	Priority
Submit Date(s)	01/30/09
Received Date(s)	01/30/09
PDUFA Goal Date	7/30/09, extended to 10/30/09 (due to a major amendment submission)
Reviewer Name(s)	Steven Lemery, M.D. Jenny Zhang, Ph.D.
Review Completion Date	09/14/09
Established Name	Ofatumumab
(Proposed) Trade Name	Arzerra
Therapeutic Class	CD20-directed cytolytic monoclonal antibody
Applicant	GlaxoSmithKline (GSK)
Formulation(s)	100 mg/5 mL single-use vial

**Dosing Regimen** 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.

b(4)

**Proposed Indication(s)** Treatment of patients with chronic lymphocytic leukemia (CLL) who have received prior therapy

## Table of Contents

<b>1 RECOMMENDATIONS/RISK BENEFIT ASSESSMENT .....</b>	<b>10</b>
1.1 Recommendation on Regulatory Action .....	10
1.2 Risk Benefit Assessment.....	11
1.3 Recommendations for Postmarket Risk Management Activities.....	13
1.4 Recommendations for Postmarket Studies/Clinical Trials.....	13
1.4.1 OMB110911.....	13
1.4.2 OMB112855 QTc Study .....	17
1.4.3 OMB110911 QTc sub-Study .....	17
1.4.4 Study Hx-CD20-406 Final Results .....	18
1.5 CMC Postmarket Commitments .....	18
<b>2 INTRODUCTION AND REGULATORY BACKGROUND .....</b>	<b>19</b>
2.1 Product Information.....	19
2.2 Tables of Currently Available Treatments for Proposed Indications.....	20
2.3 Availability of Proposed Active Ingredient in the United States .....	22
2.4 Important Safety Issues with Consideration to Related Drugs.....	22
2.5 Summary of Pre-submission Regulatory Activity Related to Submission.....	23
2.6 SGE Comments to FDA.....	25
2.7 Other Relevant Background Information.....	25
2.7.1 Background Related to CLL .....	25
2.7.2 Approval History of other CLL Drugs.....	26
2.7.3 Consideration of Unmet Medical Need (Regulatory Standard) .....	27
2.7.4 CT Scans in the Response Assessment of CLL.....	29
2.7.5 Literature Review of anti-CLL activity of Rituximab.....	30
2.7.6 Literature Review of Anti-CLL Activity of Corticosteroids .....	32
<b>3 ETHICS AND GOOD CLINICAL PRACTICES .....</b>	<b>33</b>
3.1 Submission Quality and Integrity .....	33
3.1.1 Quality.....	33
3.1.2 Integrity.....	33
3.2 Compliance with Good Clinical Practices .....	34
3.2.1 DSI Inspections .....	34
3.2.2 Protocol Violations Study Hx-CD20-406 .....	35
3.2.3 Protocol Violations Study Hx-CD20-402 .....	38
3.2.4 Protocol violations from other studies.....	38
3.3 Financial Disclosures.....	38
<b>4 SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES .....</b>	<b>39</b>
4.1 Chemistry Manufacturing and Controls.....	39
4.2 Clinical Microbiology.....	40
4.3 Preclinical Pharmacology/Toxicology .....	40
4.4 Clinical Pharmacology.....	40
4.4.1 Mechanism of Action.....	40
4.4.2 Pharmacodynamics .....	41
4.4.3 Pharmacokinetics .....	41
<b>5 SOURCES OF CLINICAL DATA.....</b>	<b>41</b>
5.1 Tables of Studies/Clinical Trials.....	41
5.2 Review Strategy .....	42
5.3 Discussion of Individual Studies/Clinical Trials.....	43

5.3.1 HX-CD20-406.....	43
5.3.2 STUDY 402 .....	53
5.3.3 Supportive safety studies.....	55
<b>6 REVIEW OF EFFICACY .....</b>	<b>57</b>
Efficacy Summary (Statistical Reviewer).....	57
Efficacy Summary (Clinical Reviewer).....	58
6.1 Indication .....	59
6.1.1 Methods.....	59
6.1.2 Demographics (Clinical Reviewer).....	59
6.1.3 Subject Disposition .....	63
6.1.4 Analysis of Primary Endpoint(s).....	63
6.1.5 Analysis of Secondary Endpoints(s) .....	85
6.1.6 Other Endpoints .....	90
6.1.7 Subpopulations.....	98
6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations.....	100
6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects .....	100
6.1.10 Additional Efficacy Issues/Analyses.....	100
<b>7 REVIEW OF SAFETY .....</b>	<b>102</b>
Safety Summary.....	102
7.1 Methods .....	103
7.1.1 Studies/Clinical Trials Used to Evaluate Safety.....	103
7.1.2 Categorization of Adverse Events.....	103
7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence .....	105
7.2 Adequacy of Safety Assessments .....	106
7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations.....	106
7.2.2 Explorations for Dose Response .....	106
7.2.3 Special Animal and/or In Vitro Testing .....	108
7.2.4 Routine Clinical Testing .....	108
7.2.5 Metabolic, Clearance, and Interaction Workup.....	108
7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class.....	108
7.3 Major Safety Results.....	109
7.3.1 Deaths .....	109
7.3.2 Serious Adverse Events.....	115
7.3.3 Dropouts and/or Discontinuations.....	125
7.3.4 Significant Adverse Events .....	131
7.3.5 Submission Specific Primary Safety Concerns .....	132
7.4 Supportive Safety Results .....	135
7.4.1 Common Adverse Events.....	135
7.4.2 Laboratory Findings.....	144
7.4.3 Vital Signs.....	165
7.4.4 Electrocardiograms (ECGs) .....	166
7.4.5 Special Safety Studies/Clinical Trials .....	167
7.4.6 Immunogenicity .....	167
7.5 Other Safety Explorations.....	167
7.5.1 Dose Dependency for Adverse Events.....	167
7.5.2 Time Dependency for Adverse Events.....	167
7.5.3 Drug-Demographic Interactions.....	168
7.5.4 Drug-Disease Interactions .....	173
7.5.5 Drug-Drug Interactions .....	173
7.6 Additional Safety Evaluations .....	174
7.6.1 Human Carcinogenicity .....	174
7.6.2 Human Reproduction and Pregnancy Data .....	176

7.6.3 Pediatrics and Assessment of Effects on Growth.....	176
7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound .....	176
7.7 Additional Submissions .....	176
<b>8 POSTMARKET EXPERIENCE.....</b>	<b>181</b>
<b>9 APPENDICES.....</b>	<b>182</b>
9.1 Literature Review/References.....	182
9.2 Labeling Recommendations.....	187
9.2.1 Indications and Usage .....	187
9.2.2 Dosage and Administration.....	188
9.2.3 Dosage Forms and Strengths.....	188
9.2.4 Warnings and Precautions .....	188
9.2.5 Adverse Reactions.....	189
9.2.6 Clinical Studies .....	189
9.2.7 Patient Information/Patient Counseling Information .....	189
9.3 Advisory Committee Meeting.....	190

## Table of Tables

Table 1: Summary of Ofatumumab Treatment Effect Size .....	12
Table 2: Currently Available Single Agent Treatments that are FDA Approved for CLL .....	21
Table 3: Combination Chemotherapy Regimens (for the Treatment of Patients with CLL).....	21
Table 4: Important Safety Issues for Rituximab .....	22
Table 5: Regulatory Meetings and Letters Pertinent to Clinical Issues associated with IND 11719.....	23
Table 6: Bases for Approval of CLL Drugs.....	27
Table 7: Literature Reports of Bendamustine Monotherapy for CLL .....	28
Table 8: Studies Reviewed Regarding Rituximab as Monotherapy for CLL.....	31
Table 9: DSI Inspections: Study 406 .....	34
Table 10: Study Hx-CD20-406 Protocol Deviations /Violations (Partial Listing).....	36
Table 11: Study Hx-CD20-402 Protocol Deviations /Violations (Partial Listing).....	38
Table 12: Listing of Clinical Trials Submitted to the BLA .....	41
Table 13: Dates of Amendments for Protocol Hx-CD20-406 .....	43
Table 14: Study Premedication Requirements (Table Copied with Modifications from the Hx-CD20-406 Clinical Protocol) .....	47
Table 15: 1996 NCIWG Criteria for Progression and Response in CLL .....	48
Table 16: Ofatumumab Doses in Study 402 .....	53
Table 17: Demographics: Study 406.....	60
Table 18: Categories of Certain Prior Therapies in Full Analysis Set.....	63
Table 19: Clinical Course of Patient Number 406147 .....	65
Table 20: Variability in Response Assessments of IRC Members (from Statistical Reviewer) .	67
Table 21: Narratives of Patients Considered as Responders at the time of the Original BLA Submission.....	68
Table 22: Summary of Applicant’s Revised ORR Results-Study 406 (Table Completed by Statistical Reviewer) .....	70
Table 23: Responding Patients (DR) per IRC, FDA Clinical Reviewer, and Investigators .....	73
Table 24: Responding Patients (DR) per IRC and FDA Clinical Reviewer; Non-responding per the Investigators .....	76
Table 25: Responding Patients per Investigators; non-Responding Patients per IRC and FDA Clinical Reviewer.....	77
Table 26: Responding Patients per Investigators and IRC; non-Responding per FDA Clinical Reviewer .....	77
Table 27: Responding Patients per IRC (per original BLA submission); non-Responding per FDA and Investigators .....	78
Patient 406157 (Table 28) in the bulky fludarabine refractory group was designated as a complete responder by the IRC despite having no confirmation of response by CT scan. On the baseline CT scan, this patient had a massive retroperitoneal lymph node measuring 39 cm <sup>2</sup> . Prior to the week 12 visit, a confirmatory CT scan showed that the retroperitoneal lesion was 50 cm <sup>2</sup> and the spleen was unchanged in size. Other measured lymph nodes on CT scan appeared to be stable in size. If CT scans were used in the response determination, the patient would have been classified as a non-responder. Table 28: Review of Patient 406157 (Complete Response per IRC).....	79

Table 29: Examples where Radiology may have provided Relevant Information for the Overall Response Assessment .....	81
Table 30: Summary of ORR Assessed by IRC, Investigator, and Sponsor Algorithm (Statistical Reviewer).....	84
Table 31: Variability in Response Assessments of IRC Members (Statistical Reviewer) .....	84
Table 32: GSK Results for DOR (Statistical Reviewer).....	85
Table 33: Investigators' Duration of Response (Statistical Reviewer) .....	86
Table 34: Applicant's Results for OS (Statistical Reviewer).....	87
Table 35: Inconsistencies in Overall Survival Data (Statistical Reviewer).....	87
Table 36: Applicant's Results for PFS and Time to Next CLL Therapy (Statistical Reviewer) .	80
Table 37: Clinical Improvements with Minimal Duration of $\geq 2$ Months with Abnormalities at Baseline (Statistical Reviewer).....	91
Table 38: Proportion of Patients who manifested a Lymphocyte Count Reduction of More than 50 Percent (any Duration).....	92
Table 39: Baseline Lymphocytes of Responding Patients (406 Study).....	94
Table 40: Neutrophil Improvements in Patients with $\geq$ Grade 3 neutrophil counts at baseline (N=23).....	95
Table 41: ORR by Baseline Characteristics (Statistical Reviewer).....	98
Table 42: Duration of Response by Weight at Baseline (Statistical Reviewer) .....	98
Table 43: ORR by Prior Rituximab Use (Table Completed by Statistical Reviewer).....	99
Table 44: Demographics: Study 402.....	100
Table 45: Examples of (Potentially) Inappropriately Coded Verbatim Events .....	104
Table 46: Explanations for AEs being deleted in CRFs (study 406).....	105
Table 47: Number of Ofatumumab Infusions Patients Received During Study 406.....	107
Table 48: Exposure Summary Data by Dose Number for Study 406.....	107
Table 49: Tabular Listing of Deaths that Occurred after the Administration of Ofatumumab in CLL studies.....	110
Table 50: Summary of Serious Adverse Events by MedDra SOC .....	115
Table 51: Study 406 SAEs by PT in Infections and Infestations SOC.....	117
Table 52: Study 406 SAEs by PT in Cardiac Disorders SOC .....	119
Table 53: Tabular Listing of SAEs Related to the Cardiac SOC that Occurred after the Administration of Ofatumumab.....	119
Table 54: Tabular Listing of SAEs Related to Immune System Disorders that Occurred after the Administration of Ofatumumab.....	122
Table 55: Patients Withdrawn from Treatment during the Treatment Period of the 406 Study	126
Table 56: Patients Who Withdrew for Reasons "Death," "Other," "Adverse Event," or "Patient Refusal" during the Treatment Period of the 406 Study .....	126
Table 57: Withdrawal from Protocol Directed Therapy in Study 403 (Parts A and B).....	129
Table 58: Adverse Reactions in Study 406 by MedDRA Preferred Term (PT) .....	135
Table 59: Adverse Reactions in Study 406 by MedDRA High Level Term (HLT).....	139
Table 60: Adverse Reactions in Study 406 by MedDRA High Level Group Term (HLGT).....	141
Table 61: Adverse Reactions in Study 406 by MedDRA Preferred Term (PT) .....	143
Table 62: Shift Table of Uric Acid Levels (mmol/L) by CTCAE Grade (Study 406)* .....	146
Table 63: Mean Creatinine by Visit (umol/L) .....	147
Table 64: Median Creatinine by Visit (umol/L) .....	147

Table 65: Shift Table of Creatinine Levels by CTCAE Grade.....	148
Table 66: Median Immunoglobulin Levels by Visit.....	149
Table 67: Shift Table of ALT Levels by CTCAE Grade*.....	151
Table 68: Shift Table of Bilirubin by CTCAE Grade*.....	153
Table 69: Shift Table of Alkaline Phosphatase by CTCAE Grade*.....	153
Table 70: Shift Table of Platelets by CTCAE Grade (Study 406).....	157
Table 71: Shift Table of Platelets by CTCAE Grade for Study 402 in the 2,000 mg dose cohort (Copied from Study 402 CSR).....	157
Table 72: Shift Table of Neutrophils by CTCAE Grade (study 406).....	160
Table 73: Shift Table of Neutrophils by CTCAE Grade for Study 402 in the 2,000 mg dose cohort (Copied from Study 402 CSR).....	160
Table 74: Shift Table of Hemoglobin by CTCAE Grade (Study 406).....	163
Table 75: Shift Table of Hemoglobin by CTCAE Grade for Study 402 in the 2,000 mg dose cohort (Copied from Study 402 CSR).....	164
Table 76: Instances of SBP < 90 mmHg and Pulse > 100 Beats per Minute (study 406).....	166
Table 77: Cases in Study 402 of Normal ECG results at Screening and an Abnormal Result at Visit 15.....	167
Table 78: Comparison of AEs by MedDRA PT by Gender.....	168
Table 79: Comparison of AEs by MedDra SOC in Patients ≥ 65 Years of Age.....	169
Table 80: Comparison of AEs by MedDra PT in Patients ≥ 65 Years of Age.....	171
Table 81: Comparison of AEs by MedDra PT in Patients by Weight.....	172
Table 82: Malignancies Reported after Ofatumumab (1,138 total patients exposed).....	175
Table 83: Number of Patients Contributing to the Updated Safety Analysis by Study.....	177
Table 84: Selected Listing of Selected SAEs (Reported in the 90 Day Safety Update).....	178
Table 85: Deaths -- Safety Update.....	180

## Table of Figures

Figure 1: Dates of Infusions during Study 406 (copied directly from the GSK 406 CSR).....	46
Figure 2: Study 406 Flow Chart Part A: Schedule of Events (copied directly from the GSK 406 CSR).....	47
Figure 3: Study 406 Flow Chart Part B: Schedule of Events (Copied directly from the GSK 406 CSR).....	48
Figure 4: Study 402 Infusion Schedule (Copied Directly from the GSK 402 CSR).....	53
Figure 5: Study 402 Calendar of Events (Copied Directly from the GSK 402 CSR).....	54
Figure 6: Distribution of Prior Therapies for DR Group (n=59).....	62
Figure 7: Distribution of Prior Therapies BFR group (n=79).....	62
Figure 8: Distribution of Prior Therapies for "Other" Group (n=16).....	62
Figure 9: OS per response in week 12 survivors [DR group (Statistical Reviewer)].....	89
Figure 10: OS per response in week 12 survivors [BFR group (Statistical Reviewer)].....	89
Figure 11: Absolute Change in Lymphocyte Counts at Visit 6 from Baseline (~4 weeks after the first dose) X 1,000/mcL (N=139).....	93
Figure 12: Absolute Change in Lymphocyte Counts at Visit 10 from baseline (~8 weeks after the first dose) X 1,000/mcL (N=129).....	93
Figure 13: GSK Analysis of Infusion Reactions by Infusion (Copied from GSK CSR).....	133
Figure 14: Scatter-plot of Baseline versus Maximum Creatinine Value for Men (in umol/L)..	148
Figure 15: Scatter-plot of Baseline versus Maximum Creatinine Value for Women (in umol/L).....	148
Figure 16: Variability Chart for IgA in g/L.....	150
Figure 17: Variability Chart for IgG in g/L.....	150
Figure 18: Variability Chart for IgM in g/L.....	150
Figure 19: ALT Values by Visit.....	152
Figure 20: Variability Chart by Week for Lymphocyte Counts (Study 406).....	154
Figure 21: Variability Chart for CD45+, CD5-, CD19+ cells in cell/mm <sup>3</sup> .....	155
Figure 22: Per Visit Variations in Per-Patient Differences in CD45+, CD5-, CD19+ Cell Counts Compared to Baseline.....	156
Figure 23: Platelet Counts by Visit (Study 406).....	158
Figure 24: Number of Days from First Dose of Ofatumumab to First Episode of ≥ Grade 3 Neutropenia (Study 406) in Patients with Baseline Normal Neutrophil Counts (N=109). .....	162
Figure 25: Neutrophil Counts over Time by Visit (Study 406).....	162
Figure 26: Hemoglobin Values by Study Visit (Study 406) in g/dl.....	165
Figure 27: Occurrence of Infections by Number of Days Following the First Dose of Ofatumumab (x-axis in days).....	168

## 1 Recommendations/Risk Benefit Assessment

Note to reader: This review is a joint review written by Dr. Lemery (clinical reviewer) and Dr. Zhang (statistical reviewer). All sections of this review were written by Steven Lemery except parts of Section 6. Parts of Section 6 written by Dr. Zhang are indicated as such. The following sections regarding regulatory actions are written by Dr. Lemery. Dr. Zhang's summary conclusions were summarized by Dr. Lemery in Section 1.2. Her full summary can be found at the beginning of Section 6.

### 1.1 Recommendation on Regulatory Action

This reviewer recommends that ofatumumab be granted Subpart E (accelerated) approval under 21 CFR 601.41:

FDA may grant marketing approval for a biological product on the basis of adequate and well-controlled clinical trials establishing that the biological product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefits or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. Approval under this section will be subject to the requirement that the applicant study the biological product further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome. Postmarketing studies would usually be studies already underway. When required to be conducted, such studies must also be adequate and well-controlled. The applicant shall carry out any such studies with due diligence.

This regulatory recommendation regarding ofatumumab is applicable under 21 CFR 601.40. This subpart applies to "certain biological products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments (e.g., ability to treat patients unresponsive to, or intolerant of, available therapy, or improved patient response over available therapy)."

This approval recommendation is applicable for the population of patients studied by GSK in the patient group refractory to fludarabine and alemtuzumab (double refractory or DR). This population of DR CLL patients constituted a population with a life-threatening illness [median survival in one literature report was 8 months (Tam et al., 2007)]. As described in the ODAC briefing document, FDA considers this DR patient population, more than 90% of whom also received prior therapy that included an alkylating agent, to be a patient population with an unmet medical need. Thus, the DR population did not have adequate available therapy. The DR population received a median of five prior treatments in the Hx-CD20-406 study. This reviewer notes that acceptance of the DR population as a population with unmet medical need was supported by the high percentage of patients who received alkylating agent therapy. It is not

clear whether FDA would have considered this population as having unmet medical need if most of the population was not exposed to alkylating agents.

The regulatory action under Subpart E of 21 CFR 601.41 is supported by an effect on a surrogate endpoint [durable objective response rate (see Section 1.2 of this review)] that is reasonably likely to predict clinical benefit. The ODAC committee voted 10 to 3 that the treatment effects observed in studies Hx-CD20-406 and Hx-CD20-402 are reasonably likely to predict clinical benefit. In CLL, FDA has considered a clinically meaningful improvement in PFS with an acceptable safety profile as evidence of clinical benefit (for example, in the bendamustine and alemtuzumab approvals).

The Subpart E approval of alemtuzumab in 2001 was based on the results of three single-arm studies enrolling 149 patients with CLL who had progressive disease following treatment with alkylating agents and fludarabine. The overall response rate (ORR) in the three studies ranged from 21% to 33% with median durations of response of 7 to 11 months. These point estimates for alemtuzumab were based on the 1996 NCI Working Group criteria. Ultimately, a controlled trial confirmed the benefit of alemtuzumab. Alemtuzumab was granted regular approval in 2007, on the basis of superior PFS [HR 0.58 (95% CI 0.43, 0.77),  $p < 0.0001$  stratified log-rank test] in a randomized active-controlled study comparing alemtuzumab to chlorambucil in previously untreated patients with CLL. Thus, based on prior FDA precedent, approval of ofatumumab is supported by a higher ORR point estimate than alemtuzumab using the same response criteria.

This reviewer acknowledges uncertainty as to the relation of the surrogate endpoint to clinical benefit (for ofatumumab). For this reason, approval of ofatumumab is only being considered for CLL patients without adequate available therapy. The uncertainty regarding the ofatumumab clinical benefit effect is partially related to the uncertainties regarding the overall surrogate endpoint effect size described in Section 6 of this review. Some of the uncertainty was due to the endpoint definition contained within the 1996 NCI Working Group criteria for CLL. Additionally, discrepant results between treatment effects on peripheral lymphadenopathy measured during physical examination and visceral lymphadenopathy measured on CT scans were observed.

Post-marketing studies are underway to further characterize the clinical benefit(s) of ofatumumab (see section 1.4).

## 1.2 Risk Benefit Assessment

This application is supported by the following effect sizes (Table 1) on objective response rate (ORR) and duration of response (DOR). These ORRs were determined by the investigators using the 1996 NCI Working Group criteria. The population under consideration for Subpart E approval is the DR population. The results in the DR population are supported by the treatment effects observed in the bulky fludarabine-resistant (BFR) population (see Section 5) and those observed in study Hx-CD20-402. The investigators' estimates are being considered by FDA for this application. The estimates obtained by the IRC are not being considered due to the reasons

described in Sections 3 and 6 of this review. Additionally, this reviewer acknowledges for reasons described in Section 6 that there is considerable uncertainty regarding the point-estimates for ORR. The lower limits of the 99% CI were considered in the review of this application.

**Table 1: Summary of Ofatumumab Treatment Effect Size**

	ORR (99% CI)	Median DOR
DR (N = 59)	42% (26, 60)	6.5 months
BFR (N = 79)	34% (21, 49)	6.5 months

These effects on ORR and DOR are surrogate effects and not considered to be clinical benefit. FDA has considered a meaningful improvement in PFS as an established surrogate for clinical benefit in the CLL population assuming the PFS improvement is of sufficient magnitude and is accompanied by an acceptable toxicity profile.

Study Hx-CD20-406 was the only study to evaluate ofatumumab at the doses and schedule for which the applicant is seeking approval. Because the data were derived from an uncontrolled study, only a descriptive analysis of safety could be performed.

Infections (including infectious deaths) occurred frequently in study Hx-CD20-406. The applicant's analysis of deaths demonstrated a 17% incidence of infectious deaths in the DR population.

In the BLA submission, GSK stated that the overall incidence of fatal infections was lower (10%) than that quoted in the literature [48% (Perkins, 2008)]. This reviewer did not agree with the implication of this statement because the cited literature report was a retrospective literature review that followed the clinical course of 27 patients over a median of two treatment regimens (versus one for the ofatumumab study). Nevertheless, this reviewer agrees that based on literature reports, the background rate of severe and fatal infections in heavily treated CLL patients is high. Patients in the Hx-CD20-406 trial frequently had a history of severe infections. Because of the high background rate of infections in this patient population and the absence of an internal control, it was not possible to determine the additional risk of infection posed by the administration of ofatumumab. However, this reviewer notes that neutropenia may increase the risk of life-threatening infections in this patient population.

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

Myocardial infarction or angina was noted in four patients within two days of a dose of ofatumumab. The population of patients with CLL, a disease occurring in an older age group, may be at higher risk for myocardial events. It was not possible in a single arm study to determine whether ofatumumab increased the risk for myocardial events in susceptible patients. Finally, patients with preexisting COPD may be at higher risk for drug related bronchospasm as was observed in 2 of 5 patients in a separate COPD study.

Ultimately, the risk-benefit determination for ofatumumab will require a randomized clinical trial. This application is only being considered for the CLL patient population refractory to alemtuzumab and fludarabine. This DR population has a life-threatening disease and does not have adequate available therapy. Because these conditions exist, there is acceptance of the uncertainty regarding the ultimate clinical benefits of ofatumumab allowing for approval under Subpart E of 21 CFR 601.41.

The uncertainty regarding the treatment effects of ofatumumab were the major concerns for the statistical reviewer (refer to Section 6). These concerns included:

- The primary trial submitted for approval consideration was a single arm study with uncertainty regarding the ORR point estimate effect size
- Reliability of ORR as a surrogate for PFS or OS
- Small sample size of the DR population in the Hx-CD20-406 study
- Prolonged time-frame for the confirmatory study

This clinical reviewer shares these concerns; however, this reviewer believes that based on the approval of other drugs for the treatment of CLL (and cancer in general), that ofatumumab has a tolerable risk-benefit profile for the intended population with this life-threatening disease (who do not have adequate available treatment options). Additionally, consideration of ORRs as an endpoint (of sufficient magnitude and duration) for patient populations with unmet medical need was directed under Vice President Gore's "Reinventing the Regulation of Cancer Drugs" initiative (1996).

### **1.3 Recommendations for Postmarket Risk Management Activities**

GSK will be required to provide progress reports as required under 21 CFR 601.70, 21 CFR 601.44, and 21 CFR 600.80.

Ofatumumab is indicated for the treatment of patients with life-threatening cancer. As such, no additional clinical post-market risk management activities are to be instituted at this time. The proposed USPI contains patient counseling information for prescribing physicians (hematologists or oncologists).

### **1.4 Recommendations for Postmarket Studies/Clinical Trials**

Because ofatumumab has an orphan drug designation, ofatumumab is exempt from the requirements under the Pediatric Research Equity Act.

#### **1.4.1 OMB110911**

Approval of a biological drug under 21 CFR 601.40-46 requires that an applicant conduct adequate and well-controlled trials to verify and describe the clinical benefit attributable to the

biological drug. In the original BLA submission, GSK identified study / intended to verify and describe the benefit attributable to ofatumumab. Study / was entitled (

During a June 23, 2009 telephone conference, GSK proposed changing the primary study intended to verify and describe the benefit attributable to ofatumumab to study OMB110911 entitled "a phase III, open label, randomized, multicenter trial of ofatumumab added to chlorambucil versus chlorambucil monotherapy in previously untreated patients with chronic lymphocytic leukemia."

b(4)

GSK requested this change due to slow accrual in study / due to the changing practice of medicine. GSK communicated by email on July 9, 2009 that study OMB110911 was likely to meet accrual deadlines and 69 patients had been registered as of July 9, 2009. Furthermore only 82 of 143 targeted sites were open at the time of GSK's communication to FDA.

b(4)

As discussed in the preceding paragraph, study OMB110911 is an ongoing study in patients with CLL. FDA sent a letter to GSK regarding study OMB110911 on December 18, 2008, prior to the BLA submission. In the letter, FDA stated that in order for ofatumumab to be licensed in combination with chlorambucil, the data obtained from the study must be applicable to the U.S. population and U.S. medical practice. FDA recommended that GSK restrict enrollment in study OMB110911 to the subset of patients who would receive first-line chlorambucil in the United States (i.e., elderly or frail).

GSK provided a proposed amended protocol OMB110911 to FDA by email on July 14, 2009. In the revision, GSK proposed limiting eligibility to those patients "considered inappropriate for fludarabine-based therapy, for reasons that include, but not limited to, advanced age or presence of co-morbidities."

After receipt of the protocol amendment, GSK agreed to the following postmarketing trial requirement under 21 CFR 601.70:

To submit a final report for ongoing clinical trial OMB110911, entitled, "A Phase III, Open-label, Randomized, Multicenter Trial of Ofatumumab Added to Chlorambucil versus Chlorambucil Monotherapy in Previously Untreated Patients with Chronic Lymphocytic Leukemia" which is intended to verify the clinical benefit of Arzerra (ofatumumab) through demonstration of a clinically meaningful effect on progression-free survival. The protocol for clinical trial OMB110911 was submitted to FDA on October 24, 2008 and as amended (Amendment 2) with submission to FDA on August 21, 2009; and began patient accrual on December 22, 2008.

The following milestones are to be met for this post-marketing requirement:

- Patient Accrual 50% Completed (222 patients) by August 30, 2010
- Patient Accrual 75% Completed (333 patients) by March 30, 2011

- **Patient Accrual Completed** by **November 30, 2011**
- **Trial Completion Date:** by **October 14, 2013**
- **Final Report Submission:** by **June 30, 2014**

The following describes the major design features of study OMB110911:

- Randomized (1:1), open-label study.
- Progression free survival (PFS), defined as the time from randomization until disease progression or death due to any cause, is the primary endpoint.
- PFS is defined using the 2008 NCIWG CLL criteria.
- A 90% power and 5% alpha to detect a 9 month improvement in median PFS in the ofatumumab plus chlorambucil arm versus the chlorambucil arm (projected median PFS of 18 months in the chlorambucil arm).
- Patients in both arms receive chlorambucil 10mg/m<sup>2</sup> orally days 1-7 every 28 days.
- Patients in the ofatumumab arm will receive ofatumumab 1,000 mg every 28 days (except cycle 1 where patients will receive 300 mg on day 1 and 1,000 mg on day 8).
- If tolerated, patients will receive a minimum of 3 cycles of treatment until best response. Patients will receive a maximum of 12 cycles of treatment. Determination for treatment discontinuation will occur prior to cycles 4, 7, and 10 and will occur according to a pre-specified decision tree contained within the protocol.
- During the treatment phase and for one month after the treatment phase, patients will undergo monthly disease status assessments.
- Following the treatment phase, patients will undergo disease status assessments every three months until CLL progression, new CLL treatment, or until five years has elapsed.
- Following disease progression, patients will be monitored for overall survival in the post-disease progression follow-up phase.

*Reviewer comment: Because the median age of patients with CLL in the United States is > 70 years-of-age, chlorambucil is a reasonable treatment option for most patients in the United States. The Rai et al., (2000) study showed that there is no OS benefit for fludarabine over chlorambucil in patients with CLL (despite better ORRs and PFS). The median age in years in the Rai study was 62 to 64, depending on the treatment group. A more recent German co-operative group study (Eichhorst et al, 2009) showed that in patients with CLL who were older than 65, PFS was no better with fludarabine than with chlorambucil. The OS trend favored the chlorambucil arm (median OS was 46 months for fludarabine versus 64 months for chlorambucil). Fatal treatment-related side effects occurred in four patients receiving fludarabine versus one patient receiving chlorambucil. Additionally, patients ≥ 70 years-of-age are less likely to complete a full course of aggressive anti-CLL therapy [46% versus 79% for patients less than 70 years-of age completed 6 courses of FCR (Tam et al., 2008)]. Based on these data, chlorambucil is a reasonable treatment option for most patients older than 70 (and possibly older than 65) in the United States.*

GSK submitted amendment 2 for study OMB110911 to IND 11719 on August 21, 2009. The amendment revised the protocol to restrict eligibility to those patients “considered inappropriate for fludarabine based therapy.” The protocol contained other revisions recommended by FDA including additional biochemistry assessments to evaluate tumor lysis-related blood chemistry effects. GSK did not incorporate all of the FDA recommendations into the revised protocol. The following recommendations were not incorporated into the protocol:

- In order to prevent differential assessment bias between the two study arms, FDA recommended that monthly disease status assessments for progression occur during the first year for all patients enrolled into OMB110911 (currently, the monthly assessment period will be determined by the length of time that a patient remains on treatment).
- FDA recommended that patients be followed for disease progression after discontinuing protocol treatment for toxicity or other reasons. Table 5 of the revised OMB110911 protocol stipulates that patients will be followed for disease progression until disease progression, alternative CLL treatment, or five years (whichever comes first).
- FDA recommend that GSK modify the 2008 NCIWG criteria (for CLL) to minimize the influence of clinical judgment in the determination of progression and response (investigator determinations of response will influence the length of treatment). Otherwise, FDA recommended that investigators and the IRC should be instructed by GSK to accept the NCIWG criteria strictly as written. FDA asked GSK to consider the following scenarios in the evaluation of the 2008 NCIWG criteria:
  - An increase in the size of only one lymph node from 1 cm to 1.5 cm will designate a progression event even if the node resolves in size at the next visit.
  - If one node increases in size from 1 cm to 1.5 cm, a patient will not be classified as a responder even if the node resolves in size at the next visit and all other nodes have decreased in size.
  - As the NCIWG criteria are written, a new node of 0.5 cm in diameter during a response will designate the patient as a non-responder.

FDA noted that a previous version of the protocol contained instructions that a lymph node of 1-1.5 cm must increase by 50% or more to a size greater than 1.5 cm in the longest axis and a lymph node of more than 1.5 cm must increase to more than 2.0 cm in longest axis in order to designate progression. Such instructions may help to clarify response and progression events and prevent differential assessment bias between arms from affecting the overall study results.

Ultimately, evaluating the differential assessments during the treatment phase of the protocol will be a review issue and may require an evaluation of data robustness through sensitivity analyses. Additionally, FDA will have to determine whether the results of study OMB110911 will be affected by the number of patients who withdraw from PFS follow-up due to alternative CLL treatments. This determination will be a review issue when the final study results are received by FDA. Finally, GSK decided to use response criteria that correspond to the 2008

NCIWG criteria without modifications as suggested by FDA. Ultimately, the degree to which the criteria were adhered to will have to be reviewed when the final data are submitted to FDA.

#### 1.4.2 OMB112855 QTc Study

GSK must conduct study OMB112855 under Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA).

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

The following milestones are to be met for this post-marketing requirement:

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

This study was required and reviewed by FDA clinical pharmacology staff. No additional comments will be made in this review regarding study OMB112855.

#### 1.4.3 OMB110911 QTc sub-Study

GSK must conduct a sub-study in OMB110911 to evaluate QTc effects under Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA).

To conduct an assessment of QTc intervals as a sub-trial in clinical trial OMB110911. The total number of patients in OMB110911 with evaluable ECG measurements will be at least 50 (25 per treatment arm). For the QTc assessments, ECGs will be collected in triplicate at baseline, at steady-state Arzerra (ofatumumab) concentrations, periodically on-therapy (e.g., every 3 months), and at the end of treatment. The final report will be a comprehensive combined report of the results (including primary data) of the sub-trial assessing QTc intervals in OMB110911 and of clinical trial OMB112855.

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

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

This study was required and reviewed by FDA clinical pharmacology staff. No additional comments will be made in this review regarding study OMB112855.

#### **1.4.4 Study Hx-CD20-406 Final Results**

GSK has committed to submitting the final results of study Hx-CD20-406 to FDA by December 31, 2011. This is not a requirement under Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA); however, this PMC is subject to reporting requirement of Section 506B. FDA is requesting a report of the final study results to ensure robustness of the ORR described in the interim report.

#### **1.5 CMC Postmarket Commitments**

The following CMC-related postmarketing commitments were agreed upon with GSK as of 8/21/2009. The rationale for these commitments will be described further in the CMC review. Note that all dates for the annual report submissions are estimates. Final agreement has not been reached at the time of the completion of this review as to the timing of the annual report submissions.

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

b(4)

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

## 2 Introduction and Regulatory Background

### 2.1 Product Information

Ofatumumab (HuMax-CD20) is a human monoclonal antibody (IgG1 kappa) that targets the CD20 molecule expressed on human B cells. The proposed trade name is Arzerra.

Ofatumumab is the second monoclonal antibody targeting the CD20 antigen on human B-cells that has been submitted to FDA for approval consideration. Rituximab was the first approved biological drug targeting the CD20 antigen on B-cells. Rituximab was first approved by FDA in 1997 and is currently approved for the treatment of B-cell non-Hodgkin's lymphoma (NHL) and rheumatoid arthritis (RA) in combination with methotrexate in adult patients with moderately-to severely-active RA who experienced an inadequate response to one or more TNF antagonist therapies. In this BLA submission, GSK is proposing that ofatumumab should receive approval for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received prior therapy.

Ofatumumab and rituximab bind to different epitopes on CD20. Ofatumumab binds to the second extracellular loop on CD20. In their September 29, 2008 pre-BLA meeting package, the applicant stated that in nonclinical models, ofatumumab induces higher complement-mediated cytotoxicity (CDC) than rituximab. Furthermore, the applicant stated that ofatumumab demonstrates slower disassociation from CD20 than rituximab. Finally, the applicant stated that antibody dependent cell-mediated cytotoxicity (ADCC) was equivalent to rituximab. *Comment: There is no evidence to date that these non-clinical differences will translate into differences in either the safety or effectiveness of either product. Ofatumumab and rituximab have not been compared against each other in clinical trials for any indication.*

GSK describes ofatumumab (Arzerra) as a clear, colorless, aqueous solution containing 20/mL of drug substance in ( ) citrate buffer with ( ) sodium chloride at a pH of 6.5. The drug product is supplied in Type 1 glass vials sealed with a ( ) / coated / ( ) rubber stopper. Each vial of ofatumumab contains 5 mL of solution for intravenous administration. The drug product is intended to be diluted into an infusion bag containing isotonic pyrogen free 0.9% sodium chloride. Prior to administration, ofatumumab is to be filtered through an in-line, low protein binding ( ) filter that is to be provided with the drug product. b(4)

The proposed product label indicates that undiluted Arzerra is to be stored in a refrigerator at 2-8 degrees Centigrade and must not be frozen. The vials are to be protected from light. The proposed product label provides instructions to dilute Arzerra in 0.9% sodium chloride, USP prior to each infusion.

For the treatment of patients with CLL, patients are to receive 300 mg of ofatumumab for the first dose. If tolerated, patients are to receive 2,000 mg of ofatumumab weekly for 7 additional doses. Subsequently, patients will be scheduled to receive 4 additional monthly (every four weeks) doses.

## 2.2 Tables of Currently Available Treatments for Proposed Indications

The proposed indication at the time of the original BLA submission was for the treatment of patients with CLL who have received prior therapy.

Table 2 lists currently (FDA) approved drugs for the treatment of patients with CLL. Table 3 lists combination chemotherapy regimens that are used by oncologists in clinical practice. The regimens listed in Table 3 are used off-label; these regimens used off-label are supported by published literature reports or oncology practice guidelines (NCCN practice guidelines, accessed June 2009). Some of the regimens in Table 3 are based on randomized phase 3 trials that have not been submitted to FDA in support of an NDA or BLA. Inclusion of these regimens in Table 3 does not indicate that these regimens are approved or recommended by FDA.

**Table 2: Currently Available Single Agent Treatments that are FDA Approved for CLL**

Drug	Class	Specific Indication(s) for CLL and Comments
chlorambucil	alkylating agent	CLL (unspecified)
bendamustine	alkylating agent	CLL (unspecified)
alemtuzumab	anti-CD52 monoclonal antibody	B-cell CLL (unspecified)
fludarabine	fluorinated nucleotide analog	Patients with CLL whose disease has not responded to or has progressed following treatment with at least one standard alkylating agent regimen
cyclophosphamide	alkylating agent	CLL (unspecified); most frequently administered as part of a combination chemotherapy regimen

**Table 3: Combination Chemotherapy Regimens (for the Treatment of Patients with CLL)**

Regimen*	Comments/Literature Sources
chlorambucil +/- P +/- R	Rituximab not currently approved for the treatment of patients with CLL; [ECOG EST 2480 (Raphael et al., 1991) for chlorambucil + P]
CVP +/- R	CVP not better than chlorambucil + P in ECOG study (Raphael et al., 1991)
CHOP +/- R	French Cooperative Group Study (Leporrier et al., 2001)
FC +/- R	FC [US Intergroup Trial E2997 (Flinn et al., 2007) and UK LRF CLL 4 (Catovsky et al., 2007)] FCR [CLL8 (Hallek et al., 2008) and REACH (Robak et al., 2008)]
F +/- R	[CALGB-9712 (Byrd et al., 2003)]
PentoCR	Pentostatin not currently approved for the treatment of patients with CLL [MAYO-MC0183 (Kay et al., 2007)]
F + chlorambucil	This regimen not frequently used: the combination of fludarabine and chlorambucil was not better than fludarabine alone, and the combination showed excess toxicity [CALGB-9011 (Rai et al., 2000)]
F + alemtuzumab	Elter et al., 2005
HyperCVAD +/- R	Second line therapy in younger patients (included in NCCN guidelines; no literature citation in guidelines)
EPOCH +/- R	Second line therapy in younger patients (included in NCCN guidelines; no literature citation in guidelines)
Oxaliplatin FAR	Second line therapy in younger patients (Tsimberidou et al., 2008)
R + HDMP	Bowen et al., 2007; Castro et al., 2008

\*Abbreviations: C=cyclophosphamide, H=doxorubicin, O=vincristine, P=prednisone, F=fludarabine, R=rituximab, E = etoposide (VP-16), Pento=pentostatin, HDMP=high dose methylprednisone

### 2.3 Availability of Proposed Active Ingredient in the United States

Ofatumumab is a new molecular entity and is not currently marketed in the United States.

### 2.4 Important Safety Issues with Consideration to Related Drugs

Rituximab is an anti-CD20 antibody approved for the treatment of B-cell non-Hodgkin's lymphoma and rheumatoid arthritis. Table 4 contains warnings associated with rituximab that are included in the product label. Specific issues related to rheumatoid arthritis will not be described in this review. In addition to the warnings described in the table below, serious infections including viral, bacterial, and fungal infections have been observed following treatment with rituximab in clinical trials. A full list of all adverse reactions can be found in the rituximab package insert.

**Table 4: Important Safety Issues for Rituximab**

Warning	Boxed Warning*	Comments
Infusion reactions	Y	Can be life threatening; most occur after the first infusion; infusions should be interrupted for $\geq$ Grade 3 infusions reactions
Tumor lysis syndrome (TLS)	Y	In NHL, TLS has occurred in patients with a high number of malignant cells ( $\geq 25,000/\text{mm}^3$ )
Severe mucocutaneous reactions	Y	Including paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis
Progressive multifocal leukoencephalopathy	Y	Fatal JC virus infection resulting in PML has occurred in patients receiving rituximab
Hepatitis B virus reactivation	N	Fulminant hepatitis and death has occurred in patients with hepatitis B virus reactivation
Viral infections	N	Reported infections have included cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis C
Cardiovascular events	N	Including life-threatening cardiac arrhythmias
Renal events	N	Renal toxicity has occurred due to TLS and in patients who received concomitant cisplatin therapy in clinical trials
Bowel obstruction and perforation	N	In post-marketing reports, the mean time to documented gastrointestinal perforation was 6 days in patients with NHL
Immunizations	N	The safety of immunizations with live viral vaccines following rituximab therapy has not been studied and is not recommended
Laboratory monitoring	N	Monitoring for cytopenias at regular intervals following rituximab therapy is recommended

## 2.5 Summary of Pre-submission Regulatory Activity Related to Submission

Table 5 summarizes regulatory activities including meetings held with the IND sponsors (Genmab and GSK). Issues of importance included identifying a patient population with unmet medical need and identifying the extent of drug activity that would be reasonably likely to predict clinical benefit. Bendamustine was not approved when the double refractory (refractory to fludarabine and alemtuzumab) CLL patient population was initially deemed by FDA as having an unmet medical need.

**Table 5: Regulatory Meetings and Letters Pertinent to Clinical Issues associated with IND 11719**

Date	Nature of Regulatory Activity	Issues
5/20/2004	IND submission	<ul style="list-style-type: none"> <li>IND 11719 submitted by Genmab A/S.</li> </ul>
12/10/2004	Fast track	<ul style="list-style-type: none"> <li>Ofatumumab received Fast Track designation for the investigation of ofatumumab in combination with fludarabine for treatment of patients with previously untreated CLL to show an improvement in progression free survival as compared with fludarabine therapy.</li> </ul>
8/26/2005	Type C meeting to discuss the acceptability of a proposed trial to support accelerated approval (AA)	<ul style="list-style-type: none"> <li>FDA recommended that Genmab conduct an additional phase 2 dose finding trial prior to studies designed to support accelerated or regular approval. Genmab stated that a second study could not be conducted prior to a "pivotal" trial.</li> <li>FDA stated that a response rate of 15% would not be sufficient to predict clinical benefit; acceptability of a response rate of 20% would depend on data that shows that this ORR provides a significant advance over available therapy and is likely to predict benefit. FDA also stated that responses should be durable (at least 4-6 months) and associated with clear measures of clinical benefit.</li> <li>FDA stated that patients should be refractory to fludarabine in order to satisfy Fast-Track requirements.</li> </ul>
11/30/2005	Type C/pre-Phase 2	<ul style="list-style-type: none"> <li>FDA identified durable objective response rate as an acceptable surrogate endpoint reasonably likely to predict clinical benefit in a patient population with an unmet medical need, i.e., no alternative therapy.</li> <li>Genmab proposed to conduct a study in patients who "failed" both fludarabine and alemtuzumab to satisfy the requirement for demonstrating benefit in patients with an unmet medical need.</li> <li>Genmab proposed a sample size of 100 patients.</li> </ul>
12/2005	406 Protocol Submission	<ul style="list-style-type: none"> <li>Study Hx-CD20-406, "A single-arm, international, multi-center trial of HuMax-CD20, a fully human monoclonal anti-CD20 antibody, in patients with B-cell chronic lymphocytic leukemia who have failed fludarabine and alemtuzumab" was submitted to FDA.</li> </ul>

Date	Nature of Regulatory Activity	Issues
2/2006	406 Protocol Amendment	<ul style="list-style-type: none"> <li>Protocol Amendment 1 introduced a bulky fludarabine refractory patient group that was not required to receive prior alemtuzumab.</li> </ul>
4/11/2006	Letter (faxed) to Genmab re: 12/2005 protocol and Amendment 1	<ul style="list-style-type: none"> <li>Included advice from FDA's expert consultant serving as a Special Government Employee (SGE) who reviewed the 12/2005 protocol.</li> <li>CLL patients who are "double refractory" (DR) to both fludarabine and alemtuzumab have an unmet medical need.</li> <li>Patients with bulky, fludarabine-refractory CLL (BFR) should be analyzed separately from the DR population.</li> <li>Overall response rates of 10-20% were unlikely to predict clinical benefit.</li> </ul>
5/5/2006	Letter to Genmab re: amended protocol Feb 2006	<ul style="list-style-type: none"> <li>In a population with unmet need, an observed response rate where the lower bound of the 95% CI for the ORR was at least 25% would be of interest.</li> <li>Median duration of response should be at least four months.</li> <li>Efficacy should be determined separately in the DR and BFR subgroups.</li> </ul>
9/2006	406 Protocol Amendment	<ul style="list-style-type: none"> <li>Protocol Amendment 2 removed the inclusion criterion specifying that patients may be intolerant to or ineligible for treatment with fludarabine (i.e., specified a fludarabine refractory population).</li> </ul>
4/2007	406 Protocol Amendment	<ul style="list-style-type: none"> <li>Specified that the trial populations (DR and BFR) were to be analyzed separately.</li> <li>Increased sample size from 100 patients total to a sample size of 66 patients each in the DR and BFR subgroups.</li> <li>Removed inclusion criteria specifying that patients may be ineligible for alemtuzumab for reasons other than being BFR (i.e., refractory).</li> </ul>
9/6/2007	Letter to Genmab	<ul style="list-style-type: none"> <li>Nonclinical reproductive and developmental toxicity studies would not be required in support of a BLA for CLL; however, these studies may be required in support of marketing authorization for any non-oncology indications.</li> <li>Genotoxicity and carcinogenicity studies would not be required in support of a BLA for CLL.</li> </ul>
10/2007	406 Protocol Amendment	<ul style="list-style-type: none"> <li>Increased the sample size in the DR and BFR groups from 66 to 100 patients.</li> <li>Revised the analysis plan to include an interim analysis for efficacy when data from 66 DR patients were available.</li> </ul>
4/2008	Sponsorship Change	<ul style="list-style-type: none"> <li>Sponsorship of study Hx-CD20-406 was transferred from Genmab A/S to GSK.</li> </ul>

Date	Nature of Regulatory Activity	Issues
9/29/2008	Pre-BLA Meeting	<ul style="list-style-type: none"> <li>• Pre-BLA meeting with GSK, Genmab, and FDA. Issues raised by FDA included:               <ul style="list-style-type: none"> <li>○ The patient population studied in the BFR group did not meet the regulatory standard for having unmet medical need; the protocol only required prior therapy with one drug (fludarabine).</li> <li>○ 1996 NCIWG criteria did not require radiographic evaluation (unless to confirm CR) and the IRC were not provided with radiographs for most patients.</li> <li>○ Independent review, which relied on investigators' measurements of lymph nodes, liver, and spleen rather than review of radiographs was not "truly independent."</li> </ul> </li> </ul>
10/15/2008	Letter to GSK	<ul style="list-style-type: none"> <li>• Letter regarding an SPA request for study / /; the SPA was denied due to lack of agreement on the proposed dose and schedule of ofatumumab</li> </ul>
12/8/2008	Protocol Submission	<ul style="list-style-type: none"> <li>• Protocol OMB110913 was submitted as the confirmatory trial to confirm clinical benefit (a phase III, open label, randomized trial of ofatumumab in combination with fludarabine-cyclophosphamide versus fludarabine cyclophosphamide combination in subjects with relapsed B-cell chronic lymphocytic leukemia)</li> </ul>

b(4)

## 2.6 SGE Comments to FDA

Additional comments were provided via email by the FDA consultant (SGE) on August 19, 2005. The consultant stated that there is not an unmet medical need in patients who were refractory to fludarabine or cladribine alone. The SGE stated that the definition of refractory (to fludarabine) should include disease progression within 6 months of starting therapy (rather than 12 months after the cessation of previous treatment).

## 2.7 Other Relevant Background Information

### 2.7.1 Background Related to CLL

Chronic lymphocytic leukemia (CLL) occurs at an age adjusted incidence rate of 4.1 per 100,000 for men and women each year (SEER database, 2009). The median age at diagnosis is 72 years and the incidence of CLL in men is approximately twice that in women (SEER database, 2009). Survival for patients with CLL can be variable with over half of patients living longer than 10 years; however, reported median survival is only two to three years for patients with high risk disease, i.e., Rai category III or IV or Binet stage 3 (SEER database, 2009, Rai et al., 2004). Survival is expected to be shorter for patients who have progressed following multiple lines of different chemotherapy. In a literature report based on single-center experience, the median survival of 54 patients refractory to alemtuzumab and fludarabine was 8 months (Tam, 2007).

As will be discussed in Section 6 of this review, patients in the double refractory group (i.e., refractory to fludarabine and alemtuzumab), most of who also received alkylating agent therapy, were enrolled into the primary study supporting efficacy.

Choice of therapy for CLL is influenced by age and co-morbid conditions. Patients who are younger than 70 and have limited co-morbidities are frequently treated with combination chemotherapy (NCCN practice guidelines, accessed June 2009).

## **2.7.2 Approval History of other CLL Drugs**

Table 6 describes the bases for approval of five drugs for the treatment of patients with CLL. In the past decade, regular approval for the treatment of CLL has been based on demonstration of superior progression-free survival (PFS), while accelerated approval has been granted based on demonstration of durable objective tumor responses in patients with CLL that has progressed following available therapy.

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

Alemtuzumab received accelerated approval (Subpart E) in 2001 based on the results of three single-arm studies enrolling a total of 149 patients with CLL and progressive disease following alkylating agents and fludarabine. The overall response rate (ORR) in the three studies ranged from 21% to 33% with median durations of response of 7 to 11 months [Campath (alemtuzumab) package insert, 2001].

Alemtuzumab was granted regular approval in 2007, on the basis of superior PFS [HR 0.58 (95% CI 0.43, 0.77),  $p < 0.0001$  stratified log-rank test] in a randomized active-controlled study comparing alemtuzumab to chlorambucil in previously untreated patients with CLL. Alemtuzumab also demonstrated an improvement in ORR (83% and 55%) and complete response rates (24% vs. 2%) compared to chlorambucil.

Bendamustine was granted regular approval in 2008 on the basis of superior PFS [HR 0.27 (95% CI 0.17, 0.43)  $p < 0.0001$ ] in a randomized active-controlled study comparing bendamustine to chlorambucil in previously untreated patients with CLL. Bendamustine also demonstrated an improvement in ORR (59% vs. 26%) and complete response rates (8% vs. <1%) compared to chlorambucil.

**Table 6: Bases for Approval of CLL Drugs**

Drug	Initial Approval	Basis for Later Approval
chlorambucil	March 18, 1957	Not described in the label
cyclophosphamide	November 16, 1959	Not described in the label
fludarabine	April 18, 1991 (regular)	ORR in two single arm studies (n=48 and 31). ORR was 48% and 32% with a median DOR of 1.75 and 1.25 years, respectively. CR rate was 13% in both studies.
alemtuzumab	May 7, 2001 (accelerated)	ORR in three single arm studies (total n = 149). ORR was 21-33% with CR rate of 0 to 2%. Median DOR was 7 to 11 months.
alemtuzumab	September 17, 2007 (regular)	Improved PFS compared to chlorambucil [HR 0.58 (95% CI 0.43, 0.77), p<0.0001 stratified log-rank test]. ORR in untreated patients was 59% with CR rate of 8%.
bendamustine	March 20, 2008 (regular)	Improved PFS compared to chlorambucil. [HR 0.27 (95% CI 0.17, 0.43) p<0.0001]. ORR in untreated patients was 59% with a CR of 8%.

### 2.7.3 Consideration of Unmet Medical Need (Regulatory Standard)

#### Double Refractory

The primary population under consideration by FDA for accelerated approval in this BLA is the double refractory (DR) CLL population studied in Hx-CD20-406. This patient population was refractory to both fludarabine and alemtuzumab. Among this group, 93% of patients had received prior alkylating agent therapy and 59% received off-label treatment with rituximab. The median number of prior therapies in this group was five, indicating heavy pretreatment. As will be described in Section 6 of this review, 88% of patients in the double refractory group received an alkylating agent other than chlorambucil alone or received a combination alkylating agent regimen (this analysis was done because single-agent chlorambucil demonstrated inferior PFS to both alemtuzumab and bendamustine in separate randomized trials).

Bendamustine was approved for CLL in 2008 based on the results of a randomized study comparing bendamustine to chlorambucil in patients with untreated CLL (Table 6).

Bendamustine is an alkylating agent drug that was studied in the first line setting. As will be shown in Section 6 of this review, over 90% of patients in study Hx-CD20-406 received alkylating agent therapy.

GSK submitted a briefing document to the BLA on April 21, 2009 describing the experience of bendamustine in patients with previously treated CLL. The briefing document stated that literature reports describing bendamustine use in patients with refractory CLL were few in number. This reviewer independently evaluated these reports and also conducted a separate PubMed search of the literature, which did not identify additional reports of bendamustine monotherapy for CLL. A summary of these reports can be found in Table 7. Few patients in

these reports had received prior fludarabine. One objective response to bendamustine (Kath et al., 2001) was reported in a patient who received prior fludarabine; however, it was not identified whether this patient was refractory to fludarabine, and this patient had received only one prior therapy. There were no responses reported among four patients who were deemed “resistant” to fludarabine in the Bergman study.

**Table 7: Literature Reports of Bendamustine Monotherapy for CLL**

Study	Population	N	Reported ORR*	Toxicity
Lissithkov et al., 2006	Pre-treated, fludarabine naive	15	40%	50% ≥ Grade 3 infection rate
Bergman et al., 2005	Pre-treated with either fludarabine or chlorambucil (four were resistant to fludarabine)	16	44%; 0% among four fludarabine refractory patients	50% ≥ Grade 3 leukopenia; 44% ≥ Grade 3 infections; 6/16 patients experienced dose limiting toxicities after one cycle
Kath et al., 2001	Rai stage III or IV (13/23 chemotherapy naive; only two received prior fludarabine)	23	65% (one of two patients previously treated with fludarabine responded)	51% ≥ Grade 3 leukopenia; three patients died due to infection; Four patients died of cardiac events

\* These response rates were derived from literature reports and not confirmed by FDA; only PRs and CRs in the literature reports were considered to be responses

Although bendamustine has shown activity (Table 7) in previously treated patients with CLL, the effects of bendamustine in patients previously treated with fludarabine (or alemtuzumab) are largely unknown. Because > 90% of the (ofatumumab) 406 double refractory study population also received an alkylating agent in addition to fludarabine and alemtuzumab, it is unlikely that an additional alkylating agent (bendamustine) would represent satisfactory alternative therapy in this patient population. Thus, this reviewer accepts that the DR group evaluated in study 406 represents a population with unmet medical need.

#### **Bulky Fludarabine Refractory**

As discussed in the ODAC briefing document, FDA does not consider the patient population studied in the separate bulky fludarabine refractory (BFR) group as meeting the *regulatory* standard for having unmet medical need; the protocol only required prior therapy with one drug (fludarabine). The Office of Oncology Drug Products (ODDP) determined that GSK will need to conduct a comparative study in order to support approval in a patient population (BFR) who were only required to be refractory to one drug. Data from the BFR patient population and from “other” CLL patients enrolled in study Hx-CD20-406 and data from patients enrolled in study Hx-CD20-402 will be considered supportive of an approval determination regarding ofatumumab for the DR patient population.

The following additional factors were considered regarding the BFR group and the regulatory criteria regarding unmet medical need:

- Approval of ofatumumab for the BFR group would imply a comparative effectiveness claim versus alemtuzumab (without comparison in a randomized clinical trial).
- Patients with bulky lymphadenopathy can have a significant response to alemtuzumab. Patients with bulky lymphadenopathy (n=33) receiving alemtuzumab in study CAM307 in the first line setting achieved a published response rate of 76% compared to 44% with chlorambucil (Hillmen, 2007).
- The extent of the data regarding patients with bulky lymphadenopathy in patients with CLL is limited. Additionally, Section 6 of this review will describe uncertainty related to the assessment of response rate in patients with CLL using the NCI Working Group Criteria.

#### **2.7.4 CT Scans in the Response Assessment of CLL**

To support this BLA, GSK used the 1996 National Cancer Institute-sponsored Working Group (NCIWG) Guidelines for CLL (Cheson et al., 1997) to define responses and progression. The specific criteria to define CR, nPR, PR, and progression can be found in section 5.3. The 1996 NCIWG criteria did not require that patients undergo follow-up CT scans to confirm a partial response or disease progression. Follow-up CT scans were required only to confirm a complete response.

Since the criteria for a partial response requires a reduction in lymphadenopathy and of either hepatomegaly or splenomegaly of  $\geq 50\%$ , an accurate assessment of lymph node, liver, and spleen size is important. Small errors in investigator measurements by physical examination may result in misclassification of response assessments.

The recently revised NCIWG CLL guidelines (Hallek et al., 2008) state that for clinical trials, CT scans are “desirable.” The revised guidelines further state that in clinical trials, CT scans are recommended to evaluate response to therapy as the intent is to maximize CRs. Furthermore, in the section describing PRs, the 2008 guidelines state that reduction in lymphadenopathy and hepato-splenomegaly should be measured by CT in clinical trials.

The following literature was evaluated to determine whether radiography adds to the accuracy of lymph node or spleen measurements compared to physical examination:

- Blum et al., 2007: This single-center retrospective review evaluated 82 patients with CLL. Using NCIWG criteria, there were 32 PRs and 5 CRs, with 7 “non-assessable” patients. Using NHL-CT criteria, there were 3 CRs, 12 unconfirmed CRs, 16 PRs, and 21 “non-assessable” patients. Thus, the ORR using NCI criteria was 45% versus 39% (representing 6% fewer responses using CT criteria). *This reviewer believes that this study did not adequately answer the question of the utility of CT scans to increase the accuracy of response determination in patients with CLL. There was no centralized review of radiographs. Furthermore, clinical investigators were not blinded to CT scan results meaning that physical examination measurements might have been influenced by the prior knowledge of radiograph results. Finally, this reviewer believes that the difference in non-assessable patients between analyses was too large to allow for an appropriate comparison.* An accompanying editorial by Thomas Kipps (2007) described situations in which CT scanning is useful in CLL including stratification

- of patients and the detection of splenomegaly. Kipps concluded that additional studies were necessary to determine the relative value of CT scans in the monitoring of patients with CLL.
- Bruneton et al., 1987: Lymph node measurements by physical examination and ultrasound were compared in the cervical, axillary, and inguinal regions in 120 patients with lymphoma. Ultrasound detected clinically impalpable lesions in 10.8% of cases in the cervicosupraclavicular region, 17.8% in the axillary region, and 4.1% in the inguinal region. Eight of 29 (28%) relapses were not detected by physical examination. *This article contradicts the findings of the Blum study because 28% of relapses were not detectable by physical examination. Because the definition of response in CLL requires a duration of at least two months, inability to detect lymphadenopathy in 28% of cases may result in an overestimation of the ORR.*
  - Gobbi et al., 2002: Data were obtained from measurements of cervical, supraclavicular, axillary, and inguinal lymph nodes using ultrasound and physical examination. The authors concluded that physical examination tended to underestimate lymph node size in all regions. Correlation was higher for cervical and inguinal nodes ( $R^2$  was 0.90 and 0.80, respectively) than for nodes in the supraclavicular and axillary areas ( $R^2$  was 0.53 and 0.37 respectively). Up to 75% of lymph node measurements in the supraclavicular region, 46% in the axillary region, 32% in the cervical region, and 19% in the inguinal region had errors greater than 50% for physical examination compared to ultrasound.
  - Gerrits et al., 1994: Data were obtained from 47 patients with malignant lymphoma. Ultrasound of the cervical area demonstrated additional pathological lymph nodes compared to physical examination in 6 of 47 patients (13%).
  - Tamayo et al., 1993: Ultrasound of the spleen was evaluated in 27 patients hospitalized with suspected HIV infection. Splenomegaly as detected by ultrasound was present in 33.3% of patients. The range of test sensitivity among three examiners was 0-64.3% for three methods of palpation and 7.7 to 75% for three methods of percussion.
  - Herrada et al., 1997: Physical examination, ultrasound, and mammography were correlated with pathological findings in a retrospective analysis of 100 patients with locally advanced breast cancer. Eighty-three patients had both a clinically detectable primary tumor and lymph node metastases. Physical examination did not correlate well with pathological findings regarding axillary lymph node size [Spearman's rank correlation coefficient ( $r$ ) = 0.318]. Ultrasound was somewhat better with an ( $r$ ) of 0.514.

*In summary, the review of the literature indicates that radiography may be necessary for the accurate response assessment of patients with CLL. The use of available radiographs for supportive efficacy results will be discussed in Section 6. These data were presented to the ODAC for discussion and considered by the Committee (see Section 9.3).*

### **2.7.5 Literature Review of anti-CLL activity of Rituximab**

As described, rituximab is an approved anti-CD20 therapy for patients with lymphoma and rheumatoid arthritis. In module 2.7.3 of the BLA submission, GSK stated that rituximab is not approved for CLL and has limited efficacy as monotherapy. Furthermore, GSK stated that response rates remained low when rituximab doses were increased from 375 mg/m<sup>2</sup> to 2,250

mg/m<sup>2</sup> in fludarabine refractory CLL. In order to assess these statements, this reviewer evaluated the literature using PubMed.

Table 8 contains (published) study results for rituximab monotherapy in CLL (the Castro study evaluated rituximab and high dose steroids). These studies show that rituximab has anti-CLL activity (however, primary data from these studies have not been verified by FDA). *Comment: This reviewer disagrees with the GSK statement that rituximab has limited efficacy as monotherapy. It would be appropriate to state that the efficacy of rituximab as monotherapy in patients with CLL (fludarabine sensitive or refractory) is unknown because of the following: rituximab monotherapy studies had small sample sizes, and the optimal dose and schedule of rituximab may not be known.*

**Table 8: Studies Reviewed Regarding Rituximab as Monotherapy for CLL**

STUDY	RESULTS
Byrd et al., 2001	33 previously treated patients (untreated patients were eligible if Coomb's positive or "not appropriate for other chemotherapy") with CLL/SLL received 1 dose of rituximab 100 mg/m <sup>2</sup> followed either 250 or 350 mg/m <sup>2</sup> three times weekly for a total of four weeks (12 doses). The reported ORR was 45% with median response duration of 10 months. The investigators reported responses in 7/17 (41%) fludarabine refractory patients.
Huhn et al., 2001	30 patients with previously treated CLL received rituximab 375 mg/m <sup>2</sup> weekly for four weeks. Seven of 28 (ORR of 25%) treatment evaluable patients showed a partial response according to the investigators.
O'brien et al., 2001	40 patients with CLL received escalating doses of four weekly infusions of rituximab. The first dose was 375 mg/m <sup>2</sup> for all patients. The overall reported response rate was 36% in patients with CLL. The investigators reported a 75% ORR at the highest doses in 8 patients with CLL (all PRs). Patients had received a median of 2 prior treatments and 53% of the population was refractory to fludarabine. The reported overall response rate in fludarabine refractory patients was lower (20%); however the number of fludarabine refractory patients who received the highest dose (n=8) was not reported.
Itala et al., 2002	24 patients with CLL received rituximab 375 mg/m <sup>2</sup> weekly for four weeks. The investigator reported ORR was 35% (all PRs). The ORR was 20% among 10 patients refractory to fludarabine.
Hainsworth et al., 2003	44 previously untreated patients with CLL received rituximab 375 mg/m <sup>2</sup> weekly for four weeks. Patients who achieved a response or had stable disease continued to receive rituximab at 6 month intervals. The published ORR after the first course was 51% with 4 CRs. The published ORR overall was 58% with 9 CRs.

Castro et al., 2008	Fourteen fludarabine-refractory patients received rituximab (375 mg/m <sup>2</sup> ) and high dose methylprednisolone (1 gm/ m <sup>2</sup> daily for five days). The investigator reported ORR was 93% with a CR rate of 36%.
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## 2.7.6 Literature Review of Anti-CLL Activity of Corticosteroids

Because corticosteroids have been used in the treatment of patients with lymphoma and CLL, the literature was reviewed to determine whether corticosteroid premedication administered during the ofatumumab clinical trials might have induced responses.

Thornton (1999) et al., studied the effects of high dose methylprednisolone at a dose of 1 gm/m<sup>2</sup> daily for five days at four weekly intervals in previously treated patients with CLL. The investigators reported that 6 of 11 evaluable patients had a partial response. The Castro study described in Table 8 showed a high reported rate of activity when high dose methylprednisolone was combined with rituximab.

One literature report (Dighiero et al., 1977) evaluated corticosteroids at doses similar to those administered as premedication to patients in the Hx-CD20-406 study submitted as evidence to support this BLA. A total of 23 controls and 51 patients (43 CLL) with lymphoid disorders received a single IV injection of 400 mg hydrocortisone (*Comment: this dose of hydrocortisone is equivalent to approximately 100 mg of prednisolone*).

In the Dighiero study, a reduction in lymphocyte counts was observed in all normal controls after receiving hydrocortisone. In CLL patients, the peripheral lymphocyte counts showed a variable response to hydrocortisone. A total of 10 of 18 patients with Rai stage 0 CLL had a reduction in lymphocyte count of greater than 20% after receiving hydrocortisone. However in advanced CLL, the following numbers of patients experienced lymphocyte count reductions of greater than 20%:

- 1 of 22 (5%) with lymph node enlargement
- 2 of 15 (13%) with splenomegaly
- 0 of 2 with hemoglobin of < 10 gm/mcL
- 0 of 4 with a platelet count < 100,000/mcL
- 2 of 25 patients with Rai stage I-IV

*In summary, corticosteroids used at doses administered as premedication for ofatumumab appear to have limited effects on patients with advanced CLL. Higher dose corticosteroids may have more pronounced lympholytic effects. This reviewer acknowledges the possibility that corticosteroid premedication might add to the anti-CLL effects of ofatumumab [such as that described in the Castro (2008) study]; however, these doses of corticosteroids as monotherapy would unlikely result in sustained responses.*

## **3 Ethics and Good Clinical Practices**

### **3.1 Submission Quality and Integrity**

#### **3.1.1 Quality**

The BLA submission was of adequate quality to allow for the review to be conducted. The following items were identified as obstacles to the conduct of a timely review:

- Absence of a separate column in the laboratory datasets indicating which lab results were selected as the baseline result.
- Multiple CRF AE pages had strike-outs removing AEs from the datasets without adequate explanation. GSK adequately responded to an FDA inquiry regarding a subset of these CRFs on May 18, 2009; however, the causes of these deletions should have been completely described in the initial BLA submission.
- There were multiple copies of certain pages of the CRFs; some with crossed-out data. The primary CRF was not stamped to allow for ease of navigation of CRFs.
- In the original BLA submission, the applicant did not provide an explanation of the approach that the independent review committee used to identify responding patients. Triggers for the consensus IRC review for applicable patients were not identified. Datasets were not provided for overall reader responses from the IRC evaluations to the original BLA. GSK responded to these deficiencies on May 19, 2009.
- The dataset for overall survival contained an error in the comments section that described the derivations of the variables OS and OS01.

#### **3.1.2 Integrity**

During the BLA review, one serious issue of integrity/quality was identified during the FDA clinical review. As described in the FDA briefing document, prior to the Oncology Drugs Advisory Committee, certain "responding" patients were identified who appeared to be considered by the IRC as responding (to ofatumumab) despite clear evidence of non-response (per the opinion of this reviewer). Two of these patients in the DR CLL population (406199 and 406203) were identified by GSK in a May 19, 2009 addendum to the BLA as being mistakenly identified as responders. Two additional patients in the BFR CLL population were also mistakenly identified as responders. These mistakes were described as a data entry error that occurred during the IRC re-consensus process. This reviewer considers these errors regarding response determinations to be a serious data integrity issue because durable response is the primary surrogate endpoint for the approval consideration of ofatumumab (refer to Section 6 of this review for additional discussion of these cases, including the FDA decision to use the investigator-determined response rate as opposed to the IRC-determined response rate for approval considerations).

Additionally, despite the identification of these patients as non-responders by GSK on May 19, 2009, these patients were classified as responders by GSK at the May 29, 2009 Oncology Drugs Advisory Committee meeting. GSK presented a 58% ORR (IRC) in the DR population as opposed to a 54% ORR that would have been valid if patients 406199 and 406203 were no longer considered as responding to ofatumumab. Ultimately, the ODAC vote was not affected by this omission because (for reasons to be described in Section 6) FDA asked the ODAC members to consider the investigator determined response rate of 42% rather than the IRC determined response rate.

### 3.2 Compliance with Good Clinical Practices

All studies submitted to the BLA contained a statement that the trial was conducted or is being conducted (for ongoing trials) in accordance with the Declaration of Helsinki and Good Clinical Practice. GSK supplied audit certificates for applicable study sites that were audited. CRFs for 154 patients were submitted for study Hx-CD20-406. All AEs in the database were audited in this review; certain demographic data were also audited. Refer to section 7 of this review for a discussion of database/CRF audit findings regarding AEs. In general, demographic data contained within the CRFs matched the data in the datasets.

#### 3.2.1 DSI Inspections

Five sites were chosen for inspection based on the number of patients enrolled at the site or a high response rate that was observed at a particular site. Three U.S. and two ex-U.S. inspections were conducted. DSI also inspected the records of the study sponsor (Genmab). Table 9 shows the sites selected for inspection and the preliminary inspection results.

**Table 9: DSI Inspections: Study 406**

Site/Clinical Investigator/Location	Number of Subjects	Inspection Dates	Preliminary Inspection Results
Site US02 Thomas Kipps UCSD Moores Cancer Center La Jolla, CA	14 Subjects	March 19 – April 1, 2009	VAI
Site US01 William Wierda MD Anderson Cancer Center Houston, TX	8 subjects	April 27 – 29, 2009	NAI – data acceptable
Site US12 Richard Furman Weill Medical College of Cornell New York, New York	10 subjects	March 31 – April 2, 2009	NAI – data acceptable

Clinical Review  
 Steven Lemery/Jenny Zhang  
 BLA 125326  
 Ofatumumab/Arzerra

Site/Clinical Investigator/Location	Number of Subjects	Inspection Dates	Preliminary Inspection Results
CZ02 Jiri Mayer Faculty Hospital Brno Brno, Czech Republic	9 Subjects	Completed May 22, 2009	NAI – data acceptable
CZ05 Tomas Kozak Faculty Hospital Kralovske Vinohrady Srobarova Prague, Czech Republic	5 Subjects	Completed May 29, 2009	NAI – data acceptable
Genmab Copenhagen, Denmark	N/A	June 15, 2009	NAI – data acceptable

A preliminary VAI (voluntary action indicated) determination was made for the US02 site based on multiple inconsistencies regarding infusion rates and infusion times and incomplete documentation (primarily regarding infusions). These deficiencies were such that although corrective actions were indicated at site US02, the deficiencies were unlikely to affect the overall study results for safety or efficacy. DSI inspection of Genmab records indicated active communication between Genmab, the CRA monitor, and this study site to bring this site into compliance.

### 3.2.2 Protocol Violations Study Hx-CD20-406

#### Inclusion/exclusion

In study Hx-CD20-406, GSK stated that 28 patients (18%) received exemptions and were included in the trial despite not formally fulfilling all inclusion and exclusion criteria. The most common protocol deviation occurred due to patients having a positive serology for hepatitis B. The protocol was subsequently amended to allow patients with a positive test for the hepatitis B surface antibody to be eligible if the surface antigen and core antibody were not present.

Two patients received alemtuzumab within 6 weeks prior to visit 2. One of the two patients was considered a responder to ofatumumab (406261) and received ofatumumab approximately one week earlier than permitted by the protocol. This patient was considered by the investigator as requiring clinical intervention at the earliest opportunity.

One ineligible patient entered in the 406 study experienced a serious adverse event related to the specific reason for ineligibility. Patient 406244 had clinically significant cardiac disease that was not intercepted at enrollment “by mistake.” This patient experienced a myocardial infarction 12.6 weeks following the start of treatment and was withdrawn from the study.

#### Exclusion from the full analysis set

Seven patients were excluded from the full analysis set because they were not treated with ofatumumab. Four were ineligible according to the selection criteria at the second designated visit (first ofatumumab infusion). One patient had disease progression prior to the first infusion.

One additional patient withdrew consent and one patient withdrew from the study due to deep vein thrombosis (DVT) prior to the first infusion. *Comment: Exclusion of these patients is acceptable for an analysis of ORR; however, in a randomized study, such patients would generally be included in an ITT analysis of PFS or OS. The exclusion of such patients is one reason that including PFS or OS results in product labeling is not appropriate for this product.*

**Additional deviations/violations**

In the listings of protocol deviations, there was a comment that stated the following: “this is part of a larger issue with the site [UK06] where it was clear that the clinicians were not necessarily being consistent in their lymph node evaluations.” The DSI inspection of Genmab noted that there was active communication between Genmab, the CRA monitor, and this study site in order to bring this site into compliance. *Comment: It is unlikely that the results from this site affected the overall study results. Of five patients enrolled at site UK06, only two were classified by investigators as responding.*

Additional examples of missing lymph node measurements can be found in Table 10 below. Most deviations not included in Table 10 would, in the opinion of this reviewer, not be expected to affect the overall study results (for example, requests to delay the date of drug infusion due to a patient receiving a blood transfusion on the same day).

**Table 10: Study Hx-CD20-406 Protocol Deviations /Violations (Partial Listing)**

Patient	Protocol Group	Deviation	Comments
406109	DR	No lymph node examination during visit 2 (first dose)	Non-responder; unlikely to affect study results
406129	DR	The patient received dexamethasone 40 mg prior to visit 21	Non-responder
406145	DR	The patient received prohibited methylprednisolone for chronic bronchitis	Non-responder
406165	DR	Wrong dosage administered during week 14 (the patient received 19 vials instead of 20)	Responder (Not expected to affect results; however this is a concern for a product that requires the administration of drug from 20 vials)
406195	DR	The patient received three doses of prednisone due to a slipped disk	Responder
406218	DR	Lymph node size was not measured for two lymph nodes at visit 21 (for new nodes)	Non-responder (responder per IRC)
406228	DR	Investigator previously identified two abdominal masses at visits 2, 6, and 10. At visit 11, the investigator could not discern the two masses and was instructed to record a confluent mass at a new location	Non-responder
406103	DR	Bone marrow examination performed 6 weeks prior to the first dose instead of two weeks	Non-responder

Patient	Protocol Group*	Deviation	Comments
406172	BFR	Received hydrocortisone three weeks prior to the first ofatumumab dose rather than 4 weeks specified by the protocol	Non-responder
406178	BFR	Received prohibited medication (prednisone) for 6 days	Responder
406183	BFR	Received prohibited methylprednisolone for palliative CLL treatment	Responder (Non-responder per IRC)
406193	BFR	Received prohibited medication prior to visit 21	Responder
406202	BFR	Lymph node at the nape of the neck was not assessed at visit 2	Non-responder
406123	BFR	Lymph nodes and ECOG status were not assessed at visit 2	Non-responder
406221	BFR	Informed consent document was lost; site inspection confirmed that the ICF was initially signed	Non-responder
406229	BFR	One dose of prednisone that would have made the subject ineligible to receive the first dose of ofatumumab was administered prior to a CT scan	Non-responder
406251	BFR	Size of new lymph nodes was not documented at visit 21 (end of study visit)	Non-responder
406106	BFR	Received prohibited medication (hydrocortisone) between visits 10 and 11 (for four days)	Responder
406151	Other	Nineteen vials were used for two infusions instead of the full 20	Responder (Not expected to affect results; however this is a concern for a product that requires the administration of drug from 20 vials)
406191	Other	At visit 10, lymph nodes were assessed by a different investigator who assessed nodes as femoral right and left (new site) versus inguinal right and left.	Responder

\* DR = double refractory; BFR = bulky fludarabine refractory; O = other; Responses are according to investigators

**Reviewer conclusions regarding Hx-CD20-406 protocol violations:**

*These violations were unlikely to affect the overall results of the study. Most patients who received prohibited corticosteroids during the course of the protocol were non-responders. Most of the responding patients received prohibited corticosteroids for too short a time to (likely) affect whether the patient responded.*

**The following problematic issues, however, were noted during the review of protocol violations:**

- *The potential for inconsistencies regarding lymph node measurements by physical examination. A more thorough review of the efficacy of ofatumumab can be found in Section 6.*

- *The potential for dosing errors due to the requirement for 20 vials of ofatumumab to prepare the entire 2,000 mg dose.*
- *The potential for medication errors and adverse events that may occur due to the in-line filter being clogged. Site US02 reported two instances of clogged filters and reported a technical complaint to the Genmab QA department. In both cases the site prepared a new infusion bag to allow for the remaining drug product to be infused.*

### 3.2.3 Protocol Violations Study Hx-CD20-402

Most protocol violations that were reported in study Hx-CD20-402 were unlikely to affect the overall study results. Potentially relevant violations/deviations can be found in Table 11. The table also describes whether these patients were considered responders as documented in the RESP dataset.

**Table 11: Study Hx-CD20-402 Protocol Deviations /Violations (Partial Listing)**

Patient	Protocol Group	Deviation	Comments
402605	A	Spleen and liver not examined during visit 11	Non-responder
402602	C	The patient was enrolled in the study too soon after completing prior therapy	Non-responder
402606	C	Physical examination was not complete during visit 11 and there was no bone marrow examination during visit 17	Responder (PR)
402610	C	Physical examination was not performed during visit 13	Non-responder
402621	C	There was no neck CT scan performed at the screening visit	Responder (PR)
402649	C	There were no details regarding lymph node size at visit 11 and visit 12	Non-responder

### 3.2.4 Protocol violations from other studies

Protocol violations from studies Hx-CD20-403 (parts A and B) and Hx-CD20-001 were reviewed specifically to determine if any instances of filter complications or medication errors occurred (for example, due to the number of vials required). No additional violations in these categories were discovered during the review.

### 3.3 Financial Disclosures

GSK submitted Form 3454 for studies Hx-CD20-406 and Hx-CD20-402. For study Gx-CD20-406, GSK checked box number 1 indicating that the sponsor certified no financial arrangements with listed clinical investigators. GSK provided a list of clinical investigators who certified that they had no financial conflicts of interest as defined in 21 CFR 54.2(a)(b) and (f).

GSK submitted one form 3455 for ( ) indicating that he had significant equity interest (\$80,000) as defined in 21 CFR 54.2(b). ( ) was a sub-investigator at US site number ( ) that enrolled ( ) who was classified by the investigator at the site as a ( ) ( ) Thus, it is unlikely that this financial conflict of interest affected the overall study results.

b(6)

In the BLA, GSK provided a list of investigators for whom the required financial information could not be obtained. GSK stated that based on internal documentation, none of these investigators had disclosable financial interests. However, updated information could not be obtained. All investigators on the list were sub-investigators who could not be located.

For study HX-CD20-402, GSK checked off box number 2 on form 3454 indicating that the study was sponsored by a firm (Genmab) other than the applicant. No financial conflicts of interest were reported as defined in 21 CFR 54.2(a)(b) and (f). Information for one sub-investigator could not be obtained.

## **4 Significant Efficacy/Safety Issues Related to Other Review Disciplines**

### **4.1 Chemistry Manufacturing and Controls**

The following issues were identified by CMC reviewers as of June 20, 2009 relating to the safety and efficacy of ofatumumab. This list should be considered a partial summary of certain pertinent CMC issues. Please refer to CMC reviews for a full description of CMC issues.

- Ofatumumab is to be administered using an infusion filter that is to be provided with the drug product.
- The preparation of the 2,000 mg dose of ofatumumab requires the contents of 20 vials. The requirement for 20 vials may potentially result in medication errors.
- As of April 6, 2009, the cell based, complement dependent cytotoxicity assay required revalidation.
- Qualified assays are available for the detection of product neutralizing antibody and isotyping antibody.
- During the review, CMC reviewers discovered out-of-specification results for the test parameter sub-visible particles greater than or equal to ( ) at 36 months from one drug product (DP) lot at ( ) and from four DP lots at 12 months at the Barnard Castle manufacturing site. As a result, a letter was issued to GSK on May 11, 2009 requesting further analysis of these sub-visible particles and identification of the root causes of these particulate formations. Also requested was information regarding leachates from container/closure systems and additional information regarding product release specification. GSK submitted their response to the May 11, 2009 letter on June 5, 2009. GSK indicated,

b(4)

based on microscopy and vibrational spectroscopy results, that the particles are likely related to drug product. Based on GSK's responses, additional information was requested on June 19, 2009. At the time of the completion of this clinical review, GSK's responses to the CMC information requests are under review by FDA CMC reviewers.

## 4.2 Clinical Microbiology

At the time of the mid-cycle meeting held on April 6, 2009, the following issues were identified: validation of hold times for protein intermediates; container closure integrity validation; and shipping validation. Minor issues included endotoxin monitoring, qualification of protein intermediates for bioburden and endotoxin tests, and bioburden limits and sample volumes. Requests regarding these issues were communicated to GSK in the 74-day letter sent to GSK on April 14, 2009. Based on GSK's responses and additional microbiology review, additional requests were made to GSK by FDA on June 19, 2009 regarding microbial control. Final review of these issues is ongoing.

## 4.3 Preclinical Pharmacology/Toxicology

GSK conducted sufficient non-clinical toxicology studies to support the refractory (alemtuzumab and fludarabine) CLL indication. Additional studies may be necessary, however, to support non-oncology indications. Pivotal non-clinical toxicology studies were limited to one species, the cynomolgus monkey, because ofatumumab did not bind to rat, mouse, rabbit, dog, or pig tissues.

As expected, ofatumumab resulted in B-cell depletion in the cynomolgus monkey. Nonclinical safety issues identified in the monkeys included an increased risk of infection, reduced immune response to KLH antigen, infusion reactions, delayed onset anemia (hemolysis), and fetal toxicity.

## 4.4 Clinical Pharmacology

### 4.4.1 Mechanism of Action

Ofatumumab is an anti-CD20 antibody directed against CLL cells that express CD20. Ofatumumab is a full length IgG1 $\kappa$  human monoclonal antibody produced in a murine transfectoma NSO cell line. Ofatumumab recognizes an epitope that encompasses both large and small extracellular loops of CD20. Ofatumumab binds to a different epitope than the epitope recognized by rituximab, an anti-CD20 antibody licensed for the treatment of patients with lymphoma and rheumatoid arthritis. The probable mechanisms of action are through antibody-dependent cellular cytotoxicity and/or complement-dependent cytotoxicity. *Comment: There is no evidence to date that any non-clinical differences between ofatumumab and rituximab will translate into differences in either the safety or effectiveness of either product. Ofatumumab and rituximab have not been compared against each other in clinical trials for any indication.*

#### 4.4.2 Pharmacodynamics

Because normal B-lymphocytes express CD20, treatment with ofatumumab results in prolonged depletion of normal B-cells. A detailed description of this pharmacodynamic action is described in section 7 (laboratory results section) of this review.

#### 4.4.3 Pharmacokinetics

As of April 6, 2009, the following pertinent issues were identified by the clinical pharmacology reviewers.

- Ofatumumab displayed dose-dependent pharmacokinetics with a large inter-subject variability.
- Clearance of ofatumumab is reduced as CD20 cells (normal or abnormal) are depleted from circulation (or tumors).
- In study 402, immunogenicity appeared to decrease clearance and increase the AUC of ofatumumab.
- No dose adjustments were necessary for special populations.

*Comment: Because the numbers of CLL patients treated with alternative doses of (single-agent) ofatumumab were small (6 total patients at two lower doses), no definitive statements can be made regarding dose-response or dose-toxicity relationships.*

### 5 Sources of Clinical Data

#### 5.1 Tables of Studies/Clinical Trials

Table 12 lists all trials submitted in support of the BLA application. Some studies were submitted as synopses or interim reports (as agreed by the Division) because they are ongoing. Only studies 402 and 406 are included in the efficacy and primary safety analyses.

**Table 12: Listing of Clinical Trials Submitted to the BLA**

Study Number	Phase	Design	Disease	N <sup>*</sup>	Dose and dose of O (mg, 3)	Control	Status
Hx-CD20-402	1/2	OL, DE	CLL	33#	O (500, 1,000 or 2,000)	None	Supportive study for efficacy (monotherapy for CLL)
Hx-CD20-406	2	OL, SA	CLL	154	O (2,000)	None	Interim results of ongoing "pivotal" CLL study
Hx-CD20-407	2	DR, PA study of O plus chemotherapy	CLL	28	O-FC (1,000)	OFC (500 mg)	Ongoing study
Hx-CD20-001	1/2	OL, DE	FL	40	O (300, 500, 700, or 1,000)	None	Completed study

Study Number	Phase	Design	Disease	N*	Dose and dose of O (mg)	Control	Status
Hx-CD20-405	2	OL, SA	FL	74	O (500 or 1,000)	None	Ongoing; the 500 mg dose cohort was discontinued
Hx-CD20-409	2	DR, PA study of O plus chemotherapy	FL	33	O-CHOP (1,000)	O-CHOP (500)	Ongoing
GEN415/DLBCL	2	OL, SA	DLBCL	4	O (1,000)	None	Ongoing
Hx-CD20-403	2	DB, PC, PA, randomized	RA	201	O (300, 700, or 1,000)	Placebo	Ongoing follow-up
GEN410	3	DB, PC, PA, randomized	RA	54^	O (700)	Placebo	Ongoing
GEN411	3	DB, PC, PA, randomized	RA	12^	O (700)	Placebo	Ongoing
GEN413	2	OL extension of 403	RA	10	O (700)	None	Ongoing
Hx-CD20-408	2	DB, PC, PA, randomized	COPD	5	O (1,000)	Placebo	Terminated prematurely

Abbreviations: O=ofatumumab; F = fludarabine; C = cyclophosphamide; CLL = chronic lymphocytic leukemia; FL = follicular lymphoma; DLBCL = diffuse large B-cell lymphoma RA = rheumatoid arthritis; COPD = chronic obstructive pulmonary disease; OL = open-label; DE = dose escalation; DR = dose ranging; SA = single arm; PA = parallel arm; DB = double blind; PC = placebo-controlled

# 27 patients received the 2,000 mg dose of ofatumumab

^ patients received ofatumumab or placebo

\$In certain studies, patients received a lower dose of ofatumumab for the first dose

\*Number of patients enrolled at the time of data cut-off

## 5.2 Review Strategy

Safety and efficacy data, including clinical study reports, CRFs, and datasets, were reviewed for studies Hx-CD20-406 and Hx-CD20-402. These two studies were the only studies submitted to the BLA that evaluated ofatumumab monotherapy in patients with CLL. All other studies submitted to the BLA were primarily reviewed for serious adverse events and deaths. These other studies were conducted in different patient populations and utilized lower doses of ofatumumab. Section 5.3 contains a detailed description of the design of study Hx-CD20-406 and a review of the design of study Hx-CD20-402. Other studies are briefly described in section 5.3.

## 5.3 Discussion of Individual Studies/Clinical Trials

### 5.3.1 HX-CD20-406

This BLA is primarily supported by results from one study, Hx-CD20-406:

A single-arm, international, multi-center trial of ofatumumab, a fully human monoclonal anti-CD20 antibody, in patients with B-cell chronic lymphocytic leukemia who have failed fludarabine and alemtuzumab

This study was an industry sponsored international trial conducted in Europe and nine sites in the United States (26% of 156 enrolled patients). The 406 clinical study report contains data from the first patient visit (visit date June 13, 2006) until the date of primary data cut-off (November 27, 2007). Table 13 shows the dates that the initial protocol and each amendment were finalized. The following section of this review describes the final 406 study design. Important details of protocol amendments are described subsequently.

**Table 13: Dates of Amendments for Protocol Hx-CD20-406**

Amendment Number	Date of Amendment
Final Protocol	16-December-2005
Amendment 1	27-February-2006
Amendment 2	26-September-2006
Amendment 3	16-April-2007
Amendment 4	31-October-2007

#### 5.3.1.1 Objectives

The primary objective of the 406 protocol was to “evaluate the efficacy of ofatumumab in patients with B-cell CLL who have failed fludarabine and alemtuzumab.” *Comment: GSK primarily measured efficacy of ofatumumab by using the surrogate endpoint of objective response rate.*

Secondary objectives described in the 406 protocol included determining the safety of ofatumumab; determining the host immune response to ofatumumab; and determining the pharmacokinetic profile of ofatumumab. *Comment: Study 406 is a single-arm study without an internal control. This lack of an internal control complicates the ability to determine whether adverse reactions are caused by ofatumumab. This lack of an internal control is especially problematic in describing any additional risk that ofatumumab confers regarding infections. Patients with CLL who have received prior fludarabine and alemtuzumab are expected to be immunocompromised and have a high background rate of infections (Tam et al., 2007).*

### 5.3.1.2 Inclusion and Exclusion Criteria (copied from the protocol with some modifications for brevity)

#### Important inclusion criteria

- B-CLL phenotype (CD5+, CD20+, and CD23+)
- Active B-CLL and an indication for treatment defined as one of the following (from NCI working group guidelines):
  - Progressive marrow failure with the development of, or worsening, anemia or thrombocytopenia
  - Massive ( $\geq 6$  cm below the left costal margin) or progressive splenomegaly
  - Massive nodal clusters ( $\geq 10$  cm in nodal diameter) or progressive lymphadenopathy
  - Progressive lymphocytosis with an increase in lymphocytes of greater than 50% over a two month period or an anticipated lymphocyte doubling time of less than 6 months
  - 10% or greater weight loss in 6 months
  - Fevers (100.5 F) for  $\geq 2$  weeks without evidence of infection
  - Night sweats without evidence of infection

*Comment: These criteria allowed for the enrollment of patients without measurable disease.*

- Failed at least one fludarabine treatment regimen (minimum of 2 cycles) as defined by failure to achieve at least a PR; disease progression while on a fludarabine regimen; or disease progression in responders within 6 months of the last dose of fludarabine
- Failed at least one alemtuzumab-containing regimen (minimum of at least 12 administrations) as defined by failure to achieve at least a PR; disease progression while on an alemtuzumab regimen; or disease progression in responders within 6 months of the last dose of alemtuzumab
- The protocol stated that subjects may forgo treatment with alemtuzumab if it was determined that such treatment would be inappropriate (one lymph node must be at least 5 cm)
- ECOG 0, 1, or 2
- Age  $\geq 18$  years

#### Important exclusion criteria

- Previous treatment with alemtuzumab within 6 weeks prior to visit 2 (planned first dose of ofatumumab)
- Autologous stem cell transplantation within 6 months prior to visit 2
- Allogeneic stem cell transplantation or radioimmunotherapy
- Received any of the following within 4 weeks prior to visit 2: anti-cancer therapy, glucocorticoids  $> 10$  mg prednisolone per day (or equivalent), or leukapheresis
- Known transformation to more aggressive B-cell malignancies
- Known CNS involvement of CLL
- Chronic or ongoing active infections requiring systemic treatment
- Clinically significant cardiac disease including unstable angina, myocardial infarction within 6 months, congestive heart failure, and arrhythmia requiring therapy
- Significant concurrent uncontrolled medical conditions
- History of significant cerebrovascular disease
- Known HIV positive

- Known positive serology for hepatitis B
- Pleural effusion or ascities as detectable by physical examination

#### **5.3.1.3 Protocol Specified Study Discontinuation Criteria**

##### **Discontinuation from treatment with ofatumumab**

- Patient wish
- Investigator judgment due to medical reasons
- Critical adverse event (CAE)
- Pregnant
- Patient receives prohibited therapy

##### **Discontinuation from study related follow-up**

- Patient wish
- Investigator judgment due to medical reasons
- Receipt of prohibited therapy

##### **CAEs requiring discontinuation of ofatumumab**

- Occurrence of a treatment related  $\geq$  Grade 3 (CTCAE) adverse event (AE) during the day of an infusion; additionally, the severity of the AE prevented the infusion from resuming
- Second occurrence of treatment related  $\geq$  Grade 3 bronchospasm during an infusion
- A third occurrence of a  $\geq$  Grade 3 AE during an infusion
- Occurrence of a treatment related non-hematologic AE  $>$  Grade 3 in severity on any non-infusion day, excluding AEs from the MedDRA SOC infections and infestations

#### **5.3.1.4 Definition of Prohibited Therapies**

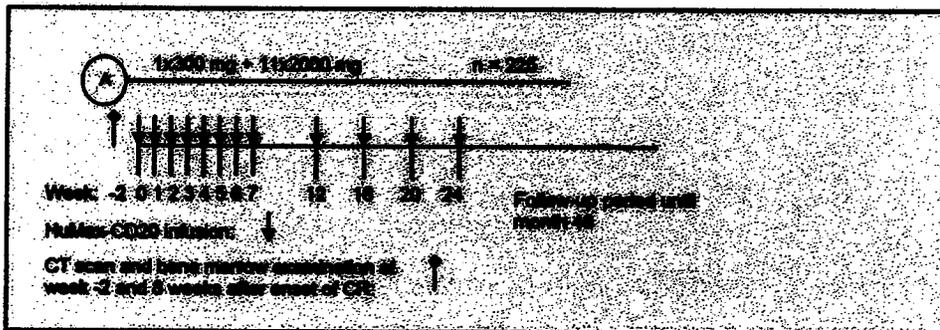
- Glucocorticoids  $>$  10 mg per day (except those given as pre-medication as stipulated by the protocol and single doses  $<$  30 mg administered for exacerbations of respiratory tract disorders)
- Any other anticancer treatment, radioimmunotherapy, stem cell transplant, or experimental therapy
- Leukapheresis

#### **5.3.1.5 Trial Design and Treatment Plan**

- Study Hx-CD20-406 is an open-label, multicenter, international, non-comparative trial to investigate the ORR and safety of ofatumumab in patients with CLL.
- The screening evaluation included blood samples; physical examination; CT scan of the neck, chest, abdomen, and pelvis; and a unilateral bone marrow examination (aspirate and biopsy).
- Patients were scheduled to receive a total of 12 doses of ofatumumab at the following doses and schedule (Figure 1):
  - 300 mg during week 0
  - 2,000 mg weekly from weeks 1 to 7, and on weeks 12, 16, 20, and 24

- The study mandated disease status evaluations every four weeks until week 28 and then every three months until disease progression or until month 24. However, repeat CT scans were only required to confirm a possible complete response 8 weeks after the onset of the complete response.
- For lymph node examinations, investigators were to assess, by physical examination, the diameter (in two planes) of the largest palpable lymph node in each of the following sites: cervical, axillary, supraclavicular, inguinal, and femoral. Hepatomegaly and splenomegaly were to be assessed as cm under the costal margin. Lymph nodes under 1 cm were to be considered normal and not described in the response evaluation.
- During each visit, patients were asked whether they experienced constitutional symptoms.
- Flow cytometry for CLL cells was to be performed at three month intervals until one value was  $\geq$  baseline or until alternative B-CLL treatments were prescribed (or until month 48).
- Prior to receiving ofatumumab, all patients were to receive premedication with an antihistamine, acetaminophen (1,000 mg or equivalent), and IV corticosteroids at doses according to the prespecified protocol as shown in Table 14.
- Patients who received alemtuzumab within the past 6 months were to continue Pneumocystis and herpes virus prophylaxis as recommended by the alemtuzumab package insert.
- Figure 2 and Figure 3 show the schedule of events in study 406.

**Figure 1: Dates of Infusions during Study 406 (copied directly from the GSK 406 CSR)**



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**Table 14: Study Premedication Requirements (Table Copied with Modifications from the Hx-CD20-406 Clinical Protocol)**

Ofatumumab Infusion Number and Dose	IV glucocorticoid dose (prednisolone or equivalent) administered 30 minutes to two hours prior to the ofatumumab infusion XX mg
1 (300 mg)	100
2 (2,000 mg)	100
3-8 (2,000 mg)	0-100*
9 (2,000 mg)	100
10-12 (2,000 mg)	50-100*

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

**Figure 2: Study 406 Flow Chart Part A: Schedule of Events (copied directly from the GSK 406 CSR)**

**2 Flow Chart**

Phase	Screening	Treatment period														Follow-Up period						Extended Follow-Up: Survival <sup>1</sup> and B-cells <sup>2</sup>	
		CLINICAL ASSESSMENTS <sup>3</sup>																					
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	FU+1	
Day/Week/Month	$\leq 14$ days prior to Visit 2	0w	1w	2w	3w	4w	5w	6w	7w	8w	12w	16w	20w	24w	28w	32w	36w	40w	44w	48w	52w	every 3 months until 48w	
Visit Window			±1d	+1w	+1w	+1w	+1w	+1	+1	+1	+1	+1	+1	+1	+2w								
Informed Consent	X <sup>4</sup>																						
Eligibility Criteria	X																						
Demographics	X																						
Medical History <sup>5</sup>	X																						
Height and Body weight	X																						X <sup>6</sup>
Physical Examination	X																						X
Lymph node/organ examination	X	X					X			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Constitutional Symptoms	X	X								X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG Performance Status	X	X					X			X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X																						
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Administration of study drug		X	X	X	X	X	X	X	X		X	X	X	X									
CT scan	X <sup>7</sup>																						
Bone marrow examination	X <sup>8</sup>																						
Response evaluation							X			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Observational contact																							X

<sup>1</sup> Survival will be followed until Month 48.  
<sup>2</sup> B-cells (CD5/CD19<sup>+</sup> and CD5/CD20<sup>+</sup>) will be followed until a value  $\pm$  the baseline value or until initiation of alternative B-CLL treatment or Month 48.  
<sup>3</sup> Details of assessments can be found in sections 8.1  
<sup>4</sup> Informed consent can be obtained outside the screening visit window (i.e. may be prior to screening date)  
<sup>5</sup> Signs and symptoms occurring between visit 1 and 2 should be recorded as Medical History  
<sup>6</sup> Body weight only  
<sup>7</sup> Only Serious Adverse Events will be collected. Only during the Extended Follow-Up period; deterioration in the study disease and signs and symptoms thereof should not be reported as AEs/SAEs unless the outcome is death.  
<sup>8</sup> Only the first alternative B-CLL treatment will be recorded.  
<sup>9</sup> To be performed for confirmation 8 weeks after a patient, for the first time, fulfills the NCIWG requirements of a CR  
<sup>10</sup> CT scan and bone marrow examination can be obtained up to 6 weeks prior to Visit 2

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**Figure 3: Study 406 Flow Chart Part B: Schedule of Events (Copied directly from the GSK 406 CSR)**

Phase	Screening	Treatment period														Follow-Up period						Extended Follow-Up Survival <sup>14</sup> and B-cell <sup>15</sup>	
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	FI+1	
Day/Week/Month	≤14 days prior to Visit 2	0w	1w	2w	3w	4w	5w	6w	7w	8w	12w	16w	20w	24w	28w	9m	12m	15m	18m	21m	24m	every 3 months until 48m	
Visit Window		±1d	±1d	±1d	±1d	±1d	±1d	±1d	±1d	±1d	+1w	+1w	+1w	+1w	+1w	+1w	+1w	+1w	+1w	+1w	+1w	±2w	
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Biochemistry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test	X																						
Flow Cytometry	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HAIHA	X																						
HACA <sup>16</sup>	X																						
Prognostic factors <sup>17</sup>	X																						
Hepatitis B	X																						
Complement (CH50)	X	X	X																				
PK <sup>18</sup>	X	X																					
Serum Sampling <sup>19</sup>	X	X				X				X	X	X	X	X	X	X	X	X	X	X	X	X	X

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<sup>14</sup> Survival will be followed until Month 48  
<sup>15</sup> B-cells (CD19<sup>+</sup> and CD20<sup>+</sup>) will be followed until a value ≥ the baseline value or until initiation of alternative B-CLL treatment or Month 48  
<sup>16</sup> Details of parameters can be found in section 8.2  
<sup>17</sup> Only for patients previously treated with rituximab  
<sup>18</sup> Both blood cells and serum will be collected and stored for one year after last patient test visit. Details of parameters to be investigated can be found in section 8.2.9  
<sup>19</sup> Serum samples are stored for one year after last patient test visit for future analyses (e.g. PK analyses or other relevant analyses)  
<sup>20</sup> Only at selected sites

**5.3.1.6 Definitions of Response:**

The NCIWG criteria (Cheson 1996) were used to define response in study 406. These criteria are described below in Table 15. *Comment: Section 6 of this review contains a discussion regarding problems using these criteria in determining ORR in patients with CLL.*

**Table 15: 1996 NCIWG Criteria for Progression and Response in CLL**

	CR	nPR	PR	Progressive Disease
Lymph Nodes	None	None	≥50% reduction (PE)	New or ≥ 50% increase
Spleen and Liver	No enlargement	No enlargement	≥50% reduction (PE)	New or ≥ 50% increase
Blood Counts	<ul style="list-style-type: none"> <li>ANC ≥ 1,500/mcL</li> <li>Plt &gt; 100,000/mcL</li> <li>Hb &gt; 11 g/dl</li> </ul>	<ul style="list-style-type: none"> <li>ANC ≥ 1,500/mcL</li> <li>Plt &gt; 100,000/mcL</li> <li>Hb &gt; 11 g/dl</li> </ul>	At least one of CR criteria or 50% improvement	N/A

	CR	sPR	PR	Progressive Disease
Lymphocytes	< 4,000/mcL	< 4,000/mcL	≥ 50% lymphocyte reduction	≥ 50 percent increase and ≥ 5,000/mcL
Bone marrow	< 30% lymphocytes; no nodules	Same as CR but lymphoid nodules	N/A	N/A
Other	NA	NA	NA	Transformation to a more aggressive histology

PE = physical examination; ANC = absolute neutrophil count; NA = not applicable

Patients not meeting criteria for response or progressive disease were considered to have stable disease. Results from radiographic images, when available, were not to be used by the IRC.

### 5.3.1.7 Statistical Design / Sample Size

The primary endpoint was objective response through week 24 as determined by an Independent Endpoints Review Committee (IRC) according to response criteria in the 1996 NCIWG guidelines.

#### Sample Size

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

#### Definition of Endpoints

- ORR: The primary efficacy endpoint in the SAP was ORR as measured over a 24 week period from the start of treatment as assessed by the IRC. The SAP allowed for the imputation of tumor measurements if they were missing (either completely missing or at one nodal site) and were preceded and followed by a visit with a measurement.
- Duration of Response: Time from the first visit where response was observed until progression or death. Duration of response (DOR) was defined as the time from the initial response to progression as assessed by the IRC, or to death. For the analysis of DOR, the following scenarios were censored: no progression at the end of the trial; treatment discontinued for undocumented progression, toxicity, or other reasons; new anti-cancer therapy started; and death or progression after two or more consecutive missed visits.
- PFS: The protocol defined PFS as the time from allocation until progression or death. The statistical analysis plan defined PFS as the time from baseline (visit 2) until progression or death as assessed by the endpoint review committee.

- Time to next CLL therapy: time from allocation until first administration of the next B-CLL treatment.
- Overall survival: time from allocation until death. GSK also subgrouped OS for responders and nonresponders. OS was censored if a patient was lost to follow-up.  
*Comment: Drug effects on PFS, time to next CLL therapy, and OS cannot be validly determined in a study that lacks an internal control. This reviewer recommends exclusion of these endpoints from the product label.*
- Reduction in tumor size: GSK summarized tumor measurements by the absolute difference before and after therapy and by the percentage change of the sum of products of the diameters.

#### Data Analysis:

- The protocol was amended on October 31, 2007 (Amendment 4) to include an interim analysis when the primary endpoint data were available for 66 patients in the DR subgroup. The data monitoring committee (DMC) conducting the interim analysis would notify Genmab if the lower limit of the 99% CI excluded a response rate of 15% or less. Over 96% of the patients were enrolled when the protocol was amended to include the interim analysis.
- The IRC charter specified that Genmab would have access to the results of the IRC assessments on an ongoing basis. IRC assessments were to be conducted after 4, 30, 60, 90, 120, 150, 180, 210, and 225 patients had reached the primary endpoint.
- The interim analysis for potential early study termination was added after approximately 60% of patients' response assessments were completed.
- The full analysis set included all patients exposed to ofatumumab. *Comment: For a single arm study evaluating response rates, this analysis population is reasonable. However, time to event endpoints may be overestimated by excluding patients who were screened (and consented) but did not receive therapy.*
- GSK planned to assess improvements in hemoglobin, platelets, and neutrophils. The protocol did not specify how transfusion would be accounted for in these analyses. The statistical analysis plan indicated that patients who received blood transfusions or concomitant medications that affect hemoglobin and were influential at that time point would be excluded from the analysis. The definition of "influential at the time point" was not provided. For platelets, patients with transfusions within five days prior to the time point were excluded. The statistical plan also stated that discontinuation of granulocyte stimulating growth therapy would be considered an improvement in neutropenia.

#### Adverse Event Reporting:

- Adverse events were to be monitored during the ofatumumab treatment period (until week 28) and at three month intervals during the follow-up period (until 24 months).
- Serious adverse events, deaths, new CLL treatment, and B-cell recovery were monitored until month 48 (extended follow-up period). Follow-up for B-cell recovery stopped if new CLL treatment was initiated.
- AEs were not to be recorded during the extended follow-up period unless the AEs were considered SAEs. *Comment: This design for the collection of AEs may have resulted in an underestimation of the incidence rate of certain AEs. For example, if a patient received*

*ofatumumab three weeks prior to starting new CLL therapy and then developed an infection, the event may not have been recorded because the patient had started alternative therapy.*

#### **5.3.1.8 Amendments:**

##### **Amendment 1 (February 27, 2006):**

Prior to the enrollment of the first patient, a protocol amendment was submitted so that patients were no longer required to receive an alkylating agent. The justification was that fludarabine had become standard of care in first-line CLL and that patients “failing fludarabine” have poor responses to regimens that contain alkylating drugs. *This reviewer evaluated the paper cited by GSK (Rai et al., 2000). The justification was based on an analysis of patients who crossed over from fludarabine (due to lack of response) to chlorambucil. Only seven percent of patients experienced a response after cross-over. It is not clear whether a more active alkylating agent (or regimen) than chlorambucil could have resulted in a higher response rate.*

Furthermore, the initial protocol allowed patients to be eligible if they were “refractory” to fludarabine and alemtuzumab or were “intolerant” to the drugs. Patients were considered ineligible for alemtuzumab if they had at least one lymph node that was greater than 5 cm or compression symptoms that required therapy.

##### **Amendment 2 (September 26, 2006):**

In amendment 2, patients were no longer eligible if they were intolerant to or “ineligible” for fludarabine (i.e., only refractory patients were enrolled). Furthermore, the minimum number of cycles required for a patient to be considered refractory to fludarabine or alemtuzumab was specified (2 cycles for fludarabine or 12 administrations for alemtuzumab).

##### **Amendment 3 (April 16, 2006):**

In amendment 3, patients could no longer be enrolled if they were intolerant to alemtuzumab (i.e., patients must have been refractory). Amendment 3 stipulated that patients must have “failed alemtuzumab” or are considered inappropriate due to the presence of at least one bulky lymph node.

Amendment 3 specified an increased number of patients because the two primary patient groups (DR and BFR) were considered separate. The original sample size was 100 for all patients; the revised sample size was 66 per group. The revised study contained a new assumption that there was an 81% power to exclude an ORR of 15% assuming a true ORR of 30%.

This amendment allowed for an administrative interim analysis (to be performed approximately 6 months prior to the final DR endpoint final analysis) that was not to influence the conduct of the trial.

##### **Amendment 4 (October 31, 2007):**

The sample size was increased from 66 to 100 for each of the two study populations. Furthermore, an interim analysis was to be conducted when data from 66 DR patients were available. The new interim analysis would include superiority and futility analyses. *The new*

*amendment did not provide justification as to why these changes were made. The changes (assuming a 30% true response rate) increased the power to exclude a 15% response rate to 92% (at 100 patients) with a 63% power after 66 patients were enrolled. According to the independent review charter, Genmab had access to ongoing response evaluations during the study (occurring when 4, 30, 60, 90, 120, 150, 180, 110, and 225 patients reached the primary endpoint).*

**Amendment 5 (July 15, 2008):**

This amendment was predominately administrative and accounted for the change in sponsorship of ofatumumab from Genmab A/S to GlaxoSmithKline.

**5.3.3.9 Independent (Radiology) Review Charter:**

Independent radiology reviews were provided by an independent imaging core laboratory ( )  
( ) One independent radiology review was to be conducted by a single board certified radiologist who would review all imaging data. Primary objectives of the reviewer were to confirm complete remissions and to define whether bulky lymphadenopathy was present at baseline. The ( ) radiologist was to be blinded in regards to institution, clinical information, and on-site treatment and outcome data. The reviewer was not to be blinded to the chronology of the scans.

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At baseline, six dominant abnormal lymph nodes or nodal masses (index lesions) were to be identified and measured on the imaging workstation. Any extranodal lesions were to be identified and measured. Lymph nodes less than 1 cm were to be considered normal and not recorded. Other assessable lesions were to be considered non-index lesions. The reviewer was to assess organomegaly documented at baseline and during follow-up.

**5.3.1.10 Independent Endpoints Review Committee Charter:**

The IRC was composed of five independent board certified oncologists or hematologists experienced with CLL. The committee was to be provided with clinical data and determine the level of response and when progression occurred according to NCIWG guidelines. CT scans were not included in the response determinations but were made available to the IRC. *Comment: This reviewer considers the IRC process to be an audit and review of available data rather than a blinded independent confirmation of tumor measurements (because confirmatory radiographs were not required for response assessments).*

Each patient's data was to undergo two parallel independent reviews by any two of the five IRC members. If a discrepancy occurred, a third member would review the case independently and blinded to the previous reviews. Concurrence of any two findings would generate the final assessment. If all three members disagreed, one of the original members plus a fourth member would convene and provide consensus as to the final determination for that patient.

### 5.3.2 STUDY 402

Study 402 was an open-label, international, multicenter, dose escalation study. The study planned to evaluate three separate dose levels of ofatumumab in patients with CLL. Eligibility required patients to have relapsed or refractory CLL (to any treatment) and a circulating lymphocyte count above 5,000/mcL. Patients received up to four weekly doses of ofatumumab according to the schedules described in Table 16.

**Table 16: Ofatumumab Doses in Study 402**

	First Dose	Final Dose
Cohort A	100 mg	500 mg
Cohort B	300 mg	1,000 mg
Cohort C	500 mg	2,000 mg

The protocol submitted with the 402 study report indicated that the following considerations were taken into account when selecting the ofatumumab doses for patients with CLL.

- A fixed dose was chosen based on the following:
  - Experience of fixed doses of rituximab in patients with rheumatoid arthritis.
  - Variability of serum concentrations observed when rituximab was administered using the mg/m<sup>2</sup> approach. *Comment: This reviewer is uncertain as to this justification for using fixed doses; fixed doses may yield even greater variability in serum concentrations than weight based dosing.*
- The absolute doses were chosen based on studies (not cited) with rituximab in NHL and CLL and the experience of ofatumumab in NHL patients.

Study 402 was designed such that dose escalation could proceed if three patients in the previous cohort were followed for four infusions and one week of follow-up without protocol defined dose-limiting toxicity (DLT). An expansion cohort of 26 patients was planned for Group C if study specific (safety based) stopping rules were not met.

Figure 4 and Figure 5 show the infusion schedule and calendar of events for study 402. Responses were judged according to international working group criteria. Despite a CT scan being conducted at week 19, responses were judged according to physical examination for lymph nodes, liver, and spleen measurements. Responses occurring up to week 27 were determined for all patients.

**Figure 4: Study 402 Infusion Schedule (Copied Directly from the GSK 402 CSR)**

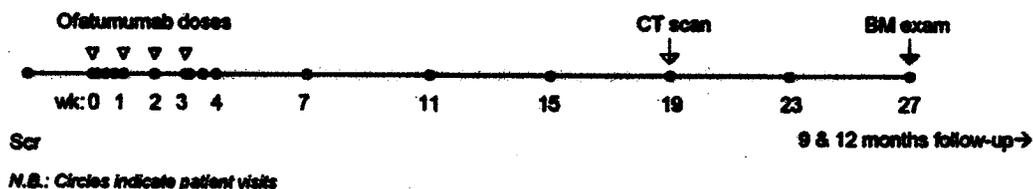


Figure 5 shows that the AE reporting period began at baseline (first dose) for AEs and on Visit 1 for SAEs. The AE reporting period ended when the patient left the study (including for reasons of progressive disease, new CLL therapy, or patient decision). The last follow-up visit was scheduled to occur at 12 months (or approximately 11 months after the last dose of ofatumumab). AEs for study 402 were coded according to MedDRA version 6.0.

Figure 5: Study 402 Calendar of Events (Copied Directly from the GSK 402 CSR)

Table 8-8: Study Procedures

Phase	Screening	Treatment							Follow-up 1								Follow-up 2		
		2	3 <sup>a</sup>	4 <sup>a</sup>	5 <sup>a</sup>	6	7	8	9 <sup>b</sup>	10 <sup>b</sup>	11	12	13	14	15	16	17	18	19
		0d	1d	3d	5d	7d	14d	21d	22d	25d	4w	7w	11w	15w	19w	23w	27w	9m	12m
Informed Consent	X																		
Inclusion/ Exclusion Criteria	X																		
Treatment Assignment	X																		
Demographics	X																		
Medical History	X																		
Treatment		X				X	X	X											
Concomitant Medication		X				X	X	X		X	X	X	X	X	X	X	X	X <sup>c</sup>	X <sup>d</sup>
Adverse Events		X				X	X	X		X	X	X	X	X	X	X	X	X	X
Constitutional Symptoms	X <sup>e</sup>									X	X	X	X	X	X	X	X	X	X
Physical Examination	X <sup>e</sup>									X	X	X	X	X	X	X	X	X	X
Vital Signs	X <sup>e</sup>	X <sup>f</sup>				X <sup>g</sup>	X <sup>g</sup>	X <sup>g</sup>											
ECG	X <sup>e</sup>														X				
CT Scans	X <sup>e</sup>														X				
Blood Smear	X <sup>e</sup>																X <sup>h</sup>		
Clinical Chemistry & Hematology	X <sup>e</sup>					X	X	X		X	X	X	X	X	X	X	X	X	X
Complement Blood Sample		X				X	X	X		X									
Flow Cytometry	X <sup>e</sup>					X				X	X	X	X	X	X	X	X	X	X

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Phase	Screening	Treatment							Follow-up 1								Follow-up 2			
		2	3 <sup>a</sup>	4 <sup>a</sup>	5 <sup>a</sup>	6	7	8	9 <sup>b</sup>	10 <sup>b</sup>	11	12	13	14	15	16	17	18	19	
Circulating CD20	X <sup>i</sup>											X				X				
HAHA	X <sup>i</sup>														X				X	
PK		X <sup>j</sup>	X <sup>j</sup>	X	X	X <sup>k</sup>	X <sup>k</sup>	X <sup>k</sup>	X <sup>k</sup>	X	X	X						X	X	X
Pregnancy Test	X <sup>i</sup>																			
Bank of Serum and Cells		X									X		X	X	X	X	X	X	X	
Bone Marrow Examination	X <sup>i</sup>																	X <sup>l</sup>		

Table notes:  
 a) Visits on days 1, 3, 5, 22 and 25 were laboratory visits for PK blood sampling  
 b) Only anticancer and anti-infection treatment were followed  
 c) Must be performed within 2 weeks prior to baseline (day 0)  
 d) See separate tables for Vital Signs/PK sampling times (Table 5-7 and Table 6-9)  
 e) Only if bone marrow aspiration was performed  
 f) 24 hours after start of infusion ± 6 hours  
 g) Only if peripheral blood lymphocyte count was  $\leq 4 \times 10^9/L$ , 8 weeks prior to the visit

**Comment:** Study 402 can only be considered as supportive for the proposed indication because of differences in dose, dosing schedule, inclusion criteria, and monitoring (compared to study 406).

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### **5.3.3 Supportive safety studies**

The following supportive studies evaluated ofatumumab in different populations or used different dosing schedules than that proposed for this BLA. In general, doses were lower than those used in the 406 study. The usefulness of these studies in the safety analysis is primarily limited to additional data regarding deaths and SAEs. The incidence of more common adverse reactions may differ in these studies due to differences in indication, concomitant chemotherapy, and doses or duration of ofatumumab administered.

#### **5.3.3.1 Hx-CD20-001**

Study Hx-CD20-001 was an open-label, uncontrolled, multicenter, dose-escalation study evaluating ofatumumab in patients with relapsed or refractory follicular lymphoma (Grade 1 to 2) in doses ranging from 300 to 1,000 mg. Patients were excluded if they were treated with rituximab and achieved less than a partial response. Ten patients were enrolled in each of four cohorts. Patients were followed up to 12 months.

#### **5.3.3.2 Hx-CD20-403**

Study 403 part A was a double-blind, placebo-controlled, dose-escalation study evaluating ofatumumab in patients with rheumatoid arthritis (RA). Patients were randomized to receive one of three doses (300, 700 or 1,000 mg) of ofatumumab or placebo in a 4:1 ratio (ofatumumab to placebo). Patients each received two infusions of ofatumumab scheduled to occur at an interval of two weeks apart. If MTD was not reached in part A, the study was to be followed by study 403 part B.

Study 403 part B was a parallel randomized study in which a total of 200 patients with RA were randomized (1:1:1:1) to one of four groups (placebo: 300 mg: 700 mg: 1,000 mg). Patients were eligible if they had RA for at least 6 months with active disease and had treatment failure with one or more disease-modifying anti-rheumatic drugs (DMARD).

The primary objective of part A was to determine the safety of ofatumumab in patients with rheumatoid arthritis. The primary objective of part B was to evaluate the efficacy of ofatumumab in patients with active RA using the ACR response assessment and disease activity score at 12 to 24 weeks after the initiation of treatment. In part B, patients were followed every 12 weeks after the week 24 visit until CD19+ cell counts normalized.

#### **5.3.3.3 Hx-CD20-405**

Study 405 is an ongoing randomized, double-blind, two arm comparison study of 500 mg and 1,000 mg ofatumumab in patients with follicular lymphoma refractory to rituximab in combination with chemotherapy. A protocol amendment, however, changed the study to a one

arm study enrolling 81 patients at the 1,000 mg dose level. Patients can receive up to 8 doses of ofatumumab weekly in combination with chemotherapy.

#### **5.3.3.4 Hx-CD20-408**

Study 408 was designed to investigate the ability of ofatumumab to decrease bronchial inflammation in patients with COPD. The study was terminated prematurely due to the occurrence of bronchospasm in two of five treated patients. The study was originally designed to enroll forty patients randomized 3:1 to ofatumumab or placebo. Patients could receive up to two doses of 1,000 mg of ofatumumab preceded by a lower dose of ofatumumab (10 to 100 mg).

#### **5.3.3.5 Hx-CD20-409**

Study 409 is an ongoing study investigating ofatumumab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (O-CHOP) in patients with previously untreated follicular lymphoma. Twenty-eight patients are planned for enrollment into one of two arms (300 mg ofatumumab followed by either 500 mg or 1,000 mg). Patients can receive up to 6 cycles of O-CHOP. The follow-up period is 24 months with an extended follow-up period of 48 months.

#### **5.3.3.6 Hx-CD20-415 (GEN415)**

Study 415 is an ongoing open-label, single-arm, multi-center study to evaluate ofatumumab in patients with relapsed diffuse large B-cell lymphoma (DLBCL) who are ineligible for transplant or who relapse after autologous transplant. Patients are to receive one dose of 300 mg followed by up to seven doses of 1,000 mg ofatumumab. The follow-up period is 24 months with an extended follow-up period of 48 months. Enrollment of up to 75 patients is planned.

#### **5.3.3.7 Hx-CD20-410 (GEN410)**

Study 410 is an ongoing double-blind, randomized, placebo-controlled, parallel-group, multi-center phase 3 study of ofatumumab in adult patients with active rheumatoid arthritis who have had an inadequate response to methotrexate therapy. Patients are randomized (1:1) to receive either ofatumumab or placebo in addition to methotrexate. Patients are scheduled to receive two ofatumumab doses two weeks apart. A total of 248 patients are planned for enrollment into this study.

### 5.3.3.8 Hx-CD20-411 (GEN 411)

Study 411 is an ongoing double-blind, randomized, placebo-controlled, parallel-group, multi-center phase 3 study of ofatumumab or placebo in patients who had an inadequate response to TNF-alpha antagonist therapy. Patients are randomized (1:1) to receive either ofatumumab or placebo in addition to methotrexate. A total of 236 patients are planned for enrollment into this study.

### 5.3.3.9 Hx-CD20-413 (GEN413)

Study 413 is an open-label extension study allowing additional doses of ofatumumab (700) mg for patients who were previously enrolled into study 403.

## 6 Review of Efficacy

### Efficacy Summary (Statistical Reviewer)

#### Summary of Major Statistical Issues and Comments

- Study 406 is a single-arm trial; the lack of a comparator arm makes it difficult to interpret and draw reliable conclusions concerning the benefit of ofatumumab on progression-free survival (PFS) or overall survival (OS). Thus, such results will only be considered descriptive in nature. Additionally, the high variability in the assessment of response rates by the IRC, investigators, and sponsor in study 406 further undermines the ability to characterize the primary endpoint (ORR) and to study the relationship between effects on ORR and effects on PFS or OS. As stated by the ODAC statistician, Dr. David Harrington, at the May 29, 2009 ODAC meeting, "There's obviously lots of uncertainty, lots of difficulty in evaluating this disease and this is where randomized trials really shine. I think despite the obvious unmet need, I think this is exactly the situation where a randomized trial is needed to understand the benefit of a therapy. There are just too many things here [in this study] that add uncertainty to accelerated approval."
- The reliability of ORR, the primary endpoint of study 406, as a surrogate for PFS or OS is difficult to assess. One possible scenario is that responders exhibit better PFS or OS not as a result of the actual treatment (ofatumumab), but because the responders are a select patient population who would have had better PFS or OS regardless of treatment (e.g. those with less aggressive disease).
- The results of the pivotal trial (study 406) in this application are from an interim analysis, in which there are only 59 patients in the DR group. Given the small sample size, caution should be taken concerning the reliability/interpretability of the results.
- As a requirement for an application to be eligible for accelerated approval, a confirmatory randomized trial must be ongoing. At the May 29, 2009 ODAC meeting, the sponsor stated that the approximate time for which results from the confirmatory trial are expected is 5

years. Given this timeframe, due diligence to complete the confirmatory trial is highly questionable.

**Efficacy Summary (Clinical Reviewer)**

Primary efficacy results were based on the results of an interim analysis that demonstrated durable objective responses among patients enrolled in a single, multicenter, parallel-group, non-comparative study, titled Hx-CD20-406 “A single-arm, international, multi-center trial of HuMax-CD20, a fully human monoclonal anti-CD20 antibody, in patients with B-cell chronic lymphocytic leukemia who have failed fludarabine and alemtuzumab.” Although the study enrolled a total of 154 patients treated according to a uniform dose and schedule of ofatumumab, the primary efficacy data for regulatory purposes were derived from a protocol-specified subgroup of 59 patients with CLL whose disease was refractory to fludarabine and alemtuzumab (“Double Refractory” or DR).

The magnitude of objective response rate (ORR) was dependent upon the assessor, with a higher response rate determined by the independent review committee (IRC) than by the investigators (54% vs. 42%) in the DR subgroup. The median duration of response using the investigators’ results was 6.5 months. This reviewer’s analysis of ORR using case report forms and datasets yielded an ORR that was similar to that of the investigators. Furthermore, because radiographs were not required for documentation of response, the IRC did not conduct an independent assessment of tumor measurements in lymph nodes, spleen, or liver but instead relied on investigator-reported tumor measurements. For these reasons and additional reasons described below, this reviewer will consider the investigators’ point estimate (and 99% CI’s) of ORR for regulatory decision making.

The durable responses in the DR population were supported by an investigator determined ORR of 34% (99% CI 21, 49) in the BFR population with a median DOR of 6.5 months. Additionally, these results were supported by a 48% ORR (95% CI 30, 70) among 27 patients receiving 2,000 mg ofatumumab in the 402 study with a median DOR of 4.4 months.

The durable responses observed in the DR population supported by responses in the BFR population and in study 402 support that ofatumumab yields anti-tumor activity in CLL when administered as a single agent. The magnitude of the anti-tumor activity was difficult to quantify due to the following factors:

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

Based on the uncertainty of the ORR, this reviewer believes that the 99% CIs must be considered in the efficacy evaluation of ofatumumab (the 99% CI was specified by the protocol at the time of the interim analysis). The lower bound of the 99% CI of the investigators’ ORR was 26% in

the DR group. This lower boundary indicates anti-tumor activity in this heavily pretreated CLL patient population. Additionally, efficacy results in the 406 study were supported by effects observed on individual components of the NCIWG criteria. Even in non-responders, anti-tumor activity was observed in some patients. However, this activity was not of sufficient duration or magnitude to be considered a response.

## 6.1 Indication

GSK proposed the following indication for ofatumumab in the original BLA submission: Arzerra is a human monoclonal antibody against CD20 indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received prior therapy. C

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*Comment: Due to the issues described in Section 2 of this review regarding unmet medical need, only the DR population will be considered for accelerated approval. Thus, this reviewer recommends that the indication statement be revised so that ofatumumab will only be indicated for the treatment of patients refractory to both fludarabine and alemtuzumab.*

### 6.1.1 Methods

#### (Clinical Reviewer)

This efficacy review contains results from two studies: Hx-CD20-402 and Hx-CD20-406 (or 402 and 406, respectively). These two studies were selected because they were the only two studies that evaluated the 2,000 mg dose of ofatumumab in patients with CLL (as monotherapy). Study Hx-CD20-406 was the more important study for the efficacy review as the 402 study did not contain a protocol-specified population that meets the regulatory criterion for unmet medical need. Furthermore, the dosing schedule proposed in the ofatumumab label was the schedule administered to patients in study Hx-CD20-406.

#### (Statistical Reviewer)

This review will focus primarily on the efficacy results of the pivotal study submitted with this application, study Hx-CD20-406. Study 406 was a single-arm, international, multi-centered trial of ofatumumab in patients with B-cell chronic lymphocytic lymphoma (CLL) who have failed fludarabine and alemtuzumab. The primary objective was to evaluate the efficacy of ofatumumab in this heavily-pretreated CLL population as assessed by objective response rate (ORR) at 24 weeks. The results presented in this application were from an interim analysis with data cutoff date May 19, 2008, at which time 154 patients were eligible for analysis [59 in the double refractory (DR) group, 79 in the bulky-fludarabine refractory (BFR) group, and 16 in the "Other" group]. Focus will be on the DR and BFR groups.

### 6.1.2 Demographics (Clinical Reviewer)

#### Note regarding grouping of study populations:

The primary interim analysis was to occur when 66 patients in the DR population were assessable for the primary endpoint. During May and June of 2008, Genmab conducted an

internal review and questioned the grouping decision for 19 patients (DR, BFR, or other). Genmab requested that the IRC re-assess the eligibility of these 19 patients and conducted the re-assessment in a face-to-face meeting with Dr. Keating and Dr. Kay. During this review, 10 patients were re-assigned into a different population group.

### Demographics of Study Hx-CD20-406

Table 17 shows that most patients enrolled in study Hx-CD20-406 were white men. *Comment: In the U.S., approximately 60% of patients diagnosed with CLL are men (SEER Statistics). The age adjusted incidence rate for CLL is higher amongst the White population compared to the Black population according to SEER Statistics [age-adjusted incidence rate of 6.0/100,000 for White men; 4.4/100,000 for Black men; 3.1 per 100,000 for White women; and 2.1 per 100,000 for Black women (<http://seer.cancer.gov/statfacts/html/clyl.html>)].* Median age was 63 years. A total of 63% of patients were Rai stage III or IV at the time of screening.

**Table 17: Demographics: Study 406**

	DR (n=52)	BFR (n=72)	Other (n=16)	Total (n=140)
<b>Sex (n, %)</b>				
Female	15 (25)	22 (28)	6 (37.5)	43 (28)
Male	44 (75)	57 (72)	10 (62.5)	111 (72)
<b>Age</b>				
≥65 yr (%)	27 (46)	33 (42)	6 (37.5)	66 (43)
Mean (SD) (yr)	63 (9)	63 (9)	65 (8)	63 (9)
Median (yr)	64	62	63	63
<b>Race (n,%)</b>				
White	56 (95)	78 (99)	15 (94)	149 (97)
Asian	1 (2)	0	1 (6)	2 (1)
Black	0	1 (1)	0	1 (<1)
Hispanic/Latino	1 (2)	0	0	1 (<1)
Other (Arab)	1 (2)	0	0	1 (<1)
<b>Time from Original CLL Diagnosis (years)</b>				
Mean (SD)	6.7 (4.1)	6.5 (3.8)	8.8 (3.5)	6.9 (3.9)
Median	6.0	5.9	7.5	6.3
<b>Rai Stage at Screening (n, %)</b>				
0	1 (2)	0	0	1 (1)
1	11 (19)	7 (9)	2 (13)	20 (13)
2	15 (25)	17 (22)	4 (25)	36 (23)
3	10 (17)	11 (14)	4 (25)	25 (16)
4	22 (37)	44 (56)	6 (38)	72 (47)
<b>Time from Last CLL Treatment (years)</b>				
Mean (SD)	0.52 (0.42)	0.68 (0.69)	0.92 (1.57)	0.65 (0.75)
Median	0.36	0.40	0.36	0.39

	DR (n=59)	BFR (n=79)	Other (n=16)	Total (n=154)
No. of patients with prognostic factors (n,%)				
CD38+ > 20% CD5,CD19+ cells (n=152)	34 (58)	34 (44)	5 (31)	73 (48)
FISH 13q- (+/-) (n=151)	26 (47)	39 (50)	6 (38)	71 (47)
FISH 13q- alone (+/-) (n=151)	5 (9)	13 (17)	1 (6)	19 (13)
FISH 11q- (+/-) alone (n=151)	24 (42)	22 (28)	4 (25)	50 (36)
FISH 17p- (+/-) (n=148)	17 (30)	14 (18)	2 (13)	33 (22)
ECOG PS (n,%)				
0	27 (46)	25 (32)	3 (19)	55 (36)
1	19 (32)	41 (52)	9 (56)	69 (45)
2	12 (20)	13 (22)	4 (13)	29 (19)
3	1 (2)	0	0	1 (1)

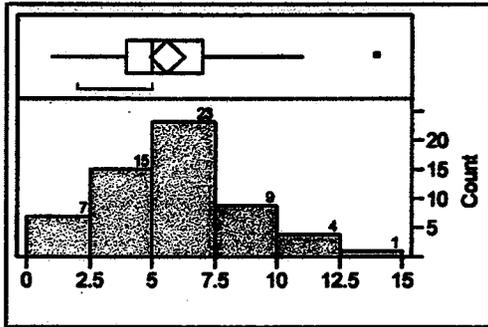
### Prior Therapies

The overall population in study Hx-CD20-406 was heavily pretreated. In the DR population (n=59), the number of prior therapies ranged from 1 to 14. Two patients in the DR group received one prior therapy; both of these patients received fludarabine combined with alemtuzumab. The median number of prior therapies in the DR group was 5 and in the BFR group (n=79) was 4. The median number of therapies in the “other” group (n=16) was 6.5. Figure 6, Figure 7, and Figure 8 show the distributions of prior therapies for the three different treatment analysis groups.

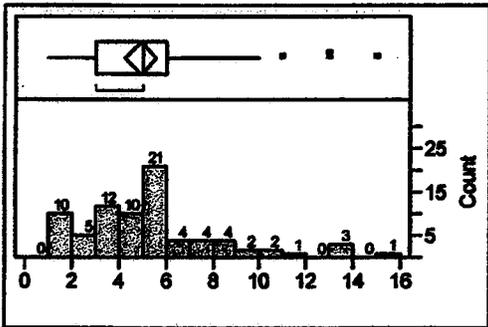
Table 18 shows that in addition to receiving fludarabine and alemtuzumab, nearly all patients in the DR subgroup, as well as the in overall study population, had received an alkylating agent-containing regimen. A total of 88% of patients received an alkylating agent regimen other than single-agent chlorambucil. A total of 81% of patients received a combination therapy regimen that included fludarabine plus one other drug. Over 50% of the patients in study Hx-CD20-406 received rituximab.

*Comment: The FDA analysis presented in the histograms below may differ (slightly) from GSK’s for the BFR group. GSK explained the difference in an amendment to the BLA submitted on March 17, 2009 as resulting from corrections in CRF pages. This reviewer considers the GSK response as acceptable and the differences between the FDA and GSK analyses were minimal.*

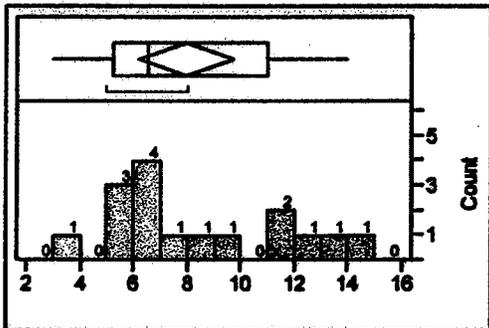
**Figure 6: Distribution of Prior Therapies for DR Group (n=59)**



**Figure 7: Distribution of Prior Therapies BFR group (n=79)**



**Figure 8: Distribution of Prior Therapies for "Other" Group (n=16)**



**Table 18: Categories of Certain Prior Therapies in Full Analysis Set**

Type of prior Regimen	IR N=57 (%)	HR N=72 (%)	Other N=10 (%)	Total N=154 (%)
Alkylating agent	93%	92%	100%	94%
Alkylating agent other than chlorambucil alone or combination regimen	88%	85%	100%	88%
Bendamustine alone or bendamustine-containing regimen	3%	6%	13%	6%
Fludarabine	100%	100%	100%	100%
Combination therapy that includes fludarabine plus at least one other drug*	85%	82%	63%	81%
Alemtuzumab	100%	19%	63%	55%
Rituximab or rituximab-containing regimen	59%	54%	63%	57%

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

### 6.1.3 Subject Disposition

Section 7.3.3 of this review contains a discussion of the reasons for patient withdrawal from the study during the treatment period including deaths and adverse events. A total of 69 patients withdrew during the treatment period. Thus, 85 patients completed treatment and were withdrawn during follow-up (n=65) or completed treatment and follow-up was ongoing at the time of data cut-off for the interim analysis. GSK cited progressive disease as the most common cause of withdrawal during the follow-up period (55/65 patients).

### 6.1.4 Analysis of Primary Endpoint(s)

#### (Statistical Reviewer)

The primary endpoint of study 406 was Independent Review Committee (IRC)-assessed ORR at 24 weeks. Responses were measured over 24 weeks, every 4 weeks, from the start of treatment following NCIWG 1996 guidelines. Responders were defined as those with a complete response (CR), nodular partial response (nPR), or partial response (PR), and non-responders were those with stable disease (SD) or progressive disease (PD). Responses were required to be maintained for at least 2 months (56 days) to be confirmed as a response. CT scans were not a requirement in the NCIWG 1996 guidelines, and were only required in this study to confirm a potential CR within 8 weeks of the initial assessment.

#### 6.1.4.1 Evaluation of the 1996 NCI Working Group Criteria for Assessing ORR in CLL (Clinical Reviewer)

##### General Overview

Responses were assessed using the 1996 NCI working group criteria. A partial response required greater than or equal to 50% reduction in lymphocytes, lymph nodes, and spleen or liver. At least one of the hematologic criteria for complete response had to be observed. To be considered a response, the response duration must last at least two months (56 days). The presence or absence of constitutional symptoms was not included as a response criterion except for complete response.

The criteria for progression specified that an increase in lymph node, spleen, or liver size of greater than or equal to 50% qualified as a progression event. For this criterion, one lymph node must have been at least 2 cm in diameter. However, for the appearance of new lymph nodes, size was not specified in the 1996 working group criteria (*the 2008 criteria did specify size for a new lymph node*).

The 1996 NCI working group criteria did not require CT scan confirmation of partial responses. The 406 protocol, however, did stipulate that confirmatory CT scans were to be performed 8 weeks after an investigator observed the onset of a complete response.

*Comment: The 1996 response criteria were written such that a strict application of the criteria would result in few responders even in a drug with notable activity. This is because, technically, any new lymph node could deem a patient as progressing, even if the node was small and enlarged due to an infection and the lymph node resolved to normal within a week.*

##### Application of the Response Criteria

The following case [406147 (Table 19)] from study 406 shows how the determination of response may differ depending on how the 1996 NCI working group criteria are interpreted. This patient first had an improvement in lymph node size and spleen size on week 4 after starting treatment with ofatumumab. For this reviewer's analysis, the more conservative requirement was used where a patient must have demonstrated evidence of response for at least two months. Because the new node found on week 12 was considered to be pathologic (by this reviewer) based on longitudinal evidence, this reviewer made the determination that this patient only had direct evidence of response at two visits, week 4 and week 8. Thus, a response duration of at least two months could not be verified.

However, if a less conservative assumption is made where this patient is considered as maintaining their response all the way until the pre-specified visit date on week 12 (*Comment: this reviewer does not agree with this interpretation used by the IRC*), this patient may have been considered a partial responder as the response duration would have lasted more than 60 days.

Additionally, an argument can be made for assigning the dates of progression at week 16 (*the beginning of nodal enlargement over two visits*) based on increasing lymph node size or week 20. The argument for assigning progression to week 20 would be made if the new lymph node

criterion used in the 2008 NCI working group criteria were used. Regardless of whether this patient is considered as responding per the 1996 working group criteria, anti-CLL activity was observed in this patient.

**Table 19: Clinical Course of Patient Number 406147**

	Baseline	Week 4	Week 8	Week 12	Week 16	Week 20
Lymphocytes (per mL)						
LN SUP (cm <sup>2</sup> )						
Liver (cm)			NP		NP	
Spleen (cm)				NP	NP	NP
New Node?	No	No	No	/		

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- LN SUP = Sum of Products of the Lymph Nodes
- NP = Not Palpable
- Weeks are approximate
- Liver and spleen measurements below costal margin

Table 20 in the next section of this review shows how frequently different independent reviewers came to different conclusions regarding overall response, date of response, or date of progression despite having access to identical data.

In the assessments of solid tumors, some variation is expected between assessors because different target lesions can be selected during the independent evaluation of radiographs. This was not the case for study 406; readers only had access to CRF data.

*After evaluating the cases in this review, this reviewer agreed with the applicant that the most strict interpretation of the 1996 criteria was not appropriate given that transient (small) enlargement of lymph nodes can occur in patients with CLL (in the setting of all other evidence indicating that the particular patient was responding to treatment).*

*Because some deviation of the response criteria was necessary in the overall response assessment, there was substantial variability in the determination of dates of response, progression, or overall response. This variability created uncertainty in the determination of the ORR in study 406.*

*This reviewer believes that the magnitude of this uncertainty will be inflated when clinicians try to compare the results of this study to other studies published in the literature. This reviewer believes that any comparisons of response rates across studies in CLL are thus not valid and should not be relied upon for marketing claims against any approved or unapproved drugs.*

#### **6.1.4.2 General Overview of IRC Process:**

##### **(Statistical Reviewer)**

The IRC consisted of 5 members, at least two of whom would independently evaluate each patient's response. For every patient visit, each reviewing IRC member was to independently determine a response by reviewing the investigator's clinical assessments and lab components of the primary efficacy data from electronic CRFs. The IRC was blinded to the investigators' response determinations. An overall objective response was then determined by the IRC based upon their clinical interpretation of all the 'per visit' evaluations. Note that when the IRC made its evaluation, they evaluated all the clinical data for all visits. CT scans, however, were not used by the IRC as part of their assessment.

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

##### **FDA Decision not to accept the IRC Determination of Overall Response for Labeling Purposes**

##### **(Clinical Reviewer)**

During the review of the BLA, this reviewer recommended that the IRC determination of ORR not be used in product labeling. The investigators' ORR was used by the Division and the ODAC in the decision making process regarding the approval of ofatumumab. The following describes the reasons for this determination.

- **Lack of independent tumor size measurements**

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

- **Genmab requests for the IRC to reconvene**

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

(four additional patients were deemed as being downgraded in a subsequent BLA amendment).  
*Comment: This reviewer believes that the request to reconvene and re-adjudicate >10% of patients during the first session indicates a lack of rigor by the IRC, who should have used strict criteria at the time of the initial response determination. This reviewer acknowledges that neither Genmab nor GSK was involved in the re-consensus process; however, the identification of the need for the re-consensus by the IRC remains problematic.*

- **Variability in IRC response assessments**

In order to have consistent application of response assessments, tumor response criteria should, ideally, be unambiguous such that given the same data, similar conclusions will be drawn by all response assessors. Table 20 shows that IRC readers frequently disagreed on response determination, date of response, or date of progression despite having access to identical lymphocyte measurements, hematology laboratory values, and investigator liver, spleen, and lymph node measurements. This variability in response assessments likely occurred as a function of the way the 1996 NCI working group criteria were written.

**Table 20: Variability in Response Assessments of IRC Members (from Statistical Reviewer)**

	Percentage of cases that went to adjudication [% (N)]
DR (N=59)	58 % (34)
BFR (N=79)	58 % (46)

- **Inconsistent use of response criteria**

IRC notes submitted by the applicant indicated that in some instances, for new nodes, the IRC used the 2008 NCI Working group criteria to designate progression (the 2008 criteria specify a new lymph node size to designate progression).

This constituted an inconsistent use of the response criteria. For comparison, the 2008 working group criteria also recommended the use of CT scans for clinical trials. Additionally, section 5.2.2 of the 2008 working group criteria stated that for partial response, there must be no increase in the size of any lymph node, and no new enlarged nodes.

The IRC charter stated that in order to compare results from the 406 trial with historical data, CT scans were not to be included in the response evaluation. *As such, this reviewer does not agree with the decision to selectively include parts of the 2008 Working Group Criteria for new lymph node size but not to include CT scans for response determination.*

• **IRC's rules for determination of response duration**

To be considered as a responder according to the NCIWG criteria, a patient must have maintained their response for at least two months (56 days). GSK's May 19, 2009, submission to the BLA stated that the IRC considered the date of onset of response until the assigned date of progression as the duration of response rather than until the date of last response. *Comment: while it might be appropriate to consider DOR from the date of response to the date of progression, this reviewer believes it is inappropriate to designate as a responder a patient who has not exhibited definitive evidence that he or she has maintained the response for at least two months.* Because response assessments occurred every four weeks, using the IRC's criteria, a patient who progressed shortly after the first confirmatory four week visit could be considered a responder because they were assigned as progressing at the next month's visit.

• **FDA Review of Specific Cases**

As was previously discussed and will be elucidated in more detail subsequently in this review, there can be significant variability in response determination using the 1996 NCIWG criteria. However, during the review, specific cases were highlighted that caused this reviewer to question the strictness with which the IRC applied the criteria. These cases were considered as responders at the time of the original BLA submission. The case in the BFR group was considered a complete responder despite having CT scan evidence that the patient had growth of a large mesenteric lymph node at the time of the response determination. *This reviewer believes that ofatumumab would be mislabeled if this patient was classified as a complete responder.*

**Table 21: Narratives of Patients Considered as Responders at the time of the Original BLA Submission.**

Patient	Case Description
406157 (BFR)	This patient was determined to be a complete responder by the IRC. At baseline, this patient had no peripheral lymphadenopathy, no hepatomegaly, no splenomegaly, and a baseline lymphocyte count of $\backslash$ mL. At baseline, this patient had a mesenteric lymph node measuring $\backslash$ cm <sup>2</sup> . This patient was designated a complete responder even though the mesenteric lymph node measured $\backslash$ cm <sup>2</sup> by CT on week 12.
406261 (DR)	In the efficacy narrative contained in the BLA, the applicant stated that this patient's (partial) remission lasted 49 days. This reviewer agreed that on the 49 <sup>th</sup> day after the initial designation of response, this patient's CLL progressed by lymphocyte criteria (lymphocyte counts more than doubled and was $\geq$ 5,000/mL), a new lymph node was palpable, and the liver became palpable. Despite the clear evidence of progression prior to 60 days, the IRC designated this patient as a partial responder.
406199 (DR)	In the efficacy narrative contained in the BLA submission, the applicant stated that this patient's (partial) remission lasted from July 18, 2007 to July 24, 2007. Less than 10 days following the first visit qualifying the patient as a responder by the lymph node criterion, the patient had increasing lymphadenopathy and a newly palpable liver edge. Despite the clear evidence of progression prior to 60 days, the IRC designated this patient as a partial responder.

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406203 (DR)	The first documented date of response for this patient occurred on visit 10 as the LN SUP (lymph node sum of the products of the diameters) decreased from $\text{cm}^2$ . At the following visit (less than 30 days later), the LN SUP was $\text{cm}^2$ and a new submandibular left node was reported by the investigator. Thus, this patient appeared to have evidence of progression prior to 60 days; however, the IRC designated this patient as having a PR. The investigator assigned this patient as having progression during this visit, due to the LN SUP more than tripling from the nadir.
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b(4)

GSK's May 19, 2009, submission to the BLA stated that two of the patients in the above table were mistakenly considered as responders (406199 and 406261) along with two additional patients in the BFR patient group. GSK stated that these mistakes occurred during the re-consensus process and the reassessments were not captured in a manual part of the IRC process. *Comment: This reviewer considers this mistake to be a BLA submission integrity issue. The primary endpoint was ORR and this reviewer believes that it was not appropriate to submit data with these substantial errors in the primary endpoint in support of a BLA. Additionally, the incorrect ORR was presented by GSK at the ODAC meeting (refer to section 3 of this review for details).* Irrespective of whether the IRC intended for these four additional patients to be classified as non-responders, these patients were initially classified as responders and not reclassified until Genmab requested the re-consensuses. For example patient 199 (less than 10 days response) was classified as a responder initially by the IRC and during the first re-consensus process. It was only at the second re-consensus process that this patient was reclassified as being a non-responder. *Comment: This reviewer questions the strictness with which the IRC applied the response criteria as exemplified by the classification of these patients (with reclassification only occurring after Genmab observed that these patients may have been classified incorrectly).*

- **Inability of FDA review staff to Determine all IRC related procedures**

At the time of the original BLA submission, it was not possible for FDA reviewers to determine the exact IRC procedures used for response determination including the procedures required for an independent adjudication (or consensus). The IRC *charter* specified that if discrepancies occurred in the determination of response or progression, a third IRC member would independently evaluate the case. However, the IRC followed the process whereas all three of the following must agree for the case not to be reviewed by an adjudicator: overall objective response assessments; onset of response date; and progression date. Datasets were also not provided in the original BLA submission that would allow FDA reviewers to determine the IRC process. The process was somewhat clarified after several teleconferences and BLA amendments.

- **Increased "consistency" over time**

During the ODAC meeting, one of the IRC members stated that there was much discussion regarding determination of responding patients during the IRC's response determinations. The IRC member went on to state that "I think that there was a lot more consistency in the

evaluations over a period of time.” This reviewer has concerns that the independence of the IRC process may have been compromised if meetings were held to ensure greater consistency.

#### 6.1.4.3 Summary of Applicant’s ORR Results-Study 406

Table 22 shows the ORR submitted by GSK. Note that the number of responders for the IRC analyses shows the proportion of responders described by GSK after the May 19, 2009 submission to the BLA (i.e., in response to the FDA 74-day letter). As described in the ODAC briefing document, the finding of a higher ORR by the IRC than by that based on the investigators’ response status was an unexpected result. The IRC identified 7 and 8 additional patients with an objective response in the DR and BFR subgroups, respectively, than did the investigators.

**Table 22: Summary of Applicant’s Revised ORR Results-Study 406 (Table Completed by Statistical Reviewer)**

	DR (N=59)	BFR (N=79)
<b>IRC</b>		
Overall Responders, N (%)	32 (54)	35 (44)
CR	0	1
PR	32	34
99% CI (%)	(37, 71)	30, 59)
<b>Investigators</b>		
Responders, N (%)	25 (42)	27 (34)
99% CI	(26, 60)	(21, 49)

#### Summary of Applicant’s ORR Results (Statistical Reviewer)

- The IRC assessed 7 and 8 more responders than the investigators in the DR and BFR groups, respectively. This is somewhat unusual since we generally expect the IRC to be more stringent than the investigator. It is worthwhile to note that in the applicant’s original submission, the IRC number of responders (%) in the DR and BRF groups were 34 (58%) and 37 (47%), respectively. In response to FDA’s question concerning the IRC assessments in the 74-day letter, the applicant identified 4 patients (2 in DR and 2 in BFR) who were not deemed responders by the IRC, but were recorded as responders erroneously (406199, 406261, 406225, 406232).
- The IRC procedure for the determination of the overall response assessment from individual IRC reader response assessments was unclear. Not until after several teleconferences and information requests were the procedures clarified. Key elements that were unclear or missing from the IRC charter were:
  - Each IRC member was asked to determine the dates of onset of response and progression for each patient.
  - The initial two IRC reviewers must agree on *all three* of the following endpoints: (i) overall objective response assessments (i.e. not per visit), (ii) onset of response dates and (iii) progression dates. If there was disagreement on at least one endpoint, then

the patient was independently adjudicated by a third IRC member. If the adjudicator's assessment did not agree with either of the two initial reviewers on all three endpoints, then a panel of at least 2 of the 5 members was to convene and review the data again to provide a consensus read.

- The one CR patient in the BFR group was patient number 406157, however, the repeat CT scan did not confirm the CR; see the Clinical Review section for details.

#### 6.1.4.4 FDA Analysis of ORR

##### (Clinical Reviewer)

In an attempt to confirm the results from GSK, this clinical reviewer conducted a case-by-case review of all patients in the DR population. CRFs, narrative summaries, and datasets were used in this analysis. Additionally, the one patient (in the BFR group) considered to be a complete responder by the IRC was also included in this analysis.

For the review of ORR, this reviewer did not use the most strict interpretation of the 1996 NCIWG criteria under which the detection of *any* new node (for example, a 1x1 cm lymph node that regressed at the next visit) would designate a progression event. However, the following considerations were made for the overall response assessment.

- If a new small node grew over time and was determined to be pathologic, the patient was deemed as progressing at the time the new node was first palpated.
- In order to consider a patient as responding, the patient must have evidence that they maintained the response for at least 56 days (rather than the more liberal interpretation of maintaining the response until the documented time of progression).
- Newly enlarged nodes (or liver/spleen size) present over multiple visits (> 1 month) were generally not considered transient [unless a node was small (~1 cm) and remained stable and there were no other signs of progression].
- A patient was not considered to have met hematological criteria if the hematologic response was clearly influenced by transfusion or growth factors.

Overall, the point estimate for ORR determined by this reviewer in the DR group was similar to that determined by the investigators (41% versus 42%). The 99% CI for this reviewer's analysis was 25 to 59%.

*Reviewer Comment: The analysis by this reviewer should not be considered as the definitive arbiter of response rate in the 406 study. However, because the ORR was similar to that of the investigators, and because of the issues described regarding the IRC review of response rate, this reviewer recommends using the investigators' ORR determination for labeling purposes (using the 1996 NCIWG criteria). In the opinion of this reviewer, significant uncertainty remains regarding the true ORR (due to the variability observed when assigning responses by the IRC and due to discrepant findings when CT scans were evaluated). The 99% CI's are useful in this regard [recognizing that the bounds of a CI interval cannot account for (known or unknown) biased results].*

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

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

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

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

#### **Case-by-Case Analysis of DR Population**

The following cases will not be summarized because they were not included in the FDA analysis (408118, 406222, 406116) or because this reviewer, the IRC, and the investigators all considered the patient as a non-responder: 406102; 406105; 406109; 406112; 406124; 406129; 406139; 406141; 406145; 406160; 406167; 406168; 406182; 406189; 406206; 406211; 406228; 406230; 406237; 406244; and 406253.

Table 23 contains brief descriptions of cases where agreement existed between the FDA (clinical) reviewer, the investigators, and the IRC that these patients experienced a PR using the 1996 NCIWG criteria. As described in the table, many of the cases could have technically been considered non-responders if strict application of the 1996 criteria were used. However, the totality of the evidence suggested that these patients did respond to ofatumumab. *In the opinion of this reviewer, the inability to strictly apply the 1996 NCIWG rules is a deficiency in the criteria themselves. This reviewer believes that criteria should be developed so that consistent application will be applied from study to study. This latitude in the interpretation of these criteria results in an inability to interpret the CLL literature for assessing ORRs.*

**Table 23: Responding Patients (DR) per IRC, FDA Clinical Reviewer, and Investigators**

Patient	Case Description
406104	Baseline: ALC / / mL; SUP (sum of the products of lymph nodes) / cm <sup>2</sup> ; and spleen / cm. This patient experienced a PR with nadir ALC of / / mL; SUP of / / cm <sup>2</sup> , and improvement in splenomegaly. Nights sweats were absent by week 8. On visit 11, the patient had a palpable spleen (from non-palpable) and new inguinal nodes; however, the LAD improved at the next visit as did the splenomegaly. <i>Comment: This reviewer agrees that the patient experienced improvements in LAD (lymphadenopathy) and the LAD and splenomegaly at visit 11 should not have designated this patient as progressing.</i>
406115	Baseline: ALC / / mL; SUP / cm <sup>2</sup> ; spleen / cm. The ALC improved to a nadir of / / mL; SUP of / cm <sup>2</sup> ; and non-palpable spleen. <i>Comment: This patient experienced a response; however, the patient experienced Grade 3 neutropenia and required G-CSF.</i>
406122	Baseline: ALC / mL; SUP / cm <sup>2</sup> . This patient had a PR and improvement in night sweats. <i>Using strict criteria, this patient could have been a non-responder according to NCI criteria. Just prior to the two month response assessment, the patient had a reappearing node and increase in SUP from / cm<sup>2</sup>. On the next visit, the SUP was / with a / cm node (technically meeting progression criteria). However, because this axillary node was palpable at all but one visit, this reviewer agrees that this patient can be considered as responding based on the totality of the evidence. The patient technically met the platelet count for response with a maximum platelet count of / mL; however, the baseline count was / mL with a screening count of / nL. Thus the hematological improvement was modest at best (in the opinion of this reviewer).</i>
406128	Baseline: ALC / mL; SUP / cm <sup>2</sup> . This patient met response criteria and reported improvements in night sweats and fevers. Reported ECOG improved from / . SUP nadir was / cm <sup>2</sup> . This patient left the study to undergo an allogeneic bone marrow transplantation. <i>Comment: This patient had low volume disease burden by peripheral LAD and lymphocytosis; however, he met response criteria. The patient was heavily pretreated including undergoing an autologous stem cell transplant. Technically, this patient could be considered a non-responder with new nodes at weeks 8 and 12; however the nodes were small (≤ 1 cm) and not increasing in size at week 12. Thus, the reviewer agreed that this patient can be considered as responding.</i>
406137	Baseline: ALC / mL; SUP / cm <sup>2</sup> ; spleen / cm. This patient experienced an improvement in spleen size by PE. The LAD improvement was modest; although the ALC improved to a nadir of / mL. The neutrophil count decreased to / mL on one visit at week 20.
406140	Baseline: ALC / mL; SUP / cm <sup>2</sup> . The ALC decreased to / mL by week 5 and the patient experienced improvements in LAD and reported improvements in night sweats. <i>Comment: This case was an example of a patient with discrepant results comparing CT scan to peripheral exam. At baseline, the peripheral LN SUP was / cm<sup>2</sup> and / cm<sup>2</sup> on CT scan. At the time of the Aug 1, 2007 scan, the patient had an SUP of / cm<sup>2</sup> on CT scan but had no palpable lymph nodes.</i>

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Patient	Case Description
406153	<p>Baseline: ALC <math>\nearrow</math> /mL; SUP <math>\nearrow</math> cm<sup>2</sup>; spleen <math>\nearrow</math> cm. This patient experienced improvements in lymphocytes and lymph node size (modestly enlarged at baseline). The spleen became non-palpable, and the patient's reported night sweats improved. <i>Comment: This is another case with discrepant CT and PE results. On March 13, 2007 (~2 months after beginning of response,) there was no LAD on physical examination; however the CT showed an SUP of <math>\nearrow</math> cm<sup>2</sup> (same as baseline). If CT were used in lieu of PE, this patient would not have been a responder; however, this reviewer agrees that the interpretation of the 1996 criteria would label this patient as a responder.</i></p>
406158	<p>Baseline: ALC <math>\nearrow</math> /mL; SUP <math>\nearrow</math> cm<sup>2</sup>; liver <math>\nearrow</math> cm. This patient experienced improvements in node size (SUP of <math>\nearrow</math> cm<sup>2</sup> at visit 6). The nodal size increased at visit <math>\nearrow</math> to an SUP of <math>\nearrow</math> cm; however, the nodes became non-palpable from visit 11 to visit 14 (&gt; 2 months), so this reviewer agrees that this patient can be considered a responder. This patient's night sweats were reported to have improved during the study. The liver edge also became non-palpable.</p>
406165	<p>Baseline ALC <math>\nearrow</math> /mL; SUP <math>\nearrow</math> cm<sup>2</sup>; no organomegaly; no constitutional symptoms. This reviewer agrees that this patient is considered a responder as the SUP decreased to <math>\nearrow</math> cm<sup>2</sup> or below for &gt; 2 months; however, the overall observed effects in this patient were modest (modest decrease in lymph node size; ALC was in the normal range at baseline).</p>
406174	<p>Baseline: ALC <math>\nearrow</math> /mL; SUP <math>\nearrow</math> cm<sup>2</sup>; no organomegaly; no constitutional symptoms. This patient experienced reduction in massive (peripheral) LAD to a nadir of <math>\nearrow</math> cm<sup>2</sup> on visit 12. The reduction in LAD lasted longer than 2 months.</p>
406195	<p>Baseline: ALC <math>\nearrow</math> /mL; SUP <math>\nearrow</math> cm<sup>2</sup>; no organomegaly. This patient had improvements in lymphocyte counts (normal range) through visit 12. The patient had fluctuations in the lymph node size (SUP was <math>\nearrow</math> cm<sup>2</sup> at baseline and decreased to <math>\nearrow</math> cm<sup>2</sup> at visit 6 increasing to <math>\nearrow</math> cm<sup>2</sup> at visit 10 and <math>\nearrow</math> cm<sup>2</sup> at visit 11). <i>Comment: A more informative evaluation of this patient's nodal burden would have involved repeated imaging of the patient's massive right iliac lymph node by CT scan (rather than the small volume peripheral lymphadenopathy).</i> This patient experienced an improvement in platelets; however, the neutrophil count was decreased and the patient received growth factor treatment.</p>
406205	<p>Baseline: ALC <math>\nearrow</math> /mL; SUP <math>\nearrow</math> cm<sup>2</sup>; spleen <math>\nearrow</math> cm; no constitutional symptoms. This patient experienced improvements in lymphocytosis (&lt;1,000/mcL) and reduction in size of the massive splenomegaly by physical examination for more than 2 months. <i>Comment: This reviewer noted that a CT scan obtained on August 2 (around the time of visit 11 evaluation showing no palpable splenomegaly) was read as "stable" spleen size.</i></p>

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Patient	Case Description
406219	Baseline: ALC [redacted] /mL; SUP [redacted] cm <sup>2</sup> ; spleen [redacted] cm; liver [redacted] cm. This patient experienced improvements in lymphocytosis (to < 1,000/mcl) and massive splenomegaly by physical examination. However, a confirmatory CT scan just prior to visit 11 showed stable portacaval lymphadenopathy and five new iliac and retroperitoneal non-measurable lesions. Additionally, the spleen remained enlarged on CT. <i>Thus, if the 2008 criteria were used, this patient would have been a non-responder; however, this patient is considered a responder by 1996 criteria.</i>
406233	Baseline: ALC [redacted] mL; SUP [redacted] cm <sup>2</sup> ; spleen [redacted] cm; The spleen became non-palpable. Night sweats were reported sporadically; there was some fluctuation in lymph node size; however nodes remained [redacted] cm or less in diameter; thus this reviewer agrees that this patient is considered a responder.
406248	Baseline: ALC [redacted] mL; SUP [redacted] cm <sup>2</sup> ; no organomegaly; no constitutional symptoms. The ALC remained < 5,000/mcl. The SUP decreased to a nadir of [redacted] cm <sup>2</sup> .
406254	Baseline: ALC [redacted] /mL; SUP [redacted] cm <sup>2</sup> ; spleen [redacted] cm; liver [redacted] cm. The ALC decreased to [redacted] mcl by visit 6 and remained less than 5,000/mcl at the time of data cut-off. The patient's lymphadenopathy, organomegaly, and night sweats resolved. Platelets improved from [redacted] /mcl. This patient did not experience a CR because of persistent bone marrow involvement (80% lymphocytes). The patient also experienced decreased neutrophil counts from week 12 to 16 (to [redacted] /mcl).
406260	Baseline: ALC [redacted] mL; SUP [redacted] cm <sup>2</sup> ; spleen [redacted] cm. The ALC improved to the normal range; The SUP improved to < 50% baseline by visit 10; night sweats reported improved. The patient had a neutrophil count of [redacted] /mcl on week 6. <i>Comment: This patient's response in LNs consisted of modest improvements in the size of multiple peripheral nodes. The overall response assessment for this patient may have benefited from independent radiological confirmation.</i>

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- Note: Spleen and liver edges are cm below the costal margin; SUP refers to lymph node sum of the products of the diameters. ALC refers to absolute lymphocyte count.

Table 24 contains a brief description of cases where the FDA clinical reviewer agreed with the IRC that the patient responded. These cases were deemed as not responding per the investigators. As described in the table, some of the cases, including 406163 and 406218 were difficult to adjudicate using the 1996 NCIWG criteria.

**Table 24: Responding Patients (DR) per IRC and FDA Clinical Reviewer; Non-responding per the Investigators**

Patient	Case Description
406149	<p>Baseline: ALC <math>\sim</math> /mL; SUP <math>\sim</math> cm<sup>2</sup>; no organomegaly. This patient had improvement in baseline small volume (peripheral) lymphadenopathy. There was no repeat imaging of the massive mesenteric lymph node. This reviewer agreed that the documentation of a new <math>\sim</math> cm axillary lymph node (at visit 6) should not have designated progression because it was not palpated at any subsequent visit. This patient did not experience sustained improvements in constitutional symptoms or hemoglobin; however, platelets increased from <math>\sim</math> 2 /mL for more than two months. This improvement may have been clinically important as this patient experienced a prior GI bleed.</p>
406163	<p>Baseline: ALC <math>\sim</math> /mL; SUP <math>\sim</math> cm<sup>2</sup>; no organomegaly. This patient was considered a responder due to improvement in lymphocyte counts and lymphadenopathy. <i>Comment: This reviewer agrees that this patient is considered a responder; however, it remains unclear to this reviewer how the IRC assigned the date of progression. Richter's transformation was documented on May 2, 2007, but the IRC assigned a progression date of May 24.</i></p> <p><i>This case was a borderline case of response, and was difficult to adjudicate. Technically, the first date of response was 2/22/2007 and the last known date of response was April 17, 2007 or 55 days (56 days was to be required for response). The known Richter's transformation occurred on May 2, 2007. The lymphocyte improvements started on week 3 [one week prior to the known first lymph node improvement denoting a probable earlier date of response (due to scheduling of the visit)], so this patient was classified as responding (with consideration given to the visit schedule).</i></p>
406192	<p>Baseline: ALC ( <math>\sim</math> /mL; SUP ( <math>\sim</math> /cm<sup>2</sup>; no organomegaly. This patient experienced modest improvements in peripheral lymph node size and improvements in lymphocyte counts. Symptoms of weight loss and night sweats were reported to have improved. There was an increase in lymph node size at visit 12; however, the lymph node size improved at the time of the next visit.</p>
406218	<p>Baseline: ALC ( <math>\sim</math> /mL; SUP ( <math>\sim</math> cm<sup>2</sup>; spleen <math>\sim</math> cm; liver <math>\sim</math> cm. This patient was considered as responding; however response determination for this case was difficult. The lymph node size fluctuated during the study and was <math>\sim</math> cm<sup>2</sup> at visit 6, <math>\sim</math> cm<sup>2</sup> at visit 10, <math>\sim</math> cm<sup>2</sup> on visit 12, <math>\sim</math> cm<sup>2</sup> on visit 13, and <math>\sim</math> cm<sup>2</sup> on visit 14 (with new nodes). There were no lymph node measurements at visit 11. The case was difficult to adjudicate due to the missed visit, followed by increase in size of lymph nodes at visit 13, followed by new nodes at visit 14 (with decreased overall size of nodal volume at this visit). Additionally, the nodal size increased again at visit 15. This reviewer considered this patient as a responder, acknowledging the uncertainty.</p>

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Clinical Review  
 Steven Lemery/Jenny Zhang  
 BLA 125326  
 Ofatumumab/Arzerra

Patient	Case Description
406239	Baseline: ALC / mCL; SUP / cm <sup>2</sup> ; no organomegaly. This patient experienced improvements in small volume cervical lymphadenopathy. This patient's platelets improved from / mCL to greater than / mCL. The hemoglobin also improved from / gm/dL to greater than / gm/dL. With hematological improvement, this reviewer considered this patient to be a responder per 1996 guidelines. <i>The investigator deemed the patient as a non-responder as he/she interpreted repeat imaging as "stable." This responding patient had relatively low disease burden (peripheral LAD and lymphocyte counts) at baseline due to prior treatment and was eligible for treatment due to constitutional symptoms.</i>
406259	Baseline: ALC / mCL; SUP / cm <sup>2</sup> ; liver / cm. This patient experienced a PR. There was an increase in size of nodes by palpation at visit 11; however, the nodes improved by the next visit.

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Table 25 describes three patients who were considered by investigators as responders; however both the IRC and FDA clinical reviewer deemed these patients to be non-responders.

**Table 25: Responding Patients per Investigators; non-Responding Patients per IRC and FDA Clinical Reviewer**

Patient	Case Description (Reason for Consideration of Patient as a Non-Responder)
406119	Spleen at baseline / cm below coastal margin. Spleen remained / cm throughout the study.
406150	Spleen was / cm at baseline and was / cm throughout study.
406168	Nodal SUP at baseline was / cm <sup>2</sup> . SUP was / cm <sup>2</sup> throughout the remainder of the study.

b(4)

Table 26 describes two instances where the FDA clinical reviewer deemed the patient as not responding despite both the IRC and independent reviewers determining these cases to be responders. The FDA clinical interpretation for both patients involved hematological criteria.

**Table 26: Responding Patients per Investigators and IRC; non-Responding per FDA Clinical Reviewer**

Patient	Case Description (Reason for Consideration of Patient as a Non-Responder)
406210	This reviewer considered this patient a non-responder because hematological lineage improvements were not sustained for at least two months (in any of the three lineages). Baseline platelets were / mCL increasing to / mCL on visit 3 (6/11) and remained above / mCL until visit 9 [7/24 (< 2 months)]. Hemoglobin was / gm/dL at baseline and did not increase above / gm/dL for two consecutive months. Baseline ANC was / mCL; the ANC did not increase above / mCL except on 2 separate non-consecutive visits and thus was not sustained.

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Patient	Case Description (Reason for Consideration of Patient as a Non-Responder)
406236	At baseline the patient had an ALC of [redacted] $\mu\text{m}^3$ and small volume peripheral LAD [redacted] $\text{cm}^3$ . Non-response was considered by this reviewer based on hematological parameters. Platelets were [redacted] $\mu\text{m}^3$ at baseline decreasing to [redacted] $\mu\text{m}^3$ at visit 3 and [redacted] $\mu\text{m}^3$ at visit 6. The platelets increased to above [redacted] $\mu\text{m}^3$ from November 7, 2007 to February 27, 2008; however, platelet transfusions were required on multiple occasions from December 3 through December 24. Platelet transfusions were also reported on March 2, 2008. The patient was also transfusion dependent for red blood cells. The patient did have a greater than 50% improvement in neutrophils documented from 11/7/2007 to 1/23/2008; however, the patient was documented to receive G-CSF from 12/1/2007 to 12/22/2007. <i>This reviewer considered this patient to be a non-responder based on hematological criteria (including worsening of platelets).</i>

b(4)

Table 27 describes seven patients in which this reviewer (and the investigator) deemed as non-responders that the IRC deemed responders (original BLA submission). Two of the seven cases were later described as non-responders by GSK. Some cases were difficult to adjudicate (in the opinion of this reviewer, including cases 406111 and 406170).

**Table 27: Responding Patients per IRC (per original BLA submission); non-Responding per FDA and Investigators**

Patient	Case Description (Reason for Consideration of Patient as a Non-Responder)
406111	At baseline the liver was not palpable. The liver edge later became palpable at weeks 12 (visit 11) and 16 (visit 12) during documentation of the response by the IRC. The liver was not palpable on visit 13. GSK (IRC) deemed the liver enlargement as transient and thus the patient did not have PD and was a responder. This reviewer considered the more conservative assessment (using the 1996 criteria) that the enlargement occurred over two visits (November 22 and December 10) and thus was not considered transient. <i>Comment: This reviewer considered this case as difficult to adjudicate. The patient did experience modest improvements in peripheral lymphadenopathy, improvement in lymphocyte counts, and improvement in night sweats.</i>
406147	This patient was described in Table 19 above. Additionally, this patient experienced no sustained improvements in hemoglobin or platelet counts (and required platelet transfusions). The patient had persistent severe neutropenia during the trial with improvement from [redacted] $\mu\text{m}^3$ at baseline to [redacted] $\mu\text{m}^3$ at visit 10, [redacted] $\mu\text{m}^3$ at visit 12, and [redacted] $\mu\text{m}^3$ at visit 13; however, this patient received pegfilgrastim every third week during the trial until just after visit 12 (no start date for pegfilgrastim was described). <i>Thus, this reviewer considered this patient to be a non-responder using both lymph node criteria and hematological criteria (requirement for growth factors).</i>
406154	This patient's ALC reached nadir on 2/20/2007 with first evidence of response on 1/30/2007. The ALC increased more than 50% on two consecutive visits with an ALC of $> 5,000$ on visit 11 (3/27/2007). Because of the increasing ALC starting on 2/27/07, this reviewer considered this patient to be a non-responder by NCIWG criteria. <i>Despite being considered as non-responding, disease activity was noted in this patient with reduction in size of lymphadenopathy. This reviewer considered progression to be measured from nadir counts rather than from baseline.</i>

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Patient	Case Description (Reason for Consideration of Patient as a Non-Responder)
406170	The ALC on visits 12 and 13 was more than 50% increased from the nadir ALC occurring at visit 11 (the patient first could be considered a responder at visit 10 by lymph nodes). Additionally, on visit 11, the SUP increased in size and there was a new node (the SUP stabilized on visit 12, but increased again at visit 13). <i>This was a difficult case to adjudicate.</i>
406199	In the efficacy narrative contained in the BLA submission, the applicant stated that this patient's (partial) remission lasted from July 18, 2007 to July 24, 2007. Less than 10 days following the first visit qualifying the patient as a responder by the lymph node criterion, the patient had increasing lymphadenopathy and a newly palpable liver edge. Despite the clear evidence of progression prior to 60 days, the IRC initially designated this patient as a partial responder. <i>GSK stated that this patient should have been considered as a non-responder in the May 19, 2009 addendum to the BLA.</i>
406203	The first documented date of response for this patient occurred on visit 10 as the LN SUP (lymph node sum of the products of the diameters) decreased from $\text{cm}^2$ / $\text{cm}^2$ . At the following visit (less than 30 days later), the LN SUP was $\text{cm}^2$ and a new submandibular left node was reported by the investigator. Thus, this patient appeared to have evidence of progression prior to 56 days; however, the IRC initially designated this patient as having a PR. The investigator assigned this patient as having progression during this visit, due to the LN SUP more than tripling from nadir. <i>GSK stated that this patient should have been considered a non-responder in a May 19, 2009 addendum to the BLA.</i>
406261	In the efficacy narrative contained in the BLA, the applicant stated that this patient's (partial) remission lasted 49 days. <i>This reviewer agreed that on the 49<sup>th</sup> day after the initial designation of response, this patient's CLL progressed by lymphocyte criteria (lymphocyte counts more than doubled and were <math>\geq 5,000/\text{mCL}</math>), a new lymph node was palpable, and the liver became palpable.</i> Despite evidence of progression prior to 60 days, the IRC designated this patient as a partial responder.

b(4)

In summary, this reviewer found a 41% ORR using the 1996 NCIWG criteria. The FDA clinical review was not a strict interpretation of the 1996 NCIWG criteria; however, the FDA review applied rules that were more conservative than the IRC. There were multiple cases that were difficult to adjudicate using the 1996 NCIWG criteria. In the FDA review, some of the difficult cases were considered as responders and some non-responders. *This difficulty in adjudicating cases underscores the uncertainty regarding the point estimate for ORR.*

Although this reviewer did not agree with the clinical investigators' assessments on a case-by-case basis, the overall response rate was similar for both analyses. Because of the multiple issues regarding the IRC described above, this reviewer believes that the investigators' ORR (and response duration) should be used for labeling purposes in lieu of the IRC's ORR.

**Evaluation of the CR in the BFR Group**

Patient 406157 (Table 28) in the bulky fludarabine refractory group was designated as a complete responder by the IRC despite having no confirmation of response by CT scan. On the baseline CT scan, this patient had a massive retroperitoneal lymph node measuring  $7.7 \text{ cm}^2$ . Prior

b(4)

to the week 12 visit, a confirmatory CT scan showed that the retroperitoneal lesion was  $\surd$  cm<sup>2</sup> and the spleen was unchanged in size. Other measured lymph nodes on CT scan appeared to be stable in size. If CT scans were used in the response determination, the patient would have been classified as a non-responder.

b(4)

Table 28: Review of Patient 406157 (Complete Response per IRC)

	Baseline	Week 4	Week 8	Week 12	Week 16	Week 20
Lymphocytes (per mL)	[Redacted]					
LN SUP (cm <sup>2</sup> )	[Redacted]					
Liver/Spleen (cm)	NP	NP	NP	NP	NP	NP
RP LN by CT (cm <sup>2</sup> )	$\surd$	-	-	$\surd$	-	-

b(4)

- LN SUP = Sum of the Products of the Lymph Nodes
- NP = Not Palpable
- Weeks are approximate
- Liver and spleen measurements below costal margin

**6.4.1.5 Consideration of CT Scans in the Overall Response Determination (Study 406)**

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

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

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

Furthermore in the DR group, 9 patients who were considered responders by the IRC underwent repeat CT scans assessment. If CT scans were used instead of physical examination for response determination, five of the patients (406140, 406153, 406205, 406219, and 406233) may have been re-classified as non-responders. *Comment: this reviewer could not make a definitive statement that all of these patients would have been non-responders. For example, the repeat CT scan for patient 140 was at month 9 and the repeat scan for patient 233 occurred at month 8. Nevertheless, this reviewer was concerned regarding the discrepancies observed between lymph node improvements observed with physical examination versus CT scans results.*

- The following examples from the DR group show how follow-up radiography may have either
- Reclassified the response category (when repeat CT scans were obtained), or
  - Assisted in the response classification of patients (who did not undergo repeat CT scans)

**Table 29: Examples where Radiology may have provided Relevant Information for the Overall Response Assessment**

Patient	Case Description
406118	At baseline, this patient had no measurable disease by physical examination (peripheral lymphadenopathy, splenomegaly, or hepatomegaly) and no lymphocytosis. Furthermore, the platelet count remained above _____ mL at baseline ensuring that, if stable, this patient would have been considered a responder (whether or not there was any actually anti-CLL activity). This patient had a lymph node in the peritoneum measuring _____ cm <sup>2</sup> on baseline CT. Although this patient was designated as PR by the IRC, there were no objective findings to support this designation and this patient was removed from the FDA analysis. Radiographic follow-up may have provided evidence of objective anti-tumor activity for this patient.
406140	By physical examination, this patient had a baseline lymph node sum of products of the diameters (LN SUP) of _____ cm <sup>2</sup> and a LN SUP of _____ cm <sup>2</sup> on study visit 16. Yet by CT scan, the baseline nodal SUP was _____ cm <sup>2</sup> versus _____ cm <sup>2</sup> on the day of visit 16. This patient had a reported complete nodal response by PE and was designated as having a partial response; however, if only CT scan was used for the LN response assessment, this patient would have not been deemed a responder.
406153	This patient had modest peripheral lymphadenopathy by PE at baseline with a LN SUP of _____ cm <sup>2</sup> . On visit 11, the LN SUP was _____ cm <sup>2</sup> by physical examination. However, the baseline and visit 11 LN SUPs by CT scan were _____ and _____ cm <sup>2</sup> , respectively. Furthermore, the patient had spleen enlargement on CT scans at baseline and follow-up. Using the 1996 NCI WG criteria, this patient is considered a responder; however, this patient may have been classified as having stable disease if repeat CT scans were required.
406195	This patient had a LN SUP (by PE) of _____ cm <sup>2</sup> at baseline, visit 6, visit 10, and visit 11. The patient was deemed a partial responder based on lymphocyte counts. This patient did not exhibit a 50% decrease in the SUP of the LNs for two months; however, this patient's peripheral LNs always were less than 1 cm <sup>2</sup> after baseline until progression. A more valid assessment of this patient's lymphadenopathy would have been a follow-up scan of a right (arterial) iliac node that measured _____ cm <sup>2</sup> at the time of the baseline CT scan.
406205	This patient, deemed a responder, had no lymph nodes at baseline, but had a spleen that was _____ cm under the coastal margin. The spleen subsequently became undetectable by physical examination and was not palpable on visit 11. A confirmatory CT scan at this time revealed stable organ (spleen) enlargement. Thus, by CT scan, this patient might have been designated a non-responder.

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Patient	Case Description
406219	<p>This patient had minimal peripheral lymphadenopathy at baseline (SUP / cm<sup>2</sup>) and had a (peripheral) nodal SUP between 6 and 7 cm<sup>2</sup> from baseline until visit 15. A porta-caval node measured 7 cm<sup>2</sup> at the baseline CT scan. A confirmatory CT scan prior to visit 11 revealed a stable porta-caval node measuring 7 cm<sup>2</sup> and five new non-measurable lymph nodes. The patient continued to have splenic enlargement by CT despite having no palpable splenomegaly. This patient was designated a responder but would be considered to have stable disease or progression using the CT scan results.</p>

b(4)

These data were presented to the Oncology Drugs Advisory Committee on May 29, 2009. One of the committee members expressed concern that in advanced CLL, peripheral lymphadenopathy may not accurately reflect anti-tumor activity of anti-CLL treatments. The committee voted, despite the concerns regarding lack of radiographic imaging, to recommend approval of ofatumumab (by a 10 to 3 vote) based on the totality of the data and prior experience using the 1996 criteria with other drugs including alemtuzumab. The Committee did recommend that CT scans be utilized in future trials designed to evaluate ORR in a refractory CLL patient population for regulatory purposes.

**6.4.1.6 Other ORR Analyses**

**(Statistical Reviewer)**

To investigate the robustness of the IRC results, the sponsor performed a computer algorithm-based analysis of the IRC response assessments. This algorithm was copied to this review below directly from the Applicant's summary of clinical efficacy. Overall, the algorithm was a strict application of the NCIWG 1996 guidelines, excluding any clinical judgment. Results are shown in Table 30.

The clinical reviewer excluded three patients from the DR group (406116, 406118, and 406222) analysis due to the inability to discern whether the patients' responses were due to anti-CLL activity; i.e., they had no detectable CLL at baseline. Thus, the number of patients (N) in the DR group for the analyses in Table 30 was 56. Please refer to the Clinical Review sections above for further explanation regarding exclusion of these patients from the analyses.

The statistical reviewer performed an additional sensitivity analysis of ORR following the FDA's interpretation of the IRC charter procedures for the determination of the final IRC response using per-visit IRC response assessments from Reader 1, Reader 2, and the Adjudicator. Specifically, the statistical reviewer required at least 2 consecutive visits, at least 56 days apart, with response present (i.e. from date of onset of response until date of last response) to confirm a response with a duration of at least 2 months. Furthermore, if the overall response determination of the initial two IRC readers were in agreement, then the adjudicator's assessment (if adjudicated) would be ignored. As shown in Table 30, the reviewer found that the number of responses obtained through this strict adherence to the IRC charter and procedures was similar to the Applicant's algorithm.

For the investigator and Applicant's algorithm determination, there was only one response assessment per visit, per patient. The corresponding reviewer's results in Table 30 were also obtained by requiring at least 2 consecutive visits, at least 56 days apart, with response present to confirm a response with duration of at least 2 months. The reviewer's results for those two analyses were generally consistent with the applicant's.

#### ***Sponsor Sensitivity Analysis***

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

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

**Table 30: Summary of ORR Assessed by IRC, Investigator, and Sponsor Algorithm (Statistical Reviewer)**

	Sponsor		Reviewer	
	DR (N=59)	BFR (N=79)	DR (N=59)	BFR (N=79)
<b>IRC</b>				
Responders, N (%)	32 (54)	35 (44)	18 (32)	21 (27)
99% CI (%)	(37, 71)	(30, 59)	(17, 50)	(15, 41)
<b>Investigator</b>				
Responders, N (%)	25 (42)	27 (34)	23 (41)	26 (33)
99% CI (%)	(26, 60)	(21, 49)	(25, 59)	(20, 48)
<b>Sponsor Algorithm</b>				
Responders, N (%)	22 (37)	24 (30)	17 (30)	22 (28)
99% CI (%)	(22, 55)	(18, 45)	(16, 48)	(16, 43)

**Statistical reviewer's comments:**

1. The clinical reviewer conducted a case-by-case review of all patients in the DR group evaluating all laboratory data, CRFs, and electronic case report forms submitted; see clinical review sections for details. The estimate of ORR in the DR group from the clinical review was 41% (23 responders) with 99% CI of (25, 59), which was similar to that of the Applicant's results for the investigators' assessment.
2. In addition to the statistical reviewer's analysis of ORR by the IRC shown in Table 30 (which required at least 2 consecutive visits, at least 56 days apart, with response present to confirm a response with duration of at least 2 months), the reviewer also repeated the analysis including a 3-week window. Allowing a 3-week window only added 2 responders to the DR group [20 (36%), 99% CI: (20, 54)] and 1 responder to the BFR group [22 (28%), 99% CI: (16, 43)].
3. As seen in Table 31, there is large variability of response assessments between IRC readers and the adjudicator.

**Table 31: Variability in Response Assessments of IRC Members (Statistical Reviewer)**

	Number of cases such that IRC reader 1 disagreed with reader 2*	# of cases that went to adjudication
DR (n = 59)	14 (24 %)	34 (58 %)
BFR (n = 79)	18 (26 %)	46 (58 %)

\*using Applicant-submitted overall response assessments for individual IRC members

**(Clinical Reviewer)**

*Comment: These algorithmic sensitivity analyses applied strict application of the response criteria without clinical judgment. The ORRs using these analyses were less than that obtained by the IRC or investigators. The lower bounds of the investigators' 99% CI was less than the point estimate of these sensitivity analyses. Importantly, anti-tumor activity was still observed in*

*the heavily pretreated DR population. The difference in ORR estimates underscores the previous comments regarding the overall uncertainty of the ORR point estimate.*

### 6.1.5 Analysis of Secondary Endpoints(s)

#### (Statistical Reviewer)

Progression-free survival (PFS) was defined as the time from baseline (visit 2) until progression as assessed by the IRC or death. Duration of response (DOR) was defined as the time from the initial response to progression as assessed by IRC or death, and was censored in the same way as PFS. For the primary analyses of PFS and DOR, the following scenarios were censored: no progression at the end of trial; treatment discontinued for undocumented progression, toxicity, or other reasons; new anti-cancer therapy started; death or progression after two or more consecutive missed visits. For the sensitivity analysis of PFS and DOR, only those patients with no progression at the end of study were censored, all other scenarios are considered as observed events.

Overall survival (OS) was defined as the time from baseline to death, and time to next CLL therapy was defined as the time from baseline to time of first administration of the next CLL treatment other than ofatumumab. Note that deaths without next CLL therapy were censored in the sponsor's analysis of time to next CLL therapy.

#### 6.1.5.1 Duration of Response (IRC)

#### (Statistical Reviewer)

The most important secondary endpoint in consideration of this review is duration of response because responses must be considered durable if they are to be considered as reasonably likely to predict clinical benefit. Table 32 shows the GSK summary results for duration of response (DOR) and the results of a GSK sensitivity analysis of DOR in which only those patients with no progression at the end of study were censored, and all other scenarios were considered as observed events. This DOR was based on the IRC analysis.

**Table 32: GSK Results for DOR (Statistical Reviewer)**

Duration of Response (mo.)	DR (N=59)	BPR (N=79)
Median (95% CI) – primary analysis	7.1, (3.7, 7.6)	5.6, (3.6, 7.0)
Median (95% CI) – sensitivity analysis	5.3, (3.7, 7.4)	5.5, (3.6, 6.4)

### Duration of Response (Investigators)

#### (Statistical Reviewer)

Given the IRC's inconsistent application/interpretation of the criteria in the NCIWG 1996 guidelines, the FDA will base its decision regarding accelerated approval of ofatumumab in patients with CLL refractory to fludarabine and alemtuzumab on the investigators' ORR. See Clinical Review sections for details.

Table 33 summarizes the duration of response (DOR) as assessed by the investigators. The sponsor defined DOR as the time from the date of onset of response until the date of progression. The statistical reviewer conducted a sensitivity analysis of DOR, defined as the time from the date of onset of response until the last date of response. The median DOR in the sensitivity analysis was about 1 month less than the applicant's; this result is expected given that tumor assessments were conducted every 4 weeks.

**Table 33: Investigators' Duration of Response (Statistical Reviewer)**

	DR (N=59)	BFR (N=79)
<i>Applicant's DOR: date of onset of response until date of progression</i>		
Median (95% CI)	6.5 (5.8, 8.3)	6.5 (5.5, 8.7)
<i>Sensitivity Analysis DOR: date of onset of response until last date of response</i>		
Median (95% CI)	5.6 (4.6, 9.2)	5.4 (4.6, 7.9)

An analysis of investigator "raw" data was conducted to confirm GSK's results for DOR. For each responding patient, the date of relapse was considered the date of PD, or if the date did not exist, the censoring date was the last visit date recorded. Using this procedure, this reviewer obtained the same DOR times as the applicant except for four patients. The dates for these four cases were within a one month window of GSK's results. The results of this sensitivity analysis would have resulted in a slightly longer DOR in the DR population and the same DOR in the BFR population. Thus, the results of GSK are acceptable.

### 6.1.5.2 Overall Survival

#### (Clinical Reviewer)

As described in FDA Guidance for Industry, "overall survival almost always needs to be evaluated in randomized controlled studies." Without a control group, effects on survival can be attributed to patient selection or improved supportive care. This reviewer recommends against including survival information in the product label.

The following additional analyses for survival were conducted by the statistical reviewer.

**(Statistical Reviewer)**

The following table summarizes the applicant's results for survival.

**Table 34: Applicant's Results for OS (Statistical Reviewer)**

	DR (N=59)	BFR (N=79)
Overall Survival (mos.) Median (95% CI)	13.7 (9.4, na)	15.4 (10.2, 20.2)

During the review, inconsistencies with respect to CRF death dates and time to death (OS) were found in the overall survival datasets. Table 35 summarizes these inconsistencies.

**Table 35: Inconsistencies in Overall Survival Data (Statistical Reviewer)**

	Visit 2 date	CRF	AE	OS	CRF death date
patient ID	(baseline)	death date	death date	(applicant)	baseline
406105				25	28
406168				195	160
406228				311	*
406250				131	134

b(6)

\*In the clinical study report, patient 406228 died on \_\_\_\_\_ which corresponds to OS of 311 days; however, the death date is missing in the survival dataset.

The applicant was asked to address the death date discrepancies in the 74-day letter sent on April 14, 2009. The following summarizes the applicant's response. The date of death was not collected as a specific item on the CRF; the "death date" variable was derived from various data items collected on the CRF (e.g. withdrawal date, follow-up date, termination date). The most accurate death information was data obtained during the SAE reporting process, thus, mortality dates recorded in the AE datasets were used as the priority in the algorithm for assessing survival. If these data were missing, then the data items collected on the CRF were considered to determine the date of death.

It was worthwhile to note that for patient 406168 in the DR group, the AE death date was 35 days later than the CRF death date.

- Censoring deaths without next CLL therapy in the definition of time to next CLL therapy could result in informative censoring. The median times (in months) to next CLL therapy including deaths as events for the DR and BFR groups were 7.3 with 95% CI (5.6, 9.3) and 7.2 with 95% CI (6.1, 8.2), respectively.
- Since study 406 was a single-arm trial, reliable conclusions concerning the benefit of ofatumumab on PFS and OS are difficult to ascertain.

**(Statistical reviewer-Comments)**

The reviewer would like to reiterate and emphasize that since Study 406 was a single arm trial, analyses of OS and PFS (Section 6.1.5.3) are very difficult to interpret and should only be

considered as descriptive.

### **12-week Responder Landmark Analysis of OS**

#### **(Statistical Reviewer)**

The applicant conducted a landmark analysis of overall survival (OS) in responders vs. non-responders to evaluate the relationship of response and OS. In a landmark analysis, only patients who survive until the analysis timepoint were included. Twelve weeks was chosen as the analysis time-point as this was the earliest time at which a response identified at week 4 could be confirmed. At week 12, 53/59 DR patients and 75/79 BFR patients were included in the landmark analysis. The median OS was not reached for responders in either the DR or BFR groups. The median OS (95% CI) for non-responders in the DR and BFR groups was 10.2 months (8.4, na) and 10.9 months (8.7, 15.4), respectively. The survival curves for the Applicant's analyses of responders vs. non-responders in the DR and BFR groups are provided in Figures 9 and 10, respectively.

#### **Comments:**

1. The value of the landmark analyses was limited; although not all available data was used in the analyses, the inferences made were applied to the entire ITT population. Additionally, it is difficult to interpret analyses where the groups are determined based on random outcomes obtained during the course of the study. The limitations of landmark analyses were recognized at the May 29, 2009 ODAC meeting. Dr. David Harrington stated that "It's difficult to interpret that sort of analysis, because you have to have survived 12 weeks -- conditional on surviving 12 weeks, then the responders do better than the non-responders. So the analysis isn't biased, but it's restricted to people who survive 12 weeks on therapy."
2. Due to the concerns with such analyses, the results should be interpreted with caution. These analyses aim to correlate OS with response; this is, however, not sufficient to argue that response in this study will reasonably likely predict that clinical benefit will later be demonstrated.

Figure 9: OS per response in week 12 survivors [DR group (Statistical Reviewer)]

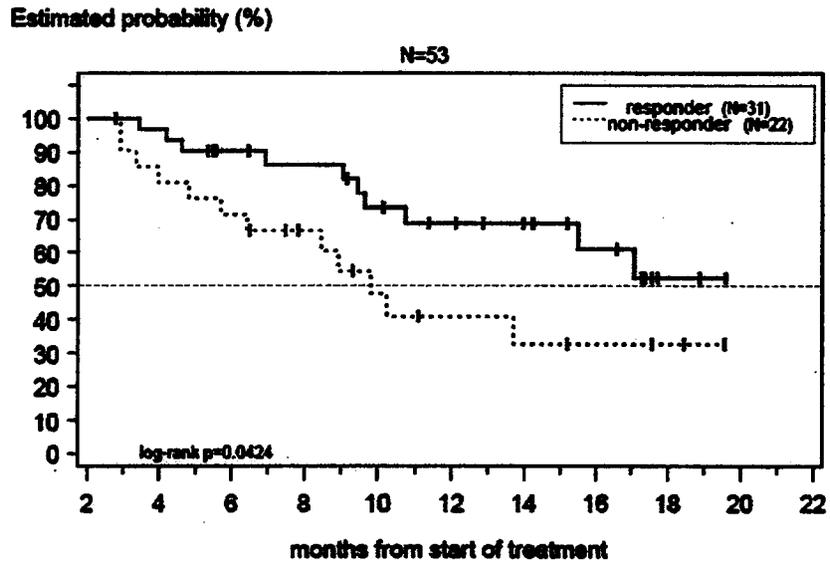
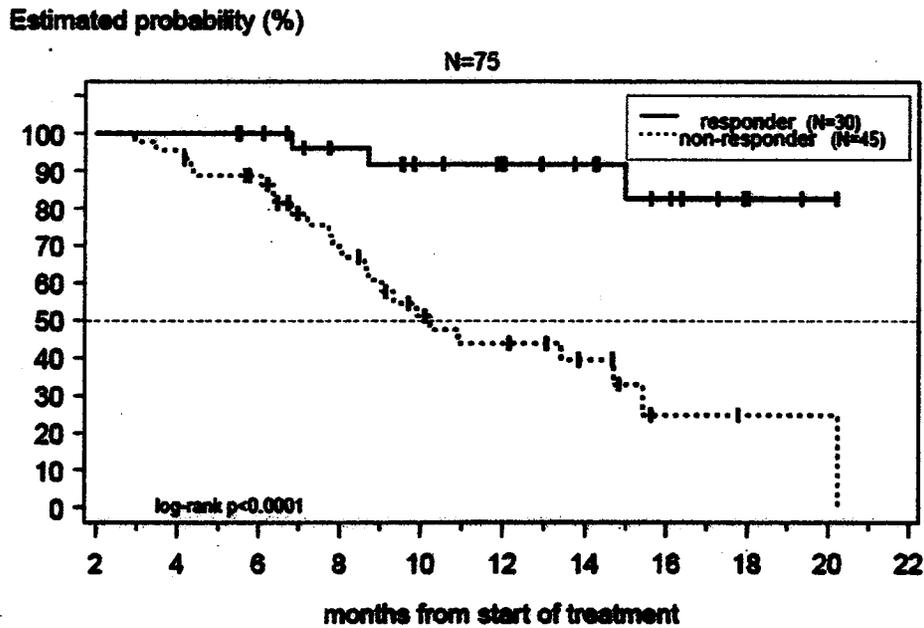


Figure 10: OS per response in week 12 survivors [BFR group (Statistical Reviewer)]



**(Clinical Reviewer)**

***Comment Regarding Survival Analyses***

*The applicant's analyses of OS in patients alive at week 12 are not informative and potentially misleading. Even with the landmark approach, the analyses still are comparing responding patients who have different disease characteristics to non-responding patients. Additionally, these analyses do not incorporate information regarding fatal drug-related events occurring prior to 12 weeks. Because these analyses are based on single arm studies without an internal control, any survival benefit in responders cannot be attributed to drug effects. Any determination of drug effect on OS in CLL must come from a randomized study with an internal control arm. Results for time-to-event endpoints will not be included in the product label.*

**6.1.5.3 Progression Free Survival and Time to Next CLL Therapy**

As described in FDA Guidance for Industry, time to event endpoints need to be evaluated in randomized controlled studies. Without a control group, effects on time to event endpoints can be attributed to patient selection or improved supportive care. This reviewer recommends against including these endpoints in the label. Table 36 summarizes the applicant's results for these endpoints.

**Table 36: Applicant's Results for PFS and Time to Next CLL Therapy (Statistical Reviewer)**

<b>Endpoint</b>	<b>DR (N=59)</b>	<b>BER (N=79)</b>
<b>Progression-free Survival (mos.)</b>		
Median (95% CI) - primary	5.7 (4.5, 8.0)	5.9 (4.9, 6.4)
Median (95% CI) - sensitivity	5.5 (4.0, 6.4)	5.5 (3.9, 6.4)
<b>Time to Next CLL Therapy (mos.)</b>		
Median (95% CI)	9.0 (7.3, 10.7)	7.9 (7.1, 9.3)

**6.1.6 Other Endpoints**

**Summary of Improvements in Individual ORR Components Compared to Baseline**

**(Statistical Reviewer)**

Table 37 tabulates the number of patients with abnormalities at baseline who experienced clinical improvements lasting at least 2 months for various hematologic and efficacy parameters, all of which were components of the composite primary response endpoint. As shown in Table 37, the reviewer was able to replicate the sponsor's results; small discrepancies were likely due to slight differences in definition (e.g. it was unclear for certain parameters what the applicant's cutoff value was to designate a patient as abnormal at baseline).

**Table 37: Clinical Improvements with Minimal Duration of  $\geq 2$  Months with Abnormalities at Baseline (Statistical Reviewer)**

Efficacy Endpoint or Hematologic Parameter	Subjects with Benefit/Subjects with Abnormality at Baseline (%)			
	DR		BFR	
	Applicant	Reviewer	Applicant	Reviewer
Lymphocyte count: $\geq 50\%$ Decrease Normalization ( $\leq 4 \times 10^9/L$ )	31/42 (74)	27/40 (68)	44/64 (69)	41/63 (65)
	20/42 (48)	17/40 (43)	26/64 (41)	22/63 (35)
Complete Resolution of Constitutional Symptoms	15/31 (48)	14/31 (45)	29/46 (63)	28/46 (61)
Lymphadenopathy: $\geq 50\%$ Decrease Complete Resolution	34/55 (62)	34/54 (63)	36/74 (49)	35/72 (49)
	9/55 (16)	8/54 (15)	8/74 (11)	6/72 (8)
Splenomegaly: $\geq 50\%$ Decrease Complete Resolution	16/30 (53)	16/30 (53)	26/46 (62)	26/46 (62)
	14/30 (47)	14/30 (47)	16/46 (35)	14/46 (30)
Hepatomegaly: $\geq 50\%$ Decrease Complete Resolution	11/18 (61)	11/18 (61)	13/21 (62)	13/21 (62)
	9/18 (50)	9/18 (50)	11/21 (52)	11/21 (52)
Hemoglobin $<11$ g/dL at baseline to $>11$ g/dL post baseline	8/26 (31)	9/28 (32)	11/42 (26)	13/44 (30)
Platelet count $<100 \times 10^9/L$ at baseline to $>50\%$ increase or $>100 \times 10^9/L$ post baseline	12/29 (41)	13/26 (50)	17/44 (39)	20/43 (47)
Neutrophils $<1.5 \times 10^9/L$ at baseline to $>1.5 \times 10^9/L$ post baseline	1/19 (5)	1/18 (6)	5/17 (29)	7/16 (44)

**Summary of Improvements in Individual ORR Components (Clinical Reviewer)**

Even though the statistical reviewer was able to replicate the applicant's results, this clinical reviewer recommends against inclusion of such information in the label. Reasons for this decision include the following:

- For hematological parameters, it is not clear that the defined parameters constitute a clinical benefit or would even be likely to predict benefit. For example, increasing platelets from 96,000/mcL to 108,000/mcL would satisfy the requirement for benefit in the table; however, such an increase would not result in a reduction of bleeding risk.
- Constitutional symptoms are considered patient reported outcomes. These endpoints were not adequately measured for regulatory purposes as per FDA's draft guidance. Additionally, it was not clear what constituted extreme fatigue (compared to fatigue).

This reviewer considers these individual component endpoints as supportive of the overall response rate claim. Additional more detailed analyses of selected endpoints are included in the review below.

**Lymphocytosis:**

A total of 116 out of 154 patients experienced a documented decrease in lymphocyte counts greater than 50% of baseline. However, 41 patients (27%) had lymphocyte counts less than 5,000/mcL at baseline. Table 38 shows the proportion of patients who experienced lymphocyte count reductions of more than 50% compared with baseline.

**Table 38: Proportion of Patients who manifested a Lymphocyte Count Reduction of More than 50 Percent (any Duration)**

	> 50% decrease (DR)	> 50% decrease (total population)
All patients	42/59 (71%)	116/154 (75%)
Baseline lymphocyte counts $\geq 5,000/\text{mcL}$	31/38 (82%)	100/113 (88%)
Baseline lymphocyte counts $\geq 10,000/\text{mcL}$	26/31 (84%)	88/97 (91%)
Baseline lymphocyte counts $\geq 20,000/\text{mcL}$	20/23 (87%)	70/75 (93%)

The 31 DR patients with baseline lymphocyte counts  $\geq 5,000/\text{mcL}$  and who had a 50% reduction in lymphocyte counts were examined to determine if the lymphocyte counts remained low for more than 2 months. The following were examples of patients in the DR group without sustained improvement in lymphocyte counts:

- Patient 170 had a lymphocyte count of \_\_\_\_\_ mcL at screening and \_\_\_\_\_ mcL on day one of therapy. The higher value was used as baseline; thus, the patient only met criteria (> 50% decrease in lymphocytes) for approximately one month. If the screening value was used (assuming the patient had progression due to CLL from screening to baseline) as the baseline, this patient would have met the lymphocyte criteria.
- Patient 211 experienced a documented > 50% decrease in lymphocyte counts from 6/20/2007 to 8/08/2007.
- Patient 228 experienced a  $\geq 50\%$  decrease in lymphocyte count on only one visit.
- Patient 237 had documented improvements in lymphocyte count measurements ( $\geq 50\%$ ) from 9/25/07 to 11/07/07.
- Patient 244 had documented improvements in lymphocyte count measurements ( $\geq 50\%$ ) from 10/10/2007 to 12/05/2007.

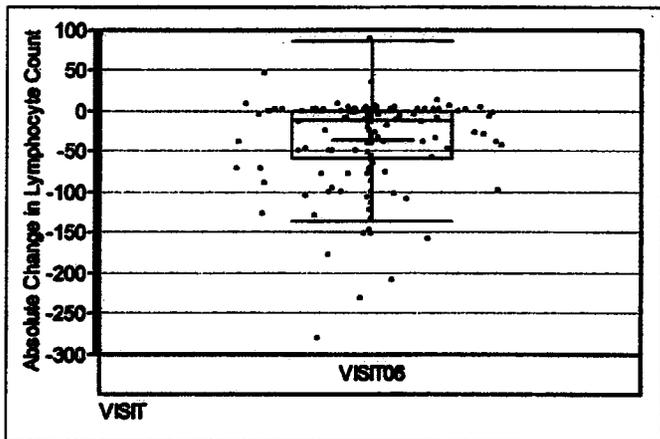
b(4)

Thus, five of 31 patients in the DR group with baseline > 5,000 lymphocytes/mcL did not meet lymphocyte count response criteria for at least 2 months.

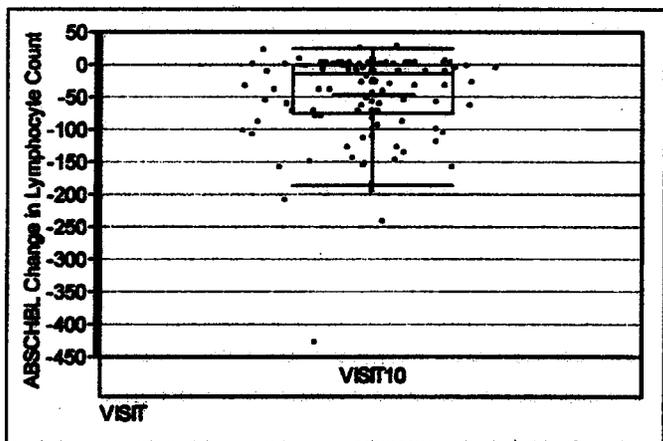
**Lymphocyte Variability by Visit (Absolute Change)**

Most patients who experienced a response in lymphocyte counts did so by visit 10. The following figures show the absolute changes for each patient compared to baseline at visit 6 and visit 10. The patients with values around 0 in the figures both represent non-responding patients as well as those who had baseline lymphocyte counts less than 5,000/mcL. The median absolute change at visit 10 in patients who had lymphocyte values measured was -14,100/mcL.

**Figure 11: Absolute Change in Lymphocyte Counts at Visit 6 from Baseline (~4 weeks after the first dose) X 1,000/mcL (N=139)**



**Figure 12: Absolute Change in Lymphocyte Counts at Visit 10 from baseline (~8 weeks after the first dose) X 1,000/mcL (N=129)**



**CD5+; CD19+; CD45+ Lymphocytosis by Flow**

Because normal B lymphocytes are not CD5 positive (CD5 is a T-cell marker), an analysis of the CD5+; CD19+; CD45+ cell counts by flow cytometry was conducted to evaluate changes in tumor cell counts over time after ofatumumab treatment. A total of 150 patients had screening flow cytometry performed prior to receiving ofatumumab. A total of 28 patients had less than 1000/mcL CD5+; CD19+, and CD45+ cells by flow cytometry. Twelve patients had counts less than 200/mcL. Six of these patients were in the DR population.

For this reviewer's analysis of improvements in CD5+; CD19+;CD45+ lymphocyte counts, only patients who had baseline counts of above 1,000/mcL were analyzed (N=122). A total of 106 of 122 (87%) patients with CD5+; CD 19+; CD45+ cells  $\geq$  1,000/mcL at baseline had

improvements greater than 50% after receiving ofatumumab. This number of patients was not notably different than that described for lymphocytes in Table 38 for the entire study population who had greater than 5,000 lymphocytes per microliter at baseline.

**Baseline Lymphocyte Characteristics of Patients who responded to Ofatumumab**

Table 39 shows the baseline lymphocyte counts of patients in the 406 study by response category. In the DR population, 30% of responders in the FDA analysis and 38% of responders in the IRC analysis had baseline lymphocyte counts less than 5,000/mcL. In general, these low lymphocyte counts appeared to be a function of prior therapy (rather than patients being classified as having small lymphocytic lymphoma). Thus, for a substantial proportion of patients, there was no ability to independently confirm any response parameters (as independent radiological confirmation was not required). *Comment: This concern was presented to the Oncology Drugs Advisory Committee. Ultimately, based on the totality of the evidence, the committee felt that the trial results in the DR group were reasonably likely to predict clinical benefit.*

**Table 39: Baseline Lymphocytes of Responding Patients (406 Study)**

	FDA DR (n=23)	IRC DR (n=34)	IRC BPR (n=37)	IRC Other (n=4)	IRC Total responders (n=90)	IRC Total Non- responders (n=74)
<b>Lymphocytes x 1000</b>						
Median (range)	19.90	19.65	43.4	75.1	40.9	15.8
Mean (SD)	46.8 (61.8)	49.9 (61.8)	75.8 (99.4)	93.5 (78.9)	66.8 (83.5)	51.8 (51.9)
N < 5,000 (%)	7 (30%)	13 (38%)	8 (22%)	2 (22%)	23 (29%)	18 (24%)

b(4)

**Neutropenia:**

As shown in Table 72 in the safety section of this review, 24 patients had  $\geq$  Grade 3 neutropenia at baseline. This reviewer conducted an analysis to determine whether these patients with moderate to severe baseline neutropenia experienced hematologic improvement. Sustained neutrophil improvements in these categories could (in-theory) constitute a surrogate for clinical benefit in that neutrophil counts greater than 1,000/mcL are associated with a decreased risk of infection/sepsis (Pizzo, 1993).

For this analysis, a patient must have had experienced improvements in hematologic parameters for at least two consecutive visits. The duration of improvement was classified on the first date of improvement to the last date recorded that the patient had an improved laboratory value. Patients with evidence of improvement and myeloid growth factor use were considered non-responders for this analysis.

Of these 24 patients with baseline  $\geq$  Grade 3 neutropenia, patient 406116 had a dual diagnosis of CLL and mantle cell lymphoma. This patient's ANC increased in value more than 500/mcL to a total ANC of  $> 1,000$ /mcL for more than two months; however, the following analysis will only include 23 patients diagnosed with CLL and not mantle cell lymphoma.

Table 40 shows that 17% of patients (n=4) with  $\geq$  Grade 3 neutropenia experienced at least a 500/mcL improvement in neutrophil counts and a total absolute neutrophil count of  $\geq 1,000$ /mcL. This excluded 6 patients who received myeloid growth factors at some point during the study. Of these four patients with improved neutrophil counts, three had neutrophil counts greater than 1,000/mcL at screening but less than 1,000/mcL at baseline.

More patients experienced decreased neutrophil counts as described in the safety section of this review compared to patients who experienced increased neutrophil counts. *This analysis showed that few patients experienced sustained (potentially) clinically meaningful improvements in neutrophil counts in the absence of growth factor therapy.*

**Table 40: Neutrophil Improvements in Patients with  $\geq$  Grade 3 neutrophil counts at baseline (N=23)**

	Yes for one or more visits N (%)	Yes $< 1$ consecutive month (30d) N (%)	Yes between 1-2 consecutive months N (%)	Yes $> 2$ consecutive months N (%)
Value $\geq 1,000$ /mcL	11 (48)	5 (22)	2 (9)	4 (17)
Value $\geq 1,000$ /mcL and $\geq 500$ /mcL increase	9 (39)	4 (17)	1 (4)	4 (17)

### Thrombocytopenia

As shown in Figure 23 in the safety section of this review, median platelet counts appeared to increase in the overall study population during the treatment period of study 406. In order to test whether some patients had clinically meaningful improvements in thrombocytopenia, patients with platelet counts less than 50,000/mcL at baseline were analyzed.

Of 10 patients with baseline Grade 4 thrombocytopenia ( $< 25,000$ /mcL), three (30%) experienced improvements in platelet counts  $> 20,000$ /mcL (a value that may decrease the risk for life threatening hemorrhage) for at least two months. Patient 256 had received prior platelet transfusions; however, there was no record of transfusions for this patient after the platelet counts increased to  $> 100,000$ /mcL.

Of 18 patients with Grade 3 thrombocytopenia, two (11%) experienced at least a 50,000/mcL improvement in platelet counts (or a count above 100,000/mcL) for at least two months. Two additional patients experienced an improvement of this magnitude for between one and two months. The 50,000/mcL increase was chosen for this analysis because patients with Grade 3

thrombocytopenia have a lower risk of immediately life-threatening hemorrhage than patients with Grade 4 thrombocytopenia (and an increase of platelets of 20,000/mcL would be less meaningful).

In summary, a total of 5 out of 28 (18%) patients with baseline  $\geq$  Grade 3 thrombocytopenia experienced prolonged (two months or more) objective improvements in platelet counts in study 406.

### Anemia

In order to determine whether treatment with ofatumumab may have resulted in improvements in hemoglobin levels in patients with severe anemia, an exploratory analysis was conducted to determine whether patients who had transfusions at baseline or baseline  $\geq$  Grade 3 anemia had improvements in hemoglobin levels. The following nineteen patients were reviewed for this analysis:

- Patient 103 received packed red blood cells (PRBCs) in July and August 2006 and again in April 2007 prior to progression. No record of ESA use was described in the CRF. This patient experienced a clear increase in reticulocyte percentage from 0.9% on visit 2 to 9.7% on visit 5. The hemoglobin level increased from  $\frac{\quad}{\quad}$  gm/dL on visit 2 to  $\frac{\quad}{\quad}$  gm/dL on visit 5 up to a maximum of  $\frac{\quad}{\quad}$  gm/dL on visit 11. The hemoglobin was greater than 12 gm/dL for more than 2 months without the need for PRBCs and prior to progression. Despite having a clear improvement in hemoglobin, this patient was classified as having stable disease. b(4)
- Patient 105 had less than one month of hemoglobin measurements and was not evaluable for this analysis.
- Patient 108 received transfusions prior to starting ofatumumab. The patient received one dose of an ESA after visit 2. Subsequently, this patient maintained hemoglobin levels  $> 12$  gm/dL from visit 10 through visit 15 without receiving other transfusions or ESAs according to the CRFs. The IRC classified this patient as responding to ofatumumab.
- Patient 110 did not have post baseline labs measured and was not evaluable.
- Patient 133 had ongoing ESA use and was not evaluable. The patient also received multiple PRBCs during the study period.
- Patient 146 had a baseline hemoglobin concentration of  $\frac{\quad}{\quad}$  gm/dL but also had a reticulocyte percentage of 7.4% at baseline. This patient had hemolysis at baseline documented on the CRF. The patient's hemoglobin increased to  $> 10$  gm/dL on visit 3 through the last visit approximately one month later. b(4)
- Patient 147 continued to have documented hemoglobin levels under 10 gm/dL except on one visit.
- Patient 159 was documented as being transfused; however all hemoglobin levels for this patient were greater than  $\frac{\quad}{\quad}$  gm/dL. Thus no sustained hemoglobin increase was documented. b(4)

- Patient 162 had a hemoglobin concentration of  $\nearrow$  gm/dL at baseline increasing to  $\nearrow$  gm/dL at visit 4 with sustained improvements above 10 gm/dL for over two months. This patient, a partial responder, received PRBCs one day following the first dose of ofatumumab. The patient received no further transfusions and there was no record of ESA use. b(4)
- Patient 169 had a hemoglobin concentration of  $\nearrow$  gm/dL at screening. The hemoglobin was  $\curvearrowright$  gm/dL at baseline. The hemoglobin levels remained under 10 gm/dL throughout the remainder of the study.
- Patient 195 remained transfusion dependent throughout the study. b(4)
- Patient 205 had a hemoglobin concentration of  $\curvearrowright$  gm/dL on visit 2 increasing to  $> 10$  gm/dL from visit 5 through visit 15. This patient classified by the IRC as responding, received one PRBC transfusion following visit 12. There were no further records of PRBC transfusions or ESA use.
- Patient 229 had a hemoglobin concentration of  $\nearrow$  gm/dL at baseline. The patient did not have sustained hemoglobin improvements of greater than 2 gm/dL for over two months. Furthermore this patient received ESAs. b(4)
- Patient 236 required numerous PRBC transfusions during the study.
- Patient 240 had a hemoglobin concentration of  $\nearrow$  gm/dL at baseline and did not have sustained hemoglobin levels of  $> 9$  gm/dL during the study. b(4)
- Patient 243 had a hemoglobin concentration of  $\nearrow$  gm/dL at baseline. This patient was considered by the IRC as being a partial responder. This patient received numerous PRBCs during the study period.
- Patient 244 had a hemoglobin concentration of  $\nearrow$  gm/dL at baseline with a history of transfusions. All other hemoglobin values were less than 10 gm/dL.
- Patient 246 had a hemoglobin concentration of  $\nearrow$  gm/dL at baseline. By visit 7, the hemoglobin values were  $> 9$  gm/dL. By visit 10, the hemoglobin values were  $> 10$  gm/dL and remained above this value through visit 15. This patient was considered a responder by the IRC; the patient received one PRBC transfusion at baseline. No other records of transfusions or ESAs were noted in the datasets. b(4)
- Patient 256 had a hemoglobin concentration of  $\nearrow$  gm/dL at baseline. This patient received transfusions through visit 10. The patient did not experience a  $> 2$  gm/dL sustained (more than 2 months) increase in hemoglobin levels while off transfusions.

In summary, few patients experienced sustained meaningful improvements in hemoglobin levels. Patients 103, 108, 162, and 246 appeared to have real benefit (i.e., reduction in transfusion requirements). The trends in increasing hemoglobin levels (like those of platelets) over time for the entire population suggest that ofatumumab may increase hemoglobin counts. However, it is likely that patients with less severe anemia are those who more commonly experience increases in hemoglobin levels.

### 6.1.7 Subpopulations

#### Summary of Main Subgroup Analyses (Statistical Reviewer)

Subgroup analyses of ORR were conducted for many baseline characteristics and prognostic factors; Table 41 tabulates the IRC ORR results for age, sex, region, and body weight (trichotomized and dichotomized). Given the small number of patients in some subgroups, the ORR was fairly consistent across subgroups.

**Table 41: ORR by Baseline Characteristics (Statistical Reviewer)**

	DR (N=79)	BR (N=79)
<b>Age, N (%)</b>		
< 65 years	20/32 (63)	22/46 (48)
≥ 65 years	14/27 (52)	15/33 (45)
≥ 70 years	6/10 (60)	8/19 (42)
≥ 75 years	2/4 (50)	3/10 (30)
<b>Sex, N (%)</b>		
Female	10/15 (67)	8/22 (36)
Male	24/44 (55)	29/57 (51)
<b>Region, N (%)</b>		
Eastern Europe	15/23 (65)	10/20 (50)
Western Europe	11/23 (48)	15/31 (48)
U.S.	8/13 (62)	12/28 (43)
<b>Body Weight, N (%)</b>		
≤ 67 kg	7/12 (58)	10/24 (42)
67-87 kg	17/34 (50)	14/35 (40)
> 87 kg	10/13 (77)	13/20 (65)
≤ 75 kg	15/30 (50)	15/41 (37)
> 75 kg	19/29 (66)	22/38 (58)

Duration of response was also assessed for the subgroup of body weight (trichotomized and dichotomized); the results are shown in Table 42.

**Table 42: Duration of Response by Weight at Baseline (Statistical Reviewer)**

Body Mass	DR group		BR group	
	# of events	Median, mos. (95% CI)	# of events	Median, mos. (95% CI)
≤ 67 kg	4/7	10.1 (7.4, 13.8)	6/10	4.6 (3.0, 7.7)
67-87 kg	12/17	5.3 (3.7, 7.6)	11/14	6.4 (5.6, 8.7)
> 87 kg	7/10	3.7 (2.8, 8.2)	11/13	3.6 (2.5, 9.6)
≤ 75 kg	11/15	3.9 (3.0, 10.1)	10/15	5.6 (3.7, 7.7)

Body Mass	DR group		ORR group	
	# of events	Median mos. (95% CI)	# of events	Median mos. (95% CI)
> 75 kg	12/19	7.1 (3.7, 7.7)	18/22	5.5 (2.8, 7.1)

**Statistical reviewer's comments:**

- Over 97% of subjects were Caucasian, thus, no meaningful comparison of anti-tumor activity could be made between racial subgroups.
- The subgroup of body weight was assessed after correspondence with the clinical pharmacology review team, who found differences between the body weight subgroups with respect to some PK parameters. The ORRs across the body weight subgroups (either dichotomized or trichotomized) were fairly consistent (Table 41). The trend in the DR group of decreasing DOR for increasing body weight seen in the trichotomized analysis was not seen in the dichotomized analysis (see Table 42). A more detailed look at the DR group data showed that patients with body weight 67-75 kg (N=7) had median DOR of 3.4 mos. (95% CI: 3.0, 3.9), and patients with body weight 75-87 kg (N=9) had median DOR of 7.4 mos. (95% CI: 5.3, 9.8); this explained the differences between the dichotomized and trichotomized analyses. However, given the low number of patients in each subgroup, these results should be interpreted with caution.

**(Clinical Reviewer)**

*Comment: This reviewer agrees that these subgroup analyses should be interpreted with caution based on the limited number of patients and the issues described in the ORR section of this review describing the uncertainty of the ORR in this patient population.*

Because ofatumumab is an anti-CD20 antibody, the following subgroup analysis was conducted to determine the ORR in patients previously exposed to rituximab. Table 43 shows that some patients responded to ofatumumab despite prior treatment with rituximab. *Because rituximab and ofatumumab bind to separate epitopes on CD20, it is feasible to speculate that the antibodies might not be cross-resistant. However, it should be noted that the results in Table 43 shows response by prior rituximab treatment status; the table does not describe how many of these patients were refractory to prior rituximab treatment. It is possible that these patients might have responded to a second course of rituximab-containing therapy.*

**Table 43: ORR by Prior Rituximab Use (Table Completed by Statistical Reviewer)**

	DR (N=35) N responding (%)	ORR (N=43) N responding (%)
IRC	19 (54)	19 (44)
Investigator	12 (34)	13 (30 %)
	<b>DR (N=33)</b>	
FDA Clinical reviewer	12 (36)	

### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

#### Clinical Reviewer

Studies that evaluated lower doses of ofatumumab (i.e., study 402) in patients with CLL contained too few patients for any conclusions to be made regarding dosing recommendations (three patients were evaluated at each of two lower dose levels). The DOR in the 406 study was longer than in the 402 study. This longer DOR may have been a function of the longer dosing schedule evaluated in study 406; however, because these studies were not comparative, no definitive conclusions can be made.

### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Refer to the DOR section of this review for persistence of efficacy effects.

### 6.1.10 Additional Efficacy Issues/Analyses

#### (Clinical Reviewer)

Supportive efficacy results from study Hx-CD20-402 (402) will be analyzed in this part of the review.

In the 402 study, patients were permitted to receive a maximum of four doses of ofatumumab as compared to a maximum of 12 doses in study Hx-CD20-406. The patients in cohort C were less heavily pretreated than patients in the Hx-CD20-406 study. Patients in cohort C received a median of 2 prior therapies and received 2,000 mg of ofatumumab. Table 44 shows the demographic profile of patients enrolled into cohort C of study 402.

**Table 44: Demographics: Study 402**

<b>Sex (n, %)</b>	
Female	12 (44)
Male	15 (56)
<b>Age</b>	
≥65 yr (%)	12 (44)
Mean (SD) (yr)	61 (13)
Median (yr)	62
<b>Race (n, %)</b>	
White	27 (100)
<b>Time from Original CLL Diagnosis (years)</b>	
Mean (SD)	6.3 (2.8)
Median	6.1
<b>Rai Stage at Screening (n, %)</b>	
0	1 (4)

1	13 (48)
2	10 (37)
3	1 (4)
4	2 (7)
<b>Time from Last CLL Treatment (years)</b>	
Mean (SD)	1.5 (1.4)
Median	0.84
<b>ECOG PS (n, %)</b>	
0	18 (67)
1	8 (30)
2	1 (4)

#### **ORR and DOR**

GSK's summary of efficacy results for cohort C are as follows: ORR 48% (95% CI: 30, 70) with a median DOR of 4.4 months.

For study 402, this reviewer evaluated responding patients in Group C who received the 2,000 mg dose (n=27). Efficacy response datasets for lymph nodes (physical examination), CT scan measurements, laboratory data, and organ size were analyzed. Case report forms were submitted and evaluated for 6 of 13 responding patients.

For the analysis of ORR, this reviewer could confirm GSK's results on all but one patient using the 1996 NCI response criteria. A response duration of at least 50 days could be confirmed for patient 621; however, based on the CRF, there was no bi-directional measurement of a specific LN on one date (thus a response duration of 56 days could not be confirmed). Because results were only questionable for this one patient, and because the one patient had a response of at least 50 days, GSK's interpretation of the results were acceptable.

#### **CT Scans:**

Nineteen patients in group C underwent baseline and repeat CT scans. In general, scans were repeated approximately 4 months after starting treatment. LN size decreased by more than 50% in only three responding patients (606, 630, and 636). One patient experienced a 41% improvement compared to baseline and one patient experienced a 48% improvement compared to baseline. One additional patient had no lymphadenopathy observed at baseline. The timing of the repeat CT scan was not optimal as at least three patients probably had the repeat CT scan obtained at the time of relapse (in the opinion of this reviewer). *In summary, these results are somewhat concerning regarding the applicability of physical examination for lymph node size determination in patients with advanced CLL. However, because serial scans were not obtained, it is possible that patients may have experienced more pronounced responses during or shortly following the end of study drug administration.*

## 7 Review of Safety

### Safety Summary

The safety database contained data from 648 patients at the time of the original BLA submission. Data from 1,138 patients were available at the time of the safety update.

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

In study Hx-CD20-406, the most common AEs (>10% incidence in the full study population) were pyrexia, cough, diarrhea, anemia, neutropenia, pneumonia, fatigue, dyspnea, rash, nausea, bronchitis, and upper respiratory tract infection.

In the BLA submission, GSK stated that the incidence of fatal infections was lower (10%) than that quoted in the literature [48% (Perkins, 2002)]. This reviewer does not agree with the implication of this statement because the cited literature report was a retrospective literature review that followed the clinical course of 27 patients over a median of two treatment regimens (versus one for the ofatumumab study). Nevertheless, this reviewer agrees that based on literature reports, the background rate of severe and fatal infections in heavily treated CLL patients is high. Patients in the Hx-CD20-406 trial frequently had a history of severe infections. Because of the high background rate of infections in this patient population and the absence of an internal control, it is not possible to determine the additional risk of infection posed by the administration of ofatumumab. However, this reviewer notes that neutropenia may increase the risk of life-threatening infections in this patient population.

Infusional toxicities were common, manifesting as fever, dyspnea, and rash despite premedication with intravenous corticosteroids (50-100 mg methylprednisolone or equivalent), an antihistamine, and acetaminophen (1,000 mg or equivalent) prior to each dose. This reviewer believes that comparisons of infusional toxicities between ofatumumab and rituximab are not appropriate because the premedication schedules for the two drugs differ (with corticosteroids administered prior to ofatumumab) and because the initial rate of the infusion is slower for ofatumumab.

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

This reviewer believes that hepatitis B reactivation should be included in the label as a warning even without observing severe hepatitis reactivation events in the safety database as patients with active hepatitis B were excluded from protocols supporting licensure of ofatumumab. Inclusion of this warning is based on the experience with rituximab. Additionally, one fatal case of

primary acute hepatitis B infection was submitted to the BLA on July 28, 2009 (subsequent to the submission of the safety update).

Due to the lack of an internal control, labeling of safety information can only be done descriptively. This lack of an internal control resulted in substantial uncertainty regarding the attribution of adverse events to ofatumumab. Results of ongoing clinical trials may allow for more definitive conclusions regarding the attribution of AEs to ofatumumab. This includes the additional risk of infection that ofatumumab confers on patients with CLL (who have a high baseline risk of infections).

## **7.1 Methods**

### **7.1.1 Studies/Clinical Trials Used to Evaluate Safety**

The total denominator of all patients used to evaluate safety in this database was 648. Table 12 in Section 5 of this review contains a listing of all studies that were submitted to the BLA containing safety data. Data from a total of 154 safety evaluable patients from study Hx-CD20-406 were available for analysis at the time of the original BLA submission. Study Hx-CD20-406 was the only study to evaluate ofatumumab at the doses and schedule for which the applicant is seeking approval.

### **7.1.2 Categorization of Adverse Events**

For study Hx-CD20-406, GSK used version 9.0 of the MedDRA coding dictionary to code adverse event data.

The Hx-CD20-406 dataset contained 1,213 individual adverse event listings. A total of 680 verbatim terms described all 1,213 of the adverse events.

Verbatim terms in the adverse event dataset were reviewed to determine whether MedDRA preferred terms were appropriately coded. In general, coding was acceptable. There were some inconsistencies applied to multiple occurrences of “tingling” in areas of the face; however, the preferred term for the inconsistent LLTs was paresthesia in each instance. Table 45 includes a list of potential inappropriately coded events. FDA requested that GSK provide explanations for the coding of these events in a communication sent by electronic mail on March 6, 2009.

**Table 45: Examples of (Potentially) Inappropriately Coded Verbatim Events**

Study ID	Verbatim Event	Preferred Term	Reviewer's Assessment	GSK's Response
103	Bilateral interstitial pneumopathy	Pneumonia	The PT was deemed acceptable because further review of this case determined that this was most likely an infection.	GSK was not asked to comment further regarding this case.
106	Neuropathy – motor (left sided weakness)	Peripheral neuropathy	Unclear if left sided weakness should actually be deemed a central neuropathy. GSK's response was acceptable; however, this reviewer remains uncertain as to whether a pure unilateral peripheral neuropathy occurred.	GSK indicated that this patient had left side weakness and rib pain without other signs of CNS involvement. The patient died of peritonitis before a CT scan could be performed.
133	Disease progression / sepsis	Disease progression	The Grade 5 event of sepsis was not included as a preferred term. The CIOMS report indicated that antibiotic treatment was started due to suspected sepsis. Thus this reviewer disagrees with the GSK assessment.	GSK stated that follow-up indicated that a clear diagnosis of sepsis was not made so GSK found the term disease progression was most appropriate to characterize this patient's death.
213	Ataxia/disease progression	Disease progression	The event ataxia was not included as a preferred term. GSK's response was acceptable.	GSK stated that disease progression caused the ataxia as confirmed by MRI.

In the audit of CRFs, this reviewer noted that multiple AE CRF pages were crossed-out without adequate explanation (for study 406). Other inconsistencies were noted between the CRFs and the database. In many cases, this reviewer discovered that AEs were crossed-out because the AE occurred before the patient received ofatumumab or occurred after new CLL treatment had commenced. On March 6, 2009, FDA requested that GSK provide explanations for five such events in order to determine whether re-auditing of all cases was necessary (Table 46).

*Comment: In general, GSKs explanations were acceptable. The potential discrepancy regarding patient 406236 would not affect the overall safety profile of ofatumumab because the patient was classified as having death due to infection (irrespective of whether it was caused by gangrene or sepsis).*

**Table 46: Explanations for AEs being deleted in CRFs (study 406)**

Patient	AE Number	Adverse Event	GSK Explanation
406234	18	Fungus in mouth	The AE was crossed-out in the CRF by the investigator who reported a normal examination on PE.
406201	2	Septic shock	Patient started new treatment for CLL prior to the AE.
406102	11	Hemolytic anemia	Patient started new treatment for CLL prior to the AE.
406147	21	Grade 3 hypotension	No blood pressure reading showed hypotension on the day of the infusion. The infusion was temporarily interrupted at the time the BP was 120 mmHg systolic.
406238	18	Eye infection	Grade 4 eye infection was noted on May 26, 2008, which was after the database cut off.
406236	Narrative summary	Death with "gangrenes" of the left and right thigh	This patient had polymicrobial septic shock and had positive cultures at the site of the gangrene and in the sputum. GSK indicated that the gangrene was likely of infectious origin. <i>Comment: it is not-clear whether gangrene could have caused the sepsis or was caused by the underlying sepsis.</i>

### 7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

The primary safety data were obtained from study Hx-CD20-406. Studies were not pooled to obtain the primary estimates of adverse events in patients treated with ofatumumab. Safety data related to serious adverse events and deaths from the other studies were evaluated. The following list describes the reasons why the data were not pooled:

- Different doses of ofatumumab among trials (only the two monotherapy CLL studies evaluated the 2,000 mg dose in patients).
- Different schedules among trials (the 406 study evaluated a more prolonged dosing schedule than in study 402: inclusion of data from patients in the 402 study could dilute the incidence of certain AEs in the total population).
- Different diseases being studied among trials (the background incidence of infections in CLL patients is higher than in RA patients).

## **7.2 Adequacy of Safety Assessments**

### **7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations**

For this BLA, data from three studies were submitted that involved the target population, CLL. This section of the review will focus on the two monotherapy studies that evaluated ofatumumab doses of 2,000 mg. The third study enrolled 28 patients at the time of data cut-off and combined ofatumumab with fludarabine and cyclophosphamide.

Study 406 allowed enrollment of patients 18 years of age or older with a performance status of  $\leq 2$ . It is unclear if the most sick patients (i.e., those in bed  $> 50\%$  of the time) would tolerate ofatumumab. Likewise the 406 study excluded patients with clinically significant cardiac disease within the past 6 months, known significant cerebrovascular disease, active infection, and significant other medical conditions considered to be uncontrolled. Furthermore, patients with pleural effusions or ascities detected by physical examination were excluded.

#### **Assessment of Size of Premarketing Safety Database**

The assessment of the pre-marketing safety database is influenced by two major factors including the duration of therapy (approximately 6 months) and the intended population (CLL refractory to fludarabine and alemtuzumab).

GSK submitted summary safety data on 181 patients who received monotherapy with ofatumumab. The size of this safety database compares with the 149 patients in the alemtuzumab safety database included in the original (accelerated) approval of alemtuzumab for the treatment of patients with CLL

(<http://www.fda.gov/cder/foi/label/2001/alemmil050701LB.htm#adver>, accessed 3/10/09).

*Comment: Based on prior FDA precedent, an adequate number of patients have been included in the BLA for the treatment of patients with refractory CLL (a life threatening malignancy) in consideration of accelerated approval. Additionally, the data from 181 patients was supported by data from a total of 648 patients in all ongoing or completed clinical trials.*

### **7.2.2 Explorations for Dose Response**

#### **Study 406**

In the 406 study, patients could receive a maximum of 12 doses of ofatumumab (over 24 weeks). The first eight doses were administered weekly; the last four doses were administered monthly. Patients were to receive 300 mg during the first dose and 2,000 mg during each subsequent dose. At the time of the interim analysis, 154 patients received at least one dose of ofatumumab. Table 47 shows that 90% of patients received all eight weekly doses of ofatumumab. A total of 55% of patients received all 12 doses.

**Table 47: Number of Ofatumumab Infusions Patients Received During Study 406**

Maximum Number of Doses	Number of Patients	% of Total
1	4	2.6
2	2	1.3
3	3	1.9
4	3	1.9
5	0	0
6	2	1.3
7	1	0.6
8	22	14.3
9	10	6.5
10	14	9.1
11	8	5.2
12	85	55.2

Table 48 shows that most patients received the full dose of each planned ofatumumab infusion. There were 19 instances where the total dose administered did not equal the planned dose during study 406. Three patients received less than the 300 mg dose planned during the first ofatumumab administration. GSK indicated that two of these three patients in the BFR group received less than the planned dose due to infusion reactions. GSK also stated that a total of three subjects received a second 300 mg infusion (rather than the planned 2,000 mg dose) due to delays in the infusion schedule and a high lymphocyte count at the time of the second infusion. GSK stated in the Summary of Clinical Safety that one patient received 150 mg during infusion number 11 due to a hypersensitivity reaction.

**Table 48: Exposure Summary Data by Dose Number for Study 406**

Dose Number	Number of Subjects	Median Dose in mg	Minimum Dose in mg	Maximum Dose in mg	Mean Dose in mg	Std Dev
1	153	300	144	300	298.0	15.7
2	149	2000	300	2000	1971.0	207.4
3	147	2000	300	2000	1974.1	200.0
4	144	2000	1972	2000	1999.8	2.3
5	141	2000	2000	2000	2000.0	0.0
6	141	2000	1960	2000	1999.6	3.6
7	139	2000	2000	2000	2000.0	0.0
8	138	2000	2000	2000	2000.0	0.0
9	117	2000	1700	2000	1997.4	27.7
10	107	2000	1900	2000	1999.1	9.7
11	93	2000	150	2000	1977.4	192.2
12	85	2000	2000	2000	2000.0	0.0

### **Study 402**

Twenty seven patients received the 2,000 mg dose of ofatumumab during the conduct of study 402. The study also included two additional cohorts of patients who received 500 mg and 1,000 mg of ofatumumab. Patients in the 402 trial were to receive a maximum of four infusions. In the Summary of Clinical Safety, GSK indicated that one of the 27 patients in the 2,000 mg cohort did not receive all four planned ofatumumab infusions. The patient withdrew after the first dose due to "cytolytic hepatitis."

### **7.2.3 Special Animal and/or In Vitro Testing**

The non-clinical assessment for cardiovascular effects (QTc) related to ofatumumab included tissue-cross reactivity studies and end-point assessments in 4-week and 7-month repeat-dose monkey studies. Because ofatumumab is a therapeutic protein, in-vitro electrophysiology studies such as the hERG assay were not conducted

Additional stand-alone special non-clinical toxicology studies were not performed.

### **7.2.4 Routine Clinical Testing**

Refer to sections 7.4.2 (laboratory monitoring) and 7.4.4 (ECG) for discussions on the adequacy of biochemistry monitoring, hematology monitoring, and ECG monitoring during studies 402 and 406.

### **7.2.5 Metabolic, Clearance, and Interaction Workup**

No formal drug-drug interaction studies were conducted during the development of ofatumumab. This product is a monoclonal antibody (biological drug) that does not undergo metabolism and excretion in a manner similar to that of small molecules.

### **7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class**

Analyses of the following adverse events are included in other sections of this review: infusion reactions, tumor lysis syndrome, progressive multifocal leukoencephalopathy, hepatitis B virus reactivation, viral infections, cardiovascular events, renal events, bowel obstruction and perforation.

#### **Severe Mucocutaneous Reactions**

On March 6, 2009 (by electronic mail), FDA requested that GSK submit an analysis of severe mucocutaneous reactions including paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis. This request was based on the presence of a warning regarding severe mucocutaneous reactions in the rituximab product label. GSK's response regarding severe mucocutaneous reactions submitted to the BLA on March 17, 2009 contained the following reply (copied directly from the GSK submission).

No SAEs with the terms listed in the above question were identified in the GSK safety database (OCEANS) for ofatumumab by the use of the Standardized MedDRA Query (SMQ) search for severe mucocutaneous adverse reactions, which was inclusive of the terms specified above.

In addition, a review of the entire AE database for the oncology studies included in the BLA through the clinical cut-off date of 20 June 2008 was performed to identify any AE or SAE  $\geq$  Grade 3 indicative of a mucocutaneous reaction. This review identified four potential cases of non-serious Grade 3 events [rash in Subject 406165, DR population (300 mg); pruritis in Subject 001451 (300 mg); rash in Subject 001465 (1000 mg); and urticaria in Subject 405157 (1000 mg)]. In all four cases, the events occurred during the first infusion, required no treatment for the events, and the subjects subsequently received all doses of ofatumumab per protocol and experienced no further dermatologic events.

These findings support the rationale why the proposed prescribing information for Arzerra does not include a statement regarding severe mucocutaneous reactions.

*Comment: This reviewer agrees that the events reported in the database most likely represent infusion reactions rather than severe mucocutaneous reactions.*

## 7.3 Major Safety Results

### 7.3.1 Deaths

#### Overview of the applicant's methods

GSK analyzed deaths separately by study and then performed a pooled analysis for patients in the two CLL studies who received the 2,000 mg ofatumumab dose. This approach is reasonable because the doses of ofatumumab in CLL monotherapy studies differ from other oncology and non-oncology indications. Additionally, the baseline characteristics of the CLL population may differ from the characteristics of other patient populations (RA or NHL) who receive ofatumumab. GSK separated deaths into "early deaths" versus "late deaths." Patients in the "early death" category were considered to have died within eight weeks after starting ofatumumab. *Comment: The "early death" classification used by the applicant is problematic because patients in the 406 study may have been receiving ofatumumab after the end of the "early death" period. Because anti-CD20 antibodies have a prolonged pharmacodynamic effect, the possibility exists that these antibodies may increase the risk of infections for months after the last dose of ofatumumab.*

In study 406, the protocol mandated that serious AEs including death were to be reported from the date the informed consent was signed until month 48. Deaths were to be reported even if caused by deterioration of the underlying disease (CLL). Following visit 21 (month 24 or end of study visit), observational contacts were to be conducted every three months to obtain data on survival until month 48.

For study 402, survival was not considered a secondary endpoint. Follow-up during this study was for 12 months.

**FDA review of deaths**

In study 406, 61 patients were reported as having died at the time of data cut-off. The median number of days of follow-up for the 93 patients who did not die was 366 days (range 8 to 615). To verify the cause of death described by the applicant, narrative summaries and SAE listings were reviewed. Additionally, the AE dataset was reviewed to evaluate AEs that occurred within 90 days of the patients' deaths to determine whether other AEs may have contributed to the cause of death. Table 49 lists patients who died in the two CLL monotherapy studies. GSK stated in the BLA submission that no patients died who were enrolled in studies Hx-CD20-407, Hx-CD20-409, GEN415, Hx-CD20-403, Hx-CD20-408, GEN410, GEN411, or GEN 413 at the time of data cut-off. Seven deaths in the two supportive FL monotherapy studies were reported at the time of data cut-off. All seven deaths were deemed to occur as a result of disease progression or infectious complications. Finally, eight deaths were reported after the clinical cut-off date but before the SAE cut off date (4 in study Hx-CD20-406, 3 in study Hx-CD20-405, and 1 in GEN415). The patients who died in study Hx-CD20-406 were enrolled after November 27, 2007 (the date that enrollment stopped for the interim analysis). Deaths in these patients were due to infections (n=2), disease progression (n=3), bladder cancer (n=1), cardiac arrest (n=1), and pulmonary edema (n=1).

**Table 49: Tabular Listing of Deaths that Occurred after the Administration of Ofatumumab in CLL studies**

Trial	Group	Center	Patient	Age	# of doses	Days since Last Dose	Brief Description of Probable Cause of Death
406	DR	UK01	406102	68	10	145	Hemolytic anemia (patient had started new CLL therapy with fludarabine)
406	BFR	FR03	406103	62	12	294	Aspergillosis (additional details were not provided)
406	DR	US02	406104	68	12	303	Respiratory failure (additional details were not provided)
406	DR	UK01	406105	76	4	7	Disseminated fungal infection
406	Other	UK03	406106	58	12	56	Perforated bowel due to adenocarcinoma
406	BFR	DE02	406107	60	9	116	Sepsis with DIC and renal failure
406	DR	SE01	406109	68	10	165	Pneumonia (narrative summary not provided—this patient had started new CLL therapy)
406	DR	CZ03	406111	61	12	119	Sepsis (narrative summary not provided—this patient had started aggressive new chemotherapy)
406	DR	US02	406112	41	4	96	Disease progression (additional details were not provided)
406	BFR	UK02	406113	62	8	567	Disease progression (additional details were not provided)
406	DR	UK03	406119	63	12	249	Sepsis (narrative summary not provided)
406	BFR	DE02	406120	84	11	288	Lower respiratory tract infection

Trial	Group	Center	Patient	Age	# of doses	Days Since Last Dose	Brief Description of Probable Cause of Death
406	DR	CZ01	406128	59	9	436	Pneumonia (atypical—additional details were not provided)
406	BFR	US06	406133	66	12	69	*Sepsis (the narrative indicated probable sepsis and disease progression; GSK ascribed this event to disease progression)
406	BFR	UK03	406135	79	4	2	Myocardial infarction
406	DR	UK06	406137	86	12	158	Pneumonia
406	DR	US02	406141	55	3	32	Fusarium infection after the patient received hyper-CVAD chemotherapy for possible Richter's transformation
406	DR	CZ03	406145	59	8	25	Pneumonia
406	DR	DE04	406147	68	11	63	Progressive multifocal leukoencephalopathy
406	BFR	DE04	406148	69	9	178	Disease progression (additional details were not provided)
406	BFR	PL01	406155	51	12	279	Disease progression
406	DR	DE04	406160	65	2	7	Presumed sepsis (culture negative; however, the patient was on prophylactic antibiotics)
406	BFR	US02	406161	79	12	127	Pneumonia (pseudomonas)
406	DR	CZ02	406163	59	10	27	Disease transformation to large cell lymphoma
406	DR	US08	406168	46	9	62	Disease progression (additional details were not provided)
406	BFR	UK03	406169	70	8	56	Sepsis (with severe neutropenia after starting CHOP chemotherapy)
406	DR	US01	406170	69	11	152	Unknown cause; the patient had disease progression prior to death
406	BFR	US11	406172	73	8	19	Pneumonia
406	Other	IT03	406177	63	12	177	Pneumonia (additional details not provided)
406	BFR	SE03	406178	76	11	139	Sepsis (additional details not provided)
406	DR	PL05	406182	43	10	33	*Progressive disease (GSK's stated cause was hemiparesis—autopsy confirmed that progressive disease in the CNS caused the hemiparesis)
406	BFR	PL03	406184	53	8	19	Disease progression
406	BFR	DE04	406185	61	7	242	Sepsis (additional details not provided)
406	BFR	UK02	406188	60	12	240	Unknown
406	DR	CZ02	406189	65	1	38	Pneumonia (pseudomonas positive blood cultures)
406	DR	US12	406195	74	10	1	Sepsis (gram-negative)

Trial	Group	Center	Patient	Age	# of doses	Days Since Last Dose	Brief Description of Probable Cause of Death
406	BFR	US02	406196	62	12	162	Respiratory failure (additional details not provided)
406	BFR	DE04	406197	79	9	89	Disease Progression (additional details were not provided)
406	DR	US01	406199	67	8	55	Unknown (patient had started other therapy)
406	BFR	PL05	406201	51	1	64	Sepsis (after starting R-CHOP chemotherapy)
406	BFR	DE07	406204	69	10	118	Sepsis
406	DR	DE08	406206	76	10	159	Brain injury; this patient had started new therapy; no additional details were provided
406	BFR	US01	406209	59	8	135	Unknown
406	DR	DK03	406211	69	8	32	Sepsis (no narrative; could not confirm cause)
406	BFR	US09	406212	69	10	133	Disease Progression (additional details were not provided)
406	BFR	US05	406213	52	11	79	*(GSK) Disease progression (CLL infiltration in the brain) -- the patient's death may have been caused more directly by pneumonia
406	BFR	US02	406214	79	8	262	Unknown
406	BFR	PL05	406215	57	9	191	Cardiac arrest (additional details were not provided)
406	DR	CZ02	406219	59	12	107	Disease Progression (additional details were not provided)
406	BFR	DE07	406221	53	3	231	Disease Progression (additional details were not provided)
406	BFR	UK02	406223	64	8	158	Sepsis (additional details not provided)
406	DR	IT03	406228	66	12	.	Disease Progression (additional details were not provided)
406	BFR	US08	406229	69	12	25	Pneumonia
406	DR	ES02	406230	65	8	31	Sepsis; possibly disseminated cellulitis; blood culture positive for Pseudomonas aeruginosa
406	BFR	US12	406231	62	3	4	Sepsis
406	Other	DE05	406235	82	9	15	*Cardiac Failure (this patient was diagnosed with acute laryngitis and required IV antibiotics two days before her death—the cause of death may have been infectious)
406	DR	FR06	406236	66	10	5	Sepsis; sources could include gangrene or a pulmonary source

Trial	Group	Center	Patient	Age	Time of Death	Time to Death	Probable Cause of Death
406	BFR	US01	406240	62	8	84	Unknown (patient had disease progression prior to death)
406	BFR	UK03	406242	66	8	75	Unknown
406	DR	US14	406244	68	8	32	Pneumocystis jiroveci pneumonia (Pseudomonas aeruginosa and Clostridium difficile may have also complicated this patient's clinical course).
406	BFR	SE01	406250	74	8	84	Disease progression
402	N/A	FR22	402613	82	4	29	Pneumonia (interstitial): PCR of bronchoalveolar wash was positive for mycoplasma
402	N/A	FR21	402610	59	4	~ 4 mo	Pneumonia after administration of subsequent chemotherapy
402	N/A	PL22	402646	71	4	~ 11 mo	Disease progression; the patient had subsequently received FC chemotherapy; pneumonia may have also contributed to his death

\* the cause of death may have differed from the cause ascribed by GSK

**Review of the GSK Analysis and Conclusions Regarding Patient Deaths**

GSK indicated that 24 out of 61 deaths during study 406 (n = 154) occurred during treatment or follow-up and 37 were reported during extended follow-up. Thirty of the 37 deaths occurring during extended follow-up occurred after the initiation of new CLL therapy. The most common cause of death other than disease progression was infection. GSK indicated that 16 of the 24 deaths occurring during the treatment or follow-up periods were due to infections (10% of the overall study population). The percentage of the 24 patients who died of infections in the DR population was higher (17%) than the BFR population (6%). It is unclear if this difference was due to chance or was caused by more severe immunosuppression in the DR group from prior alemtuzumab therapy.

GSK stated on page 176 of the Summary of Clinical Safety that "in study Hx-CD20-406, the analyses of infections demonstrated that the underlying disease, rather than ofatumumab, was the major risk factor for Grade 3, Grade 4, or fatal infections." GSK stated that ≥ Grade 3 infections occurred more frequently in patients with higher Rai stage and > 2 prior therapies. GSK stated that the incidence of fatal infections was lower (10%) versus that quoted in the literature (Perkins et al., 2002).

*In this reviewer's opinion, the comparison of deaths occurring in the ofatumumab clinical trial to that quoted in the literature report was not valid. The Perkins literature report was a retrospective analysis that followed the clinical course of 27 patients. The median number of treatment regimens that patients received in the Perkins study was two after being considered*

*fludarabine refractory. Thus, infectious deaths in the Perkins study were counted from the time of being considered fludarabine refractory through more than one treatment course (different from how GSK classified infectious deaths in the 406 Summary of Clinical Safety). Furthermore, there were at least three cases (406235, 406213, 406133) where there was evidence in the narrative summaries that infection may have contributed to the patient's cause of death. In a retrospective study specifically evaluating infections, these three cases may have been attributed to infections rather than disease progression (or other causes of death). Furthermore, because seven patients in Table 49 had unknown causes of death and because there was limited information submitted for patients who had disease progression, it cannot be determined whether infection may have contributed to the death of more patients than that described by GSK.*

*Based on differential ascertainment of study populations and differential follow-up between studies, this reviewer cannot determine whether the rate of infectious deaths caused by ofatumumab might be similar to or lower than a historically controlled population (as contended by the applicant). Nevertheless, the literature reports (Tam et al., 2007 and Perkins et al., 2002) cited by the applicant are valid in that patients with advanced CLL experience a high background rate of severe and fatal infections. A review of the narrative summaries indicated that some of the patients who died of infections had a prior history of severe infections prior to starting treatment with ofatumumab.*

*In summary, the most common causes of fatal events after ofatumumab therapy were disease progression and infections. For comparison, the rituximab label accessed on 2/26/2008 (<http://www.fda.gov/cder/foi/label/2008/103705s5256lbl.pdf>) states that infections were increased after rituximab treatment in patients with follicular or low-grade NHL and patients with diffuse large B-cell lymphoma. It cannot be determined at this time to what extent, if any, that ofatumumab increases the risk for fatal infections over the baseline risk of infections for patients with CLL who previously received fludarabine with or without alemtuzumab.*

*The proposed label for ofatumumab contains an additional warning regarding Progressive Multifocal Leukoencephalopathy. For rituximab, PML is included in a boxed warning; however, the two biological drugs differ in that rituximab is approved for non-oncology indications. This reviewer agrees that PML should be included as a warning in the ofatumumab label based on the severity of the AR; one fatal event of PML occurred during the 406 clinical trial. Refer to section 7.3.2 for additional discussion of the patient diagnosed with PML.*

#### **Label**

GSK included the following language in Section 6.1 of the draft label:

C

2

b(4)

*In the label, GSK indicated that the denominator for the number of infections was 181 (the number of patients in both the 402 and 406 trials who received 2,000 mg of ofatumumab). Comment: Because the DR population is the specific population of unmet medical need under consideration for AA, this reviewer recommends that the label contain the experience of this*

population under the AE section. GSK's review found that 17% of (10/59) patients in the DR group died due to infections.

Furthermore, at least three patients (406133, 406213, and 406235) died with infection likely contributing to the cause of death. This reviewer recommends revising the label to state that 19/154 patients (13%) had fatal infections.

### 7.3.2 Serious Adverse Events

Both the 402 and 406 protocols defined a serious adverse event (SAE) as an AE that requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; results in a congenital anomaly or birth defect; is medically important; results in death; or is life threatening. *This definition is in accordance with ICH E6 Good Clinical Practice Guidelines.* During the extended follow-up period for study 406, deterioration in the study disease or signs and symptoms of CLL were not to be reported as an SAE unless the event resulted in death.

A total of 82 patients experienced a total of 152 SAEs as described in the 406 AE dataset. Table 50 summarizes the number of per-patient SAEs that occurred per MedDRA SOC (System Organ Class). In general, the number of SAEs was consistent across the three designated 406 treatment groups. One exception was that patients in the "other" group had a higher incidence of "blood and lymphatic disorders" and "general disorders and administration site conditions". Table 50 only includes AEs that occurred during the treatment or follow up phases (events in the extended follow-up phase were excluded). Thus, events occurring > 24 months following the first dose of ofatumumab or occurring after CLL progression were excluded.

Following Table 50 is a summary of specific SAEs occurring in each MedDRA SOC. The summary of SAEs occurring by SOC also includes SAEs observed in other studies submitted to the BLA.

**Table 50: Summary of Serious Adverse Events by MedDra SOC**

MedDRA SOC	DR (N=59)		BER (N=79)		Other (N=16)		Total (N=154)	
	N	%	N	%	N	%	N	%
INFECTIONS AND INFESTATIONS	22	37	23	29	6	38	51	33
BLOOD AND LYMPHATIC SYSTEM DISORDERS	6	10	6	8	6	38	18	12
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	5	8	7	9	3	19	15	10
CARDIAC DISORDERS	2	3	4	5	1	6	7	5
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	2	3	2	3	1	6	5	3
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2	3	2	3	1	6	5	3
GASTROINTESTINAL DISORDERS	1	2	2	3	.	.	3	2

MedDRA SOC	DR (N=59)		BFR (N=79)		Other (N=16)		Total (N=154)	
	N	%	N	%	N	%	N	%
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	2	3	2	3	.	.	4	3
VASCULAR DISORDERS	1	2	2	3	.	.	3	2
EYE DISORDERS	1	2	1	1	.	.	2	1
IMMUNE SYSTEM DISORDERS	1	2	1	1	.	.	2	1
METABOLISM AND NUTRITION DISORDERS	1	2	1	1	.	.	2	1
EAR AND LABYRINTH DISORDERS	1	2	.	.	.	.	1	1
INVESTIGATIONS	2	3	.	.	.	.	2	1
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	.	.	.	.	1	6	1	1
NERVOUS SYSTEM DISORDERS	4	7	.	.	.	.	4	3
PSYCHIATRIC DISORDERS	2	3	.	.	.	.	2	1

**Infections and Infestations:**

The most commonly reported SAEs were related to infections, occurring in 33% of patients during the course of study 406. A total of 51 patients experienced 67 SAEs due to infections. Infections due to bacteria, viruses, and fungi were reported. The GSK study report described a 12% overall incidence rate of pneumonia using the MedDRA preferred term. If the high-level term “lower respiratory tract and lung infections” is used, then 16% (n=25) of patients had lower respiratory tract infections.

As discussed in section 7.3.1, one patient died of JC virus infection (progressive multifocal leukoencephalopathy).

Using the HLT sepsis, bacteriemia, viraemia, and fungemia, 12 patients experienced sepsis (versus 7 using the PT). A review of the verbatim terms; however, showed that two of the events were more likely related to chest infections. Thus up to 6% of patents experienced sepsis (classified as an SAE).

Table 51 shows SAEs by MedDRA preferred term that occurred more than twice. As previously described, pneumonia/lower respiratory tract infections occurred most commonly followed by sepsis. Besides PML, other infections signifying severe immunosuppression in study 406 included Herpes zoster infection (n=3); aspergilloma (n=1); fusarium infection (n=1); Pneumocystis jiroveci pneumonia (n=1); and fungal pneumonia (n=1). Other unusual infections related to immunosuppression reported in other ofatumumab studies included Pneumocystis jiroveci (n=1; study 405); fungal pneumonia (n=1; study 407); human herpes virus 6 (n=1; study 407); candidiasis (n=1; study 409); and tuberculosis of the knee (n=1; study 403).

**Table 51: Study 406 SAEs by PT in Infections and Infestations SOC**

Preferred Term Infections SAEs	N	% of SA
PNEUMONIA	19	12
SEPSIS	7	5
BRONCHOPNEUMONIA	3	2
HERPES ZOSTER	3	2
NEUTROPENIC SEPSIS	3	2
SINUSITIS	3	2
URINARY TRACT INFECTION	3	2

In study 402, two SAEs due to infections were reported among 27 patients who received the 2,000 mg dose of ofatumumab.

*In summary, serious infections occur frequently following ofatumumab treatment in patients with CLL. Section 7.3.2 of this review contains a discussion regarding the difficulty in describing the relative increase in risk that ofatumumab might confer in this patient population utilizing the results of a single-arm study.*

*The incidence of infectious SAEs was 29% of the 181 patients who received 2,000 mg of ofatumumab. The incidence of infections was lower in the 402 study. This lower incidence of infections may have been related to the shorter total duration of treatment of ofatumumab in the 402 study. Additionally, patients were less heavily pretreated in the 402 study than in the 406 study.*

**Progressive multifocal leukoencephalopathy:** As described in the deaths section of this review, one case of progressive multifocal leukoencephalopathy was reported in study 406. Patient 406147 was a 69-year-old man diagnosed with CLL in 2002 and received ofatumumab from November 30, 2006 to April 26, 2007. Previous treatment included chlorambucil, fludarabine, radiation therapy, reduced dose fludarabine with cyclophosphamide, and alemtuzumab. Prior to being treated with ofatumumab, this patient demonstrated that he was immunocompromised and was diagnosed with "multiple" pneumonias during alemtuzumab therapy. Prior to receiving alemtuzumab, he was treated for suspected aspergillus pneumonia.

Twenty-seven days after the last dose of ofatumumab treatment (174 days after the first dose), the patient experienced gait disturbance. The patient experienced neurological progression including hemianopsia, memory disturbance, and sensory aphasia. MRI was suspicious for PML and repeat spinal fluid analyses confirmed the diagnosis of PML; two samples were positive for JC virus by polymerase chain reaction (PCR).

GSK proposed the following warning in the ofatumumab label: Progressive multifocal leukoencephalopathy (PML)

b(4)

*Reviewer Comment: This reviewer agrees with the inclusion of PML in the label based on the one case that occurred during the 406 clinical trial because PML is uncommon and causes serious morbidity and death.*

*This reviewer notes that FDA actions regarding PML have differed between drugs. Natalizumab, for example, requires enrollment in a restricted distribution program (TOUCH). In the natalizumab example, PML occurred in three patients in the early clinical program involving patients with multiple sclerosis (a non-oncology indication), a disease where PML is rarely diagnosed.*

*Rituximab contains a boxed warning describing PML. The action regarding the box warning was placed in the rituximab label after patients with SLE developed PML [a non-oncology disease (and off-label indication)].*

*Alemtuzumab is approved for CLL (an oncology indication) and a warning about infections is contained in the product label. PML is listed in the post-marketing section of the alemtuzumab label.*

*The incidence of PML in patients with CLL treated with fludarabine has been reported to be as high as 3.3% (Garcia-Suarez et al., 2005). Garcia-Suarez et al., (2005), found that of 24 consecutive patients with lymphoproliferative disorders who developed PML after 1990, 11 had B-cell CLL. Thus, in contrast to patients with MS receiving natalizumab, it is difficult to determine to what extent that anti-CD20 antibody therapy increases the risk for PML in patients who are already severely immunocompromised due to CLL and other prior therapies.*

**Blood and Lymphatic Disorders:**

A total of 18 patients experienced SAEs in the blood SOC. Most cases involved cytopenias (neutropenia, thrombocytopenia, and anemia) that are described in more detail in section 7.4.2 of this review.

Three instances (SAEs) of hemolytic anemia were reported in study 406 (patients 118, 193, and 220). The hemolysis in patient 193 was considered to be related to massive splenomegaly caused by CLL. Patient 118 had a positive direct Coombs test and low haptoglobin levels at screening. Patient 220 had a viral infection one week prior to the hemolysis event and this patient re-initiated ofatumumab following treatment of the hemolysis. *Comment: Immune cytopenias occur in patients with CLL and are considered an indication for treatment with chemotherapy or chemoimmunotherapy if refractory to glucocorticoids or other second-line autoimmune hemolysis therapies (Hallek et al., 2008). At this time, there is not sufficient evidence to support that hemolysis is related to ofatumumab rather than being caused by CLL.*

In study 402, there were two SAE reports of neutropenia and one report of hemolytic anemia.

**General Disorders and Administration Site Conditions:**

In study 406, all SAEs in the General Disorders SOC were related to disease progression (n=9) or pyrexia (n=1). The verbatim term for patient 213 was ataxia/disease progression. Review of this patient's narrative summary showed that this patient had a brain MRI consistent with lymphomatous infiltration. No SAEs were reported for the General Disorders SOC for study 402. *The inclusion of pyrexia in the adverse event table is acceptable in that it describes the overall incidence of pyrexia by CTCAE Grade.*

**Cardiac Disorders:**

In study 406, seven patients experienced 9 cardiac events (Table 52). Two cardiac events were reported during infusion days. Table 53 shows all SAEs related to cardiac events in studies 406 and 402. The SAE reports from all studies submitted to the BLA were reviewed and one additional cardiac report from study 403 is included in Table 53.

**Table 52: Study 406 SAEs by PT in Cardiac Disorders SOC**

AEPT	N Rows (N = 154)
MYOCARDIAL INFARCTION	3
CARDIAC FAILURE	2
MYOCARDIAL ISCHAEMIA	2
MYOPERICARDITIS	1

**Table 53: Tabular Listing of SAEs Related to the Cardiac SOC that Occurred after the Administration of Ofatumumab**

Trial	Group	Center	Patient	Age	Brief Description of SAE
406	BFR	UK03	135	79	A 79 year-old man with hypertension and peripheral edema received ofatumumab on the day that he tripped at home. He was hospitalized with rib fracture and pain. He developed worsening dyspnea and died the next day due to myocardial infarction.
406	BFR	PL01	142	56	This man had 2 SAEs due to ischemia and one due to infarction. After the ninth infusion, the patient had an ECG suggestive of silent MI due to prior myocardial ischemia. He had a prior history of coronary artery disease.
406	BFR	CZ05	143	61	This man had diabetes and paroxysmal atrial fibrillation. This patient was hospitalized with dyspnea and perimyocarditis after echocardiography showed a pericardial effusion. Microbial tests were negative, and the event ultimately resolved.
406	Other	DE05	235	82	This patient died of "heart failure" two days after hospitalization with acute laryngitis.
406	DR	US14	244	68	A patient with CAD, hypertension, and diabetes developed chest pain two days after the sixth infusion of ofatumumab. This patient had a confirmed myocardial infarction by enzymes.

Trial	Group	Center	Patient	Age	Best Description of SAE
406	BFR	UK06	258	76	A patient with CAD and angina developed myocardial ischemia during the forth infusion of ofatumumab. The event resolved after treatment.
406	DR	UK01	261	62	This patient with COPD, CAD, and PVD was hospitalized six days after the first infusion due to worsening heart failure.
402	B	US21	651	62	This man with CAD developed angina pectoris at an unspecified time < 1 month after the last dose of ofatumumab.
403	-	-	302	-	This woman with a history of DM, smoking, and hypertension developed cardiac ischemia approximately four months after the last ofatumumab dose. MI was ruled out.
403	-	-	818	-	This person with RA developed atrial fibrillation twice (on June 30, 2006 and September 27, 2006).

GSK proposed the following warning for

[REDACTED]

b(4)

*Comment: The rituximab label contains a similar warning as the one proposed by GSK. A review of the overall safety database for arrhythmias showed that five infusions were temporarily stopped due to either tachycardia or bradycardia. Three instances of atrial fibrillation that were not SAEs were included in the 406 AE database. One additional report of atrial fibrillation was noted, but the verbatim term was listed as supraventricular arrhythmia-AF. Finally one additional case of supraventricular tachycardia was reported. The instances of AF or SVT occurred  $\geq 5$  days after the last dose of ofatumumab.*

*This reviewer recommends adding a statement that angina and myocardial infarctions can occur on the day of or shortly after ofatumumab infusions. Alternatively, ischemic events can be described in the infusion reactions warning of the label. In the 406 clinical trial, four out of 154 patients developed MI or angina within two days of receiving a dose of ofatumumab. The population of patients with CLL (older age) may be at higher risk for myocardial events. It is not possible in a single-arm study to determine whether ofatumumab may increase the risk for myocardial events in susceptible patients.*

**Ear and Labyrinth Disorders:**

One SAE caused by Grade 3 vertigo was reported from study 406 (patient number 111). The patient made a full recovery without a documented cause being established. No other serious event in this SOC was reported from other trials submitted to this BLA.

**Eye Disorders:**

Two SAEs caused by diplopia (Grade 1 and 2) were reported during the 406 clinical study (patients 123 and 116). Patient 123 experienced Grade 1 diplopia in conjunction with being hospitalized for fever. The diplopia recovered fully. Patient 116 recovered and the CIOMS report stated that the diplopia was speculated to be caused by paralysis of the "right nervus

trochlearis.” Other serious events in this SOC were not reported from other trials submitted to this BLA.

**Gastrointestinal Disorders:**

Three SAEs in the Gastrointestinal Disorders SOC were reported from study 406. Two (patients 129 and 133) were coded to the preferred term small intestinal obstruction. Patient 129 had a prior history of small bowel obstruction and (reported) CLL invasion of the celiac plexus. The patient also had multiple bulky masses in the mesentery and retroperitoneum. Patient 133 underwent surgical resection and had no tumor involvement in the bowel. No definitive cause of the intestinal obstruction could be identified. Additional serious adverse events in the GI SOC included enteritis (n=1; study 406; patient 107); nausea (n=1; study 409; patient 106); abdominal pain secondary to enlarged lymph nodes (n=1; study HxCD20-001; patient PL3405); gastritis (n=1; study 403; patient 426) and vomiting (n=1; study 405; patient 112).

Based on the two cases of small bowel obstruction in the clinical study, GSK proposed to include a warning regarding bowel obstruction. *Comment: Based on the bowel obstruction cases observed in the 406 clinical trial and the known experience with rituximab as described in the rituximab product label, this reviewer agrees with the inclusion of a warning regarding bowel obstruction in the ofatumumab label.*

Additionally, one SAE (patient number 614) was reported in study 402 regarding a case of “cytolytic hepatitis.” After the first infusion of ofatumumab, this patient developed increased hepatic enzymes with an alanine aminotransferase of 218 U/L and an aspartate aminotransferase of 575 U/L. The patient had elevated liver enzymes at screening that improved prior to the first infusion. During the infusion, the patient developed hypoxia (oxygen saturation of 80%), fever, and hyperuricemia. The patient was considered as recovered from the event three days following the adverse event. A March 19, 2009 submission to the BLA (based on an FDA request for further information) indicated that this patient did not undergo hepatitis screening at baseline (screening was not required at the time that this patient was enrolled).

GSK stated (March 19, 2009 submission) that of the 648 patients submitted to the BLA, only 15 (2%) were either positive for hepatitis B surface antigen or hepatitis B core antibody. Thus, the safety database is not large enough to determine whether patients previously infected with hepatitis B are at risk for hepatitis B reactivation.

GSK proposed the following warning in the ofatumumab label regarding hepatitis B reactivation:

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b(4)

*Comment: this reviewer notes that fulminant hepatitis due to hepatitis B reactivation has not been observed in the ofatumumab clinical trials. However, an FDA draft guidance (<http://www.fda.gov/cder/guidance/5538dft.htm>, accessed 3/2/2009) describes situations where a warning can be included in the label even if the adverse reaction has not been observed with that drug. In the case of ofatumumab and hepatitis B reactivation, the AR is serious and clinically significant because it can lead to fulminant hepatitis and death. Furthermore, the AR is expected based on the similar prolonged B-cell depleting effects (pharmacodynamic effects) observed after both rituximab and ofatumumab and the known association of hepatitis B reactivation with rituximab. Thus, this reviewer recommends that hepatitis B reactivation remain a warning in the ofatumumab label.*

*This reviewer, however, does not believe that the proposed label should include language that*

*Finally, this reviewer believes the label should be revised to indicate that fatal primary hepatitis infection may occur (if exposed) following ofatumumab treatment based on a report submitted to the BLA on July 28, 2009 (in a patient with RA).*

**Immune System Disorders:**

This reviewer reclassified (by SOC) some serious adverse events that occurred on the day of an infusion that (in the opinion of this reviewer) may have been related to an infusion reaction. For example, bronchospasm or rash occurring on the day of an infusion were likely to be related to an infusion reaction so were reclassified to the Immune System Disorders SOC for the purposes of this review. The reclassified events are marked with an asterisk in Table 54 below. These reclassified SAEs were not double counted in the review of their primary SOC's in this SAE analysis.

**Table 54: Tabular Listing of SAEs Related to Immune System Disorders that Occurred after the Administration of Ofatumumab**

Total	Center	Events	Age	Description of SAE
406	DE07	221	53	"Cytokine Release Syndrome": This patient experienced chills, high blood pressure, bronchospasm, hypoxia, and fever five hours into the first infusion. Four hours later, the symptoms improved and the infusion was restarted.
406	DE07	221	53	"Cytokine Release Syndrome": During the second infusion, the patient experienced flushing, dyspnea, chills and fever. The symptoms resolved after temporary discontinuation of ofatumumab and steroids.
406	DE07	147	68	This patient experienced Grade 3 bronchospasm during the 10 <sup>th</sup> infusion and then experienced Grade 3 bronchospasm, urticaria, angioedema, hypertension, and tachycardia with the 11 <sup>th</sup> infusion (hypersensitivity reaction). The patient was subsequently withdrawn from treatment.

b(4)

Trial	Center	Patient	Age	Brief Description of SAE
407*	-	102	76	Wheezing and Grade 3 bronchospasm occurred about 3 hours into the first infusion. The patient was withdrawn from treatment. The patient had a prior history of bronchospasm.
407*	-	106	77	During the second infusion, the patient became dyspneic and developed bronchospasm. The patient withdrew from treatment. FEV1 dropped from 56% to 35% during the infusion. He was treated with IV adrenaline, terbutaline, ipratropium, tavegyl, and solumedrol. He was receiving ipratropium prior to receiving ofatumumab.
403	-	109	57	Anaphylactoid reaction (Grade 4) with urticaria, hypotension, loss of consciousness, and vomiting (about 20 minutes into the infusion).
403*	-	115	56	About 25 minutes after the start of ofatumumab, the patient developed Grade 2 urticaria, Grade 3 periorbital edema, and Grade 3 hot flushes. The patient was withdrawn from treatment.
403	-	422	37	Infusion reaction with hypoxia and dyspnea 2 hours and 39 minutes into the infusion.
403	-	608	55	One hour after the start of infusion, the patient experienced an infusion reaction with Grade 3 dyspnea, Grade 2 rash, and hypertension (SBP 190).
403*	-	631	44	Bronchospasm and wheezing about one hour into the first ofatumumab infusion. This patient had a history of asthma. She responded to treatment with solumedrol, diphenhydramine, and albuterol.
403*	-	903	53	About 1.5 hours after the start of the first ofatumumab infusion, the patient experienced rash, pruritus, throat tightness, and dizziness.
403	-	927	53	Infusion reaction with rash and throat tightening during study drug infusion. The patient recovered after treatment with hydrocortisone, an antihistamine, and overnight observation.
Hx-CD20-001*	-	UK2443	26	Laryngeal edema, dyspnea, heaviness in chest, difficulty swallowing, stridor, fever, and tachycardia about one hour after the start of an ofatumumab infusion. The patient was withdrawn from treatment and the toxicity resolved after treatment with steroids and ofatumumab discontinuation.
415#	-	035	79	Grade 4 infusion reaction (termed anaphylactic reaction): This woman with aortic stenosis developed rash, hypotension, seizure, and loss of consciousness after the first dose of ofatumumab.

\*SAE reported in an alternative SOC because the SAE more likely represents an infusion reaction event  
 # post-BLA submission safety report

*Comment: This reviewer agrees that infusion reactions should be included as a warning in the ofatumumab label. Bronchospasm and laryngeal edema should be included in the infusion reactions section. Because patients are often monitored in infusion centers or hospitalized on the day of infusions, some severe reactions occurred (≥ Grade 3) that were not considered SAEs.*

*A more in-depth discussion regarding infusion reactions can be found in Section 7.3.5 of this review.*

**Injury, Poisoning, and Procedural Complications:**

SAEs occurring during study 406 in the Injury SOC included 2 instances of falls, one instance of accidental acetaminophen overdose, fever after vertebroplasty, and blood transfusion reaction. In study 405, one patient (121) was hospitalized secondary to prostate-related symptoms after using Actifed. One patient in study 403 (520) underwent shoulder arthroplasty and spinal decompression.

**Investigations:**

In study 406, two SAEs occurred in the investigations SOC. One was related to an elevated LDH and one was related to low neutrophils.

**Metabolism and Nutrition Disorders:**

In study 406, one SAE due to hypercalcemia was reported and one SAE due to decomposition of diabetes mellitus was reported. The cause of the hypercalcemia was not postulated in the CIOMS report.

**Musculoskeletal and Connective Tissue Disorders:**

One SAE due to back pain was reported in study 406 (patient 191). The CIOMS report for patient 191 indicated that this 66-year-old woman had a history of osteoporosis and vertebral fractures. An MRI showed two vertebral fractures in addition to older fractures. Additional SAEs reported in this SOC included local osteoarthritis, lumbar spinal stenosis, and rheumatoid arthritis in study 403 (this study is for the treatment of rheumatoid arthritis).

In study 407, there was one report of rhabdomyolysis five days after the first infusion of ofatumumab. The patient experienced severe myalgia and a CPK as high as 1,989 U/L. Creatinine was increased. The patient recovered fully after administration of fluids. Additional serious events of rhabdomyolysis were not reported for this patient despite re-treatment with ofatumumab and chemotherapy (fludarabine and cyclophosphamide).

**Neoplasms Benign, Malignant, and Unspecified:**

Refer to section 7.6.1 for a discussion of SAEs occurring in this SOC.

**Nervous System Disorders:**

In study 406, four SAEs in the Nervous Systems Disorders SOC were reported. Patient 111 was a 61-year-old man with a history of hypertension who experienced a presumed ischemic stroke 27 days after the last dose of ofatumumab. Patient 116 was a 63 year-old-man who developed presumed Bell's palsy 68 days after the last dose of ofatumumab. Patient 137 was an 88-year-old woman with a medical history of coronary artery disease and transient ischemic attack (TIA) who experienced an SAE of TIA 38 days after the last dose of ofatumumab. Finally, patient 182 developed hemiparesis caused by presumed CLL infiltration in her brain as documented by medical imaging.

In study 402, one 69-year-old man (612) developed symptoms of carotid artery stenosis three months after receiving the last dose of ofatumumab. In study 408, one 68-year-old patient experienced a cerebrovascular accident (CVA) six days after the last dose of ofatumumab. Finally, one patient in study 407 developed a CVA two weeks after the second dose of ofatumumab (in combination with fludarabine and cyclophosphamide).

*Comment: All but one case of cerebrovascular disease occurred two or more weeks following a dose of ofatumumab. There is not enough evidence at this time to declare an association of cerebrovascular disease with ofatumumab.*

#### **Psychiatric Disorders:**

In study 406, there were two SAEs related to psychiatric disorders. In both cases, the MedDRA preferred term was confusion. Patient 109 was a 68-year-old man who had prior episodes of confusion and had no MRI changes at the time of hospitalization. Polypharmacy was the reason provided for the confusion of patient 195.

#### **Vascular Disorders:**

In study 406, two SAEs related to deep venous thrombosis were reported. One occurred 35 days (patient 180) after the last dose. Further inspection of the CIOMS report for patient 214 indicated that this patient experienced DVT on July 11, 2007 and started ofatumumab on June 13, 2007. Additional details regarding the event were not provided.

#### **Respiratory, Thoracic, and Mediastinal Disorders:**

In study 406, five SAEs in the respiratory SOC were reported. None appeared to be related to infusion reactions. Patient 102 experienced hypoxia possibly related to a resolving pneumonia. Patient 130 experienced a pleural effusion of unknown cause. Patient 135 experienced pulmonary edema. Patient 209 experienced hemoptysis, and patient 219 experienced pulmonary emboli 52 days after the last dose of ofatumumab. One additional patient experienced pulmonary emboli in study 405 (patient number 133) during hospitalization for Pneumocystis infection. *Comment: Based on the time-course of venous thromboembolic events (in the vascular disorders SOC or respiratory SOC), it is unlikely that the cases of VTE were related to ofatumumab. The one possible exception was patient 406214 who experienced DVT two days after ofatumumab treatment. Because VTEs frequently occur in patients with cancer, there is insufficient evidence to conclude that VTE is reasonably caused by ofatumumab.*

### **7.3.3 Dropouts and/or Discontinuations**

#### **Study 406**

The 406 CSR (Figure 7.1 of the CSR) stated that of the 154 patients, 20 completed treatment and are ongoing in follow-up (at the time of the submission of the BLA). The WITHDRAW dataset contains data on 136 patients and 69 of the patients were withdrawn during the treatment period.

Table 55 describes the reasons (as derived from the WITHDRAW dataset) that patients withdrew from treatment in study 406. The number of patients included in the WITHDRAW dataset differed from that described in the CSR. The differences can be ascribed to the source of the

information in the CRFs. The WITHDRAW dataset was derived from the "Withdrawal from Treatment" CRF page, but the CSR included data listed on the "AE" CRF page.

Using the more conservative approach, a total of 21 patients (14%) withdrew from treatment because of an AE (this does not include patients in the "other" or "refusal" categories). Of these 21 patients, 16 (10%) withdrew due to infections or infectious death (including patient 235), one withdrew due to cardiac causes, three withdrew due to possible infusion symptoms (2%), and one withdrew due to neutropenia.

**Table 55: Patients Withdrawn from Treatment during the Treatment Period of the 406 Study**

Reason for Withdrawal	N	N (406 CSR)
Progression of study disease	40	35
Death	10	13
Other	9	8
Adverse Event	5	8
Patient Refusal	5	5

Table 56 describes the specific reasons why patients withdrew during the treatment period of the 406 study. Among the 9 patients categorized as "other," at least 6 were likely withdrawn due to reasons related to CLL (disease progression, lack of response to treatment, or new CLL therapies). One patient withdrew due to poor functional status. Two patients were withdrawn by investigators from the study due to unclear reasons. One patient had Grade 3 urinary infection prior to treatment discontinuation; thus, this patient will be classified as having been withdrawn due to an AE for the purposes of this review.

Five patients refused further therapy. The reasons for such refusals were not clear. Two patients refused therapy after the first or second doses after experiencing mild to moderate infusion reactions associated with ofatumumab. One patient (237) experienced sepsis prior to discontinuing. It was unclear why patient 200 refused further therapy.

**Table 56: Patients Who Withdrew for Reasons "Death," "Other," "Adverse Event," or "Patient Refusal" during the Treatment Period of the 406 Study**

SUBJID_	AGE	Group 1 = DR 2 = BFR 3 = other	Center	Reason for Withdrawal in WITHDRAW dataset	Additional explanation from CRFs or AE dataset
406105	76	1	UK01	Death	Death due to fungal pneumonia
406107	60	2	DE02	Adverse Event	Death due to sepsis with DIC and renal failure

<b>SUBJID_</b>	<b>AGE</b>	<b>Group 1 = DR 2 = BFR 3 = other</b>	<b>Center</b>	<b>Reason for Withdrawal in WITHDRAW dataset</b>	<b>Additional explanation from CRFs or AE dataset</b>
406110	73	3	IT03	Patient Refusal	Patient experienced neutropenia, Grade 1 fever, and blood transfusions prior to discontinuation. Withdrew after second dose.
406120	84	2	DE02	Other	Withdrew due to poor functional status (ECOG = 03)
406128	59	1	CZ01	Other	Patient removed from study to undergo an allogeneic stem cell transplant
406129	64	1	US02	Patient Refusal	Stopped after experiencing intestinal obstruction symptoms/ileus
406135	79	2	UK03	Death	Death due to myocardial infarction
406141	55	1	US02	Other	Died of fusarium infection; patient had received additional chemotherapy for Richter's transformation
406145	59	1	CZ03	Death	Death due to pneumonia
406146	53	3	UK06	Adverse Event	Investigator withdrew this patient because of Grade 2 neutropenia
406147	68	1	DE04	Adverse Event	AE: infusion reaction (later developed PML)
406160	65	1	DE04	Death	Death due to sepsis
406163	59	1	CZ02	Progression of study disease	Richter's transformation
406167	70	1	FR07	Patient Refusal	Withdrew after second dose. Experienced Grade 2 urticaria associated with the infusion.
406172	73	2	US11	Death	Death due to pneumonia
406182	43	1	PL05	Progression of study disease	Death due to disease progression (hemiparesis caused by lymphoma)
406184	53	2	PL03	Progression of study disease	Death due to disease progression
406189	65	1	CZ02	Adverse Event	Withdrew after Grade 3 herpetic skin infection and bilateral pneumonia
406195	74	1	US12	Death	Death due to gram negative sepsis
406200	60	2	US02	Patient Refusal	Specific reason not specified: no AEs reported during the last month prior to discontinuation
406209	59	2	US01	Other	Withdrew due to lack of response to treatment

SUBJID_	AGE	Group 1 = DR 2 = BFR 3 = other	Center	Reason for Withdrawal in WITHDRAW dataset	Additional explanation from CRFs or AE dataset
406213	52	2	US05	Progression of study disease	Death due to disease progression
406214	79	2	US02	Other	Disease progression – started new CLL treatment
406230	65	1	ES02	Death	Death due to septic shock (from cellulitis)
406231	62	2	US12	Death	Sepsis
406234	60	3	FR06	Other	Unclear reason for study withdrawal. Patient had Grade 2 bone pain at the time of study discontinuation.
406235	82	3	DE05	Death	Cardiac failure (this patient was diagnosed with acute laryngitis and required IV antibiotics two days before her death)
406236	66	1	FR06	Adverse Event	Died (septic shock)
406237	72	1	UK02	Patient Refusal	Patient had Grade 3 sepsis less than one month prior to withdrawal
406242	66	2	UK03	Other	Disease transformation
406244	68	1	US14	Death	Death due to Pneumocystis pneumonia
406251	76	2	US01	Other	This patient started new CLL treatment
406258	76	1	UK01	Other	Investigator decision: AE possible (Grade 3 urinary infection and transfusions prior to withdrawal)

Section 11.1.4 of the GSK 406 CSR stated that 21 patients (14%) experienced 23 AEs leading to withdrawal from treatment. Of the 21 patients, three were actually discontinued due to disease progression (reported as AEs). This section of the CSR included one patient who withdrew due to an AE other than disease progression who was not listed as withdrawing due to an AE in the WITHDRAW dataset. Patient 169 was listed as withdrawing due to progressive disease in the dataset and death due to neutropenic sepsis in table 11-6 in the CSR (a bone marrow biopsy for this patient showed 90% CLL involvement of the bone marrow).

The FDA review of the 18 patients who withdrew during the treatment period due to a reason other than disease progression showed that one patient (182) actually withdrew due to a disease related symptom. Four patients who withdrew due to patient refusal or “other” may have withdrawn from the study due to drug related symptoms or adverse effects. Patient 237 refused after experiencing Grade 3 sepsis in the prior month. Two patients (110, 167) refused further therapy after one or two doses of ofatumumab after experiencing mild to moderate infusion symptoms; however, patient 167 most likely discontinued therapy due to interstitial pneumonia.

**Study 402:**

In study 402, all patients received all four planned doses of ofatumumab in the Group A and B cohorts. In group C, patient 614 developed cytolytic hepatitis one day after receiving a dose of ofatumumab and was withdrawn.

**Study 403:**

Table 57 lists reasons that patients withdrew from studies 403 (parts A and B) prior to receiving both doses of ofatumumab. Patients who withdrew due to worsening RA were not included in the table.

**Study 403 Part A**

GSK indicated in the CSR that 33 of the 39 patients completed two planned infusions of ofatumumab. Five of the 39 (13%) patients withdrew due to infusion reaction symptoms.

**Study 403 Part B**

A total of 169 patients received active drug in the safety population of study 403 part B. All patients in the placebo group and 149 (88%) of the actively treated patients completed two planned infusions of ofatumumab. Two additional patients refused further therapy (507 and 651) for unknown reasons. Of the 18 patients known to have discontinued therapy due to an AE, all did so due to infusion related symptoms (11%).

**Table 57: Withdrawal from Protocol Directed Therapy in Study 403 (Parts A and B)**

Trial	Patient	Age	Amendment	Dose (mg)	SAE	Event Description of Event Leading to Withdrawal
403A	109	57	NA	300	Y	Grade 4 anaphylactoid reaction
403A	110	49	NA	300	N	Grade 3 bronchospasm during first dose of ofatumumab
403A	112	58	NA	300	N	Herpes simplex
403A	115	56	NA	300	Y	Grade 3 periorbital edema; Grade 3 hot flush; Grade 2 conjunctival hyperaemia; Grade 2 urticaria during the first dose
403A	209	56	NA	700	N	Grade 2 urticaria, Grade 3 chest discomfort; Grade 3 bronchospasm on the day of the first infusion.
403A	306	56	NA	1000	N	Grade 2 urticaria; Grade 2 dyspnea; Grade 1 dysphagia on the day of the first infusion
403	407	52	7	700	N	Grade 2 pruritus; Grade 1 glossodynia; Grade 1 urticaria; Grade 1 congestion; Grade 2 hypertension on the day of the first infusion
403	408	38	NL	300	N	Grade 1 nasal congestion; Grade 1 rash; and Grade 1 pruritus on the day of the first infusion
403	422	37	6	1000	Y	Grade 3 infusion reaction with dyspnea and hypoxia on the day of the first infusion
403	518	62	8	300	N	Grade 3 throat tightness and Grade 2 urticaria on the day of the first infusion

Clinical Review  
 Steven Leemery/Jenny Zhang  
 BLA 125326  
 Ofatumumab/Arzerra

Trial	Patient	Age	Amend-ment	Dose (mg)	SAF	Brief Description of Event Leading to Withdrawal
403	521	59	NL	1000	N	Grade 2 urticaria and Grade 2 pruritus occurring on the day of the first infusion
403	531	39	8	1000	N	Grade 3 hypersensitivity on the day of the first infusion
403	608	56	6	1000	Y	Grade 3 infusion related reaction on the day of the first infusion
403	626	37	7	700	N	Grade 2 dyspnea and Grade 2 urticaria on the day of the first infusion
403	631	44	7	700	Y	Grade 3 bronchospasm on the day of the first infusion
403	643	45	NL	1000	N	Grade 2 dyspnea on the day of the first infusion
403	675	67	8	1000	N	Grade 3 rash on the day of the first infusion
403	702	52	NL	1000	N	Grade 2 rash on the day of the first infusion; also laryngeal edema and hypertension
403	704	44	NL	700	N	Grade 2 pruritus and rash on the day of the first infusion
403	818	45	NL	1000	N	Grade 2 pruritus and Grade 2 dysphagia on the day of the first infusion
403	903	52	8	700	Y	Grade 2 urticaria on the day of the first infusion
403	927	53	7	1000	Y	Grade 3 infusion related reaction on the day of the first infusion
403	938	33	8	700	N	Grade 3 infusion related reaction on the day of the first infusion
403	952	66	NL	1000	N	Grade 1 dyspnea, erythema, and stomatitis on the day of the first infusion

During the 403 study, premedication regimens and infusion rates were modified three times. In the first iteration of the study, corticosteroids were not administered on the day prior to ofatumumab treatment but were administered 30 minutes prior to the first dose of ofatumumab. In amendment 6, prednisolone was administered the day prior to- and 60-120 minutes prior to ofatumumab. A higher dose of prednisolone was administered the day prior to the first dose of ofatumumab in amendment 7. Finally, in amendment 8, the rate of the second infusion was increased. Table 57 lists the protocol amendments associated with each patient as described in table 11-6 of the study 403 CSR.

*It is unclear why the number of patients withdrawing due to infusion reactions was higher for the RA population compared to the CLL population. Possible explanations include differences in gender backgrounds of the study populations (more men in studies 402 and 406 and more women in study 403); differences in the first dose of ofatumumab (CLL compared to RA); differences in practices between oncologists and rheumatologists (patients with life threatening cancer may be more likely to endure drug related toxicities and not stop a drug due to infusion reactions); or differences in immunological function due to prior therapies (or underlying diseases).*

#### **Study 407**

Six of 28 patients withdrew due to AEs. Patient 115 was withdrawn due to autoimmune hemolytic anemia. Patient 118 was withdrawn due to CVA. Patient 122 was withdrawn due to chest discomfort (Grade 1) and urticaria (Grade 2) during the second ofatumumab infusion. The other three patients were withdrawn from therapy due to cytopenias or febrile neutropenia (this study is evaluating ofatumumab plus fludarabine and cyclophosphamide).

#### **Study 408 (COPD)**

Two of five patients withdrew from study 408 due to serious adverse events (Grade 3 bronchospasm for both patients). Thus in patients with COPD, 2 out of 5 (40%) developed Grade 3 bronchospasm associated with an infusion of ofatumumab.

#### **Study 409**

At the time of data cut-off, 33 patients have been exposed to ofatumumab and 13 received all 6 planned infusions. No patients had been withdrawn from therapy to date.

#### **Study Hx-CD20-001**

All but one patient received four planned doses of ofatumumab. One patient in the 500 mg dose group was withdrawn from the study due to an SAE of laryngeal edema, Grade 2 dysphagia, and Grade 1 pyrexia on the day of the first infusion.

### **7.3.4 Significant Adverse Events**

ICH E3 includes marked hematological or other lab abnormalities not meeting the definition of serious to be considered significant adverse events. These lab abnormalities are described in Section 7.4.2 of this review.

Furthermore, ICH E3 considers other potentially important abnormalities not meeting the above definition of serious and not leading to death or modification of therapy. A discussion of such severe adverse events ( $\geq$  Grade 3 CTCAE) is included in the common adverse events section of this review. The following section describes a review of the 406 safety database using MedDRA Standardized MedDRA Queries (SMQs).

#### **MedDRA SMQ's Study 406**

Using FDA MAED software, narrow scope MedDRA SMQs were analyzed to assess additional (potential) safety signals. All SMQ events described in 6 or more patients (in study 406) were further evaluated. However, the following terms were analyzed elsewhere in this safety review: Hematopoietic cytopenias, leucopenia, malignancies, malignant or unspecified tumors, hypertension, and agranulocytosis (neutropenia). The terms "gastrointestinal nonspecific inflammation and dysfunction conditions" and "gastrointestinal nonspecific symptoms and therapeutic procedures" are non-specific and the more common PTs included in these SMQs (diarrhea and nausea) are described in the label.

The following additional terms were analyzed:

**Angioedema:** 12 of 15 patients identified under this SMQ had urticaria. One patient experienced Grade 1 throat swelling, 1 patient experienced Grade 1 eyelid edema, and one patient experienced Grade 2 swelling of the face. These three patients had no associated angioedema terms included in the SMQ. Thus, there was no evidence of severe angioedema in study 406.

**Haemodynamic oedema, effusions and fluid overload:** This SMQ was predominately reflected by the PT peripheral edema.

### **7.3.5 Submission Specific Primary Safety Concerns**

#### **Infusion Reactions**

Because infusion reactions commonly occur with monoclonal antibodies including rituximab, this reviewer performed an analysis of AEs potentially related to infusion reactions. To perform this analysis, all AEs in the AE dataset that occurred on day 0 or 1 after an infusion of ofatumumab were initially identified for review. However, AEs in the following SOC were removed due to the low likelihood that they are related to an immunological infusion reaction: infections, neoplasms, blood and lymphatic disorders, investigations, metabolism and nutrition disorders, and injury.

The following additional PTs were removed from the analysis (because it is unlikely that these signs/symptoms were related to an infusion): palatal dysplasia, hemorrhoids, faeces discoloured, deep vein thrombosis, thrombophlebitis superficial, pallor, petechiae, ecchymosis, actinic keratosis, skin lesion, hemoptysis, epistaxis, interstitial lung disease, pleural effusion, hematuria, pollakiuria, insomnia, depression, anxiety, tendonitis, extravasation, catheter related complication, rectal hemorrhage, and stomatitis.

The remaining 84 PTs in the dataset formed the basis of the analysis of infusion reactions. This should be considered a conservative analysis of infusion reactions, recognizing that it is not possible to be completely accurate in the attribution of these AEs.

A total of 106 (69%) out of 154 patients had an AE on day 0 or 1 after an infusion that was possibly attributable to an infusion related reaction. A total of 9 (6%) of 154 patients had a total of 14  $\geq$  Grade 3 adverse reactions. These adverse reactions included myocardial infarction, pulmonary edema, myocardial ischemia, bronchospasm, dyspnea, hypersensitivity, macular rash, vasovagal syncope, back pain, cytokine release syndrome, throat irritation, and myocardial ischemia.

The number of potential infusion related AEs was not markedly different if only AEs that occurred on the day of an infusion were identified. A total of 100 (65%) patients had a potential infusion reaction on the day of an infusion. Eight out of 154 (5%) patients had a total of 12  $\geq$  Grade 3 infusion related adverse reactions.

The following analysis was performed based on infusion days. Any of the above potentially infusion related AEs that occurred on day 0 or 1 after an infusion were evaluated. A total of 67 (44%) patients experienced potential infusion reactions after the first infusion. Three patients (2%) experienced  $\geq$  Grade 3 adverse reactions that were potentially infusion related.

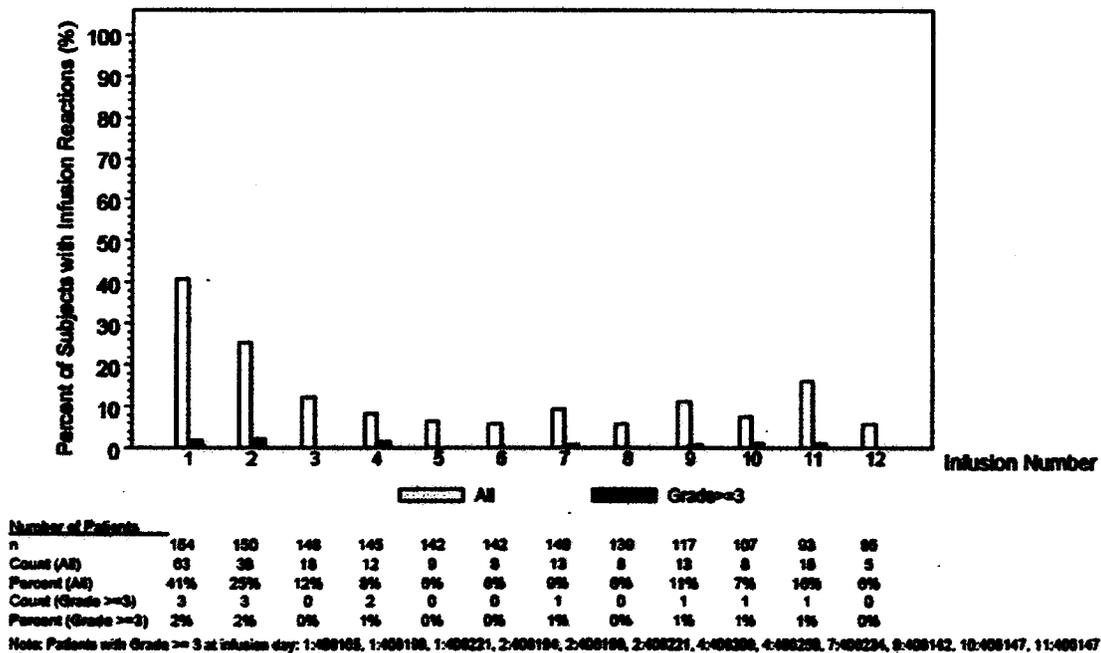
After the second dose, a total of 44 (29%) of 150 patients (150 patients received more than 1 infusion) developed a potentially infusion related AE on day 0 or 1 after the second infusion. Three patients (2%) experienced  $\geq$  Grade 3 adverse reactions that were potentially infusion related after the second dose

The frequency of infusion reactions decreased after the third dose. Eighteen of 148 patients (12%) developed an infusion-related symptom after the third dose.

The ninth dose was associated with a similar rate of infusion-related adverse reactions as the third dose (13%). The ninth dose was the first of the monthly doses of ofatumumab.

The results obtained by FDA were similar to the results provided by GSK. GSK's CSR (Figure 13) showed a 41% incidence rate of infusion reactions occurring after the first infusion of ofatumumab (with three Grade 3 events). The 46% incidence rate described in the FDA review above used a more conservative analysis that included adverse events on day 0 or 1 after the infusion. When evaluating the incidence of infusion reactions on day 0, the incidence of infusion reactions obtained by this reviewer was 41% (same as GSK's analysis).

Figure 13: GSK Analysis of Infusion Reactions by Infusion (Copied from GSK CSR)



### **Tumor Lysis Syndrome**

GSK stated in module 2 of the BLA submission that there were no reports of TLS at the time of the interim analysis cut-off date in any studies. After the data cut-off date, one SAE due to tumor lysis syndrome was reported from study Hx-CD20-406:

406274: A 55 year-old man with B-CLL (absolute lymphocyte count of 75,000/mcL), hyperuricemia, and renal impairment received his first dose of ofatumumab on January 30, 2008. The reported lab data from January 30 did not indicate if the labs were drawn before or after the infusion. On the day of the infusion, the patient experienced Grade 2 palpitations, tachycardia, and hypertension. The infusion was paused and restarted at a lower dose. The patient received IV hydration and allopurinol.

On January 30, the patient had a creatinine of 146.7 umol/L, lactate dehydrogenase 699 iu/L, potassium of 4.5 mmol/L, uric acid of 0.66 mmol/L, calcium of 2.35 mmol/L, and phosphate of 1.2 mmol/L.

On February 02, 2008, potassium was 4.1 mmol/L, creatinine was 119 umol/L, calcium was 2.02 mmol/L, phosphate was 1.02 mmol/L, and lactate dehydrogenase was 681 iu/L.

*Comment: This report appeared to be a case of an infusion reaction. There was no hyperkalemia, hyperphosphatemia, or hypocalcemia reported. The patient had high uric acid levels at baseline (urate on February 2 was lower than January 30). The creatinine was reported to be elevated at baseline and was lower on February 2 than January 30 (the creatinine on January 23, 2008 was 143 umol/L).*

At the time of the 90 day safety update, no additional cases of TLS were reported by GSK.

Additionally, for the 406 study, all cases of hyperkalemia, hyperuricemia, hypocalcemia, hyperphosphatemia, increased creatinine, or renal failure that were reported following the initial infusion were searched. No patient had a combination of more than one of these AEs being reported by investigators on the same day (after the initial infusion or any other infusion). Patient 406361 had a reported AE of Grade 2 renal failure; there was not a corresponding lab value in the dataset, and there were no other labs indicating that tumor lysis was the cause of renal failure. One AE of Grade 1 hypocalcemia occurred on the day of the first infusion for one patient (406162); however, the AE report did not include a time for the AE and it was deemed by the investigator as unrelated to ofatumumab (*it could not be determined whether the lab result occurred prior to or after the first dose of ofatumumab*). Finally, one patient had hyperuricemia reported 14 days after the first dose; however, this patient had hyperuricemia at baseline and throughout the study.

In the 402 study, there were no reports of renal failure and no reports of electrolyte disorders in the metabolism SOC.

**Conclusion:** There is no evidence that severe or serious TLS occurred during the conduct of study Hx-CD20-406. Additional cases of TLS were not reported by GSK in the other oncology

studies. *Comment: Although there were no reports of severe TLS, the 406 study did not obtain laboratory data within a week of the first infusion. Thus, evidence of subclinical TLS may have been missed.*

### Proprietary Name Review

DMEPA submitted a review of the proprietary name to DBOP on May 15, 2009. At the time of the review, DMEPA had no objections to the use of the proprietary name, Arzerra, for ofatumumab. DMEPA had identified and evaluated a total of 27 drug names and determined that Arzerra was not vulnerable to name confusion that could lead to medication errors with any currently marketed products.

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

#### STUDY 406

Common adverse events were evaluated based on the preferred term, high level term, and high level group term of the MedDRA hierarchy for study Hx-CD20-406. The most common AEs (>10% incidence in the full study population) were pyrexia, cough, diarrhea, anemia, neutropenia, pneumonia, fatigue, dyspnea, rash, nausea, bronchitis, and upper respiratory tract infection.

The original proposed label included adverse reactions that occurred at an incidence rate of  $\geq 5\%$  of patients with CLL who received 2,000 mg of ofatumumab. *In this reviewer's opinion, the adverse reactions table should only include data from study 406 and not combined data from studies 406 and 402. The shorter infusion schedule and follow-up time in study 402 may result in a dilution of the incidence of AEs described in the 406 study. Furthermore, the datasets did not include all levels of the MedDRA hierarchy for study 402. Table 58 lists adverse reactions occurring by MedDRA preferred term. GSK used the cut-off of  $\geq 5\%$  for inclusion in the product label. The cut-off for inclusion in the label was 8 events in the total study population (7 events was only  $\geq 5\%$  after rounding to the nearest percentage). This reviewer recommends removing            from the adverse reactions table in the product label because this AE is more accurately described in a separate laboratory section of the product label (using data from the laboratory datasets).*

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**Table 58: Adverse Reactions in Study 406 by MedDRA Preferred Term (PT)**

Adverse Event Preferred Term MedDRA V.9.0	All Grades n(%)		≥ Grade 3 n(%)		DR All Grades n(%)		DR ≥ Grade 3 n(%)	
	n	%	n	%	n	%	n	%
<b>PYREXIA</b>	31	20	4	3	15	25	3	5
<b>COUGH</b>	30	19	0	0	11	19	0	0
<b>DIARRHOEA</b>	28	18	0	0	11	19	0	0
<b>ANAEMIA</b>	25	16	8	5	10	17	5	8

Adverse Event Preferred Term MedDRA V 9.0	All Grades n=134		≥ Grade 3 n=134		DR All Grades ≥ 2 n=92		DR ≥ Grade 3 n=92	
	n	%	n	%	n	%	n	%
NEUTROPENIA	25	16	19	12	9	15	6	10
PNEUMONIA	25	16	16	10	10	17	6	10
FATIGUE	23	15	0	0	9	15	0	0
DYSPNOEA	22	14	3	2	11	19	3	5
RASH	19	12	0	0	8	14	0	0
NAUSEA	17	11	0	0	7	12	0	0
BRONCHITIS	17	11	1	1	11	19	1	2
UPPER RESPIRATORY TRACT INFECTION	17	11	0	0	2	3	0	0
OEDEMA PERIPHERAL	14	9	1	1	5	8	1	2
CHILLS	13	8	0	0	6	10	0	0
NASOPHARYNGITIS	12	8	0	0	5	8	0	0
BACK PAIN	12	8	2	1	7	12	1	2
URTICARIA	12	8	0	0	3	5	0	0
INSOMNIA	11	7	0	0	6	10	0	0
HEADACHE	10	6	0	0	4	7	0	0
DISEASE PROGRESSION	9	6	6	4	1	2	1	2
HERPES ZOSTER	9	6	2	1	4	7	1	2
TACHYCARDIA	8	5	1	1	4	7	1	2
SINUSITIS	8	5	3	2	2	3	1	2
MUSCLE SPASMS	8	5	0	0	2	3	0	0
HYPERHIDROSIS	8	5	0	0	3	5	0	0
HYPERTENSION	8	5	0	0	5	8	0	0
HYPOTENSION	8	5	0	0	2	3	0	0
ABDOMINAL PAIN	7	5	0	0	3	5	0	0
LOWER RESPIRATORY TRACT INFECTION	7	5	0	0	1	2	0	0
RHINITIS	7	5	0	0	4	7	0	0
SEPSIS	7	5	7	5	3	5	3	5
PARAESTHESIA	7	5	0	0	3	5	0	0
PRURITUS	7	5	0	0	3	5	0	0
ABDOMINAL PAIN UPPER	6	4	0	0	3	5	0	0
VOMITING	6	4	0	0	2	3	0	0
BRONCHOPNEUMONIA	6	4	3	2	2	3	2	3
URINARY TRACT INFECTION	6	4	2	1	2	3	1	2
ARTHRALGIA	6	4	0	0	3	5	0	0
NASAL CONGESTION	6	4	0	0	5	8	0	0
PHARYNGOLARYNGEAL PAIN	6	4	0	0	2	3	0	0
CONSTIPATION	5	3	0	0	1	2	0	0
FEELING HOT	5	3	0	0	2	3	0	0
CYTOKINE RELEASE SYNDROME	5	3	1	1	3	5	0	0
INFECTION	5	3	3	2	2	3	1	2
PHARYNGITIS	5	3	0	0	5	8	0	0
MUSCULOSKELETAL PAIN	5	3	0	0	2	3	0	0

Adverse Event Preferred Term MedDRA V 9.0	All Grades n=54		Grade 3 n=14		DR All Grades 1-59		DR ≥ Grade 3 n=59	
	n	%	n	%	n	%	n	%
PRODUCTIVE COUGH	5	3	0	0	3	5	0	0
FLUSHING	5	3	0	0	1	2	0	0
LYMPH NODE PAIN	4	3	0	0	2	3	0	0
ABDOMINAL DISCOMFORT	4	3	0	0	1	2	0	0
CHEST DISCOMFORT	4	3	0	0	3	5	0	0
LUNG INFECTION	4	3	2	1	3	5	1	2
ORAL HERPES	4	3	0	0	0	0	0	0
DECREASED APPETITE	4	3	0	0	3	5	0	0
HYPOKALAEMIA	4	3	1	1	1	2	1	2
BONE PAIN	4	3	0	0	3	5	0	0
PERIPHERAL SENSORY NEUROPATHY	4	3	0	0	2	3	0	0
BRONCHOSPASM	4	3	1	1	2	3	1	2
DRY THROAT	4	3	0	0	2	3	0	0
ATRIAL FIBRILLATION	3	2	1	1	1	2	1	2
MYOCARDIAL INFARCTION	3	2	3	2	1	2	1	2
CONJUNCTIVITIS	3	2	0	0	2	3	0	0
ABDOMINAL DISTENSION	3	2	0	0	1	2	0	0
STOMATITIS	3	2	0	0	0	0	0	0
ASTHENIA	3	2	0	0	2	3	0	0
OEDEMA	3	2	0	0	1	2	0	0
HYPERSENSITIVITY	3	2	1	1	3	5	1	2
EAR INFECTION	3	2	0	0	2	3	0	0
FOLLICULITIS	3	2	0	0	2	3	0	0
GASTROENTERITIS	3	2	1	1	1	2	0	0
INFLUENZA	3	2	0	0	2	3	0	0
NEUTROPENIC SEPSIS	3	2	3	2	1	2	1	2
VIRAL INFECTION	3	2	0	0	1	2	0	0
HAEMOGLOBIN DECREASED	3	2	1	1	0	0	0	0
HYPERURICAEMIA	3	2	0	0	2	3	0	0
DIZZINESS	3	2	0	0	0	0	0	0
HYPOAESTHESIA	3	2	0	0	1	2	0	0
LETHARGY	3	2	0	0	2	3	0	0
NEUROPATHY PERIPHERAL	3	2	0	0	1	2	0	0
ANXIETY	3	2	0	0	1	2	0	0
CONFUSIONAL STATE	3	2	2	1	2	3	2	3
DEPRESSION	3	2	0	0	1	2	0	0
DYSPNOEA EXERTIONAL	3	2	0	0	1	2	0	0
EPISTAXIS	3	2	0	0	1	2	0	0
HYPOXIA	3	2	0	0	3	5	0	0
SINUS CONGESTION	3	2	0	0	2	3	0	0
SNEEZING	3	2	0	0	2	3	0	0
THROAT IRRITATION	3	2	1	1	2	3	0	0
DRY SKIN	3	2	0	0	0	0	0	0

Adverse Event Preferred Term MedDRA V 9.0	All Grades n=54		≥ Grade 3 n=14		DR All Grades n=52		DR ≥ Grade 3 n=59	
	n	%	n	%	n	%	n	%
ERYTHEMA	3	2	0	0	1	2	0	0

Table 59 lists adverse events by MedDRA high level term. In the label, GSK summarized the adverse event rash by HLT rather than PT (*this reviewer does not object to this characterization*). This reviewer further analyzed all HLT events with a  $\geq 10\%$  incidence rate and any additional AE with a  $\geq$  Grade 3 incidence rate of 5% or higher. Based on this analysis, this reviewer recommends revising the product label to include a sepsis term and revise the incidence rate of the pneumonia term. Details of the HLT analyses are described below.

b(4)

- Lower respiratory tract and lung infections: The incidence of this term is markedly higher than the PT pneumonia described in the label (32% versus 16%). The PTs bronchitis, bronchopneumonia, lobar pneumonia, lower respiratory tract infection, lung infection, and pneumonia comprise the HLT lower respiratory tract and lung infections. *Comment: Bronchitis should not be included with the term pneumonia because of the lack of alveolar involvement. Furthermore, lower respiratory tract infection may encompass both bronchitis or pneumonia. Thus, this reviewer performed an analysis of the PT's bronchopneumonia, lobar pneumonia, lung infection, and pneumonia to determine the incidence rate of pneumonias. For the entire study population, the incidence rate was 23% (14%  $\geq$  Grade 3). For the DR study population, the incidence rate was 25% (15%  $\geq$  Grade 3).*
- The PTs acute tonsillitis, laryngitis, nasopharyngitis, rhinitis, sinusitis, tracheitis, and upper respiratory tract infection comprised the HLT upper respiratory tract infections. The label describes the incidence of the three most common PTs comprising this HLT: upper respiratory tract infection, rhinitis, and sinusitis. Seven patients were reported to have rhinitis; however, none were  $\geq$  Grade 3 in severity. Revisions to the label based on this HLT does not notably add to the safety information already included in the label regarding ofatumumab.
- The incidence of the HLT coughing and associated symptoms was similar to that of the PT cough (23% versus 19%). None of the additional events were severe in nature ( $\geq$  Grade 3).
- The incidence of the HLT febrile disorders matches that of the PT pyrexia.
- The percentage of patients with asthenic conditions was similar to that of patients who reported fatigue (17% versus 15%, respectively).
- The percentage of patients with breathing abnormalities (HLT) was similar to that of patients with dyspnea (PT) (16% versus 14% respectively). The percentage of patients with  $\geq$  Grade 3 events is unchanged.
- The percentage of patients with nausea and vomiting symptoms (HLT) was similar to that of patients who experienced the PT nausea (12% versus 11%). The incidence rate was the same for the DR population.
- The percentage of patients with the HLT diarrhea was the same as the number with the PT diarrhea (18%).

b(4)

- The HLT body temperature sensation comprises disparate terms (chills, heat sensation, rigors, feeling of warmth) and thus should not be grouped together (*in this reviewer's opinion*).
- The most common PT in the HLT category ' ( ) was disease progression; this HLT should not be included as an adverse event in the product label.
- The HLT ' ( ) refers to various pain symptoms and is non-descriptive. The most common PT in this HLT category was back pain and is included in the label. Addition of this vague HLT will not add to the information contained in the product label.
- The HLT ( ) and the PT "edema peripheral" are similar in incidence (11% and 9%).
- The HLT of "sepsis, bacteraemia, viraemia and fungemia" was evaluated because of the 8% overall incidence of ≥ Grade 3 events. The PTs that comprised the HLT were limited to sepsis, neutropenic sepsis, bacteremia, and septic shock. *Because these terms are similar, and because the incidence of ≥ Grade 3 events was > 5%, this reviewer recommends that this HLT be included in the product label.*

b(4)

b(4)

**Table 59: Adverse Reactions in Study 406 by MedDRA High Level Term (HLT)**

Adverse Event High Level Term	All Grades n=154		≥ Grade 3 n=154		DR All Grades n=59		DR ≥ Grade 3 n=59	
	n	%	n	%	n	%	n	%
<b>LOWER RESPIRATORY TRACT AND LUNG INFECTIONS</b>	50	32	22	14	22	37	9	15
<b>UPPER RESPIRATORY TRACT INFECTIONS</b>	43	28	3	2	15	25	1	2
<b>COUGHING AND ASSOCIATED SYMPTOMS</b>	35	23	0	0	13	22	0	0
<b>FEBRILE DISORDERS</b>	31	20	4	3	15	25	3	5
<b>DIARRHOEA (EXCL INFECTIVE)</b>	28	18	0	0	11	19	0	0
<b>NEUTROPENIAS</b>	28	18	22	14	9	15	6	10
<b>ASTHENIC CONDITIONS</b>	26	17	0	0	10	17	0	0
<b>ANAEMIAS NEC</b>	25	16	8	5	10	17	5	8
<b>BREATHING ABNORMALITIES</b>	24	16	3	2	11	19	3	5
<b>RASHES, ERUPTIONS AND EXANTHEMS NEC</b>	21	14	1	1	10	17	1	2
<b>NAUSEA AND VOMITING SYMPTOMS</b>	19	12	0	0	7	12	0	0
<b>BODY TEMPERATURE PERCEPTION</b>	18	12	0	0	8	14	0	0
<b>GENERAL SIGNS AND SYMPTOMS NEC</b>	17	11	6	4	6	10	1	2
<b>MUSCULOSKELETAL AND CONNECTIVE TISSUE SIGNS AND SYMPTOMS NEC</b>	17	11	2	1	9	15	1	2
<b>OEDEMA NEC</b>	17	11	1	1	6	10	1	2
<b>HERPES VIRAL INFECTIONS</b>	14	9	2	1	6	10	1	2
<b>UPPER RESPIRATORY TRACT SIGNS AND SYMPTOMS</b>	14	9	1	1	6	10	0	0

Adverse Event High Level Term	All Grades n=124		>Grade 3 n=34		DR All Grades n=49		DR > Grade 3 n=59	
	n	%	n	%	n	%	n	%
SEPSIS, BACTERAEMIA, VIRAEMIA AND FUNGAEMIA NEC	13	8	12	8	6	10	6	10
GASTROINTESTINAL AND ABDOMINAL PAINS (EXCL ORAL AND THROAT)	12	8	0	0	6	10	0	0
URTICARIAS	12	8	0	0	3	5	0	0
DISTURBANCES IN INITIATING AND MAINTAINING SLEEP	11	7	0	0	6	10	0	0
HEADACHES NEC	11	7	0	0	4	7	0	0
RATE AND RHYTHM DISORDERS NEC	11	7	2	1	5	8	1	2
INFECTIONS NEC	10	6	5	3	3	5	2	3
APOCRINE AND ECCRINE GLAND DISORDERS	9	6	0	0	3	5	0	0
BACTERIAL INFECTIONS NEC	9	6	0	0	3	5	0	0
MUSCLE RELATED SIGNS AND SYMPTOMS NEC	9	6	0	0	3	5	0	0
VASCULAR HYPERTENSIVE DISORDERS NEC	8	5	0	0	5	8	0	0
VASCULAR HYPOTENSIVE DISORDERS	8	5	0	0	2	3	0	0
ABDOMINAL AND GASTROINTESTINAL INFECTIONS	7	5	3	2	1	2	0	0
DERMAL AND EPIDERMAL CONDITIONS NEC	7	5	0	0	1	2	0	0
FUNGAL INFECTIONS NEC	7	5	2	1	4	7	2	3
PARAESTHESIAS AND DYSAESTHESIAS	7	5	0	0	3	5	0	0
PRURITUS NEC	7	5	0	0	3	5	0	0
SENSORY ABNORMALITIES NEC	7	5	0	0	2	3	0	0
URINARY TRACT INFECTIONS	7	5	2	1	2	3	1	2
APPETITE DISORDERS	6	4	0	0	3	5	0	0
JOINT RELATED SIGNS AND SYMPTOMS	6	4	0	0	3	5	0	0
NASAL CONGESTION AND INFLAMMATIONS	6	4	0	0	5	8	0	0
PERIPHERAL NEUROPATHIES NEC	6	4	0	0	3	5	0	0
BRONCHOSPASM AND OBSTRUCTION	5	3	1	1	3	5	1	2
EAR INFECTIONS	5	3	0	0	2	3	0	0
FLATULENCE, BLOATING AND DISTENSION	5	3	0	0	2	3	0	0
GASTROINTESTINAL ATONIC AND HYPOMOTILITY DISORDERS NEC	5	3	0	0	1	2	0	0
IMMUNE AND ASSOCIATED CONDITIONS NEC	5	3	1	1	3	5	0	0
PAIN AND DISCOMFORT NEC	5	3	0	0	4	7	0	0
PERIPHERAL VASCULAR DISORDERS NEC	5	3	0	0	1	2	0	0
POTASSIUM IMBALANCE	5	3	1	1	1	2	1	2
SUPRAVENTRICULAR ARRHYTHMIAS	5	3	1	1	1	2	1	2

Adverse Event High Level Term	All Grades n=154		≥ Grade 3 n=59		DR All Grades n=59		DR ≥ Grade 3 n=59	
	n	%	n	%	n	%	n	%
BONE RELATED SIGNS AND SYMPTOMS	4	3	0	0	3	5	0	0
DERMATITIS AND ECZEMA	4	3	0	0	2	3	0	0
DISTURBANCES IN CONSCIOUSNESS NEC	4	3	1	1	2	3	0	0
GASTROINTESTINAL SIGNS AND SYMPTOMS NEC	4	3	0	0	1	2	0	0
ISCHAEMIC CORONARY ARTERY DISORDERS	4	3	4	3	1	2	1	2
LYMPHATIC SYSTEM DISORDERS NEC	4	3	0	0	2	3	0	0
NEUROLOGICAL SIGNS AND SYMPTOMS NEC	4	3	0	0	0	0	0	0
NON-SITE SPECIFIC INJURIES NEC	4	3	2	1	0	0	0	0
PARANASAL SINUS DISORDERS (EXCL INFECTIONS AND NEOPLASMS)	4	3	0	0	2	3	0	0

The following table shows the results for the HLGT analysis. These HLGTs are non-granular terms that, in general, do not accurately describe a specific event that would be informative in the label. Nevertheless, because of the frequency of severe events (≥ 5% Grade 3 or higher in the general population), the following HLGTs were analyzed in more detail:

- The most common HLGT was infections (pathogen unspecified). In the infections section of the label, the overall incidence of infections is described; thus the label does not require amending to describe this HLGT.
- This HLGT “general ( ) disorders” includes disparate PTs including fatigue, ( ) ( ) Thus, this HLGT term is not appropriate for inclusion in the product label.
- Most of the AEs comprising the HLGT ( ) in study 406 were caused by neutropenia. Neutropenia is a better descriptive term than white blood cell disorders. Likewise anemia was the most common PT in the anemia HLGT category.

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**Table 60: Adverse Reactions in Study 406 by MedDRA High Level Group Term (HLGT)**

Adverse Events by High Level Group Term	All Grades n=154		≥ Grade 3 n=59		DR All Grades n=59		DR ≥ Grade 3 n=59	
	n	%	n	%	n	%	n	%
INFECTIONS - PATHOGEN UNSPECIFIED	95	62	42	27	37	63	19	32
RESPIRATORY DISORDERS NEC	59	38	4	3	24	41	3	5
GENERAL SYSTEM DISORDERS NEC	53	34	7	5	20	34	2	3
BODY TEMPERATURE CONDITIONS	45	29	4	3	20	34	3	5
EPIDERMAL AND DERMAL CONDITIONS	38	25	1	1	17	29	1	2
GASTROINTESTINAL SIGNS AND SYMPTOMS	35	23	0	0	15	25	0	0

GASTROINTESTINAL MOTILITY AND DEFAECATION CONDITIONS	31	20	0	0	12	20	0	0
WHITE BLOOD CELL DISORDERS	30	19	24	16	9	15	6	10
ANAEMIAS NONHAEMOLYTIC AND MARROW DEPRESSION	26	17	8	5	11	19	5	8
VIRAL INFECTIOUS DISORDERS	23	15	3	2	12	20	2	3
NEUROLOGICAL DISORDERS NEC	21	14	1	1	6	10	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS NEC	17	11	2	1	9	15	1	2
CARDIAC ARRHYTHMIAS	15	10	3	2	6	10	2	3
BACTERIAL INFECTIOUS DISORDERS	14	9	1	1	5	8	1	2
UPPER RESPIRATORY TRACT DISORDERS (EXCL INFECTIONS)	14	9	0	0	8	14	0	0
ANGIOEDEMA AND URTICARIA	12	8	0	0	3	5	0	0
FUNGAL INFECTIOUS DISORDERS	12	8	4	3	6	10	3	5
HEADACHES	12	8	0	0	5	8	0	0
MUSCLE DISORDERS	12	8	0	0	5	8	0	0
SLEEP DISORDERS AND DISTURBANCES	11	7	0	0	6	10	0	0
SKIN APPENDAGE CONDITIONS	9	6	0	0	3	5	0	0
DECREASED AND NONSPECIFIC BLOOD PRESSURE DISORDERS AND SHOCK	8	5	0	0	2	3	0	0
VASCULAR HYPERTENSIVE DISORDERS	8	5	0	0	5	8	0	0
ALLERGIC CONDITIONS	7	5	1	1	5	8	1	2
ELECTROLYTE AND FLUID BALANCE CONDITIONS	7	5	2	1	2	3	1	2
PERIPHERAL NEUROPATHIES	7	5	0	0	3	5	0	0
APPETITE AND GENERAL NUTRITIONAL DISORDERS	6	4	0	0	3	5	0	0
HAEMATOLOGY INVESTIGATIONS (INCL BLOOD GROUPS)	6	4	3	2	2	3	2	3
JOINT DISORDERS	6	4	0	0	3	5	0	0
URINARY TRACT SIGNS AND SYMPTOMS	6	4	0	0	0	0	0	0
BRONCHIAL DISORDERS (EXCL NEOPLASMS)	5	3	1	1	3	5	1	2
IMMUNE DISORDERS NEC	5	3	1	1	3	5	0	0
LOWER RESPIRATORY TRACT DISORDERS (EXCL OBSTRUCTION AND INFECTION)	5	3	1	1	1	2	0	0
OCULAR INFECTIONS, IRRITATIONS AND INFLAMMATIONS	5	3	0	0	4	7	0	0
VASCULAR DISORDERS NEC	5	3	0	0	1	2	0	0
BONE DISORDERS (EXCL CONGENITAL AND FRACTURES)	4	3	0	0	3	5	0	0
BONE, CALCIUM, MAGNESIUM AND PHOSPHORUS METABOLISM DISORDERS	4	3	1	1	1	2	1	2
CORONARY ARTERY DISORDERS	4	3	4	3	1	2	1	2
DENTAL AND GINGIVAL CONDITIONS	4	3	0	0	3	5	0	0
INJURIES NEC	4	3	2	1	0	0	0	0

ORAL SOFT TISSUE CONDITIONS	4	3	0	0	0	0	0	0
SPLEEN, LYMPHATIC AND RETICULOENDOTHELIAL SYSTEM DISORDERS	4	3	0	0	2	3	0	0

**Study 402**

Table 61 shows the incidence of adverse reactions by MedDRA preferred term (version 6.0) that were derived from the datasets provided by GSK. Adverse events occurring in 5% or more of patients in Group C (2,000 mg cohort) are listed. The following adverse events occurred more frequently in study 402 (Group C) than in study 406 [only those AEs occurring at a 5% or greater (absolute) incidence rate between studies are included]: rash, rigors, headache, sweating increased, arthralgia, dizziness, flushing, somnolence, tinnitus, gastroenteritis, influenza, and palpitations. All but two of these AEs in study 402 were Grade 2 or less (there were two episodes of ≥ Grade 3 dizziness). Most of these adverse events including rash, headache, and rigors were infusion related. *This reviewer notes that the doses of glucocorticoids were increased in study 406 compared to that originally specified in the 402 protocol.*

**Table 61: Adverse Reactions in Study 406 by MedDRA Preferred Term (PT)**

Adverse Event Preferred (MedDRA V 6.0)	Group A % N=3	Group B % N=3	Group C % N=27	Group C ≥ Grade 3 % N=27
RASH NOS	33	0	33	0
RIGORS	33	33	30	0
FATIGUE	100	0	19	0
PYREXIA	33	33	19	7
DYSPNOEA	0	33	15	0
HEADACHE	67	0	15	0
SWEATING INCREASED	33	0	15	0
ARTHRALGIA	0	0	11	0
DIARRHOEA NOS	0	0	11	0
DIZZINESS	33	0	11	4
FLUSHING	33	0	11	0
NASOPHARYNGITIS	33	33	11	4
SOMNOLENCE	33	0	11	0
TINNITUS	0	0	11	0
URTICARIA NOS	0	33	11	0
BACK PAIN	0	0	7	0
BODY TEMPERATURE INCREASED	0	0	7	0
COUGH	0	0	7	0
DRY MOUTH	0	0	7	0
GASTROENTERITIS NOS	0	0	7	0
HYPERTENSION NOS	0	0	7	0
HYPOTENSION NOS	0	33	7	0
INFLUENZA	0	0	7	0

Adverse Event Preferred (MedDRA V 6.0)	Group A % (N=3)	Group B % (N=3)	Group C 1% (N=27)	Group C 2 Grade 3 % (N=27)
INSOMNIA	0	0	7	0
NEUTROPENIA	0	0	7	7
PALPITATIONS	0	0	7	0
PARAESTHESIA	0	33	7	0
SINUSITIS NOS	0	0	7	0
THROMBOCYTOPENIA	0	33	7	7
UPPER RESPIRATORY TRACT INFECTION NOS	0	0	7	0
VOMITING NOS	0	0	7	0

## 7.4.2 Laboratory Findings

### Biochemistry

In the CSR for study 406, GSK indicated that biochemistry parameters (albumin, alkaline phosphatase, creatinine, glucose (random), alanine aminotransferase, potassium, sodium, and uric acid) were measured at screening, baseline, every four weeks during the treatment period, and every three months during follow-up (for up to two years). GSK indicated that “marked outliers” were considered to be any biochemistry value  $\geq$  Grade 3 in severity (NCI CTCAE). In addition to the laboratory results for scheduled visits, the BIOCHEM dataset contained results for up to four unscheduled visits per patient. *Comment: In the opinion of this reviewer, the biochemistry monitoring was not optimal for an NME because the first biochemistry assessment occurred one month following the first dose of ofatumumab. The monitoring schedule employed by the protocol may have missed early signs of tumor lysis syndrome. Additionally, calcium and phosphorus levels were not monitored during the conduct of study Hx-CD20-406; thus, additional early signs of tumor lysis syndrome may have been missed.*

*In regards to the adequacy of hepatic monitoring, only indirect bilirubin was measured during the 406 and 402 studies. In the CLL population, direct bilirubin levels should have been measured in order to exclude hemolysis (or Gilbert’s syndrome) as possible causes of hyperbilirubinemia.*

*Additional Note: The laboratory datasets provided by GSK did not have a separate column specifying baseline labs. Thus, there were (minimal) differences in the shift-table results between FDA and GSK analyses. The differences in numbers did not appear to affect the overall safety profile of ofatumumab for any of the labs reviewed. The shift tables in this review also contain the results submitted by GSK in the CSR.*

### Sodium

GSK submitted sodium results in mmol/L. The lower limit of normal in the 406 BIOCHEM dataset was 133 mmol/L, and the upper limit of normal was 145 mmol/L. During study 406, three subjects experienced  $\geq$  Grade 3 sodium abnormalities ( $< 130$  mmol/L or  $> 155$  mmol/L).

No subjects experienced Grade 2 hyponatremia (CTCAE version 3 does not have a Grade 2 designation for hyponatremia). All  $\geq$  Grade 3 sodium abnormalities post-baseline involved low sodium levels and all occurred towards the end of study drug therapy (week 12, week 16, and month 9 visits).

#### *Potassium*

Grade 2 or higher potassium abnormalities contained in the BIOCHEM dataset were evaluated (occurring after visit 2). One patient had a Grade 2 low potassium level at week 8. Twelve patients experienced Grade 2 or higher potassium levels during the 406 study. One patient had a Grade 2 potassium elevation at week four and one patient had a potassium elevation at week 8. Other  $\geq$  Grade 2 potassium elevations occurred at week 12 or later. GSK provided narrative summaries for patients who had baseline Grade 0-2 hyperkalemia that progressed to Grade 3 or 4 hyperkalemia during the 406 trial (n=4). No cardiac events were associated with these episodes of hyperkalemia. Each event was a single increased potassium level that returned to normal limits by the subsequent visit.

In study 402, there was one potassium measurement of 7.0 mmol/L in the 2,000 mg dose group that occurred during the four week ofatumumab treatment period.

*Comment: Because potassium levels were not measured consistently during the first week after ofatumumab treatment, clinically significant potassium levels associated with TLS cannot be ruled out.*

#### *Glucose*

No post-baseline glucose levels that were CTCAE Grade 3 or above  $> 250$  mg/dl were contained in the BIOCHEM dataset. Seven patients who had Grade 0 glucose levels at baseline had Grade 1 or 2 glucose levels measured during the course of study 406 (five Grade 1 and two Grade 2 high glucose levels). *Comment: Hyperglycemia did not appear to be associated with ofatumumab. However, corticosteroids are administered as pre-medication prior to the administration of ofatumumab. Thus, hyperglycemia may have occurred more frequently than described in the BIOCHEM dataset as glucose levels were not obtained in the 24 hour period following ofatumumab administration.*

#### *Uric Acid*

The BIOCHEM dataset submitted by GSK contained uric acid values in mmol/L. The normal range for uric acid levels in the BIOCHEM dataset was 0.15 to 0.35 mmol/L for women and 0.21 to 0.41 mmol/L for men. The NCI CTCAE specified that Grade 3 uric acid abnormalities are associated with physiological consequences and that Grade 4 elevations occur at a uric acid level above 0.59 mmol/L. The dataset did not indicate whether patients did in-fact experience physiological consequences associated with hyperuricemia. *Comment: GSK stated on March 17, 2009 that they took a conservative approach to uric acid measurements and classified all uric acid elevations as Grade 3 if they were less than 0.59 mmol/L whether or not physiological consequences occurred. Thus, most of these events were probably Grade 1 in nature. GSK indicated that no patients experienced signs or symptoms of hyperuricemia including gout, renal insufficiency, arrhythmias, or seizures. Table 62 shows results for patients with baseline Grade 0*

uric acid levels who progressed to Grade 3 or 4 (32% of 114 patients). The results for this analysis using the BIOCHEM dataset differs slightly from the GSK results provided in the 406 CSR. The differences did not appreciably alter the safety profile of the drug.

Increased uric acid levels were observed throughout the study and there was not a predominance of increased uric acid levels at visit 6 (the first post-baseline visit). Five instances of increased uric acid levels occurred at visit 6 (among patients with baseline Grade 0 levels) and 10 instances of increased uric acid levels occurred at visit 10. *Comment: Because uric acid levels were not measured during the first week after treatment with ofatumumab, this reviewer cannot rule out early hyperuricemia associated with tumor lysis.*

In general, the shift table submitted by GSK for the 402 study was consistent with the results of the 406 study. Five of 19 patients who had baseline Grade 0 uric acid levels developed Grade 3 hyperuricemia according to the applicant. Two instances of Grade 4 hyperuricemia occurred; however, the two patients had Grade 3 hyperuricemia at baseline.

**Table 62: Shift Table of Uric Acid Levels (mmol/L) by CTCAE Grade (Study 406)\***

Baseline CTCAE Grade	Maximum CTCAE Grade		
	0	3	4
0	82 (81)	31	1
3	5	23	5
4	0	1	0

\* The data included in the GSK CSR are included in parentheses when they differed from the FDA analysis using JMP.

In the 90 day safety update, GSK provided an additional response to the FDA query dated March 6, 2009 regarding whether elevated uric acid levels were accompanied by physiological consequences. GSK submitted two analyses using a programmed algorithm to identify patients with elevated uric acid levels who had physiological consequences. Using the more conservative analysis, GSK identified three patients with Grade 3 elevated uric acid levels at the time of the BLA submission and 5 patients with Grade 3 elevated uric acid levels at the time of the safety update who possibly had physiological consequences associated with hyperuricemia.

***Creatinine***

GSK submitted creatinine values measured in umol/L, and the upper limit of normal was considered 102.9 umol/L for men and 84.9 umol/L for women.

Table 63 and Table 64 show the mean and median creatinine values by visit for the 406 study population from visit 2 (baseline visit) to visit 16 (~ four months following the last dose). In general, creatinine values did not increase in a clinically significant manner from visit to visit. A trend upward was observed in the mean creatinine values for the final two visits; however, the number of patients observed at these time-points was notably fewer than at the start of treatment.

Figure 14 and Figure 15 show scatter-plots of per-patient values from baseline creatinine to maximum creatinine. The plots are near linear, with at least two outliers (both Grade 2) in the scatter-plot of male patients. One of the patients with Grade 2 creatinine elevation (patient 406197) experienced the creatinine elevation at week 10. The other patient had a creatinine value of 229 umol/L (patient 406161) during the week 16 visit.

No elevations in creatinine above Grade 2 were observed in the dataset for study 406. Table 65 is a shift table derived from the BIOCHEM dataset submitted by GSK. The clinical study report for study 402 contained a shift table for creatinine values. No creatinine values  $\geq$  Grade 2 were observed in the study 402 shift tables.

In summary, severe renal toxicity was not observed during the course of studies 402 or 406. A small number patients did experience elevations in creatinine with three patients having normal values at baseline and progressing to Grade 2. One event was considered to be Grade 2 renal failure in the CRF. *Comment: Despite the absence of severe renal failure, the 406 study was too small to rule out drug related renal failure as a rare event. Furthermore, the 406 protocol did not mandate biochemistry evaluations until one month after the first dose. This protocol design may have missed early signs of TLS in this population of patients.*

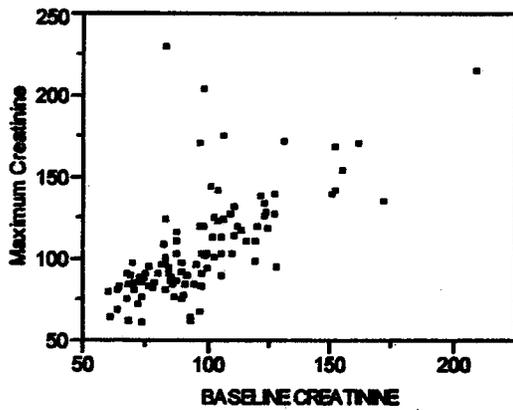
**Table 63: Mean Creatinine by Visit (umol/L)**

SEX	VISIT 02	VISIT 06	VISIT 10	VISIT 11	VISIT 12	VISIT 13	VISIT 14	VISIT 15	VISIT 16
N with a creatinine measured	153	140	131	118	107	92	86	69	35
Creatinine (Female)	74.5	73.9	77.1	71.3	70.5	69.4	69.6	72.2	75.0
Creatinine (Male)	96.5	89.0	93.3	89.1	91.0	89.0	88.5	91.7	99.0

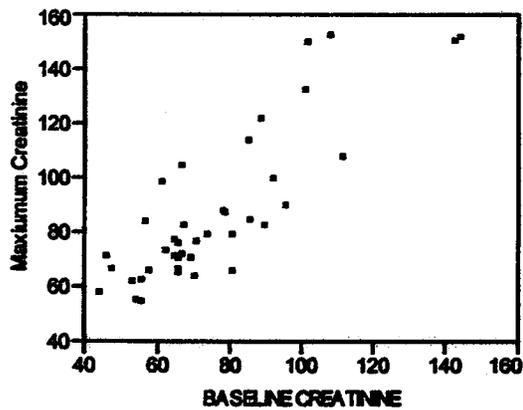
**Table 64: Median Creatinine by Visit (umol/L)**

SEX	VISIT 02	VISIT 06	VISIT 10	VISIT 11	VISIT 12	VISIT 13	VISIT 14	VISIT 15	VISIT 16
N with a creatinine measured	153	140	131	118	107	92	86	69	35
Creatinine (Female)	67.2	70.3	73.4	70.7	66.8	65.4	61.9	66.8	72.5
Creatinine (Male)	92.8	82.2	84.9	82.2	85.7	83.1	84.9	88.4	84.9

**Figure 14: Scatter-plot of Baseline versus Maximum Creatinine Value for Men (in umol/L)**



**Figure 15: Scatter-plot of Baseline versus Maximum Creatinine Value for Women (in umol/L)**



**Table 65: Shift Table of Creatinine Levels by CTCAE Grade**

Baseline CTCAE Grade	Maximum CTCAE Grade		
	0	1	2
0	87 (86)	14	3
1	7	25	6
2	0	2	4

\* The data included in the GSK CSR are included in parentheses when they differ from the FDA analysis using JMP.

**Immunoglobulins**

Immunoglobulin levels (measured in g/L) were evaluated during study 406 at screening, week 16 (visit 12), and month 9 (visit 16).

The normal range for IgA described in the BIOCHEM dataset was 0.7 to 4.0 g/L. For IgG, the normal range of values in the BIOCHEM dataset was 6.5 to 16 g/L. For IgM, the normal range of values in the BIOCHEM dataset was 0.5 to 3 g/L.

Table 66 shows that the median immunoglobulin levels for the study population was below the lower limit of normal for all visits including the screening visit. *Comment: Patients with CLL have underlying immunosuppression and hypogammaglobulinemia related to the underlying disease and due to the effects of prior treatments (in this study fludarabine +/- alemtuzumab).*

In this analysis of immunoglobulin levels, median values for IgA and IgM levels are approximations due to numerous values in the dataset being below the lower level of detection. The following conversion was performed in order to conduct the analyses in Table 66, Figure 16, Figure 17, and Figure 18: when a lab result in the dataset was listed as a character value (i.e., "< 0.24"), it was converted to a numeric value that was 0.01 g/L below the stated character value (for example, the character value "< 0.24" was converted to 0.23).

Figure 16, Figure 17, and Figure 18 show the variability in immunoglobulin levels by visit. The blue solid line across the visits represents the mean immunoglobulin levels. Table 66 describes the number of patients per visit with immunoglobulin values presented in the three figures below. *The figures show that, in general, mean immunoglobulin levels are reduced after ofatumumab treatment; however, no definitive conclusions can be made regarding immunoglobulin levels after ofatumumab treatment because the baseline levels of immunoglobulins were below the lower limit of normal.*

**Table 66: Median Immunoglobulin Levels by Visit**

	Visit 1 (Screening)		Visit 12		Week 16	
	N	Median	N	Median	N	Median
Median IgA (g/L)	153	0.39	107	0.39	34	0.39
Median IgG (g/L)	153	5.1	107	4.27	34	4.14
Median IgM (g/L)	152	0.31	106	0.21	34	0.19

Figure 16: Variability Chart for IgA in g/L

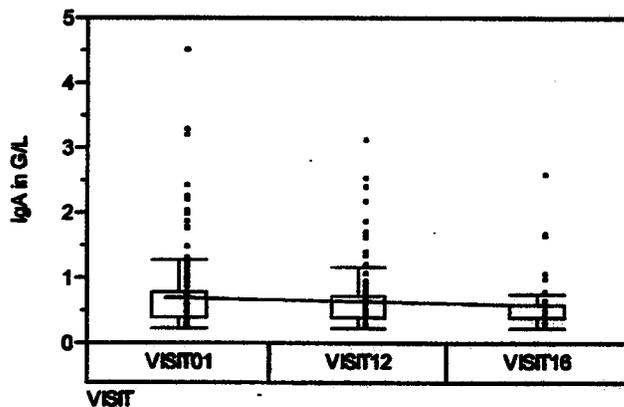


Figure 17: Variability Chart for IgG in g/L

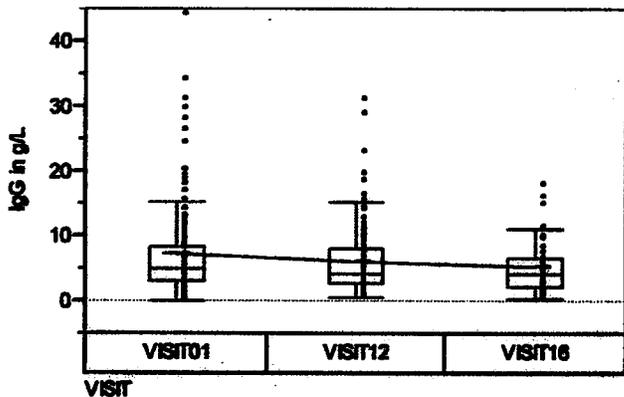
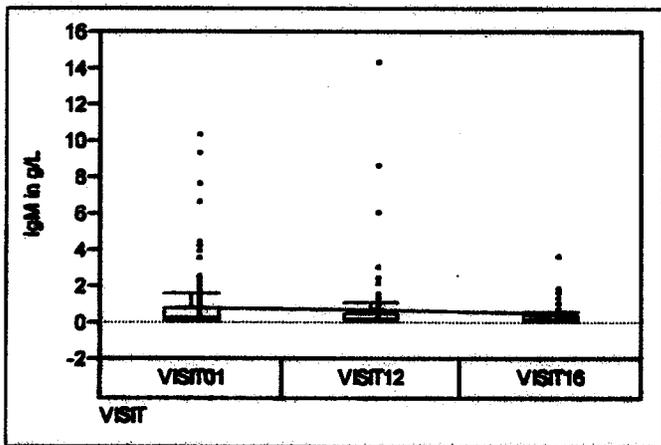


Figure 18: Variability Chart for IgM in g/L



**Hy's Law [(Alanine Aminotransferase (ALT) and Bilirubin)]**

A review of the dataset found no cases of Hy's law that occurred after screening or baseline visits. This review used a broad search strategy to include all patients with  $\geq$  Grade 2 ALT ( $> 2.5 \times$  ULN) and bilirubin elevations ( $>1.5 \times$  ULN) that occurred at the same time-point.

**ALT**

For ALT measurements, GSK assigned the range of normal values from 1 to 30 U/L for women and 1 to 39 U/L for men. Table 67 shows shifts in ALT values for patients who had both a baseline lab result and at least one post-baseline result as derived from the BIOCHEM dataset. There was one patient (116) without a baseline lab-value at week two who had a Grade 3 ALT elevation at week 16 and progressed to Grade 3 ALT elevation at week 20. This patient had liver enlargement at baseline and a subsequent elective liver biopsy showed fibrosis and steatosis in the liver and mantle cell lymphoma (with lymphoma lesions in the liver).

In regards to patients with Grade 2 ALT elevations, the following were observed during this review. Patient 103 experienced one instance of Grade 2 ALT elevation at the time of progressive disease. Patient 147 experienced Grade 2 ALT at week 16, and the ALT improved to normal at the time of the next scheduled visit. Patient 149 experienced an increased ALT at baseline and the ALT fluctuated between Grade 1 and 2 throughout the study. Patient 164 experienced Grade 2 ALT during week 12 that improved to Grade 1 at week 16. Patient 239 experienced one episode of Grade 2 ALT elevation that subsequently improved to normal.

In summary, there were no instances of life-threatening ALT elevations or sustained elevations of ALT that were Grade 2 or above during the course of the 406 study. The interpretation of causality of minor increases in ALT in this patient population is complicated by the underlying disease (hepatomegally is common in CLL) and other co-morbid conditions (or medications).

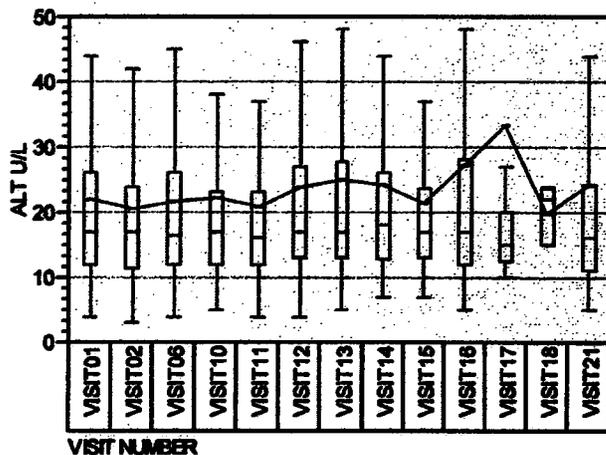
**Table 67: Shift Table of ALT Levels by CTCAE Grade\***

Baseline CTCAE Grade	Maximum CTCAE Grade			
	0	1	2	3
0	105 (104)	19	5	1
1	6	10	1	0
2	0	1	0	0

\* The data included in the GSK CSR are included in parentheses when they differ from the FDA analysis using JMP.

Figure 19 shows that median ALT values did not markedly fluctuate over time. The mean values increased at the week 16 and 17 visits; however, there were fewer data-points at these visits.

Figure 19: ALT Values by Visit



Visit													
# Observations	151	153	140	131	118	107	92	86	69	35	17	5	86

**Bilirubin**

Table 68 shows shifts in bilirubin values during study 406. The shift-table shows that few patients experienced elevated bilirubin levels. Because bilirubin was not fractionated, the cause of these patients' hyperbilirubinemia cannot be accurately determined (for example, hepatic versus hemolysis). Note that the maximum value for normal bilirubin was considered to be 18.7 umol/L.

Patient 205 experienced Grade 2 bilirubin elevation during the week 12 visit followed by Grade 2 or 3 elevated bilirubin levels during the rest of the study. This patient's elevated bilirubin was not associated with increased ALT levels or alkaline phosphatase levels. LDH levels were not uniformly elevated and haptoglobin levels were not uniformly low during this period, so the cause of this patient's elevated hyperbilirubinemia was not clear. This patient's bilirubin returned to normal by the end of the study.

There were five additional patients with normal baseline bilirubin levels who experienced Grade 2 bilirubin abnormalities during study follow-up. Patient 151 had normal bilirubin levels until week 28. Patient 156 had a normal bilirubin at baseline but had Grade 1 levels throughout the trial except for Grade 2 hyperbilirubinemia during week 16. Patient 162 did not experience Grade 2 hyperbilirubinemia until week 28. Patient 206 had normal bilirubin levels until week 20.

In summary, sustained elevations in bilirubin levels  $\geq$  Grade 3 in severity were not observed during the conduct of study 406. Most patients who experienced Grade 2 abnormalities did so after being enrolled in the study for more than four months.

**Table 68: Shift Table of Bilirubin by CTCAE Grade\***

Baseline CTCAE Grade	Maximum CTCAE Grade			
	0	1	2	3
0	117 (116)	12	5	1
1	2	3	3	0
2	1	2	2	0

\* The data included in the GSK CSR are included in parentheses when they differ from the FDA analysis

**Alkaline Phosphatase**

Mild elevations (Grade 1) of alkaline phosphatase were observed during the conduct of study 406; however only one patient experienced a post-baseline alkaline phosphatase that was  $\geq$  Grade 2 who had a baseline level of Grade 1 or below. Additionally, the GSK shift-table for study 402 was reviewed. No patient in study 402 had a  $\geq$  Grade 2 alkaline phosphatase level post-baseline.

**Table 69: Shift Table of Alkaline Phosphatase by CTCAE Grade\***

Baseline CTCAE Grade	Maximum CTCAE Grade			
	0	1	2	3
0	84 (83)	25	1	0
1	14	21	0	0
2	0	1	0	0
3	0	0	1	1

\* The data included in the GSK CSR are included in parentheses when they differ from the FDA analysis using JMP.

**Hematology**

During the conduct of study 406, hematology labs were to be obtained weekly for the first eight weeks, followed by monthly labs until week 28. Hematology labs were then obtained every three months until month 24. The hematology lab panel consisted of a white cell count with differential (lymphocytes, neutrophils, eosinophils, monocytes, and basophils), hemoglobin, hematocrit, reticulocytes, and platelets.

*Note that the previous comment in the biochemistry review section pertaining to differences in results presented in shift tables also pertains to the hematology section of this review. The differences in number of events were minimal and did not appear to affect the overall safety profile of ofatumumab for any of the labs reviewed.*

*The hematology section of GSK's CSR included results of improvements in cell counts for some hematology parameters. Because this section of the FDA review focuses on safety, analyses of lab results in this section will be limited to the review of worsening cell counts over time.*

**Lymphocytes**

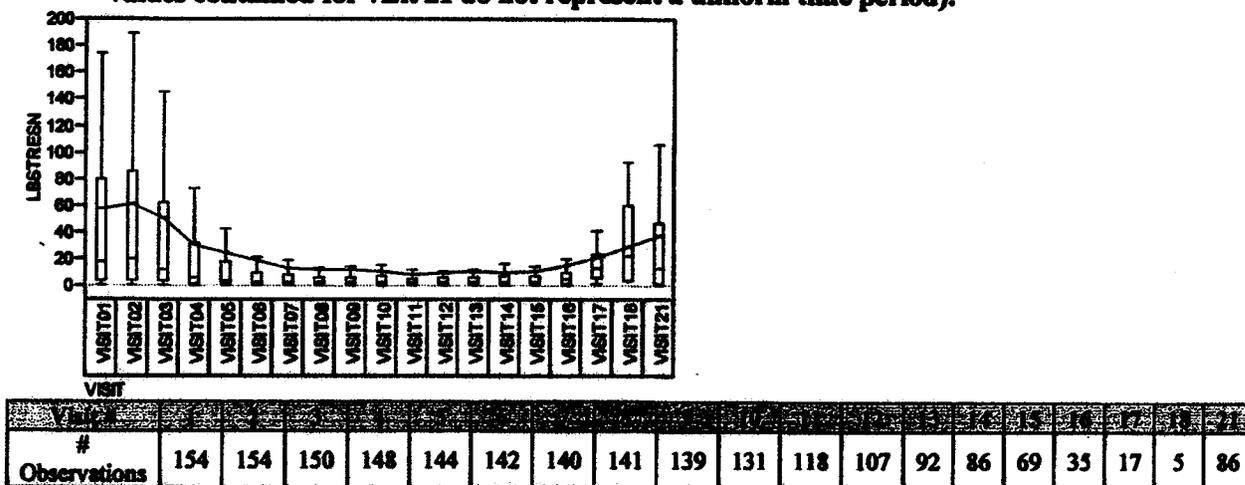
**Comment:** *The review of lymphocytes in this application is complicated by the following:*

- *Prolonged lymphocytopenia is a known and expected pharmacodynamic effect of anti-CD20 antibodies (for example, rituximab).*
- *The basic hematology panel cannot differentiate what proportion of the lymphocyte count consists of normal lymphocytes versus monoclonal lymphocytes related to the underlying malignancy. The normal lymphocyte range was specified in the 406 dataset as 1,500 to 4,000 cells per mm<sup>3</sup>. Because these lymphocytes may be malignant, recovery to normal does not necessarily mean that normal lymphocytes have returned in the patients' circulation. Flow cytometry is required to determine recovery of normal B-cell counts versus malignant cells.*

As discussed above, an analysis of lymphocyte counts in CLL is complicated by the underlying disease. Nevertheless, the variability chart in Figure 20 shows that median lymphocyte counts appeared to decrease after visit 2 (the first visit that ofatumumab was administered). The median lymphocyte counts were observed to start rising at approximately visit 17 (and possibly after visit 16). Visit 17 occurred about 6 months following the end of ofatumumab treatment. This prolonged lymphocyte depleting effect is consistent with the known lymphocytopenia associated with rituximab.

**Figure 20: Variability Chart by Week for Lymphocyte Counts (Study 406)**

**Y axis = lymphocyte count X 1,000/mm<sup>3</sup>. The blue line represents mean values with the box plot representing median values and intra-quartile ranges. (Note that visit 21 was the visit at the end of the follow-up period or following progression; thus, the values contained for visit 21 do not represent a uniform time period).**

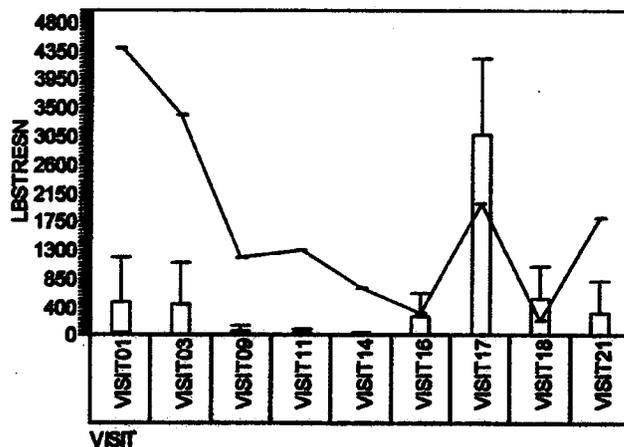


Because the lymphocyte counts in Figure 20 were composed of normal B-cells, T-cells, and malignant cells, a separate analysis of GSK's flow cytometry dataset was performed for the population of B-cells that were CD45+, CD5-, and CD19+. Figure 21 shows the variability in

CD45+, CD5-, and CD19+ B-cells over time (note that the units in the y-axis differ from Figure 20). Mean cell counts by week represented by the blue line were affected by outliers (points not visible in the figure). The median values for this cell population were close to zero immediately after ofatumumab treatment. This median count was influenced by the number of patients without lymphocytosis at baseline.

Some patients had large CD45, CD5- and CD19+ cell populations despite ofatumumab treatment. It was not clear if these patients had refractory malignant prolymphocyte populations that were not reduced in number by ofatumumab.

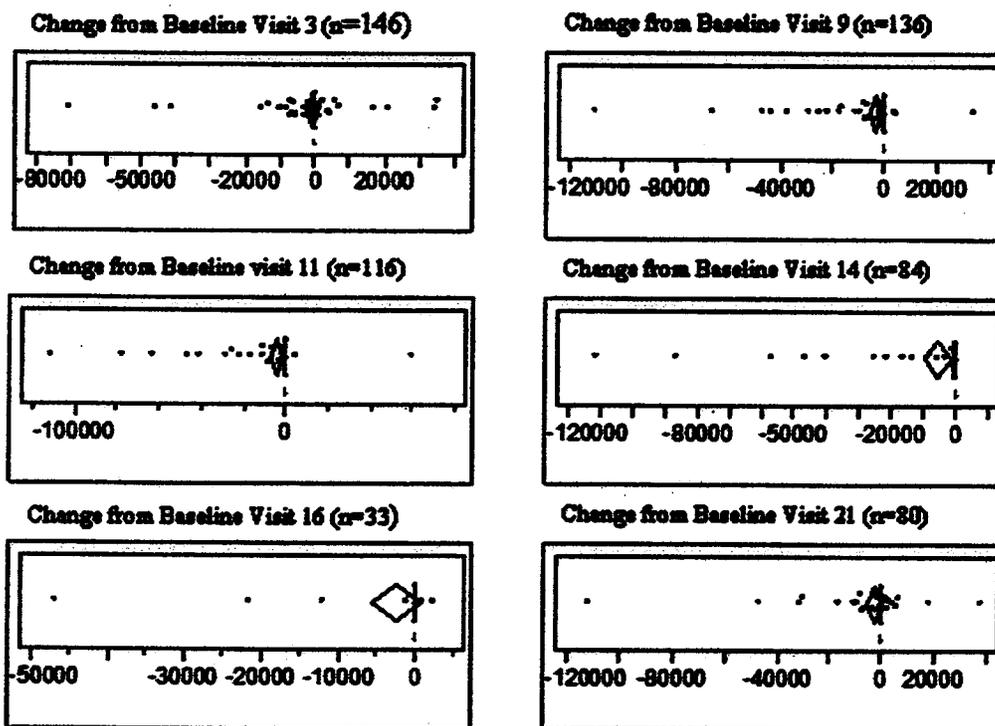
Figure 21: Variability Chart for CD45+, CD5-, CD19+ cells in cell/mm<sup>3</sup>



Visit									
# Observations	155	150	139	118	86	35	17	5	86

Figure 22 also shows that the CD45+, CD19+, CD5- cell populations remained below baseline through visit 17. The numbers of patients in Figure 21 and Figure 22 differ because the analysis in Figure 22 was a paired analysis. The paired analysis required a data-point at visit one and an additional data-point at the subsequent visit shown in the figure. The median CD45+, CD19+, CD5- counts were 0 during visits 16, 17, and 18 (one month, four months, and seven months) following the last scheduled dose of ofatumumab. Figures for visits 17 and 18 were not shown below because they included only 17 and 5 patients respectively.

Figure 22: Per Visit Variations in Per-Patient Differences in CD45+, CD5-, CD19+ Cell Counts Compared to Baseline



*Comment: In summary, lymphocyte and CD45+, CD5-, and CD19+ cells appear to be reduced in number following ofatumumab therapy. Normal B-cell recovery may take up to six months or longer in some patients.*

#### **Eosinophils**

Hyper eosinophilia was infrequently observed during study 406 in patients who had normal eosinophil counts at baseline. Patient 153 experienced an elevated eosinophil count during weeks 7 and 8 that normalized by week 12. Two patients experienced elevated eosinophil counts (157 and 115) at visit 21 (over one year following the end of ofatumumab treatment). Patients 162 and 164 experienced unsustained elevated eosinophil counts during week 8 and weeks 5-6, respectively. *Comment: No safety signal of severe or sustained hyper eosinophilia was observed in study 406.*

#### **Platelets**

GSK defined the normal range of platelets as 144,000/mm<sup>3</sup> to 440,000/mm<sup>3</sup>. The risk of spontaneous life-threatening hemorrhage is elevated in patients with Grade 4 thrombocytopenia (less than 25,000/microliter) and is greatest in patients with a platelet count less than 10,000/microliter (Rebulla et al., 1997). Nevertheless, less severe thrombocytopenia may also be

important for certain patients based on other factors, such as requirements for surgery, presence of a lesion at risk for bleeding (for example, gastrointestinal ulcer), or coagulopathy. Platelets of at least 50,000/microliter are considered necessary for major surgery (Schiffer et al., 2001), although higher platelets may be required for neurosurgery. Grade 3 thrombocytopenia is defined as less than 50,000 platelets per microliter.

Table 70 shows the number of patients who developed worsening thrombocytopenia during the 406 study. For comparison, Table 71 shows the number of patients in the 2,000 mg cohort of the 402 study who developed worsening thrombocytopenia. Of 101 patients in study 406 with baseline Grade 0 or Grade 1 platelet counts at baseline, 7 developed  $\geq$  Grade 3 thrombocytopenia (7%) and 2 developed Grade 4 thrombocytopenia (2%).

**Table 70: Shift Table of Platelets by CTCAE Grade (Study 406)**

Baseline CTCAE Grade	Highest Post-Baseline CTCAE Grade				
	0	1	2	3	4
0	17	24	0	1	0
1	1	42	10	4	2
2	0	2	11	9	2
3	0	1	1	9	7
4	0	0	0	1	9

**Table 71: Shift Table of Platelets by CTCAE Grade for Study 402 in the 2,000 mg dose cohort (Copied from Study 402 CSR)**

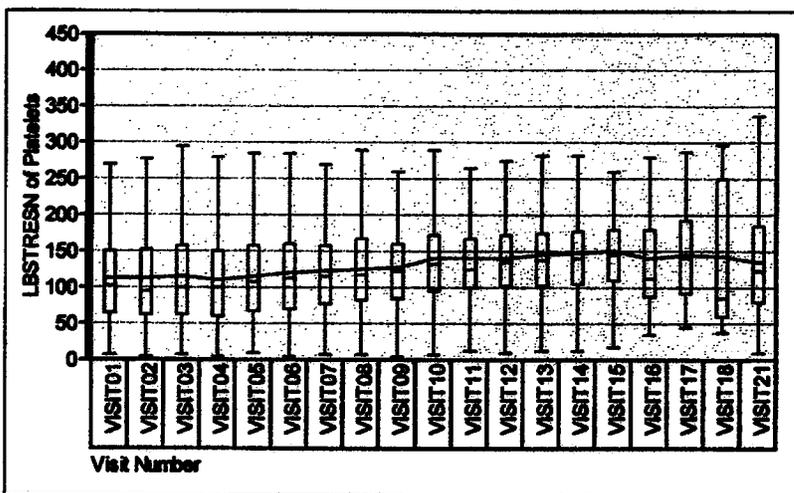
Baseline CTCAE Grade	Highest Post-Baseline CTCAE Grade				
	0	1	2	3	4
0	14	4	0	0	0
1	1	5	1	1	0
2	0	0	0	1	0
3	0	0	0	0	0
4	0	0	0	0	0

Because Grade 4 thrombocytopenia is considered life-threatening, an analysis of patients who experienced Grade 4 thrombocytopenia was conducted. Twenty patients developed Grade 4 thrombocytopenia. However, only four patients with Grade 2 or less thrombocytopenia at baseline developed Grade 4 thrombocytopenia. Patient 141 had Grade 2 thrombocytopenia at baseline and progressed to Grade 4 during week 2 of the study (71,000 to 21,000/microliter). This patient had suspected Richter's transformation and was taken off study due to new CLL treatment. Patient 143 had Grade 1 thrombocytopenia at baseline and progressed to Grade 4 at the month 18 visit. This patient's severe thrombocytopenia was unlikely to have been caused by ofatumumab because treatment had ceased over one year prior to the event. Patient 170 had Grade 2 thrombocytopenia at baseline (52,000/microliter) that progressed to Grade 4 for one visit

(week 4) and otherwise stayed in the 30 to 45,000/microliter range during the remainder of the study. Patient 211 had Grade 1 thrombocytopenia at screening that progressed to Grade 4 at week 12 for an indeterminate amount of time. Patient 211 was considered to have progressive disease at the time of Grade 4 thrombocytopenia.

Figure 23 shows that mean (solid blue line) and median platelet counts did not decrease over time.

Figure 23: Platelet Counts by Visit (Study 406)



Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	
# Observations	150	151	149	145	140	140	139	139	139	130	117	107	90	85	67	35	17	5	85			

*Comment: Life threatening (Grade 4) thrombocytopenia was infrequently observed during the 406 study. Approximately 6% of patients experienced a  $\geq 2$  Grade increase in thrombocytopenia by CTCAE. For patients with baseline Grade 2 or less thrombocytopenia, instances of Grade 4 thrombocytopenia (n=4) could be attributed to causes other than ofatumumab. Because study 406 was non-comparative, definitive conclusions regarding whether thrombocytopenia may be caused by ofatumumab cannot be made.*

#### Neutrophils

Neutropenia is a known complication of anti-CD20 therapy and this adverse reaction is included in the rituximab label (occurring in 6% of patients receiving rituximab monotherapy for NHL). Furthermore, increased rates of neutropenia were observed when rituximab was combined with chemotherapy (compared to control arms without rituximab).

Additionally, a distinct entity of delayed onset neutropenia after rituximab treatment has been described in multiple literature reports. Dunleavy et al., (2005) found that 6 of 76 patients who received rituximab developed late onset neutropenia at a median onset of 175 days. The median duration of neutropenia was 14 days in this report. The authors found that late-onset neutropenia

may have been caused by perturbations in stromal derived factor-1 caused by rapid B-cell recovery following prolonged rituximab related lymphopenia. Tesfa et al., (2008) however found that 8 of 113 lymphoma patients developed late-onset neutropenia at a median 88 days after the last rituximab dose (range 1-9 months). Tesfa et al., found that late-onset neutropenia was associated with maturation arrest of granulopoiesis at the promyelocyte stage. The median duration of the late onset neutropenia was 54 days in this group. A third group (Terrier et al., 2007) found that late-onset neutropenia was caused by hematopoietic lineage competition due to excessive BAFF-induced B-cell recovery. Other theories proposed for rituximab-associated late-onset neutropenia included infection and immune related causes (McLaughlin 2006 and Christopheit 2008). Notably the incidence rate of late-onset neutropenia varied depending on the cut-off points for neutropenia, the underlying disease, and the choice of concomitant chemotherapy regimens. Nitta et al., (2007), observed a late-onset neutropenia incidence rate of 24.9% among 107 patients (median 106 days following chemotherapy).

Because neutropenia is caused by CLL, effects of ofatumumab on neutrophil levels are difficult to interpret in a single-arm study. Neutropenia can occur in patients with CLL through either bone marrow dysfunction or autoimmune causes (Dearden, 2008).

GSK defined the normal range of neutrophils as  $1,700/\text{mm}^3$  to  $8,800/\text{mm}^3$ . GSK's conclusion in the 406 CSR regarding neutrophil counts was that ofatumumab was associated with a decrease in neutrophil counts and that the decreased counts appeared to be mild and occurred relatively early after initiation of ofatumumab treatment. Table 72 shows that of 109 patients with normal neutrophil counts at baseline, 26 (24%) and 20 (18%) developed Grade 3 or 4 neutropenia, respectively during the 406 clinical trial. For comparison across trials, Table 73 shows GSK's derived shift tables from study 402 (2,000 mg dose cohort). *Comment: Based on these results, this reviewer does not agree with the conclusion that decreases in neutrophil counts were usually mild.*

The difference between the GSK and FDA analyses in Table 72 is attributable to patient 162. The baseline value at visit 2 for this patient was 0.0/mcL; however, the neutrophil count was 9,000/mcL two weeks earlier at screening and 11,400/mcL one week following treatment with ofatumumab. The patient subsequently had two additional values of 0.0/mcL at visits 5 and 6, followed by a neutrophil count of 1,400/mcL on visit 7. Per the CRF, this patient did not receive myeloid growth factors. Because the value of 0.0/mcL at baseline was not consistent with screening or week 1 labs (and there was a comment in the dataset regarding an issue with the baseline lab sample), the screening value was used for the FDA analysis.

**Table 72: Shift Table of Neutrophils by CTCAE Grade (study 406)**

Baseline CTCAE Grade	Highest Post-Baseline CTCAE Grade				
	0	1	2	3	4
0	28	8	27	26	20 (19)
1	1	1	1	2	0
2	0	0	2	11	2
3	0	1	1	4	6
4	0	0	0	2	10 (11)

\* The data included in the GSK CSR are included in parentheses when they differ from the FDA analysis.

**Table 73: Shift Table of Neutrophils by CTCAE Grade for Study 402 in the 2,000 mg dose cohort (Copied from Study 402 CSR)**

Baseline CTCAE Grade	Highest Post-Baseline CTCAE Grade				
	0	1	2	3	4
0	12	1	7	2	3
1	1	0	0	0	0
2	0	0	0	0	0
3	1	0	0	0	0
4	0	0	0	0	0

In order to characterize ofatumumab-associated neutropenia, this review focused on 46 patients (42%) with baseline Grade 0 neutrophil counts who progressed to  $\geq$  Grade 3 neutropenia. Thus patients must have experienced  $> 500/\text{microliter}$  reduction in neutrophil counts to be included in this analysis.

In this subgroup of patients with baseline Grade 0 lymphocyte counts, the median number of days from visit 2 to the first onset of  $\geq$  Grade 3 neutropenia was 28 (range 7 to 140 days). Figure 24 shows the number of days from first dose of ofatumumab to the first episode of  $\geq$  Grade 3 neutropenia. Most episodes occurred during the treatment window of the first 60 days.

To assess for the possibility of late onset neutropenia, patients in this group were evaluated with a first day of  $\geq$  Grade 3 neutropenia onset that was greater than 30 days following the first dose of ofatumumab. A total of 18 out of 46 patients were evaluated for late onset neutropenia. Most recorded episodes of  $\geq$  Grade 3 neutropenia were within 30 days of the *last* dose of ofatumumab. Patient 138 experienced Grade 3 neutropenia during ofatumumab treatment followed by normal neutrophil counts. About five weeks after the last dose, the patient experienced Grade 4 neutropenia at the final visit; however, the neutropenia was complicated by disease progression at this visit. Patient 156 experienced Grade 3 neutropenia about four months following the last dose of ofatumumab. The neutrophil count was 1,000/mcL at the prior and following visits; no record of growth factor use was described in the datasets. *Reviewer's comment: Despite the absence of severe ( $\geq$  Grade 3) late-onset neutropenia (except for possibly patients 138 and 156),*

*late-onset neutropenia cannot be excluded because the follow-up intervals of every three months (visits 15 to 21) were insufficient to document neutropenia lasting for shorter intervals.*

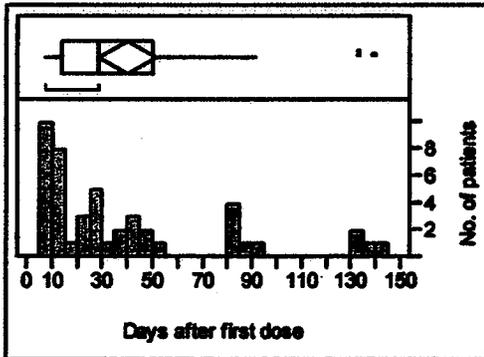
Documentation of Grade 4 neutropenia of prolonged duration is important as this is the neutrophil count where patients are at higher risk for life-threatening infections (Pizzo 1993). The Group of 46 patients with baseline Grade 0 neutropenia was evaluated to determine whether some patients experienced sustained Grade 4 neutropenia. Twenty of the 46 patients experienced Grade 4 neutropenia. The following cases of prolonged Grade 4 neutropenia were observed:

- Patient 226 experienced prolonged Grade 4 neutropenia over 6 consecutive weekly visits.
- Patient 216 experienced Grade 4 neutropenia over 7 consecutive weekly visits.
- Patient 204 experienced Grade 4 neutropenia over 4 consecutive weekly visits.
- Patient 195 experienced Grade 4 neutropenia at the week 20 visit (final lab record); this patient died of gram negative sepsis and the patient had prior Grade 3 neutropenia (ANC of 700/mcL) for two consecutive visits.
- Patient 184 experienced Grade 4 neutropenia over 2 consecutive weekly visits and again during 4 consecutive weekly visits.
- Patient 163 had neutropenia for an indeterminate amount of time [ $\leq 29$  days; (not 2 consecutive visits)].
- Patient 138 had Grade 4 neutropenia for an indeterminate amount of time (noted only at the last visit at the time of disease progression).
- Patient 134 experienced Grade 4 neutropenia over 7 consecutive weeks and again at study week 20 (for  $\leq 4$  weeks).

*Comment: At least five (226, 216, 204, 184, and 134) out of 109 patients with baseline Grade 0 neutropenia developed sustained Grade 4 neutropenia that could potentially be life-threatening after ofatumumab treatment. Additionally, patient 195 had Grade 4 neutropenia for one visit at the time of the patient's death.*

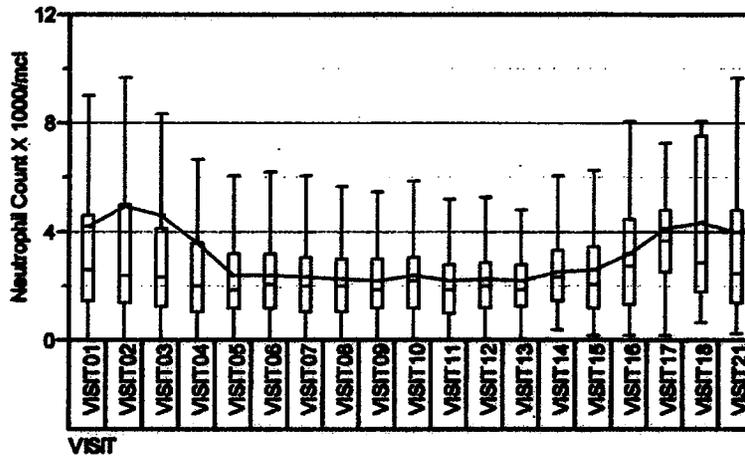
In the 406 CSR, GSK summarized AE's associated with  $\geq$  Grade 3 neutropenia. Of the patients described above with persistent severe neutropenia, patient 216 was hospitalized with febrile neutropenia; patient 184 was hospitalized with Grade 3 sepsis; patient 163 experienced Grade 3 sinusitis; patient 134 had multiple infections associated with neutropenia (periodontal abscess, wound infection, and campylobacter infection) and patient 195 died of gram negative sepsis.

Figure 24: Number of Days from First Dose of Ofatumumab to First Episode of  $\geq$  Grade 3 Neutropenia (Study 406) in Patients with Baseline Normal Neutrophil Counts (N=109).



Additionally, Figure 25 below clearly shows that the neutrophil counts over time decrease after the first and second doses of ofatumumab. The solid blue line refers to mean neutrophil counts, and the box plots show median values.

Figure 25: Neutrophil Counts over Time by Visit (Study 406)



Visit #	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	21
# Observations	150	151	150	146	142	139	139	139	137	129	118	106	91	86	67	34	17	5	85

**Reviewer Summary:** The overall incidence of neutropenia that occurred during study 406 was high. Forty-six (42%) patients experienced  $\geq$  Grade 3 neutropenia who had normal neutrophil counts at baseline. This proportion is substantially higher than the 13%  $\geq$  Grade 3 neutropenia AR rate proposed in the ofatumumab product label (adverse reactions described by

investigators). This rate of neutropenia was also higher than that observed in monotherapy trials with rituximab. This reviewer believes that the neutrophil counts described in the shift tables and laboratory datasets should supersede the numbers of AEs reported by study physicians in the product label.

Furthermore, Warning 5.8 in the proposed label contains the following statement:

This reviewer believes that the label should be revised to state that complete blood counts should be obtained at regular intervals because prolonged severe neutropenia and thrombocytopenia can occur following ofatumumab treatment. Additionally, the label should contain language that more accurately reflects the incidence of new onset Grade 3 or 4 neutrophil counts in patients who receive ofatumumab.

b(4)

**Hemoglobin**

Because anemia is caused by CLL, effects of ofatumumab on hemoglobin levels are difficult to interpret in a single-arm study. Table 74 and Table 75 are shift tables for hemoglobin levels for studies 406 and 402 respectively. The shift tables show that the number of patients who experienced two or more CTCAE Grade shifts for worsening hemoglobin were few in study 406 [n=11 (GSK's review)].

**Table 74: Shift Table of Hemoglobin by CTCAE Grade (Study 406)**

Baseline CTCAE Grade	Higher than Baseline CTCAE Grade				
	0	1	2	3	4
0	5	14	2	0	0
1	0	53	23 (21)	3 (4)	1
2	0	1	22 (24)	13	4
3	0	0	6	4 (3)	1
4	0	0	0	0	1

\* The data included in the GSK CSR are included in parentheses when they differ from the FDA analysis using JMP.

**Table 75: Shift Table of Hemoglobin by CTCAE Grade for Study 402 in the 2,000 mg dose cohort (Copied from Study 402 CSR)**

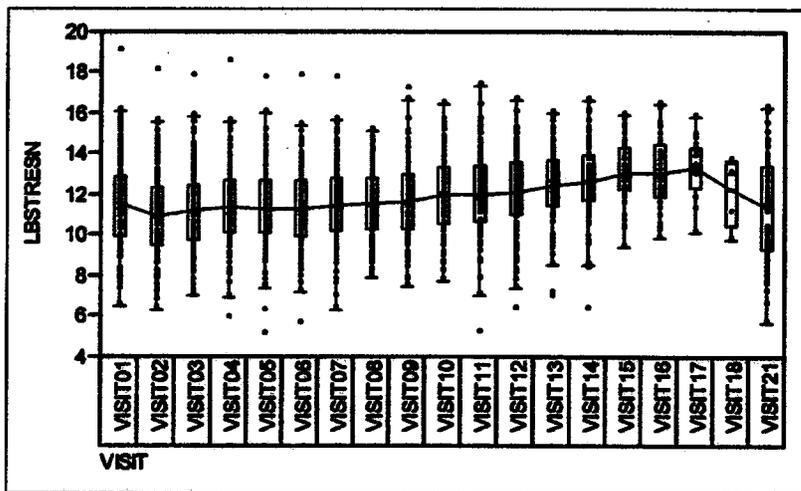
Baseline CTCAE Grade	Highest Post-Baseline CTCAE Grade				
	0	1	2	3	4
0	6	10	0	0	0
1	0	8	1	1	0
2	0	0	1	0	0
3	0	0	0	0	0
4	0	0	0	0	0

The following describes patients who developed Grade 4 anemia and who had at least a two Grade shift in hemoglobin levels

- Patient 118: This patient experienced Grade 3 hemoglobin levels on two occasions (visits 5 and 11). There were no records of transfusions or ESA use. Hemoglobin levels were Grade 2 at the prior and following visits. This patient experienced prior documented autoimmune hemolytic anemia. It is not clear if the Grade 4 anemia was related to time-limited exacerbations of hemolytic anemia, lab error, or other causes (assuming this patient did not receive any transfusions).
- Patient 193 developed hemolytic anemia and required transfusions more than 4 months after starting treatment with ofatumumab.
- Patient 197 required transfusions at baseline.
- Patient 216 had a one time decrease in hemoglobin to less than 6 g/dL. One week later, the hemoglobin was 8.69 g/dL. There were no records of transfusions at the time. Subsequently, this patient received an ESA.
- Patient 244 required transfusions at baseline.

In summary, reasons for severe worsening of anemia included hemolysis and artifact (due to elevated hemoglobin levels following a red blood cell transfusion). There was no systematic pattern of worsening red blood cell counts related to ofatumumab treatment. Figure 26 shows that during study 406, mean (solid blue line) and median hemoglobin levels remained stable during the ofatumumab treatment period. The allowance of erythropoietic stimulating agents and the administration of transfusions confound the interpretation of increased hemoglobin levels over time.

Figure 26: Hemoglobin Values by Study Visit (Study 406) in g/dl



### 7.4.3 Vital Signs

Vital signs were measured during each infusion and at visit 21 (end of study visit).

#### Fever:

A total of 10 (6.5%) patients developed a temperature of  $\geq 38$  degrees Celsius that was recorded during the 406 clinical trial. One of the patients (211) had fever at screening prior to the first dose of ofatumumab and then experienced fever during visits 2 through 3. Three additional patients (103, 167, 246) experienced fever during the first infusion of ofatumumab. No patient experienced a temperature over 40 degrees Celsius. Four patients experienced tachycardia with fever. Patient 236 experienced a heart rate of 154/minute and a temperature of 39.1 degrees Celsius during visit 12. This same patient experienced a systolic blood pressure of 81 mmHg with a temperature of 38.4 degrees Celsius during visit 4.

#### Hypotension:

A total of 42 patients experienced a systolic blood pressure less than 90 mm Hg during the conduct of study 406. GSK's review focused on reported AEs related to hypotension rather than describing the total incidence of hypotension as described in the (vital sign) datasets. The highest number of cases of abnormal systolic blood pressure were observed during baseline ( $n=15/154$ ) and during week 1 ( $n=18$ ). Week one was the first week that the 2,000 mg dose of ofatumumab was administered.

Because a simple analysis of SBP less than 100 mmHg does not account for baseline blood pressure, a second analysis of patients who had a SBP less than 90 mmHg and a heart rate above 100 per minute was conducted. There were 10 instances of this combination of vital signs among a total of 7 patients. Table 76 shows that among these patients, one (236) was a baseline

measurement for the day. Patient 112 had a low blood pressure at baseline although the heart rate increased during study drug treatment.

**Table 76: Instances of SBP < 90 mmHg and Pulse > 100 Beats per Minute (study 406)**

Patient	Visit Number (note visit 2 corresponds to the first infusion of ofatumumab)	SBP before infusion on the day of the infusion (mmHg)	SBP at time of hypotension and tachycardia (mmHg)	HR at start of infusion (beats per minute)	HR at the time of hypotension and tachycardia (beats per minute)
112	2	78	87	89	105
112	2	78	85	89	112
184	4	100	76	125	127
184	4	100	85	125	117
184	4	100	88	125	114
203	3	109	74	86	105
204	2	140	86	80	101
205	3	121	86	82	109
221	2	96	71	89	103
236	5	81	81	105	105

**Hypertension:**

A total of 77 patients experienced at least one episode of hypertension with a systolic blood pressure (SBP) > 150 mmHg. Of those 77 patients, 25 had a SBP greater than 150 mm/Hg at the time of the screening visit. Of these instances of hypertension, investigators deemed 6 patients as having hypertension related AEs. GSK conducted an analysis of mean and median blood pressures comparing baseline values to those obtained during visit 21 (month 24 or end of study visit). The mean change in BP was - 1.9 mm Hg and the median change for all patients was - 2.5 mm Hg. Thus, ofatumumab does not appear to be associated with sustained hypertension in most patients.

**7.4.4 Electrocardiograms (ECGs)**

A 12-lead ECG was obtained at screening during the conduct of study 406; however, additional follow-up ECGs were not required by the study protocol. Only the results of screening ECGs were included in the 406 datasets submitted by GSK.

For study 402, ECGs were obtained at screening and at visit 15. Limited details regarding ECGs were provided in the ECG dataset. Table 77 shows patients who had a normal ECG at screening and an abnormal ECG at visit 15. The table shows two instances of sinus bradycardia that were not noted at baseline. Heart rates were not provided in the dataset nor were QTc intervals.

**Table 77: Cases in Study 402 of Normal ECG results at Screening and an Abnormal Result at Visit 15**

Patient	Age	Ofatumumab Dose Cohort	ECG result
605	57	A	Sinus bradycardia at visit 15
606	55	C	Sinus bradycardia at visit 15

*Summary: A safety signal from ECG readings was not observed; however, the data submitted in the BLA were not sufficient to rule out such a signal. Refer to section 1.4 of this review for PMRs related to additional ECG monitoring.*

#### **7.4.5 Special Safety Studies/Clinical Trials**

There was no separate “special” safety study submitted to this BLA.

#### **7.4.6 Immunogenicity**

GSK found no instances of positive human anti-human antibodies (HAHAs) during the conduct of study 402. GSK found no positive HAHAs at the time of the interim analysis for study 406. GSK stated in the 406 CSR that 53 samples for HAHA were negative and with no ofatumumab present in the sample. *Conclusion: The numbers of samples for immunogenicity were limited at the time of the original BLA submission; however, there does not appear to be a signal for a high incidence of immunogenicity based on the negative testing done to this point. Furthermore, per the Clinical Pharmacology Review, the overall risk of immunogenicity is expected to be low in this patient population.*

### **7.5 Other Safety Explorations**

#### **7.5.1 Dose Dependency for Adverse Events**

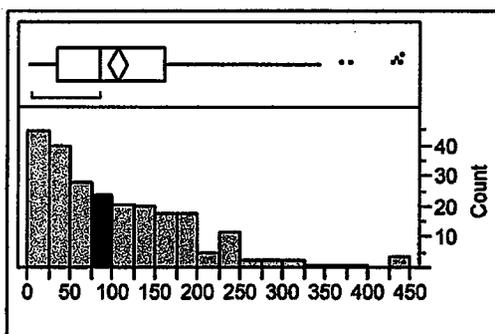
A formal analysis of dose dependency for adverse events was not possible. All patients in study 406 were treated with a uniform dose level of ofatumumab. The number of patients treated in study 402 at the lower doses was too few to conduct any formal comparisons.

#### **7.5.2 Time Dependency for Adverse Events**

Section 7.3.5 contains a discussion regarding the time dependency for infusion related symptoms. In general, infusion related symptoms most commonly occurred after the first and second doses of ofatumumab.

The time dependency for infections reported in the 406 dataset (by Infections SOC) was analyzed (one outlier with a reported start date prior to screening was removed). The median time for reported infections was 83 days after the first dose of ofatumumab. The incidence of infections appeared to decrease over time; however, this may have been a function of not continuing to document all infections after new CLL treatment.

**Figure 27: Occurrence of Infections by Number of Days Following the First Dose of Ofatumumab (x-axis in days)**



### 7.5.3 Drug-Demographic Interactions

#### Race

Because the race classification of 97% of the 406 study population was White, explorations of differences in AEs based on race would not be informative.

#### Gender

Table 78 shows the incidence of AEs by PT and by gender (study 406). Most AEs had similar per-patient incidence rates between genders. Women had a higher rate of anemia, cough, pyrexia, diarrhea, nausea, peripheral edema, abdominal pain, hypokalemia, hypotension, vomiting, and muscle spasms. Men had a higher rate of fatigue and bronchitis. Because the study did not have an internal control, such comparisons should be considered exploratory. There were not large differences observed in the per-patient incidence of  $\geq$  Grade 3 events.

**Table 78: Comparison of AEs by MedDRA PT by Gender**

AE/PT	% AEs All Grades Female N=43	% AEs All Grades Male N=111	% $\geq$ G3 AEs Female N=43	% $\geq$ G3 AEs Male N=111
ANAEMIA	26	13	7	5
COUGH	26	17	0	0
PYREXIA	23	19	0	4

AEPT	% AEs All Grades Female N=43	% AEs All Grades Male N=111	% ≥ G3 AEs Female N=43	% ≥ G3 AEs Male N=111
DIARRHOEA	21	17	0	0
NAUSEA	16	9	0	0
NEUTROPENIA	16	16	16	11
PNEUMONIA	16	16	12	10
DYSPNOEA	14	14	2	2
OEDEMA PERIPHERAL	14	7	2	0
RASH	12	13	0	0
ABDOMINAL PAIN	9	3	0	0
BACK PAIN	9	7	2	1
HEADACHE	9	5	0	0
HYOKALAEMIA	9	0	2	0
HYPOTENSION	9	4	0	0
MUSCLE SPASMS	9	4	0	0
UPPER RESPIRATORY TRACT INFECTION	9	12	0	0
VOMITING	9	2	0	0
ABDOMINAL PAIN UPPER	7	3	0	0
BRONCHITIS	7	13	2	0
CHILLS	7	9	0	0
FATIGUE	7	18	0	0

#### Age

A total of 43% of the total study population was ≥ 65 years in age. Because the total number of patients ≥ 65 years of age was less than 100 (and because there was no comparison to an internal control in either CLL study), no definitive conclusions can be made regarding the safety of ofatumumab in older patients. Table 79 shows an exploratory analysis of AEs by MedDRA SOC in patients 65 years or older compared to patients younger than 65. The incidence of AEs in both groups was similar. No SOC had a ≥ 10% difference in AE incidence except for the metabolism and nutrition disorders SOC. Much of this difference was due to increased reports of hyperuricemia and decreased appetite in older patients.

**Table 79: Comparison of AEs by MedDra SOC in Patients ≥ 65 Years of Age**

ADVERSE EVENT TERM BY MedDRA SOC	% AEs ≥ 65 Years (N=66)	% AEs < 65 Years (N=88)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	39	30
CARDIAC DISORDERS	17	11
EAR AND LABYRINTH DISORDERS	2	2
EYE DISORDERS	6	7
GASTROINTESTINAL DISORDERS	39	39
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	56	49

ADVERSE EVENT TERM BY MedDRA SOC	% AEs ≥ 65 Years (N=66)	% AEs < 65 Years (N=88)
HEPATOBIILIARY DISORDERS	0	2
IMMUNE SYSTEM DISORDERS	11	7
INFECTIONS AND INFESTATIONS	76	67
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	9	2
INVESTIGATIONS	17	9
METABOLISM AND NUTRITION DISORDERS	21	8
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	26	20
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	5	6
NERVOUS SYSTEM DISORDERS	27	23
PSYCHIATRIC DISORDERS	14	10
RENAL AND URINARY DISORDERS	6	5
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	2	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	48	40
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	35	34
VASCULAR DISORDERS	17	15

Table 80 shows AEs by MedDRA PT that occurred at a per-patient incidence rate of 10% or higher in the population who was ≥ 65 years of age. The largest discrepancy among AEs was for the dyspnea preferred term (a 22% difference in the per-patient incidence rate). There were 3 AEs of ≥ Grade 3 dyspnea (5% incidence) in the ≥ 65 years old population. Patient 137 experienced Grade 3 dyspnea 35 days after the last dose of ofatumumab. There was no report of concomitant pneumonia in this patient; however, three days later, the patient experienced a transient ischemic attack/CNS event. Patient 147 experienced multiple episodes of dyspnea. This patient's Grade 3 (dyspnea) event was considered to be infusion related; the patient also had bronchospasm during the event. Patient 147 had a medical history of sleep apnea syndrome. Patient 236 experienced Grade 3 dyspnea 20 days after the most recent previous dose of ofatumumab. Three days later, the patient was diagnosed with a Pseudomonas infection.

A large proportion of the difference in dyspnea in patients ≥ age 65 was due to dyspnea that was potentially infusion related (occurred on the day of a dose of ofatumumab). There were 11 such cases (17%) among patients 65 or older compared to three (3%) in patients younger than 65. All such cases were Grade 2 or less. The proposed label contains a warning regarding infusion reactions.

Notably there was also a 14% absolute difference in the rate of pneumonia in patients ≥ 65 years of age compared to patients less than 65 years of age. The total numbers of patients being compared was low, however.

**Table 80: Comparison of AEs by MedDra PT in Patients ≥ 65 Years of Age**

Adverse Event Preferred Term	≥ 65 Years % AEs All Grade N=27	< 65 Years % AEs All Grade N=111	< 65 Years % AEs ≥ Grade 3 N=111	≥ 65 Years % AEs N=27
DYSPNOEA	27	5	5	0
PNEUMONIA	24	10	14	8
COUGH	23	17	0	0
ANAEMIA	21	13	6	5
NEUTROPENIA	21	13	15	10
FATIGUE	21	10	0	0
PYREXIA	18	22	3	2
DIARRHOEA	17	19	0	0
OEDEMA PERIPHERAL	17	3	2	0
NAUSEA	15	8	0	0
NASOPHARYNGITIS	14	3	0	0
BACK PAIN	12	5	3	0
RASH	12	13	0	0
URTICARIA	12	5	0	0

**Weight**

Because of the variability in AUC observed in study 406 (refer to clinical pharmacology review) and the utilization of uniform dosing, an exploratory analysis of AEs by weight was conducted. The median weight among the 154 patients in study 406 was 75 kg. Thus for this analysis, weight was dichotomized between ≥ 75 kg and less than 75 kg. Table 81 provides a comparison of AEs by MedDRA PT in patients ≥ 75 kg and patients less than 75 kg.

Anemia was more common in lighter weight patients. Certain common infusion related symptoms were more frequent in patients who weighed less: dyspnea (18 versus 10%), nausea (14 versus 8%), urticaria (11 versus 5%), hypotension (9 versus 1%), vomiting (8 versus 0%), chills (12 versus 5%), and bronchospasm (5 versus 0%). The per-patient incidence rate of pyrexia was higher in heavier patients (24 versus 16%). Most of these symptoms were non-severe in nature; exceptions included dyspnea [4 (< 75 kg) versus 0% ≥ Grade 3] and pyrexia [0% (< 75 kg) versus 5% in heavier patients].

*Common: This reviewer notes that the higher rate of dyspnea observed in older patients could potentially be a function of weight (and differences in drug exposure).*

**Table 81: Comparison of AEs by MedDra PT in Patients by Weight**

AE/PT	All Patients (N=75)	All Grades (N=75)	Grade 1 (N=75)	% ≥ Grade 3 AEs ≥ 75 kg N=75
ANAEMIA	24	9	5	5
COUGH	21	18	0	0
DYSPNOEA	18	10	4	0
DIARRHOEA	17	19	0	0
NEUTROPENIA	17	15	14	10
PNEUMONIA	17	15	11	10
PYREXIA	16	24	0	5
FATIGUE	14	15	0	0
NAUSEA	14	8	0	0
RASH	13	12	0	0
CHILLS	12	5	0	0
OEDEMA PERIPHERAL	12	6	1	0
BRONCHITIS	11	12	0	1
UPPER RESPIRATORY TRACT INFECTION	11	12	0	0
URTICARIA	11	5	0	0
ABDOMINAL PAIN	9	0	0	0
HEADACHE	9	4	0	0
HYPOTENSION	9	1	0	0
INSOMNIA	9	5	0	0
ABDOMINAL PAIN UPPER	8	0	0	0
BACK PAIN	8	8	1	1
MUSCLE SPASMS	8	3	0	0
SINUSITIS	8	3	4	0
VOMITING	8	0	0	0
HERPES ZOSTER	7	5	1	1
HYPERHIDROSIS	7	4	0	0
NASOPHARYNGITIS	7	9	0	0
SEPSIS	7	3	7	3
BRONCHOSPASM	5	0	1	0
DECREASED APPETITE	5	0	0	0
LOWER RESPIRATORY TRACT INFECTION	5	4	0	0
MUSCULOSKELETAL PAIN	5	1	0	0
NASAL CONGESTION	5	3	0	0
PARAESTHESIA	5	4	0	0
PRURITUS	5	4	0	0
TACHYCARDIA	5	5	1	0
URINARY TRACT INFECTION	5	3	1	1

#### **7.5.4 Drug-Disease Interactions**

##### **Pulmonary Disease**

Because of the differences in dyspnea observed in older patients with CLL who were enrolled into study 406, an analysis was performed to determine whether this difference was due to the possibility that older patients had an increased incidence of respiratory disorders at baseline. To perform this analysis, patients who had a history (current at the time of study entry) of respiratory and thoracic disorders were evaluated against other patients without such disorders. Only pulmonary disorders related to the lung were included in this analysis (the following terms were excluded as having a history of respiratory disorders: epistaxis, nasal congestion, nasal mucosal disorder, postnasal drip, rhinitis allergic, and rhinorrhea). Fifty-four such patients had a medical history of respiratory disorders that was reported by GSK.

Compared with patients without a history of respiratory disorders, patients with a history of respiratory disorders had a higher incidence of dyspnea (17% versus 13%); however, the difference in the rate of dyspnea among patients with pulmonary disorders could not completely account for the difference in the rate of dyspnea among older patients. All three cases of severe (Grade 3) dyspnea were in patients who had a history of respiratory disorders at baseline. The one report of Grade 3 bronchospasm occurred in a patient with an underlying respiratory disorder. Reports of hypoxia and exertional dyspnea were higher in patients with underlying respiratory disorders (4 versus 1% for each category).

A separate study (Hx-CD20-408) in patients with COPD was stopped due to Grade 3 bronchospasm in two of five patients. Patients enrolled in study 408 had an FEV1/FVC less than 70% predicted. Patients were to be GOLD stage 3 prior to the first amendment (with the FEV1 between 30 and 50%). After amendment 1, this inclusion criterion was changed to require patients' FEV1 to be between 30 and 60% predicted (GOLD stage 2). Enrolled patients were not to be on long term home oxygen therapy. Both events of Grade 3 bronchospasm occurred on days of ofatumumab infusions. One patient with an FEV1 at baseline of 56% was treated with IV adrenaline and 80 mg solumedrol in addition to oxygen, ipratropium, terbutaline, and tavegyl.

#### **7.5.5 Drug-Drug Interactions**

Based on the pharmacodynamic effects of ofatumumab (depletion of B cells), an exploratory analysis was conducted to determine if prior CLL treatment affected the overall incidence rates of infections. Overall, the total number of infections was similar whether patients received 4 or fewer prior therapies (70% of 63 patients) compared to 5 or more (71% of 91 patients). The percentage of Grade 3 infections was higher in patients who had received 5 or more therapies (32% versus 25%).

Regarding previous alemtuzumab therapy, the overall number of infections was similar (71% for prior alemtuzumab versus 70% for no ofatumumab); however, the per-patient incidence of severe ( $\geq$  Grade 3 infections) infections was higher in patients who received prior alemtuzumab (37% versus 20%).

*Comment: Patients who received prior treatment with drugs causing profound immunosuppression (i.e. alemtuzumab) were more likely to experience severe infections after receiving ofatumumab. Because study 406 lacked an internal control, it cannot be determined whether ofatumumab increased the risk of infections in these patients or if the patients were at higher baseline risk due to having severe baseline immunosuppression.*

## 7.6 Additional Safety Evaluations

### 7.6.1 Human Carcinogenicity

GSK stated in the BLA submission (module 2.4) that because ofatumumab would not directly interact with DNA or chromosomal material, that standard genotoxicology studies would not be appropriate. Additionally, non-clinical carcinogenicity testing was not performed. Table 82 shows second malignancies reported after ofatumumab treatment. In the original BLA submission, there were three reports of lymphoproliferative disorders including Richter's transformation, mantle cell lymphoma, and Hodgkin's disease.

Secondary lymphoid malignancies may occur in up to 3% of CLL patients and include Hodgkin's disease (Robak, 2004). Additionally, Molica (2005) described the SEER database that showed a higher incidence of non-lymphoid neoplasms in the CLL population (observed to expected ratio of 1.20). Reasons postulated for an increased rate of malignancies included CLL disease phenomena, CLL therapy associated immunodeficiency, treatment with suspected carcinogens (for example, alkylating agents), increased risk factors (age), and increased medical surveillance compared to healthy controls.

Other studies of patients with CLL have shown a high rate of secondary malignancies. In two (Dighiero et al., 1998) French randomized studies of 1535 patients assessing the benefits of chlorambucil in patients with CLL, 206 second cancers were diagnosed (median follow-up for the two trials was 6 and 11 years. Sites of second cancers were diverse and included skin cancers, breast cancer, colon cancer, and lung cancer. Keating et al., (1998) reported five secondary solid tumor malignancies among 174 patients treated with fludarabine including lung cancer (2), ovarian cancer, colon cancer, and head and neck cancer. Cheson et al., (1999) performed a retrospective analysis of 724 patients with CLL who received fludarabine. A total of 83 malignancies were reported among the 724 patients (34 occurred prior to protocol therapy). Sites of secondary cancers in this study were diverse. The authors concluded that fludarabine did not confer a significantly elevated risk of secondary malignancies in CLL patients. More recently, a (historically controlled) study by Tsimberidou et al., 2009, showed that patients with CLL have more than twice the expected risk of expected tumors compared to the number in the SEER database. Among 2,028 patients, 216 patients developed a second cancer after the diagnosis of CLL. The median follow-up of patients who developed a second cancer was 6.3 years. Forty-two of the cancers were non-Hodgkin's lymphoma and five cases of Hodgkin's lymphoma were reported. Twenty cases of breast cancer were reported.

**Table 82: Malignancies Reported after Ofatumumab (1,138 total patients exposed)**

Trial	Days Since First Dose	Ofatumumab Indication	Patient	Age	Brief Description of Probable Cause of Death
406	2	CLL	106	58	GI-other (adenocarcinoma) – Detected two days after the first infusion (thus would not expected to be caused by ofatumumab)
406	96	CLL	116	62	Mantle Cell Lymphoma: the patient had both mantle cell lymphoma and CLL and was hospitalized for liver biopsy
406	99	CLL	163	59	Large Cell Lymphoma, Richter's Syndrome Hodgkin's Disease
406	164	CLL	188	60	
406	183	CLL	207	68	Breast Cancer – 7 m nodule of invasive ductal carcinoma detected on routine mammogram
Hx-CD20-001	-	FL	PL01434	74	Ovarian cancer was detected by CT scan about 3 months after the first dose of ofatumumab
Hx-CD20-001	-	FL	DK2413	64	Endometrioid adenocarcinoma of the ovary was diagnosed about 17 months after the last dose of ofatumumab; on retrospect the tumor was observed in an ultrasound prior to the first dose of ofatumumab
Hx-CD20-001	-	FL	UK01444	55	Ductal carcinoma in situ of the breast was diagnosed about three years after the last dose of ofatumumab.
403	-	RA	427	62	Breast cancer diagnosed about four months following the first dose of ofatumumab
406*	-	CLL	406302	67	Breast cancer was diagnosed four days after the eight weekly infusion of ofatumumab.
407*	597	CLL	407102	50	Melanoma (in situ)
409*	-	FL	409117	54	Ovarian cancer (borderline) diagnosed 25 days after cycle 6 of 0-CHOP
405*	224	FL	405514	76	Grade 3 epidermoid skin (squamous) carcinoma

\*Submitted in safety update

*In summary, secondary cancers occur more frequently in patients with CLL compared to the general population. In regards to patients described in this BLA, it is unlikely that ofatumumab would cause detectable (solid) tumors in less than a six month time period due to immunosuppression. Two solid tumors were diagnosed over one year following treatment with ofatumumab. Based on the natural history of increased incidence of tumors in patients with CLL, there is not sufficient data to support an increased risk of tumor formation caused by ofatumumab [when compared to literature reports showing frequent diagnoses of secondary malignancies (greater than 10% over 6 years in one study)]. Controlled trials will be necessary to assess whether ofatumumab increases the risk for secondary cancers.*

### **7.6.2 Human Reproduction and Pregnancy Data**

No studies were conducted of ofatumumab in pregnant or lactating women. Such studies are usually not required for drugs intended to treat patients with advanced cancer.

### **7.6.3 Pediatrics and Assessment of Effects on Growth**

Studies with safety data pertaining to pediatric patients were not submitted to the BLA. GSK requested a full waiver of pediatric use studies to remain in compliance with the Pediatric Research Equity Act. GSK stated in the request that according to data from the U.S. Surveillance, Epidemiology, and End Results (SEER) program, less than 0.1% of patients with CLL will be less than 20 years old. *Comment: This reviewer confirmed this statement from the SEER web site (<http://seer.cancer.gov/statfacts/html/clyl.html>, accessed March 10, 2009.); of patients diagnosed with CLL between the years 2001 and 2005, 0.0% were pediatric patients (age < 20 years).*

*This reviewer agrees that a full waiver would be appropriate because the necessary studies in patients with CLL would be inappropriate because the number of children with CLL is too small. FDA guidance (<http://www.fda.gov/cder/guidance/3578dft.htm>) states that the Pediatric Rule does not require pediatric studies for the pediatric use of a drug for indications for which the sponsor has not obtained, or does not seek, approval. At this time, GSK is not seeking approval of any non-CLL indications.*

Additionally orphan-drug approval was granted to ofatumumab for "treatment of chronic lymphocytic leukemia" on March 10, 2009. Because ofatumumab has been granted orphan-drug approval, submission of pediatric data is not required for this application and a waiver is not required (under 21 CFR 601.27d).

*No further comment can be made on the potential for ofatumumab related growth effects or effects on children as children were not enrolled into clinical trials supporting this BLA.*

### **7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound**

There is no expected drug abuse potential for this biological drug. No data is available to determine the effects of overdose in patients with CLL. The maximum dose administered was 2,000 mg in the 406 study.

### **7.7 Additional Submissions**

#### **Safety Update**

This section will address the results of the safety update submitted on April 30, 2009. This update is a 90-day safety update in lieu of the 120-day safety update. FDA agreed to the timing of this update. For the safety update, data from a total of 1,138 patients were reported as compared to 648 in the original BLA submission. This includes data from 550 patients in

completed or ongoing oncology studies. Table 83 shows the number of patients contributing to the updated safety analysis by study. The table shows that data from five new studies were included in this analysis: two in CLL, one in follicular lymphoma, one in multiple sclerosis, and one in patients with rheumatoid arthritis.

**Table 83: Number of Patients Contributing to the Updated Safety Analysis by Study**

Study Number	Disease	No. of BLA Patients	No. of Updated Safety Analysis Patients
Hx-CD20-402	CLL	33#	33
Hx-CD20-406	CLL	154	206
Hx-CD20-407	CLL	28	61
Hx-CD20-001	FL	40	40
Hx-CD20-405	FL	74	110
Hx-CD20-409	FL	33	58
GEN415/DLBCL	DLBCL	4	33
Hx-CD20-403	RA	201	201
GEN410	RA	54^	250
GEN411	RA	12^	57
GEN413	RA	10	39
Hx-CD20-408	COPD	5	5
Hx-CD20-416	CLL	0	2
OMB110911	CLL	0	4
OMB111148	FL	0	3
OFA110867	RA	0	16
GEN414	MS	0	20

Abbreviations: CLL = chronic lymphocytic leukemia; FL = follicular lymphoma; DLBCL = diffuse large B-cell lymphoma; RA = rheumatoid arthritis; COPD = chronic obstructive pulmonary disease; MS = multiple sclerosis  
 # 27 patients received the 2,000 mg dose of ofatumumab  
 ^ patients received ofatumumab or placebo

The following is a brief description of oncology studies that were not submitted to the original BLA:

- GEN416: This is an extension study evaluating re-treatment or additional treatment in patients with CLL who previously received ofatumumab and who progressed following response or stable disease. Eligible patients were those who tolerated at least 8 doses of ofatumumab in the 406 study.
- OMB110911: This study is a randomized controlled study comparing PFS duration among patients treated with chlorambucil and with or without ofatumumab.
- OMB111148: This study is an ongoing monotherapy study evaluating two doses of ofatumumab in Japanese patients with follicular lymphoma or chronic lymphocytic leukemia.

**Safety Update Disposition (406 study):**

At the time of data-cut off for the safety update, the proportion of patients who discontinued ofatumumab prematurely was the same (45%) as in the BLA.

**Exposure (406 study):**

The number of patients who received at least eight weekly infusions of ofatumumab (89%) was similar to that described in the original BLA submission (90%). The number of dose interruptions occurring during an infusion was similar (within 1 percentage point) for all infusions comparing the data from the original BLA to the data in the safety update.

**Overview of all AEs (406 study):**

The following AE comparisons all had a per-patient incidence rate in the original BLA submission that was similar to or higher than the per-patient incidence rate in the safety update report:  $\geq$  Grade 3 AEs (57% versus 56%); infusion-related AEs (64% versus 60%); infection AEs (70% versus 66%), SAEs (53% versus 53%); AEs leading to treatment withdrawal (14% versus 10%); and fatal SAEs (16% versus 14%).

Of the most common AEs, most were within 2 percentage points of those described in the original BLA. The exception was chills: the total incidence of chills was 13% in the safety update versus 8% at the time of the original BLA submission. Most of these events (chills) were  $\leq$  Grade 2 in severity. The proportion of patients who experienced potentially infusion-related adverse events was within 2% comparing the data in the original BLA to the data in the safety update. The only exception was for chills/rigors.

**Overview of SAEs (All studies):**

In the safety update report for study 406, SAEs occurring in two or more patients were either less frequent (by  $< 5\%$ ) or were as frequent as the SAEs reported to the original BLA. No additional cases of myocardial infarction were reported in study 406. One additional case of breast cancer was reported. No additional infusion reaction SAEs were reported in the 406 study. Table 84 lists additional SAEs that were reported in all studies at the time of the safety update. The table does not include SAEs related to infection, pyrexia, cytopenias, or disease progression (including autoimmune hemolytic anemia occurring in CLL patients). SAEs related to arthritis/musculoskeletal symptoms in patients with RA are not included in the table. Table 84 also does not list deaths as these cases are described in Table 85. Only SAEs that were reported within 3 months of the last dose of ofatumumab are included in the table. Inclusion in the table does not imply causality.

**Table 84: Selected Listing of Selected SAEs (Reported in the 90 Day Safety Update)**

Subject	Study	Age	Number of Courses*	Number of Patients	SAE
406271	406	87	9	29	Vertebral compression fracture
406284	406	69	8	19	Diabetes mellitus
40627	406	69	8	15	Grade 3 chronic diarrhea (resolving 28 days later)
406296	406	73	2	3	Cough/bronchospasm (presumed infectious)
406302	406	67	8	4	Breast cancer

Subject	Study	Age	Number of Courses	Number of Doses	SAE
406311	406	67	6	7	Arthralgia (scans negative; presumed muscle strain)
407136	407	51	2*	~60	Eczema and dermatitis from presumed scabies
407156	407	61	2*	1	Acarodermatitis Grade 2
407158	407	57	2*	4	Nausea, vomiting, and hyperglycemia
407158	407	57	2	8	Myocardial infarction
405153	405	64	N/A	N/A	Grade 3 anasarca and hypoalbuminemia (presumed by the investigator due to lymphomatous involvement of the bowel)
405500	405	79	8	34	Spontaneous loss of teeth
405530	405	67	5	2	Grade 2 constipation
405535	405	43	8	61	Grade 3 pleural effusion (patient withdrawn from the study on the same day due to progressive disease)
409117	409	54	6*	25	Grade 4 ovarian cancer (with post surgical peritonitis / small bowel perforation)
409134	409	47	2*	3	Grade 2 headache
409139	409	60	2*	0	Grade 2 cytokine release syndrome (this was the investigator's verbatim term: the symptoms were not described although the patient had dyspnea; the symptoms resolved after the rate of the infusion was reduced)
409143	409	60	1*	9	Vasovagal syncope
409152	409	56	4*	14	Increased ALT (669 U/L)
415012	409	53	2	1	Eyelid ptosis (Grade 2); no abnormalities reported in MRI or lumbar puncture; however, one month later, the patient was diagnosed with leptomeningeal metastases
001509	OFA110634	39	N/A	0	Grade 3 anaphylactic reaction: symptoms included rash, dyspnea, and bronchospasm and resolved following treatment
006002	OFA110634	47	1	2	Grade 2 hypersensitivity resolving with steroids (dyspnea, redness in face)
002550	OFA110635	53	1	0	Grade 2 angioedema (symptoms were rash, pruritus, laryngeal pruritus, face swelling, and mild dyspnea)
008101	OFA110635	67	1 (2 doses)	~60	Pulmonary embolism
413692	GEN413	39	1	0	Grade 3 allergic reaction characterized by rash

**Overview of Deaths (All studies):**

The overall proportion of patients dying reported in the original BLA submission was similar to that reported in the safety update. Narratives for these additional cases were reviewed for patients who died within 90 days of the last dose of ofatumumab and are described in Table 85.

In general, causes of death in the oncology population were mostly related to either infection or disease progression (similar to the original BLA submission). In study 406, the proportion of patients dying of infection was similar to the proportion of patients who died at the time of the data cut-off for the original BLA submission.

**Table 85: Deaths -- Safety Update**

Subject	Study	Age	Number of Courses	Days Since Last Dose (N/A) Date	Cause of Death
406312	406-DR	59	1	5	Sepsis due to Escherichia coli infection
406298	406-DR	64	9	7	Richter's transformation
406280	406-DR	68	10	10	Neutropenic sepsis / bronchopneumonia
406311	406-DR	67	7	59	Disease progression
406290	406-DR	65	7	11	Pulmonary edema (presumed due to refractory CLL)
406295	406-BFR	69	4	11	Pneumonia/organ failure
406293	406-BFR	52	5	25	Septic shock/typhlitis/enterococcus
406277	406-BFR	64	9	43	Unspecified
406304	406-N/A	52	1	7	Pneumonia/sepsis
407137	407	54	2*	19	Died at home -- unknown cause
407148	407	67	6*	50	Presumed septic shock
415004	415	76	3	45	Unknown
415009	415	78	4	6	DLBCL (disease progression)
415011	415	71	4	9	Disease progression -- neutropenic sepsis
415012	415	53	6	27	Neutropenic sepsis (Pseudomonas) at time of progression
415015	415	87	8	22	Pneumonia/sepsis
415022	415	42	5	3	Cardiac failure reported (true cause of death unknown; the patient presented with atrial fibrillation, anuria, and low blood pressure). CK and myoglobin elevated but CK-MB normal. Autopsy was not performed.
415027	415	64	2	8	Disease progression
415028	415	58	5	1	Disease progression
002516	OFA110635	59	1	11	Acute pyelonephritis
005509	OFA110635	51	2	N/A	About 2.5 months after the last dose of blinded drug, the patient died of interstitial lung disease

\* Also received chemotherapy in addition to ofatumumab

**Overview of Mucocutaneous Reactions:**

GSK was asked by FDA to conduct an analysis of severe mucocutaneous reactions because these are reported in the rituximab label. No events of paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, or toxic epidermal necrolysis were reported. In study 406, there were two mucocutaneous events reported as SAEs. Both events

were Grade 2 in severity: one event was folliculitis, and one event was infectious (*Citrobacter* cellulitis).

**Safety Update Summary:**

In general, the AE profile in the safety update was consistent with that submitted in the original BLA and described in the product label. The most common SAEs and deaths were related to disease progression and infection. Cytopenias were also a frequent cause of SAEs. No additional labeling changes are required based on the safety update.

**Post Safety Update Submission**

On July 28, 2009, GSK submitted a safety report describing a 54-year-old woman with rheumatoid arthritis who received ofatumumab on February 7, 2008; February 21, 2008; July 24, 2008; August 6, 2008; March 3, 2009; and March 17, 2009. She was also receiving methotrexate therapy. On April 29, 2009 (36 days following the last dose of ofatumumab), the patient developed jaundice and elevated liver enzymes. She was diagnosed with severe hepatitis B infection (new infection) and died on ( ) She was negative at study screening for hepatitis B surface antigen, hepatitis B surface antibody, and hepatitis B core antibody. Liver function tests were not elevated prior to the acute hepatitis B infection. Autopsy confirmed massive total liver necrosis. She also had intracranial hemorrhage which may have been caused by coagulopathy related to un-measurable prothrombin levels. *Based on this case, this reviewer recommends that the label be revised to state that hepatitis B infection (including fatal infections) can occur following ofatumumab treatment. This warning will be in addition to the statement regarding hepatitis B reactivation proposed by GSK in the original BLA submission.*

b(6)

## **8 Postmarket Experience**

Ofatumumab has not been approved so there is no post-marketing experience associated with this product.

## 9 Appendices

### 9.1 Literature Review/References

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## **9.2 Labeling Recommendations**

This section of the review will focus on general high-level labeling recommendations. All sections of the label were revised for clarity and brevity. Only notable content changes will be discussed in this section. Additionally, other sections of this review contain applicable discussions of labeling recommendations. Only sections dealing with clinical information will be described below (sections pertaining to CMC or non-clinical issues will not be included).

### **9.2.1 Indications and Usage**

The indications statement in the original BLA submission was revised to indicate that the Accelerated Approval indication would be for the specific population meeting the regulatory criterion for unmet medical need (patients with chronic lymphocytic leukemia (CLL) refractory to alemtuzumab and fludarabine). Additionally, this reviewer agrees with adding a statement that "The effectiveness of Arzerra is based on the demonstration of durable objective responses. No data demonstrate an improvement in disease-related symptoms or increased survival with Arzerra."

### 9.2.2 Dosage and Administration

- This reviewer agrees with reformatting of this section for clarity. The administration section should include the proposed rate of ofatumumab in mg/hour in addition to mL/hour.
- The proposed recommended dosing schedule was revised for clarity. The proposed schedule was for an initial dose of ofatumumab of 300mg followed by subsequent doses of 2,000 mg (seven total weekly doses followed 4-5 weeks later by a 2,000 mg dose followed by three additional doses every four weeks for a total of 12 doses). The Hx-CD20-406 protocol specified that patients receive the first of the every four week doses five weeks after the last weekly dose. For ease of administration however, the decision was made to specify that the dose be administered four weeks after the last weekly dose. This schedule was deemed easier for patients and clinicians to follow, and based on the PK/PD profile of ofatumumab, should have no detrimental effects on either the safety or effectiveness of ofatumumab.
- The label was revised to instruct clinicians to stop the current infusion of ofatumumab for a Grade 4 infusion reaction. Grade 4 reactions are life-threatening.

### 9.2.3 Dosage Forms and Strengths

The proposed dosage form (and strength) is a 100 mg/5 mL single-use vial. DMEPA recommended that the word "injection" follow the word "vial" in this section of the label. This reviewer recommends that this word not be included in the USPI for two reasons. The first is based on DBOP precedent with lack of inclusion of the word "injection" in the dosage form and strength section of the labels for alemtuzumab, bevacizumab, rituximab, cetuximab, and panitumumab. The second reason is the safety concern that health practitioners could mistake the intent of the word injection and administer the product as an intravenous bolus rather than as an infusion.

### 9.2.4 Warnings and Precautions

- **Infusion Reactions:** this section was revised to specify the most severe or serious reactions occurring after ofatumumab administration. Cardiac infarction/ischemia was added to the list. Additionally, a description of the experience in moderate to severe COPD clinical trial was added to this list (with the caveat that ofatumumab is not approved for this indication).
- 
- **Laboratory Monitoring** was moved to the second Warning because of the incidence of Grade 4 neutropenia. The revised section specifically states that prolonged severe neutropenia and thrombocytopenia can occur with ofatumumab treatment.
- **Progressive multifocal leukoencephalopathy:** refer to SAE section of this review.
- **Hepatitis B Reactivation:** This reviewer agrees with the inclusion of hepatitis B reactivation in product label as described above in this review. However, there was no evidence

b(4)

submitted supporting the applicant's proposal that <sup>c</sup> <sup>j</sup>  
D. Additionally, fatal hepatitis B infection <sup>b(4)</sup>  
occurring after ofatumumab treatment was added to the label based on a case reported in an  
ongoing clinical study (safety report submitted after the safety update).

### 9.2.5 Adverse Reactions

The label was revised to describe only the safety results of the 406 study in the adverse reactions section rather than describing the results of the integrated analysis from studies 406 and 402.

This decision was made for the following reasons:

- The 402 study occurred over a shorter duration. This shorter duration influenced the per-patient incidence of AEs (especially infections).
- Different coding was used for the two studies, making a formal integrated analysis problematic.

Table 3 (per-patient incidence of AEs in study 406) was revised as follows: <sup>b(4)</sup>

- <sup>c</sup> <sup>j</sup>
  - The term pneumonia should include the PTs pneumonia, lung infection, lobar pneumonia, and bronchopneumonia.
  - The term sepsis should be added and include the PTs sepsis, neutropenic sepsis, bacteremia, and septic shock.

The section describing infections was revised to include the incidence of fatal infections in the DR group.

### 9.2.6 Clinical Studies

As described elsewhere in this review, a decision was made to use the investigators' estimate of ORR and DOR in the clinical studies section. Additionally, as described in section 6 of this review, the table that included components of the 1996 NCIWG criteria (refer to Section 6 of this review for justification) was removed. The clinical studies section was revised so that the primary data presented was that of the DR population (the population under consideration for Accelerated Approval).

### 9.2.7 Patient Information/Patient Counseling Information

Because ofatumumab is an infusion administered by trained medical personnel, the decision was made by the Division that the inclusion of Patient Information to be given by the pharmacist to the patient with each prescription was not practical. Instead, the Patient Counseling Information Section was broadened so that it includes important instructions for clinicians to discuss with their patients.

### **9.3 Advisory Committee Meeting**

The Oncology Drugs Advisory Committee met on May 29, 2009 to discuss the ofatumumab application.

After discussing the overall effect size, safety profile, and uncertainties regarding the effect size due to lack of CT scans, the committee voted 10 to 3 that an ORR of 42% (99% CI 26,60) and a median DOR of 6.5 months (in the DR population) is an effect size that is reasonably likely to predict clinical benefit in patients with CLL (refractory to fludarabine and alemtuzumab).

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

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

# CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 125326      Applicant: GlaxoSmithKline      Stamp Date: 1/30/2009

Drug Name: ofatumumab      NDA/BLA Type: BLA

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

	Content Parameter	Yes	No	NA	Comment
<b>FORMAT/ORGANIZATION/LEGIBILITY</b>					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			(eCTD)
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
<b>LABELING</b>					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			Cursory view of label appears to be in an acceptable PLR format
<b>SUMMARIES</b>					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			(Integrated for single-arm CLL studies; this is acceptable)
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			X	Biological drug (submitted under the provisions of 21 CFR 601.2)
<b>DOSE</b>					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: Study Title: HxCD20-C-402 Sample Size: 33      Arms: refer to submission Location in submission: FSR study HxCD20-C-402		X		Three patients received ofatumumab at the 500 and 1,000 mg dose levels. Thus, it is unclear whether lower dose levels may have demonstrated similar activity as the 2,000 mg dose level.
<b>EFFICACY</b>					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	X			This is an application for accelerated approval for patients

File name: 5\_Clinical Filing Checklist for NDA\_BLA or Supplement 010908

## CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Pivotal Study #1 Hx-CD20-406 Indication: CLL refractory to fludarabine and alemtuzumab <input type="checkbox"/>				with refractory CLL. There is one "pivotal study" with supportive evidence in a second study. Both are single arm studies.
	Supportive Study #2 Hx-CD20-402 Indication: <input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/> refractory CLL				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			ORR in single arm studies have been accepted by the agency for approval of drugs to treat patients with refractory cancer according to FDA guidance
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		The "pivotal" study was conducted in the U.S. and abroad
<b>SAFETY</b>					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			On initial inspection
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?		X		The applicant has proposed a study to conduct an assessment of the QT interval as a post-marketing commitment
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			On initial inspection
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) been exposed at the dose (or dose range) believed to be efficacious?			X	Not applicable for drug intended to treat patients with refractory cancer
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			

b(4)

<sup>1</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

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23.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?	X			All verbatim and preferred terms are included in an .XPT file.
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?		X		A comment will be sent to the applicant to perform an analysis of severe mucocutaneous reactions at the 120-day safety update.
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			On initial inspection of study Hx-CD20-406. Corresponding MedWatch style reports were also submitted.
<b>OTHER STUDIES</b>					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
<b>PEDIATRIC USE</b>					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			The applicant has requested a waiver
<b>ABUSE LIABILITY</b>					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	Not relevant
<b>FOREIGN STUDIES</b>					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		
<b>DATASETS</b>					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			Appears acceptable during the early review of the datasets
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?		X		It appears that some patients are missing from the investigator response assessment dataset (the independent review dataset appears complete). A comment regarding

<sup>2</sup> The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

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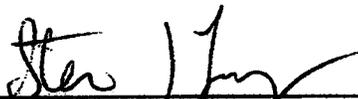
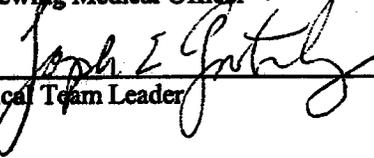
	Content Parameter	Yes	No	NA	Comment
					this issue will be sent to the applicant for correction.
34.	Are all datasets to support the critical safety analyses available and complete?	X			On initial review
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			On initial review
<b>CASE REPORT FORMS</b>					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			However, source lab data were not included in the submission.
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
<b>FINANCIAL DISCLOSURE</b>					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
<b>GOOD CLINICAL PRACTICE</b>					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			One unifying statement regarding GCP could not be found during the initial inspection. However, each stud report contained in the BLA contains a statement that the trial was conducted or is being conducted (for ongoing trials) in accordance with the Declaration of Helsinki and Good Clinical Practice.

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE?**     Yes    

If the Application is not fileable from the clinical 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.

**CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement**

	2/23/09
_____ Reviewing Medical Officer	_____ Date
	2/25/09
_____ Clinical Team Leader	_____ Date