Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Ofatumumab

Proprietary Product Name: Arzerra

Sponsor: GlaxoSmithKline Australia Pty Ltd

February 2011

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	New biological entity
Decision:	Approved
Date of Decision:	15 December 2010
Active ingredient(s):	Ofatumumab
Product Name(s):	Arzerra
Sponsor's Name and Address:	GlaxoSmithKline (GSK) Australia Pty Ltd 1061 Mountain Highway, Boronia VIC 3155
Dose form(s):	Concentrated solution for injection
Strength(s):	100 mg/5mL
Container(s):	10 mL vial
Pack size(s):	10 vials and 3 vials
Approved Therapeutic use:	Arzerra, as a single agent, is indicated for the treatment of patients with B-cell chronic lymphocytic leukaemia (CLL) refractory to fludarabine and alemtuzumab.
Route(s) of administration:	Intravenous (IV) infusion
Dosage:	The proposed dosage regimen is: · An initial dose of 300 mg; · A further 7 doses of 2000 mg, at weekly intervals; · A further 4 doses of 2000 mg at 4-weekly intervals. In all, a total of 12 infusions are given over a period of 24 weeks.
ARTG Number (s)	163702

Product Background

Ofatumumab is a novel immunoglobulin G1κ (IgG1κ) human monoclonal antibody that specifically recognises a distinct epitope encompassing both large and small extracellular loops on the human CD20 molecule expressed on B cells and binds to this site with high affinity with a dissociation half-life ($t_{1/2}$) of 3 hours. Ofatumumab binds specifically to a distinct epitope encompassing both the small and large extracellular loops of the CD20 molecule. The CD20 molecule is a transmembrane phosphoprotein expressed on B lymphocytes from the pre-B to mature B lymphocyte stage and on B cell tumours. The B cell tumours include CLL, that generally expresses lower levels of CD20, and non-Hodgkin's lymphomas, with high CD20 expression occurring on >90% tumours. The CD20 molecule is not shed from the cell surface and is not internalised following antibody binding.

The binding of ofatumumab to the membrane-proximal epitope of the CD20 molecule induces recruitment and activation of the complement pathway at the cell surface, leading to complement-dependent cytotoxicity (CDC) and resultant lysis of tumour cells. Ofatumumab has been shown to induce appreciable lysis of cells with high expression levels of complement defence molecules. Ofatumumab has also been shown to induce cell lysis in both high and low CD20 expressing cells and in rituximab-resistant cells. In addition, the binding of ofatumumab allows the recruitment of natural killer cells allowing the induction of cell death through antibody-dependent cell-mediated cytotoxicity

The ability of ofatumumab to efficiently lyse B cells *in vitro* with a relatively low expression of CD20 molecules (such as B chronic lymphocytic leukaemia (CLL) cells) via CDC and antibody dependent cell-mediated cytotoxicity (ADCC) mechanisms led to a clinical development plan for ofatumumab in CLL. The medical need is in patients with advanced disease that have exhausted their therapeutic options. Therefore, clinical studies were initiated in CLL patients who are refractory to both fludarabine and alemtuzumab or were not appropriate candidates for alemtuzumab therapy due to bulky lymphadenopathy.

B cell chronic lymphocytic leukaemia is a subtype of mature peripheral B cell neoplasms, characterised by the accumulation of circulating malignant lymphocytes that typically express cell surface markers CD5, CD20 and CD23. No therapy has been shown to be curative for CLL or to prolong survival, so the treatment objective is disease control, mitigation of symptoms and prolongation of progression-free survival. Treatment is initiated when the patient presents with active disease. Although most patients with CLL will achieve responses with initial therapy, nearly all patients relapse and require further treatments. Advanced age, more than two prior therapies (Wierda, 2005), and the presence of chromosomal abnormalities such as 17p and 11q deletions (Döhner, 2000) are associated with decreased response to therapy.

The purine analog fludarabine, alone or in combination with other agents, can be considered as the backbone of CLL therapy in both the frontline and subsequent lines of therapy (Rai, 2000; Catovsky, 2007), and is indicated for alkylator resistant CLL. Alemtuzumab, an anti-CD52 monoclonal antibody, was recently approved for the treatment of patients with CLL for whom fludarabine combination chemotherapy is not appropriate (Hillmen, 2007).

For patients who are refractory to fludarabine the prognosis is poor. Alemtuzumab has shown a 2% complete remission (CR) and 31% partial remission (PR) rate with a median time to progression of 4.7 months but is associated with significant infectious complications, including a 19% incidence of opportunistic infections, and 13% incidence of fatal infections (Keating, 2002)[1]. For double-refractory (DR) patients, who no longer respond to fludarabine and alemtuzumab, there are no approved or other standard therapies are available. In a retrospective study of 58 fludarabine and alemtuzumab refractory CLL patients, treated at a single institution, the overall response rate to 20 different salvage therapies was 20%, and no responses were seen with monoclonal antibody therapies as single agents (0 responses in 14 subjects) (Tam *et al.*, 2007[2]). A wide range of salvage therapies have been used clinically but no standard of care has emerged due to limited efficacy (20% - 26% overall response rates) and substantial toxicity (13% incidence of early deaths and a 54% incidence of major infections) as published by Tam *et al*., 2007.

There is one other registered anti-CD20 monoclonal antibody which is registered in Australia – rituximab (Mabthera). The registered indications for rituximab include the treatment of patients with CD20 positive CLL *in combination with chemotherapy*. This indication encompasses both first and second-line use, but does not include use as monotherapy.

Other registered therapies for the treatment of CLL include:

- Alemtuzumab (MabCampath) – indicated for "the treatment of patients with B-cell CLL";

[1] Keating MJ *et al.* (2002). Therapeutic role of alemtuzumab (Campath-1H) in patients who have failed fludarabine: results of a large international study. *Blood.*99(10):3554-61.

[2] Tam CS *et al*., (2007). The natural history of fludarabine-refractory chronic lymphocytic leukemia patients who fail alemtuzumab or have bulky lymphadenopathy. *Leuk Lymphoma.*48:1931-1939.

- Fludarabine (Fludara) - "the treatment of B-cell CLL";
- Cladribine (Leustatin) - "the treatment of patients with B-cell CLL in whom treatment with alkylating agents has failed".

Proposed indications for use

Ofatumumab is proposed for use as monotherapy as a second-line therapy for CLL. The proposed indication restricts use to patients with *refractory* disease (that is, it does not include patients who have had an initial response to therapy and then have relapsed.

Regulatory Status

Arzerra has been approved in the USA (26 October 2009) and the European Union (EU) (19 April 2010).

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

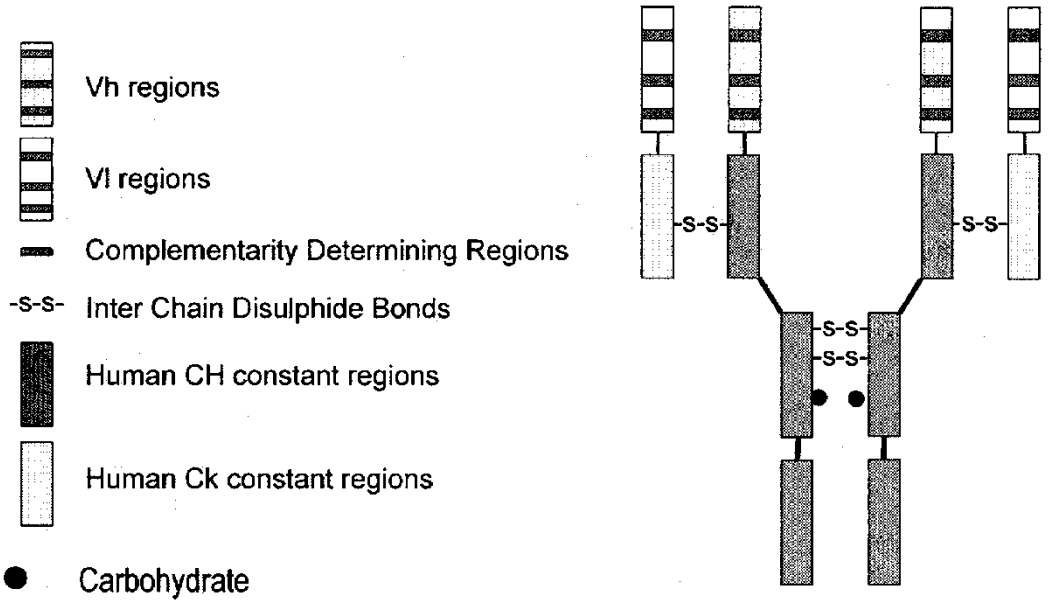
II. Quality Findings

Drug Substance (active ingredient)

Structure

Ofatumumab is a human monoclonal antibody produced in a murine cell line, using standard mammalian cell cultivation and purification technologies. The drug substance has the following structure:

Figure 1.



Ofatumumab is an IgG1κ human monoclonal antibody that specifically recognizes an epitope on the human CD20 molecule on B-cells. The molecular mass of the antibody is approximately 149 kilo Dalton (kDa) with the molecular weight (MW) of the light chain approximately 25 kDa and the MW of the heavy chain approximately 50 kDa. Carbohydrates constitute approximately 2% of the molecular weight of the ofatumumab antibody. Glycosylation is N-linked at asparagine $(Asn)_{302}$ of the heavy chain and primarily consist of fucosylated biantennary structures with varying amounts of terminal galactose.

Manufacture

The cell line for ofatumumab production is of murine origin transfected with a glutamine synthetase vector carrying antibody genes derived from the human anti-CD20 hybridoma cell line (2F2). Cell banking processes are satisfactory.

The drug substance is manufactured by expansion of cells from the working cell bank. Cells are progressively increased prior to transfer into a 2000L production bioreactor. The harvested and clarified material is concentrated then purified followed by low pH treatment. The antibody is concentrated and diafiltered then purified. The flow through material is filtered prior to concentration/diafiltration into the final formulation buffer. The drug substance is sterilised prior to testing and release. All viral/prion safety issues have been addressed, including use of animal-derived excipients, supplements in the fermentation process and in cell banking.

Quality Summary and Conclusions

There are no objections to the registration of Arzerra on Quality grounds.

III. Nonclinical Findings

Introduction

Nonclinical data include pharmacology studies, repeat-dose toxicity studies and an embryofetal toxicity study. The nonclinical program was constrained by the pharmacology of ofatumumab that does not bind to rodent or canine CD20 homologues. The cynomolgus monkey was the sole species used in toxicity studies. Pivotal toxicity studies were conducted according to Good Laboratory Practice (GLP)., The dossier submitted was largely in accordance with the EU note for guidance on nonclinical safety evaluation of biotechnology-derived pharmaceuticals (EMEA/CPMP/ICH/302/95).

Pharmacology

Primary pharmacology

Rationale and mechanism of action

The transmembrane protein, CD20, which has a role in B-cell proliferation and differentiation, is expressed on one-third of B-cell precursors and the majority of mature lymphocytic leukaemia blasts (80-90%; Leone *et al.*, 2006). The binding of a monoclonal antibody, such as ofatumumab, to CD20, induces its translocation into lipid rafts. Through interactions of the Fc region of the antibody with complement components and natural killer (NK) cells, B-cell lysis can be induced by complement-dependent cytotoxicity (CDC) and antibody dependent cytotoxicity (ADCC). Therefore, the use of ofatumumab is intended to specifically deplete B-cells with limited toxicity to other tissues in patients with CLL.

Efficacy

Pharmacology studies with ofatumumab focussed on the requirements for anti-lymphoma activity – CD20 binding and the induction of CDC and ADCC. Ofatumumab bound to CD20 (the 50% Effective Concentration (EC_{50}) was 287 ng/mL) on human peripheral blood mononuclear cells and induced its movement into lipid rafts. Once bound to cell-associated CD20, ofatumumab bound the complement factors, C1q and C3 and induced CDC (maximum at 2 μg/mL). Maximal ADCC by peripheral blood mononuclear cells (that is, 51% cell lysis) was observed *in vitro* with 0.1 μg/mL ofatumumab. These levels are considerably lower than the peak clinical plasma concentration of 1482 μg/mL.

In vivo, there was a dose-dependent prolongation of survival of mice grafted with human B-ALL (acute lymphocytic leukaemia) or Burkitt's lymphoma at ≥2 μg/mouse (≥1 μg/mL).

Greater efficacy was observed at 5 days rather than 14 days after engraftment, approximately100% compared to 66-77% tumour growth inhibition, respectively. The plasma levels of ofatumumab were lower than expected in the latter mice suggesting tumour load may have an effect on the pharmacokinetics. Acceleration of tumour growth was observed when ofatumumab plasma levels dropped below 0.4 µg/mL (Bleeker *et al.*, 2007).

Ofatumumab did not bind to mouse, rat, rabbit, dog or pig CD20 homologues but showed an affinity for CD20 from non-human primates similar to that observed for the human molecule, EC_{50} 97-139 ng/mL compared to 287 ng/mL. As expected, this resulted in significant depletion of $CD20^+$ B lymphocytes in the peripheral blood and lymph node of healthy cynomolgus monkeys at >1.25 mg/kg or 100 times lower than the clinical area under the concentration versus time curve (AUC) from a 2000 mg dose. Re-population of B-cell compartments occurred when ofatumumab levels dropped below 10 µg/mL. This was suggested to be the threshold plasma concentration for sustained biological activity (Bleeker *et al.*, 2007)[3].

Secondary pharmacodynamics and safety pharmacology

In an *ex vivo* study, ofatumumab bound only to $CD20^+$ tissues with limited cross-reactivity with other tissues at concentrations up to 20 µg/mL. *In vivo*, ofatumumab treatment did not change the pool of other cell phenotypes, including T cells[4], natural killer (NK) cells, neutrophil or monocyte populations within the blood or lymph node compartments at exposures almost twice that expected clinically. However, evidence for haemolysis and a positive Coombs' test[5] were seen in the 7 month repeat dose toxicity study.

No dedicated cardiovascular, renal or central nervous system (CNS) safety studies were submitted but, as some of these end points were included in repeat-dose toxicity studies, this is considered acceptable (ICH S6, EMEA/CPMP/ICH/302/95). Ofatumumab is a monoclonal antibody and unlikely to inhibit hERG channels (Vargas *et al.*, 2008)[6] and there were no treatment-related electrocardiogram (ECG) effects in cynomolgus monkeys at doses up to 100 mg/kg with an apparent maximum serum or plasma concentration (C_{max}) *ca* 6 times that expected clinically. In the pivotal study, signs of increased heart force and heart rate were observed during infusion and for approximately30 min post-dose from Week 15 of dosing. This was considered by the study author to be incidental but the occurrence only in ofatumumab-treated animals, the proximity to dosing on more than one occasion, and with incidences of tachycardia reported in clinical data, suggests these findings are likely to be treatment-related and clinically-relevant and may be an indication of cytokine release syndrome (see Local tolerance).

There were no clinical signs indicating CNS toxicity in repeat-dose studies at doses resulting in *ca* 6 fold the anticipated clinical C_{max}. As ofatumumab is a monoclonal antibody and, due

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[3] Bleeker, W.K. *et al.* (2007). Estimation of dose requirements for sustained *in vivo* activity of a therapeutic human anti-CD20 antibody. *Br. J. Haematol.* **140:** 303-312.

[4] A principal type of white blood cell that completes maturation in the thymus and that has various roles in the immune system, including the identification of specific foreign antigens in the body and the activation and deactivation of other immune cells. Also called *T lymphocyte.*

[5] The Coombs' test looks for antibodies that may bind to your red blood cells and cause premature red blood cell destruction (hemolysis).

[6] Vargas, H.M. *et al.* (2008) Scientific review and recommendations on preclinical cardiovascular safety evaluation of biologics. *J. Pharmacol. Toxicol. Methods* **58:** 72-76.

to its size and the presence of an Fc domain, is unlikely to cross the blood-brain barrier or be present in the brain in an appreciable amount (Zhang and Pardridge, 2001)[7]. An effect of released cytokines on the CNS cannot be dismissed as perivascular inflammatory cells in the brain and sciatic nerve were seen in treated monkeys after 7 months treatment.

There was no evidence of renal toxicity in repeat-dose toxicity studies.

Pharmacokinetics

In brief, there were no gender differences in systemic exposure to ofatumumab in cynomolgus monkeys. An apparent drug accumulation was observed after daily and weekly, but not fortnightly, administration of ofatumumab. This was most likely a result of its long elimination half-life (100-380 h). The plasma kinetics of ofatumumab were affected by the presence of anti-drug antibodies (ADAs) which occurred in a small number of animals.

Ofatumumab had a small (nonlinear) volume of distribution in both monkeys and humans (approximately0.1 L/kg). With respect to metabolism, the chemical nature of this compound (protein) would suggest that it would involve proteolytic cleavage. There were however no submitted studies which investigated the metabolic fate of ofatumumab.

Toxicology

General toxicity

Repeat-dose studies were conducted with ofatumumab administered *via* the intended clinical route (IV) in cynomolgus monkeys, a species in which ofatumumab is pharmacologically active,. All pivotal studies were GLP compliant and of adequate duration for a biopharmaceutical (7 months), The numbers of animals used were appropriate and the findings were consistent across all studies. The dosing frequency in the pivotal study was similar to that proposed clinically. A recovery period was included in the majority of studies with plasma concentrations of ofatumumab and ADAs monitored. Nonclinical batches were stated to be comparable to the intended clinical substance.

Doses used in the studies, however, resulted in exposures at or below the clinical exposure (see **Table 1**). Despite this there was almost complete depletion of B cells attained at all doses in each study, demonstrating that a near maximum pharmacodynamic response had been achieved. Based on the specificity of ofatumumab for its intended target, the doses used might be considered to be acceptable for this application. However, as there was limited toxicity observed in the submitted studies, at least one study with higher doses would have been desirable.

[7] Zhang, Y., and W.M. Pardridge. (2001) Mediated efflux of IgG molecules from brain to blood across the blood-brain barrier. *J. Neuroimmunol.* **114:** 168-172.

Table 1. Relative exposure of ofatumumab in repeat-dose toxicity studies[a]

Table.1. Relative exposure of ofatumumab in repeat-dose toxicity studies[b]

Study	Species & strain	Treatment duration [frequency]	Dose (mg/kg)	$AUC_{0-\infty}$ (mg.h/mL)	ER_{AUC}	C_{max} (mg/mL)	ER_{Cmax}
22804	**Monkey** (Cynomolgus)	4 days [daily]	1.25	4.2	0.01	106	0.1
			6.25	45	0.1	474	0.3
			12.5	179	0.3	724	0.5
23542	**Monkey** (Cynomolgus)	4 weeks [weekly]	20	190	0.3	918	0.6
			100	1189	1.8	8101	6
25052	**Monkey** (Cynomolgus)	7 months [8 weekly + 5 monthly]	20	241	0.4	951	0.6
			100	1168	1.7	4975	3.4
Clinical study HuMax-CD20-406	**Human** (B-CLL patients)	8 weeks [weekly]	40[a]	674	-	1482	-

[a] A 2000 mg does to a 50 kg individual; [b] Averaged from various time points; ER_{AUC} = animal:human exposure ratio based on AUC; ER_{Cmax} = animal:human exposure ratio based on C_{max}

Toxicities observed were consistent with a depletion of $CD20^+$ cells with atrophy of the germinal centre and lymphoid follicles of the spleen, the germinal centres of the mesenteric and mandibular lymph nodes, Peyer's patch and tonsils. Atrophy occurred with dose related severity. These findings were reversible or showed a trend to reversion. Decedents in the pivotal toxicity study had all received ofatumumab. These animals had signs of haemolytic anaemia or clinical or immunological evidence of gastrointestinal infection by *Campylobacter jejuni*. The increased incidence of GI infection was likely to have been due to a depletion of B cells compromising the immune status of the animals (see **Immunotoxicity**).

Signs of haemolytic anaemia (reduced haemoglobin, haematocrit and red blood cells with concomitant increases in reticulocyte levels) were present in a number of surviving animals after 7 months treatment at all doses. This was not seen in animals treated for 4 weeks suggesting longer treatment duration was required to show evidence of anaemia. Based on a direct Coombs' test and subsequent analyses, the observed anaemia was suggested to be due to an ofatumumab-induced humoral response leading to complement deposition on erythrocyte CR1 (complement receptor type 1) resulting in red blood cell destruction. High serum iron and bilirubin levels observed were also consistent with haemolytic anaemia. The observed anaemia was reversible. While neutrophils also contain CR1 receptors, there was no evidence of neutropenia in the nonclinical studies. The clinical relevance of these findings is unclear. CR1 receptors are also expressed on human erythrocytes suggesting anaemia may also occur after prolonged use clinically.

Genotoxicity and carcinogenicity

As is usual for most biotechnology-derived pharmaceuticals (ICHS6[8]), no genotoxicity or carcinogenicity studies were submitted. Ofatumumab is not expected to interact directly with deoxyribonucleic acid (DNA) and therefore has a low potential for genotoxic effects. Ofatumumab is not pharmacologically active in species typically used for carcinogenicity studies (mice and rats) and therefore such studies would not provide meaningful information. Given the target patient population, the absence of genotoxicity and carcinogenicity studies is considered acceptable.

[8] International Conference on Harmonization (ICH) Topic S 6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals. Note for guidance on preclinical safety evaluation of biotechnology-derived pharmaceuticals. (CPMP/ICH/302/95)

Reproductive toxicity

The sponsor provided the following justification for the absence of fertility studies: No specific histopathological changes were observed in the reproductive tissues in toxicity studies. CD20 is not expressed in tissues associated with fertility and binding to reproductive tissues was not observed in the human cross-reactivity study. Given the proposed indication and patient group and the sponsor's justification, the absence of fertility studies is considered acceptable.

An embryofetal study in cynomolgus monkeys was submitted. Pregnant monkeys were treated during the period of organogenesis (Gestation Day (GD) 20 to 50). Fetuses were clearly exposed to ofatumumab with concentrations of 8.6 and 66 µg/mL which were detectable in cord blood samples 50 days after the final dose of 20 and 100 mg/kg, respectively. This was not unexpected as it is well-documented that the active transplacental transport of IgG1 antibodies via the Fc receptor occurs during gestation (Sidiropoulos *et al.*, 1986; Roopenian and Akilesh, 2007[9]). Other than the expected evidence of pharmacological activity in the fetus (lower splenic weights and depleted B cells), there were no apparent treatment related changes in fetal body weight, body measurements or external, visceral or skeletal defects. The NOEL for teratogenicity was the highest tested dose, 100 mg/kg (***Table 2***). However, as this dose provides only an exposure marginally greater than the anticipated clinical exposure, effects on the developing fetus may not have been fully revealed and, as there was no apparent dose limiting toxicity, higher study doses may have been feasible.

The long term effects of low B cell levels and low splenic weights during fetal development are unclear. As the no observed effect level (NOEL) for these pharmacological effects resulted in an exposure below that expected clinically (Exposure Ratio based on AUC (ER_{AUC})=0.23), caution should be exercised in clinical practice. Haemolytic anaemia was observed in adult monkeys treated with ofatumumab and with its ability to cross the placenta, the potential for haemolytic anaemia in neonates also exists.

Table 2. Relative exposure of ofatumumab in reproductive toxicity studies[b]

Study	Species & strain	Treatment duration [frequency]	Dose (mg/kg)	$AUC_{0-¥}$ (mg.h/mL)	ER_{AUC}	C_{max} (mg/mL)	ER_{Cmax}
2148-010	**Monkey** (Cynomolgus)	GD20-GD50 [weekly]	20	160	0.23	694	0.5
			100	1092	1.6	4390	3
Clinical study HuMax-CD20-406	**Human** (B-CLL patients)	8 weeks [weekly]	40[a]	674	-	1482	-

[a] A 2000 mg does to a 50 kg individual; [b] Average from various time points; ER_{AUC} = animal:human exposure ratio based on AUC; ER_{Cmax} = animal:human exposure ratio based on C_{max}

No peri/postnatal studies were submitted. As ofatumumab is an antibody, it is likely to be excreted in milk. The effects of B cell depletion on the immunity of neonates and the potential adverse effects associated with the possibility of neonatal haemolytic anaemia need to be considered. The limited assessment of reproductive toxicity of ofatumumab is considered acceptable if the proposed indication is constrained to CLL patients with a median age 65-70 years, considered beyond reproductive activity. However, any extensions of

[9] Sidiropoulos, D., U. Hermann Jr, A. Morell, G. von Muralt and S. Brandun. (1986). Transplacental passage of IV immunoglobulin in the last trimester of pregnancy. *J. Pediatr.* **109:** 505-508. Roopenian, D.C. and S. Akilesh. (2007) FcRn: the neonatal Fc receptor comes of age. *Nature Rev. Immunol.* **7:** 715-725.

indication for ofatumumab to a younger population group will require a re-assessment of its reproductive toxicity.

Local tolerance

No dedicated local tolerance studies were submitted. There were no reported reactions at injection sites in repeat dose toxicity studies but these studies were not specifically designed to evaluate this.

Immunogenicity

Ofatumumab is a recombinant monoclonal antibody. In one comparative study in monkeys, more animals seroconverted with rituximab (6/6) than with ofatumumab (2/6). It is unclear if these results are predictive of the clinical situation but it is suggested that lower immunogenicity would be expected with greater humanisation (reviewed in Lobo *et al.*, 2004).

A higher number of monkeys had anti-ofatumumab antibodies following subcutaneous (SC) administration than after IV administration. This confirms previously published reports and may reflect differences in systemic absorption by the two routes of administration (reviewed in Lobo *et al.*, 2004). Systemic absorption *via* the SC route occurs primarily through the lymphatic system (Lobo *et al.*, 2004) so there is likely to be greater exposure to antigen presenting cells. Re-evaluation of immunogenicity after SC administration would need to be conducted if future applications include SC administration.

There were no apparent differences in the frequency or severity of responses between treated and control animals in delayed-type hypersensitivity reactions assessed in the 7 month repeat-dose toxicity study.

Immunotoxicity

T and NK cell populations were generally unaffected by ofatumumab treatment and there was no evidence of changes in cellular immune function. As expected, B cell populations were depleted in ofatumumab treated animals. The B cell populations affected were predominantly the non-memory B cells ($CD27^-CD21^+CD20^+$) at doses resulting in subclinical exposures based on AUC. At higher doses (ER_{AUC}=1.7) some depletion of memory B cells ($CD27^+CD21^+CD20^+$) was observed but these findings are confounded by the low basal level of memory B cells which could be expected for animals raised in a relatively protected environment. While the ability to mount an immune response was still evident in treated animals, IgG titres were considerably lower (approximately10% of control levels) during the treatment period and still low after 6 months recovery (approximately2-4% the level of control animals) suggesting an impairment of immune function. In the 7 month study, a number of treated animals, including premature decedents, had clinical or immunological signs of gastrointestinal infection by *Campylobacter jejuni*. While this bacterium is not uncommon in non-human primate colonies (Brady, 1998)[10], the severity of disease in treated animals, in some cases leading to death, may be a direct result of reduced immune function.

[10] Brady, A.G. and D.G. Morton. (1998) Digestive system (Chapter 10). *In:* Nonhuman primates in biomedical research, Diseases. Bennett, B.T., C.R. Abee and R. Henrickson. (ed). American College of Laboratory Animal Medicine Series.

As patients with CLL already have an increased susceptibility to infection (Cheson, 2001)[11], it is unclear if ofatumumab-treatment would increase this susceptibility.

There was limited evidence of the "cytokine-release syndrome" which has been observed clinically with rituximab, ofatumumab and other monoclonal antibodies (Greenberger, 2006)[12]. This syndrome is characterised by fever, chills, nausea and urticaria, and is believed to be due to the release of cytokines, such as tumour necrosis factor alpha (TNF-α), interleukin (IL)-6 and IL-8 from target cells, and activation of complement and neutrophils via Fc effector functions. While there was limited release of IL-6 in monkeys, with some evidence of tachycardia (see **Safety pharmacology**), reactions in the cynomolgus monkey appear to be poor predictors for anti-CD20-mediated cytokine-release syndrome.

Nonclinical Summary and Conclusions

- According to the relevant guidelines, the Sponsor has conducted adequate studies on the pharmacology, pharmacokinetics and toxicity of ofatumumab..

- *In vitro*, at concentrations several fold lower than the peak clinical plasma concentrations, ofatumumab bound to cell-associated CD20, induced its movement into lipid rafts and induced both complement dependent cytotoxicity and antibody dependent cytotoxicity. *In vivo*, there was a dose dependent prolongation of survival of mice grafted with B-ALL (acute lymphocytic leukaemia) or Burkitt's lymphoma. Acceleration of tumour growth was observed when ofatumumab plasma levels dropped below 0.4 μg/mL.

- Ofatumumab did not bind to mouse, rat, rabbit, dog or pig CD20 homologues but showed an affinity for CD20 from non-human primates similar to that observed for the human molecule. The threshold plasma concentration for the depletion of $CD20^+$ B lymphocytes in the peripheral blood and lymph node of healthy cynomolgus monkeys was 10 μg/mL, approximately 150 times lower than the peak clinical plasma levels.

- In monkeys, there were no signs of CNS or renal toxicity or treatment-related changes in ECG parameters at plasma concentrations 6 fold the anticipated clinical C_{max}. Treatment related increases in heart rate were observed occasionally during infusion and may be indicative of a hypersensitivity reaction.

- With respect to the pharmacokinetic profile of ofatumumab, there were no gender differences in systemic exposure to ofatumumab in monkeys. In xenografted mice there were indications tumour load negatively affected plasma levels. In both monkeys and humans, ofatumumab had a small volume of distribution (approximately0.1 L/kg) and a long plasma elimination half-life (100-380 h).

- Repeat dose toxicity studies up to 7 months duration were conducted in a species for which ofatumumab is pharmacologically active, the cynomolgus monkey. Doses used in the studies resulted in exposures at or below the clinical exposure but a near maximum

[11] Cheson, B.D. (2001) The chronic lymphocytic leukaemias. *In:* DeVite, V.T. Jr, S. Hellman, S.A. Rosenberg (ed). Cancer principles and practice of oncology. 6th edition, Vol 2. Lippincott Williams and Wilkins. p 2447-2465.

[12] Greensberger, PA. (2006) Drug Allergy. *J. Allergy Clin. Immunol.* 117(2 Suppl Mini-Primer): S464-470.

pharmacodynamic response was demonstrated. Toxicities observed were consistent with a depletion of $CD20^+$ cells with atrophy of the germinal centre and lymphoid follicles of the spleen, the germinal centres of the mesenteric and mandibular lymph nodes, Peyer's patch and tonsils. All of these findings were reversible. Additional findings included an increased incidence of infection as a result of impaired immunity and signs of anaemia consistent with complement-mediated erythrocyte destruction.

- No genotoxicity or carcinogenicity studies were submitted. This is usual for most biotechnology derived pharmaceuticals.

- No fertility or peri/postnatal studies were submitted. An embryofetal study in the cynomolgus monkey demonstrated ofatumumab crossed the placenta and was pharmacologically active in the fetus. No treatment related external, visceral or skeletal defects were observed at the highest tested dose resulting in exposures marginally greater than those expected clinically. However, the NOEL for embryofetal effects (lower splenic weights and depleted B cells) produced exposures below those expected clinically. The long term effects of these fetal findings are unknown.

- In treated monkeys, there was some evidence of cytokine release syndrome, with IL-6 release and occasional episodes of tachycardia.

- Treated animals showed an increased incidence of infection and lower IgG titres were induced in response to keyhole limpet haemocyanin challenge suggesting the reduction in B cell populations compromised the immune competence of treated animals.

Recommendations

- Nonclinical pharmacology studies support the proposed indication.

- While the majority of toxicity findings were consistent with the pharmacology of ofatumumab, haematological changes indicate patients may be more susceptible to infection and at greater risk of anaemia.

- The limited reproductive toxicity assessment is considered acceptable for the proposed indication and patient group. However, any future extensions of indication for ofatumumab will require a re-assessment of its reproductive toxicity.

- There are no objections on nonclinical grounds to the registration of ofatumumab for the proposed indication.

IV. Clinical Findings

Introduction

The efficacy and safety data in support of the application for registration of ofatumumab are primarily derived from the results of an interim analysis of an ongoing pivotal study (Study Hx- CD20-406). This study is a single arm, open-label, multicentre study of ofatumumab in subjects with CLL who were refractory to both fludarabine and alemtuzumab (DR), or were fludarabine refractory and considered inappropriate for alemtuzumab due to bulky lymphadenopathy (bulky fludarabine refractory, BFR).

Additional supportive evidence of safety and efficacy was provided by a Phase I/II study (Study Hx-CD20-402) of ofatumumab in subjects with relapsed/refractory CLL. The findings from this Phase I/II study served as the rationale for the ongoing pivotal study (Hx-CD20-406).

Further supportive safety data on ofatumumab in this application comes from other studies in CLL follicular lymphoma (FL), diffuse large B Cell Lymphoma (DLBCL), rheumatoid arthritis (RA), and chronic obstructive pulmonary disease (COPD) subjects.

National Agency scientific advice was sought on the acceptability of the overall programme to support licensure from the following countries: Germany, Sweden, Denmark and the UK. However, scientific advice from the European Medicines Agency (EMA) has not been sought.

All studies were undertaken in accordance with the principles of Good Clinical Practice.

Pharmacokinetics

Pharmacokinetic data were provided from the following studies: Hx-CD20-406 (CLL), Hx-CD20-402 (CLL), Hx-CD20-403 Part A and Hx-CD20-403 Part B (active rheumatoid arthritis [RA]), Hx-CD20-001 (follicular lymphoma [FL] Grade 1-2), and Hx-CD20-408 (chronic obstructive pulmonary disease [COPD]).

Study Hx-CD20-402

Serum ofatumumab concentrations were measurable up to 4 weeks after last infusion in the lower dose groups and up to approximately 7 months post-infusion in a small number of subjects in the highest dose group. Table 3 summarises the ofatumumab serum pharmacokinetic parameter values after the first and fourth infusions.

Table 3: Summary of Ofatumumab Serum Pharmacokinetic Parameter Values after the First and Fourth Infusions (Study Hx-CD20-402).

Cohort	n	Cmax (µg/mL)	tmax (h)	AUC(0-∞) (µg.h/mL)	CL (mL/h)	Vss (mL)	t½ (h)
First Infusion							
A 100 mg	3	8 (220)	6.9 (6.6-7.0)	447, 463[a]	215, 216[a]	3066, 4557[a]	9.7, 15.5[a]
B 300 mg	3	42 (41)	10.4 (7.1-11.8)	1135 (86)	264 (86)	4778 (78)	12.0 (13)
C 500 mg	27	136 (56)	7.7 (5.3-14.7)	7848 (141)	63.7 (140)	3241 (44)	31.3 (109)
Fourth Infusion							
A 500 mg	3	155 (36)	7.6 (5.8-9.3)	17060 (822)	35.3 (562)	2398 (57)	55.1 (353)
B 1000 mg	3	288 (32)	5.5 (5.2-6.0)	29341 (76)	37.8 (61)	3079 (9)	59.5 (89)
C 2000 mg	26	1061 (30)	6.2 (4.7-10.2)	420840[b] (103)	8.5[b] (98)	1727[b] (44)	276[b] (77)

Data are presented as geometric mean (%CVb – between-subject coefficient of variation) except tmax, which is presented as median (minimum-maximum)

a. n=2
b. n=24

After the first infusion, geometric mean area under the concentration time-curves from time zero to infinity ($AUC_{(0-\infty)}$) and C_{max} values tended to increase more than proportionally with dose. Half-life values were similar in the two lower dose groups (geometric mean half-life

($t_{½}$) = 12-13 hours) but were longer in the highest dose group (geometric mean t½ = 31 hours). Similar relationships between the pharmacokinetic parameter values across the three dose groups were seen after the fourth infusion; however, the number of subjects in the two lower dose groups was small (n=2 or 3), making it difficult to reach firm conclusions about dose proportionality.

Statistically significant differences between male and female subjects were found for AUC, clearance (CL), and Cmax values after both the first and fourth infusions, combining data in all dose groups; t½ values were not different. Geometric mean exposure values (AUC and Cmax) in female subjects in Group C (500 mg first infusion, followed by three 2000-mg infusions at weekly intervals) were approximately twice those of male subjects in Group C.

CL and t½ values were significantly different between the first and fourth infusions combining data in all dose groups (see Table 3). Ofatumumab exposure increased during the four weeks of infusions more than the expected accumulation based on first infusion data. These significant differences may be explained by rapid and sustained depletion of CD20+ B cells after the first infusion, leaving a reduced number of B cells available for the antibody to bind at subsequent infusions.

The relationships between ofatumumab pharmacokinetics and clinical response were also examined for pharmacokinetic parameter values adjusted for body weight and adjusted for body surface area, with similar results. Ofatumumab AUC and CL values correlated with duration of response, time to progression, and time to next anti-CLL therapy, with higher AUC values and lower CL values associated with longer duration of response, delayed time to progression, and delayed time to next anti-CLL therapy.

No relationship was seen between ofatumumab pharmacokinetics and occurrence of infections in exploratory analyses. There were no detectable anti-ofatumumab antibodies using the F(ab')2[13] assay.

Pivotal Study Hx-CD20-406

Pharmacokinetic data on 146 subjects in Study Hx-CD20-406 were included in the interim analysis. Because of the sparse sampling approach used in this study, a population pharmacokinetic model combining the data from Study Hx-CD20-402 and Study Hx-CD20-406 was used to generate individual pharmacokinetic parameter estimates after the eighth (Week 7) and twelfth (Week 24) infusions for the subjects in Study Hx-CD20-406.

Table 4 summarises the ofatumumab pharmacokinetic parameter values after the first, eighth, and twelfth infusions. The geometric mean half-life value after repeated administration was approximately 14 days (379 h (range 212-1477 h) and 334 h (range 217-701 h)) after the last weekly and last monthly infusions, respectively. Geometric mean clearance values after eight or twelve infusions were approximately 10 mL/h.

[13] A portion of an IgG molecule, produced by pepsin digestion, that contains two Fab fragments, that is two light chains and portions of two heavy chains, joined by disulfide bonds in the hinge region. Contains two antigen-combining sites.

Table 4: Summary of Ofatumumab Serum Pharmacokinetic Parameter Values after the First, Eighth, and Twelfth Infusions (Study Hx-CD20-406).

Parameter	n	First infusion (300 mg)	n	Eighth infusion (2000 mg)	n	Twelfth infusion (2000 mg)
Cmax (µg/mL)	143	63 (84)	130	1482 (50)	79	881 (42)
tmax (h)	143	7.4 (0.3-34.0)	130	4.5 (3.9-7.3)	79	4.5 (3.9-100.2)
AUC(0-∞) (µg.h/mL)		NE	127	674463 (85)	77	265707 (79)
CL (mL/h)		NE	127	9.5 (50)	77	10.1 (47)
Vss (mL)		NE	127	5127 (42)	77	4680 (30)
t½ (h)		NE	127	379 (40)	77	334 (26)

Data are presented as geometric mean (%CVb) except tmax, which is presented as median (minimum-maximum)
NE = not estimated

Pharmacokinetic parameter values were comparable between the DR and the BFR groups; for example, $AUC_{(0-\infty)}$ and C_{max} values at the eighth infusion in the DR and BFR groups were 666,461 µg.h/mL and 1467 µg/mL and 639,501 µg.h/mL and 1440 µg/mL, respectively. Ofatumumab exposure appeared to decrease as body weight, body surface area, and baseline creatinine increased, and exposure appeared to be higher in female subjects. Geometric mean exposure values (Cmax and AUC) after the eighth and twelfth infusions were approximately 50 to 80% higher in female subjects compared with male subjects.

Ofatumumab exposure was higher at the eighth infusion (last weekly infusion) in subjects who responded (37% higher $AUC_{(0-\infty)}$, 23% higher C_{max}, and 91% higher minimum or "trough" concentration in plasma (C_{min}) values) than in subjects who did not respond, as assessed by objective response from screening to Week 24; however, there was substantial overlap in exposure values between subjects who responded and who did not respond. No differences in exposure were seen at the twelfth infusion (last monthly infusion) between subjects who responded and subjects who did not respond.

Lower CL values at the twelfth infusion were associated with longer duration of response. Longer progression-free survival was associated with higher exposure ($AUC_{(0-\infty)}$, C_{max}, and C_{min} values) at both the eighth and twelfth infusions. In exploratory analyses, no relationships were seen between ofatumumab exposure and the time to first infection.

There were no detectable anti-ofatumumab antibodies using the whole ofatumumab assay.

Study Hx-CD20-001

Table 5 summarises the ofatumumab pharmacokinetic parameter values after the first and fourth infusions. After the first or fourth infusion, geometric mean $AUC_{(0-\infty)}$ and C_{max} values tended to increase more than proportionally with dose. A similar trend was seen with AUC and C_{max} values after the fourth infusion adjusted for either body weight or body surface area. There was no apparent difference in CL and $t_{½}$ values between the dose groups after the first or fourth infusion. $AUC_{(0-\infty)}$, CL, C_{max}, and $t_{½}$ values after the first or fourth infusion were analysed for gender differences, both by dose group and combining dose groups. There were few statistically significant differences; the one significant difference was 15% and 40% higher C_{max} values at 1000 mg after the first and fourth infusions in female subjects compared

to male subjects. $AUC_{(0-\infty)}$, C_{max}, CL, and $t_{½}$ values were statistically significantly different between the first and fourth infusions in all dose groups. Ofatumumab exposure increased during the four weeks of infusions more than the expected accumulation based on first infusion data. These significant differences may be explained by rapid and sustained depletion of CD20+ B cells after the first infusion, leaving a reduced number of B cells available for the antibody to bind at subsequent infusions.

Table 5: Summary of Ofatumumab Serum Pharmacokinetic Parameter Values after the First and Fourth Infusions (Study Hx-CD20-001) (M2.7.2, v2, p29)

Dose	n	Cmax (µg/mL)	tmax (h)	AUC(0-∞) (µg.h/mL)	CL (mL/h)	Vss (mL)	t½ (h)
First Infusion							
300 mg	10	76 (12)	4.5 (1.2-6.8)	9983 (32)	30.1 (32)	4603 (28)	111 (56)
500 mg	9	122 (25)	4.3 (2.5-5.8)	12426 (95)	40.2 (94)	2526 (18)	69 (105)
700 mg	10	209 (22)	4.9 (3.0-6.3)	29106[a] (54)	24.1[a] (54)	4372[a] (30)	131[a] (61)
1000 mg	10	339 (15)	4.7 (3.1-5.7)	50069 (52)	20.0 (52)	4017 (23)	143 (54)
Fourth Infusion							
300 mg	10	132 (12)	3.6 (2.7-5.3)	77959 (62)	7.6 (79)	2497 (10)	438 (31)
500 mg	9	193 (45)	3.4 (2.8-5.6)	56044 (165)	15.1 (114)	2798 (39)	239 (103)
700 mg	9	361 (24)	3.4 (2.9-5.3)	154440 (64)	9.8 (45)	2226 (34)	362 (40)
1000 mg	10	614 (27)	3.4 (2.4-25.4)	488107 (108)	3.8 (116)	2155 (28)	450 (77)

Data are presented as geometric mean (%CVb) except tmax, which is presented as median (minimum-maximum)
a. n=9

Study Hx-CD20-403 Part A and Part B

Table 6 summarises the serum pharmacokinetic parameter values after the first and second infusions for Part A of the study. After the first and second infusion, $AUC_{(0-\infty)}$ and C_{max} values increased more than proportionally with dose. Half-life values did not change systematically with dose. CL values were similar at the two lower dose levels, with a trend toward lower CL values at the high dose (1000 mg). As in other studies CL values were lower and $t_{½}$ values were higher after the second infusion compared to the first infusion in all active dose groups. There were no detectable anti-ofatumumab antibodies using the F(ab')2 assay.

Table 7 summarises the serum pharmacokinetic parameter values after the first and second infusions for Part B of the study. After both the first and the second infusions, $AUC_{(0-\infty)}$ and C_{max} values increased proportionally with dose. Half-life and CL values did not appear to change with dose. CL values were lower and $t_{½}$ values were higher after the second infusion compared to the first infusion in all active dose groups. Ofatumumab pharmacokinetic behaviour was not different between subjects who were positive for rheumatic factor (RF) at baseline and those who were negative (RF+ and RF-).

Table 6: Summary of Ofatumumab Serum Pharmacokinetic Parameter Values after the First and Second Infusion (Study Hx-CD20-403 Part A).

Dose	n	Cmax (µg/mL)	tmax (h)	AUC(0-∞) (µg.h/mL)	CL (mL/h)	Vss (mL)	t½ (h)
First Infusion							
300 mg	9	82 (20)	4.6 (3.0-8.4)	16904 (29)	17.7 (28)	4001 (30)	167 (25)
700 mg	9	192 (19)	6.3 (4.3-8.5)	38615 (28)	18.1 (28)	4423 (18)	172 (19)
1000 mg	9	415 (20)	6.7 (3.7-8.9)	75275 (39)	13.3 (39)	2976 (18)	159 (31)
Second Infusion							
300 mg	8	106 (22)	4.6 (3.8-5.4)	33493 (33)	11.1 (33)	3010 (30)	270 (16)
700 mg	9	244 (16)	5.2 (3.8-8.4)	97798 (40)	9.2 (33)	3238 (15)	338 (39)
1000 mg	9	514 (20)	5.5 (3.4-7.2)	171150 (51)	7.5 (49)	2233 (38)	312 (24)

Data are presented as geometric mean (%CVb) except tmax, which is presented as median (minimum-maximum)

Table 7: Summary of Ofatumumab Serum Pharmacokinetic Parameter Values after the First and Second Infusions (Study Hx-CD20-403 Part B).

Dose	n	Cmax (µg/mL)	tmax (h)	AUC(0-∞) (µg.h/mL)	CL (mL/h)	Vss (mL)	t½ (h)
First Infusion							
300 mg	55	117 (24)	4.7 (3.2-8.8)	18166[a] (33)	16.5[a] (33)	2819[a] (26)	123[a] (23)
700 mg	50	292 (22)	5.2 (4.2-7.8)	47640[b] (31)	14.7[b] (31)	2644[b] (23)	130[b] (23)
1000 mg	44	421 (21)	5.2 (3.9-7.8)	72709[c] (24)	13.7[c] (24)	2570[c] (24)	134[c] (20)
Second Infusion							
300 mg	55	151 (28)	4.1 (3.1-6.4)	54193[d] (42)	7.3[d] (40)	2314[d] (23)	316[d] (25)
700 mg	50	366 (22)	4.3 (3.3-7.5)	146968[e] (42)	6.5[e] (38)	2367[e] (21)	358[e] (27)
1000 mg	44	532 (22)	4.2 (3.3-6.1)	224528 (34)	6.3 (33)	2440 (25)	406 (25)

Data are presented as geometric mean (%CVb) except tmax, which is presented as median (minimum-maximum)

a. n=51
b. n=40
c. n=37
d. n=54
e. n=49

Study Hx-CD20-408

Study Design

Study Hx-CD20-408 was a double-blind, randomised, partial crossover, placebo-controlled, Phase I/II study to evaluate the safety, efficacy, and pharmacokinetic profile of ofatumumab in subjects with moderate to severe chronic obstructive pulmonary disease (COPD). Subjects

were randomised to receive either 100 mg ofatumumab or placebo on Day 0 and 1000 mg or placebo at Week 1 and Week 3 as IV infusions; after protocol amendment, the Day 0 dose was divided to 10 mg or placebo on Day 0 and 90 mg or placebo on Day 1. After completion of the blinded portion of the study, placebo subjects were to be allowed to receive the active regimen described above.

Forty subjects were to be randomised 1:1 active:placebo. Serial blood samples were collected after the third infusion (Week 1) and the fourth infusion (Week 3) for the determination of plasma concentrations of ofatumumab; samples were to be collected using a similar schedule for placebo subjects who crossed over to ofatumumab treatment after the blinded portion of the study. The study was terminated due to adverse events after five subjects had enrolled (two serious adverse events of Grade 3 bronchospasm attributed to treatment). Because of the small number of subjects and limited number of samples per subject, pharmacokinetic analysis was not performed. C_{max}, C_{min}, and time to maximal plasma concentration (t_{max}) values were estimated directly from the concentration-time data.

Results

Only two of the five subjects received ofatumumab and had pharmacokinetic samples collected after dosing as planned. In those two subjects, C_{max} values of 352 and 605 mg/L were observed at Week 3 (after the second 1000 mg dose).

Pharmacokinetics in Special Populations

Age: Age was not found to be a significant factor accounting for inter-individual variability in ofatumumab pharmacokinetics in analyses of patients ranging in age from 21 to 86 years of age. No dose adjustment is recommended.

Size: Increases in measures of body size (height, weight, and/or body surface area) were associated with small increases in clearance and volume of distribution, with the effects ranging from 5 to 16% with 10-kg increases in weight or $0.1m^2$ increases in body surface area. These differences are not considered clinically relevant, and no dose adjustment is recommended.

Gender: Gender accounted for a small amount (14-25%) of inter-individual variability in ofatumumab pharmacokinetics after accounting for differences in body size. These differences are not considered clinically relevant, and no dose adjustment is recommended.

Race: Almost all (96%) of the subjects were Caucasian; therefore, the influence of race or ethnicity could not be assessed.

Renal Impairment: High molecular weight molecules are excluded from glomerular filtration, and IgG molecules are not subject to tubular secretion. Therefore, changes in renal function are unlikely to have any effect on the elimination of ofatumumab. Baseline calculated creatinine clearance was not found to be a clinically significant factor accounting for inter-individual variability in ofatumumab pharmacokinetics with calculated creatinine clearance values ranging from 33 to 287 mL/min. No dose adjustment is recommended for mild to moderate renal impairment (creatinine CL (CLcr) >30 mL/min).

Hepatic Impairment: No pharmacokinetic data are available in subjects with hepatic impairment. IgG1 molecules such as ofatumumab are catabolised by ubiquitous proteolytic enzymes that are not restricted to hepatic tissue; therefore, changes in hepatic function are unlikely to have any effect on the elimination of ofatumumab. No dose adjustment is recommended.

Diagnosis: Ofatumumab clearance and volume of distribution differed between subjects with the different diseases, with the highest values observed in subjects with CLL. The differences in clearance values between the diagnoses decreased with later infusions. These differences suggest that therapeutic doses of ofatumumab as monotherapy should be higher in CLL than in FL and RA.

Clinical Immunogenicity Data

Out of the 274 subjects who received ofatumumab in Study Hx-CD20-001, Study Hx-CD20-402, and Study Hx-CD20-403 Part A and B, only two samples were positive. Although encouraging, conclusions regarding these results are limited in that the assay used to measure anti-ofatumumab antibodies (the F(ab')2 binding antibody clinical assay) was restricted to detection of antibodies of just one isotype (IgG1) and was not capable of detecting antibodies to the CH2 and CH3 domains.

Summary of Pharmacokinetics and Pharmacodynamics

Pharmacokinetics

- Ofatumumab is eliminated in two ways: a target-independent route as with other IgG molecules and a target-mediated route related to binding to B cells.
- Clearance and volume of distribution values were low and half-life values were long for ofatumumab, as seen with other monoclonal antibodies.
- Clearance values decreased and half-life values increased following repeated administration in all diseases. In the two studies in subjects with CLL, the geometric mean values for CL and t½ were 63.7 mL/h and 1.3 days (31.3 h) after the first infusion, 8.5 mL/h and 11.5 days (276 h) after the fourth infusion, 9.5 mL/h and 15.8 days (379 h) after the eighth infusion, and 10.1 mL/h and 13.9 days (334 h) after the twelfth infusion. These changes in pharmacokinetic parameter values with repeated dosing may be explained by rapid and sustained depletion of CD20+ B cells after the first infusion, leaving a reduced number of CD20+ B cells available for the antibody to bind at subsequent infusions.
- Ofatumumab volume of distribution (Vss) values were low (geometric mean Vss values of 1.7 to 5.1 L across studies, dose levels, and infusion number); this is consistent with distribution largely in the systemic circulation.

Significant covariates on ofatumumab pharmacokinetics were identified:

- Diagnosis (CLL, FL, or RA): Clearance values were higher in CLL than in FL or RA, especially at the first infusion (for example, 369%). Clearance values were 62% higher in FL than in RA at first infusion. In general, Vss values were higher in CLL (22-65%) than in FL or RA; higher Vss values (35%) were seen in FL than in RA at first infusion.
- Measures of Body Size: Increases in measures of body size (height, weight, and/or body surface area) were associated with small increases in clearance and volume of distribution, with the effects ranging from 5 to 16% with 10-kg increases in weight or $0.1m^2$ increases in body surface area. These differences are not considered clinically relevant, and no dose adjustment is recommended.
- Gender: Gender accounted for a small amount (14-25%) of the inter-individual variability in ofatumumab clearance and Vss values; however the differences are not likely to be clinically relevant, and no dose adjustment is recommended.

Pharmacodynamics

Response:

- In subjects with relapsed or refractory CLL (Study Hx-CD20-402), the primary efficacy endpoint was objective response over the period from screening to Week 19. One of the

three subjects (33%) in Group A (Week 1 100 mg, Weeks 2-4 500 mg) responded, 0 of 3 subjects (0%) in Group B (Week 1 300 mg, Weeks 2-4 1000 mg) responded, and 13 of 27 subjects (48%) in Group C (Week 1 500 mg, Weeks 2-4 2000 mg) responded to ofatumumab.

- In Study Hx-CD20-406 the objective response rates (99% Confidence Interval (C.I.)) from screening to Week 24 were 58% (40-74%) in the group of subjects refractory to both fludarabine and alemtuzumab (double-refractory (DR); n=59) and 47% (32-62%) in the group of subjects refractory to fludarabine and considered not suitable for alemtuzumab therapy due to bulky adenopathy (bulky fludarabine-refractory (BFR); n=79).
- In subjects with FL (Study Hx-CD20-001), there was no apparent relationship between ofatumumab dose level (300 to 1000 mg infused weekly for four weeks; n=9 or 10 per dose level)) and clinical response rate (response from screening to Week 19).
- In subjects with RA (Study Hx-CD20-403), all active doses induced a clearly higher response rate than placebo (n=7 to 12 per group in Part A; n=54 to 58 per group in Part B). There was no clear dose-response relationship between the active doses (300 to 1000 mg, two infusions two weeks apart). Although there were trends toward higher response rates at higher doses.

B-cell counts:

- Rapid, efficient, and sustained depletion of peripheral B cells was observed for the majority of subjects with CLL, FL, or RA at all dosing regimens tested, with the decrease beginning with the first ofatumumab infusion.
- In subjects with refractory CLL in Study Hx-CD20-406, the median decrease in B cell counts was 23% after the first infusion (300 mg) and 92% after the eighth infusion (2000 mg). Peripheral B-cell counts remained low throughout therapy in most subjects and gradually increased after the end of ofatumumab therapy, with the median decrease in B-cell counts remaining 68% below baseline three months after the last infusion.

Drug Interactions

No specific drug-drug interaction studies were submitted.

Pharmacodynamics

Pharmacodynamic data were provided from the following studies: Hx-CD20-406 (CLL), Hx-CD20-402 (CLL), Hx-CD20-403 Part A and Hx-CD20-403 Part B (RA), and Hx-CD20-001 (FL Grade 1-2).

Pivotal Study Hx-CD20-406

Study Design

Study Hx-CD20-406 is an ongoing, single arm, open-label, multi-centre study of ofatumumab in subjects with B-CLL who are either refractory to both fludarabine and alemtuzumab, or who are refractory to fludarabine and were considered inappropriate for alemtuzumab treatment due to bulky lymphadenopathy. Single agent ofatumumab was administered as 8 weekly infusions followed by 4 monthly infusions over 24 weeks. The primary endpoint was response rate over a 24 week period.

A non-randomised study design was chosen for several reasons. CLL patients who are refractory to fludarabine containing regimens have a poor prognosis. As discussed earlier, a wide range of salvage therapies have been used clinically but no clear standard of care has emerged. A comparison against “physician’s choice” could have been an option; however, the early results from the dose ranging Phase I/II study Hx- CD20-402 clearly indicated activity with a 48% response rate in the 2000 mg dose group. In light of the favourable Phase I/II results with ofatumumab in comparison to the low response rates and substantial

toxicities with salvage therapies, investigators indicated that subjects would have been reluctant to be randomised to a comparator other than ofatumumab. The non-randomised study design was discussed with CLL experts who reviewed the safety and efficacy of ofatumumab in Study Hx-CD20-402 in the context of the limited efficacy and toxicities of other salvage therapies and it was agreed that such a design would be acceptable to confirm the Study Hx-CD20-402 data.

Adult subjects were eligible for participation if they had active CLL and were refractory to prior therapy defined as a minimum of 2 cycles of fludarabine and at least 12 administrations of alemtuzumab (DR). Subjects were also eligible if they were refractory to prior therapy defined as a minimum of 2 cycles of fludarabine and were considered inappropriate candidates for alemtuzumab treatment due to the presence of bulky lymphadenopathy, defined as lymph node size of >5 cm (BFR).

All subjects were scheduled to receive eight weekly infusions of ofatumumab from Week 0 to Week 7, followed five weeks later by one infusion of ofatumumab every four weeks from Week 12 through Week 24, for a total of 12 infusions. The first infusion of ofatumumab was 300 mg; all subsequent infusions of ofatumumab were 2000 mg. The ofatumumab 2000 mg therapeutic doses were adopted from the dose ranging Study Hx-CD20-402.

This is an ongoing trial planned to be conducted in approximately 225 CLL patients (target population of at least 100 DR patients and 100 BFR patients). This dossier contained the interim report of the data from the pre-specified interim analysis (cut-off day 2008). This interim analysis was triggered when the sponsor assessed that primary endpoint data from 66 double-refractory patients were available. The trial consisted of 3 periods as described below:

Treatment (up to 24 weeks): Patients eligible for this trial were allocated to 8 weekly infusions of ofatumumab (first dose: 300 mg; second – eighth dose: 2000 mg) followed by 4 monthly infusions of ofatumumab (ninth – twelfth dose: 2000 mg). The first monthly infusion was administered 5 weeks after the last weekly infusion and the following 3 monthly infusions were administered every 4 weeks. Thus, the first dose was administered at Week 0 (Visit 2) and the last dose was administered at Week 24 (Visit 14). Patients who withdrew from treatment were assessed according to Visit 21 and End-of-study procedures (Visit 21 is the last visit in the Follow-up period). Hereafter, the patient could continue in Extended Follow-up period.

Follow-up (Week 28 to Month 24): Patients who completed the treatment period at Week 28 (Visit 14) entered the Follow-up period and their disease status was evaluated every 3 months until Month 24 (Visit 21). Hereafter, End-of-study procedures were completed and the Extended Follow-up period initiated.

Extended Follow-up: After completion of Month 24 (Visit 21) visit, patients were monitored every 3 months for survival and malignant B-cell values. Monitoring continued until the B-cell values reached baseline level or above, or until alternative CLL therapy was initiated, or Month 48. Patients were allowed to enter the Extended Follow-up period following withdrawal from Treatment- or Follow-up period.

Study Objectives

Primary Objective

· To evaluate the efficacy of ofatumumab in patients with B-cell CLL who have failed fludarabine and alemtuzumab

Secondary Objectives

· To determine the safety of ofatumumab

- To determine the host immune response to ofatumumab
- To determine the pharmacokinetic profile of ofatumumab

Inclusion and Exclusion Criteria

The trial population included patients with CLL who were ≥18 years of age. The patients were to be either refractory to fludarabine and alemtuzumab treatment (DR group) or, refractory to fludarabine and considered inappropriate for alemtuzumab treatment due to bulky (>5 cm) lymphadenopathy (BFR group). The patients were to have active disease, as defined and confirmed according to the 1996 National Cancer Institute-Working Group (NCI-WG) guideline, with the exception that only 1 criterion for 'active disease' had to be met (as in the updated in the 2008 NCI-WG guideline)[14].

Study Population

A total of 198 subjects were screened for this study. As of the clinical cut off date for the interim analysis for this study (19 May 2008), 154 subjects with planned or completed Visit 2 before 27 November 2007 had data available for the interim analysis of the primary efficacy (response data) endpoint. Subject assignment based on the Independent endpoints Review Committee (IRC) assessment included 59 exposed DR subjects, 79 exposed BFR subjects, and 16 exposed CLL subjects assigned as 'Other'. A total of 86 subjects remain on the study (20 in Follow-up period and 66 in Extended Follow-up period) and 68 have withdrawn from all study activities inclusive of 61 subjects who died.

The median age of the subjects was 64 years (range: 41 to 86 years) and the majority of subjects were Caucasian (97%) and male (72%).

The overall disease characteristics of subjects in this study population were consistent with subjects with refractory CLL. The subjects had CLL for a median duration of 6.3 years. The median number of prior CLL therapies was 5. The median time from last anti-CLL treatment was 4.7 months (range: 1 to 78 months).

ECOG performance status[15] for each subject assessed at baseline was similar in each population subgroup. Approximately two-thirds of all subjects had an impairment of their daily living abilities with a performance status of 1 or 2. The majority of subjects in each

[14] Hallek *et al*. 2008. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) updating the National Cancer Institute-Working Group (NCI-WG) 1996 guidelines. http://docs.google.com/viewer?a=v&q=cache:lvfOiubHcg4J:www.bloodmed.com/contentimage/guidelines/3182.pdf+CLL+NCI-WG+1996+guidelines&hl=en&gl=au&pid=bl&srcid=ADGEESjjFRv541MyOiMSJ0XGMgflGsUksHhY7EV-xxvTZ97EKVM8l2NHqzQITs7ud1zbgnuMOkwCoWp6i2Q7Yrl230PkqPP0Qds6gUxYGLe_xMuoWpXZcJjsy3ja1GFdD8DjUSkYkscn&sig=AHIEtbSiURY1Zdlb-RAX5NPS41qSEoLw2A

[15] ECOG Performance Status. The Eastern Cooperative Oncology Group (ECOG) has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used: 0 - Fully active, able to carry on all pre-disease performance without restriction, 1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work, 2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours, 3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours, 4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair, 5 - Dead

subgroup had high risk CLL at screening by Rai stage (III or IV was 16% and 47%, respectively) or by Binet stage (B or C was 34% and 58%, respectively)[16].

Cytopaenia observed at baseline was consistent with advanced stage CLL. The overall median lymphocyte count was above normal at baseline (19.7 x 10^9/L; normal laboratory range: 1.5 to 4.0 x 10^9/L), with the lowest median lymphocyte count in the DR group. Subjects in the DR group were exposed to a greater number of prior therapies than those in the BFR group, which may account for the lower median lymphocyte count. Median platelet counts were below normal (96.5 x 10^9/L, normal laboratory range: 144 to 440 x 10^9/L), median haemoglobin levels were below normal (10.9 g/dL, normal laboratory range: 12 to 16 g/dL), and median neutrophil counts were within the normal range (2.5 x 10^9/L, normal laboratory range: 1.7 to 8.8 x 10^9/L).

In relation to medical history, the following were most frequently reported: history of hypertension (28% of subjects), anaemia (21% of subjects), thrombocytopaenia (13% of subjects), drug hypersensitivity (12% of subjects), cough (12% of subjects) and fatigue (11% of subjects).

Pharmacodynamic Results

Clinical Response

In Study Hx-CD20-406, the objective response rates (99% C.I.) were 58% (40- 74%) in the DR group (n=59) and 47% (32-62%) in the BFR group (n=79), according to the 1996 NCI-WG guidelines as confirmed by the Independent Review Committee.

CD19+ B cells

In subjects with refractory CLL in Study Hx-CD20-406, the median decrease in B-cell counts was 23% after the first infusion and 92% after the eighth infusion. Peripheral B-cell counts remained low throughout the remainder of therapy in most subjects and gradually increased after the end of ofatumumab therapy, with the median decrease in B-cell counts remaining 68% below baseline three months after the last infusion.

The median CD5+CD19+ count at baseline was 14,167 x 10^6 /L (range 5-427,015 x 10^6/L). A median reduction of 23% in CD5+CD19+ count was observed after the first infusion; at Week 7 and Week 24, the median reduction in CD5+CD19+ count from baseline was 92% at both time points, demonstrating that the reduction in cell count was sustained during treatment. CD5+CD19+ cell counts gradually increased after the end of ofatumumab therapy, with the median reduction in B-cell counts remaining 68% below baseline three months after the last ofatumumab infusion.

Exposure-Response Relationships

In Study Hx-CD20-406, ofatumumab exposure was higher at the eighth infusion (last weekly infusion) in subjects who responded (37% higher AUC, 23% higher C_{max}, and 91% higher C_{min} values) than in subjects who did not respond, as assessed by objective response from screening to Week 24; however, there was substantial overlap in exposure values between subjects who responded and who did not respond. No differences in exposure were seen at the twelfth infusion (last monthly infusion) between subjects who responded and subjects

[16] The Rai and Binet staging systems are a standardized way to summarize information about how far a cancer has spread. The Rai system is used more often in the United States and the Binet system is used more widely in Europe.

who did not respond. Longer progression-free survival was associated with higher exposure (AUC, C_{max}, and C_{min} values) at both the eighth and twelfth infusions.

Supportive Study Hx-CD20-402

Study Design

Study Hx-CD20-402 was an open-label, multicentre, dose-escalating Phase I/II study in which ofatumumab was given to subjects with relapsed or refractory CLL. The primary objective was to evaluate the safety and efficacy of ofatumumab in subjects with CLL. The primary efficacy endpoint was response rate (RR) according to the CLL NCI-WG 1996 guidelines during the period from screening to Week 19. Efficacy assessments were performed at all visits from Week 4 to Week 27 and evaluated by the international coordinating investigator.

The subject population was less heavily pre-treated compared to Study Hx-CD20-406.

Adult subjects were eligible if they had active CLL with a circulating lymphocyte count of >5 x 10^9/L, verified by flow cytometry to be CD5+, CD20+, and CD23+. Subjects were excluded if they had previous treatment with rituximab, alemtuzumab, or autologous stem cell transplantation within 6 months prior to screening; allogeneic stem cell transplantation at any time; anticancer therapy, radiotherapy, or glucocorticosteroids within 4 weeks prior to screening; or known or suspected transformation of CLL (Richter's syndrome).

In this dose-escalation trial, subjects were allocated in consecutive order to Group A, Group B, and Group C to receive weekly treatment for four weeks. The next dose level was started when the first 3 subjects in a lower dose level group had received all four infusions plus one week of follow-up without dose-limiting toxicity (DLT). Subjects in Group A received 100 mg ofatumumab as first infusion, and 500 mg ofatumumab for the second, third, and fourth infusion. Subjects in Group B received 300 mg ofatumumab as the first infusion and 1000 mg ofatumumab for the second, third, and fourth infusion. Subjects in Group C received 500 mg ofatumumab for the first and 2000 mg ofatumumab for the second, third, and fourth infusion.

Stopping rules based on DLT were pre-defined and based on the number of DLT cases observed and the number of subjects treated in each treatment group. The number of subjects planned was 3 subjects each in Groups A and B, and 27 in Group C. If one DLT was observed among the first 3 subjects in Group A or B, an additional 3 subjects were to be evaluated at that dose level before dose escalation. No DLT occurred in Group A or B, and the study was enrolled as planned. The study was subsequently amended to omit a planned interim analysis.

The primary efficacy endpoint was response rate (RR) during the period from screening to Week 19, according to the CLL NCI-WG 1996 guidelines. Efficacy assessments were performed at all visits from Week 4 to Week 27 and evaluated by the international coordinating investigator to determine response.

Study Objectives

Primary Objective

- To evaluate the safety and efficacy of ofatumumab in patients with CLL.

Secondary Objective

- To determine the pharmacokinetics after a single dose and after 4 weekly doses of ofatumumab in patients with CLL.

Study Population

A total of 33 subjects were enrolled in Study Hx-CD20-402. Of these, 3 subjects were allocated to Group A (500 mg), 3 subjects to Group B (1000 mg) and 27 subjects to Group C (2000 mg). Thirteen (39%) of the 33 subjects completed the study and 20 (61%) subjects discontinued from the study due to disease progression (19 subjects, including 3 subjects listed under 'Other' reasons) and death (1 subject).

All subjects in Hx-CD20-402 had relapsed/refractory CLL. However, the disease was less advanced in these subjects as compared with subjects in Study Hx-CD20-406. Subjects in Study Hx-CD20-402 received fewer pre-treatments. The median age of all subjects was 61 years. A total of 13 subjects (39%) were ≥65 years of age, and 2 (6%) were ≥75 years of age. A total of 19 (58%) subjects were male and all subjects were Caucasian.

According to the Rai and Binet staging systems, most of the subjects (85% to 88%, respectively) in this study were in the low-risk or intermediate-risk group. The most common prior CLL therapy was single agent cytotoxics, such as chlorambucil, cladribine or cyclophosphamide (29 of 33 subjects, 88%).

Pharmacodynamic Results

Clinical Response

In Study Hx-CD20-402 the primary efficacy endpoint was objective response over the period from screening to Week 19 after the first infusion, according to the 1996 NCI-WG guidelines. One of the three subjects (33%) in Group A (Week 1 100 mg, Weeks 2-4 500 mg) responded, 0 of 3 subjects (0%) in Group B (Week 1 300 mg, Weeks 2-4 1000 mg) responded, and 13 of 27 subjects (48%) in Group C (Week 1 500 mg, Weeks 2-4 2000 mg) responded to ofatumumab.

Exposure-Response Relationships

In Study Hx-CD20-402 statistically significant associations were seen between objective response and ofatumumab exposure after the fourth infusion (241% higher AUC, 43% higher C_{max}, and 94% higher C_{min} values in subjects who responded compared to those who did not respond); higher AUC values were associated with longer duration of response, delayed time to progression, and delayed time to next anti-CLL therapy.

The median CD5+CD19+ count at baseline was 47,713 x 10^6 /L (range 5,523-220,427 x 10^6 /L). In Group C, a median reduction of 55% in CD5+CD19+ count was observed after the first infusion (500 mg); after the fourth infusion (2000 mg), the median reduction in CD5+CD19+ count from baseline was 97%. CD5+CD19+ cell counts gradually increased after the end of ofatumumab treatment. Rapid, efficient, and sustained depletion of malignant and normal B cells was observed in the majority of subjects during the study.

Study Hx-CD20-001

Study Design

Study Hx-CD20-001 was an open-label, international multicentre, dose escalating, Phase I/II study of ofatumumab in patients with relapsed or refractory follicular lymphoma Grade I-II. This dose escalating clinical trial comprised 4 cohorts of patients receiving 4 weekly doses of 300, 500, 700 or 1000 mg ofatumumab. Some 10 patients in succession were enrolled at each dose level. Dose escalation took place when the 10th patient in the previous dose level was allocated, the first 3 patients had one week of follow up after 4th infusion, the 6th patient had one week of follow up after 1st infusion and less than 2 DLTs in the first 6 patients were observed.

Patients were scheduled for a screening visit (V1), 7 visits during the 3-week treatment phase (V2-8) and 9 visits during the follow up period (V9-17) which lasted until Month 12. Some 40 patients were enrolled; 10 at each dose level (42 patients were screened of whom 2 were ineligible).

Study Objectives

Primary objective

· To establish the safety and efficacy of ofatumumab in patients with relapsed or refractory follicular lymphoma Grade 1-2.

Secondary objective

· To determine the pharmacokinetics after a single dose and after 4 doses of HuMax-CD20 at weekly intervals in patients with relapsed or refractory follicular lymphoma Grade 1-2.

Inclusion and Exclusion Criteria

The main criteria for inclusion were: relapsed or refractory follicular lymphoma Grade 1-2, defined according to the World Health Organization (WHO); tumour verified to be CD20-positive from excisional lymph node biopsy; CT scan in screening phase showing: 2 or more clearly demarcated lesions with a largest diameter ≥ 1.5 cm, or 1 clearly demarcated lesion with a largest diameter ≥2.0 cm.

Study Population

All 40 patients (20 males and 20 females; all Caucasian) are included in the Full Analysis Set (FAS). The Per Protocol (PP) population comprised 39 patients. Median age was 58.5 years ranging from 34-75. Median duration of follicular lymphoma was 4. 5 years ranging from 0.7-17.1 years.

Pharmacodynamic Results

Clinical Response

There was no apparent relationship between ofatumumab dose (300 to 1000 mg infused weekly for four weeks) and clinical response in Study Hx-CD20-001 (FL). Ofatumumab induced objective responses (CR, CRu and PR) in all dose groups with response rates from 20% - 63%. The objective response rates were 63% (5/8) at 300 mg, 33% (3/9) at 500 mg, 20% (2/10) at 700 mg, and 50% (5/10) at 1000 mg. The overall response rate was 41% across all dose groups.

Based on Kaplan-Meier estimates the median time to progression for all patients was 8.8 months (95% CI 5.4-20.0) and the median duration of response was 29.9 months (95% CI 19.7-36.1). The time to next anti-FL therapy and was not reached during the study.

The median CD19+ count at baseline was 85 x 10^6 /L (range 7-939 x 10^6 /L). Most subjects in all dose groups had a profound depletion of CD19+ cells after the first infusion. CD19+ cells remained nearly undetectable until approximately 6 to 10 months post-treatment, followed by a slow and gradual recovery. Rapid, efficient, and sustained B-cell depletion was seen in all dose groups.

Study Hx-CD20-403 Part A and Part B

Study Design

Study Hx-CD20-403 is a double-blind, randomised, placebo-controlled, dose escalation, multicentre, Phase I/II trial of ofatumumab in patients with active rheumatoid arthritis who have previously failed one or more disease modifying anti-rheumatic drugs.

This trial comprised sequential enrolment into 3 dose groups (4:1 active:placebo). Dosing in the next dose group was initiated when the DMC evaluated dose-limiting toxicities (DLTs) for all patients in the previous dose group, followed for at least 3 days after the second infusion.

The dose-escalation study is referred to as Part A. It was followed by a parallel-group part with randomisation into one of 4 treatment arms (referred to as Part B).

Patients received 2 infusions of ofatumumab (300 mg, 700 mg, or 1000 mg) or placebo, 2 weeks apart, and were followed for safety, efficacy, and pharmacokinetic measurements for 24 weeks. Ofatumumab/placebo was administered as an IV infusion via an infusion pump. Patients were scheduled for a screening visit (V1), the first infusion (V2) and follow-up after one and 7 days (V3+V4), the second infusion (V5) and follow-up after one and 7 days (V6+V7) and then 6 additional visits (V8-V13) up until the final assessments at 24 weeks. Hereafter patients were followed every 12 weeks until B-cells (CD19+ cells and by association, CD20+) normalised/returned to baseline levels.

Study Objectives

Primary objective

- To evaluate the safety of ofatumumab in patients with active rheumatoid arthritis (RA)

Secondary Objectives

- To evaluate the efficacy of ofatumumab in patients with active RA by measuring the degree and duration of B-cell depletion
- To determine the pharmacokinetic profile of ofatumumab in patients with active RA
- To determine host immune response, Human Anti Human Antibodies (HAHA) against ofatumumab

Inclusion and Exclusion Criteria

The main criteria for inclusion were: diagnosis of rheumatoid arthritis according to the American College of Rheumatology (ACR) criteria of at least 6 months duration; active disease at the time of screening as defined by: six or more swollen joints (of 28 joints) and 6 or more tender joints (of 28 joints) and Erythrocyte Sedimentation Rate (ESR) $\geq$ 22 mm/h (using Becton Dickinson Seditainer) and/or C-Reactive Protein (CRP) $\geq$ 10 mg/L (1 mg/dL); RA functional class I, II, or III and treatment failure to one or more disease modifying anti rheumatic drug (DMARD)s either due to intolerance at any time or insufficient efficacy after a minimum of 3 months of DMARD treatment.

Study Population

***Part A*:** Ten patients were planned to be enrolled in each of 3 successive dose groups. 64 patients were screened. The full analysis set comprised 39 patients. Thirty-three of the 39 patients completed the 2 infusions within a window of 80%-120% of the doses planned.

Baseline values were as follows (median and range): age 56 (30-88) years; time since diagnosis of RA: 7.3 (1-39) years and all but 2 patients were Functional Class II+III. The vast majority were Caucasian and female. Thirty-six patients were RF-positive. Thirty-one patients were taking methotrexate in weekly doses ranging between 10 and 25 mg (median in actively treated was 15 mg) and continued to do so during the trial.

The median number of prior RA therapies was 4. Fourteen actively treated patients had received 5 or more prior RA therapies; one as many as 14. With respect to TNF-inhibitors (adalimumab, infliximab, and etanercept), 26 patients (21 of the actively treated) had received ≥ 1 of these therapies. Seven patients had received 2 and 5 patients all 3 therapies.

Part B: The majority of patients were Caucasian (211/225), female (187/225), and RF-positive (187/225). The median (range) duration of RA was 7.4 (1-53) years. Treatment groups were generally well balanced with respect to baseline characteristics including clinical measures of disease activity. Median and range at baseline were: 28-joint Disease Activity Score (DAS28): 6.4 (4.1- 8.6); serum-CRP: 12.0 (1.0-191.9) mg/L; Swollen Joint Count: 10 (0-26); Tender Joint Count: 14 (0-28); Health Assessment Questionnaire: 1.8 (0.0-2.9). The median number of prior RA therapies was 2. Seventy-two (43%) of actively treated patients had received 3 or more prior RA therapies including one patient who had 12; 73 (32%) had previously tried TNF- inhibitor therapies; 179 (80%) were using methotrexate (MTX) (mean weekly dose 14.2 ±4 mg) and 138 (61%) patients were using oral corticosteroids (mean daily prednisolone equivalent dose 7.4 ± 4 mg) and continued to do so during the trial.

Pharmacodynamic Results

In Study Hx- CD20-403 Part A and Part B, there was no clear dose-response relationship between ofatumumab dose (300 to 1000 mg, two infusions two weeks apart) and response as assessed by or American College of Rheumatology Criteria (ACR) 2017 scores at Week 24 as well as other outcome measures, although there was a trend toward higher response rates at higher doses; all dose levels showed activity compared to placebo.

Part A: B-cell depletion: As expected, ofatumumab caused profound, selective, and prolonged reductions in CD20 positive cells within one week of the first infusion. Recovery started after approximately 18-24 weeks. In 13 patients (in whom follow-up is still performed), depletion lasted longer than the time to Follow-Up Visit 3.

Clinical efficacy scores: Based on examination of the ACR and DAS28 scores and their individual components, there is no apparent difference between the active doses, a clear effect of active treatments versus placebo, and more responders with time (from Week 12 to 24).

ACR: the proportion of actively treated patients who reached ACR20, ACR50 and ACR70 at week 12 was 44%, 9% and 3%, respectively and these proportions increased by Week 24 to 63%, 34% and 16%. None of the placebo treated patients reached an ACR20 response.

[17] The terms ACR 20, ACR 50, and ACR 70 are used to describe improvement in RA disease according to preset ARC criteria. ACR 20 means that patients achieved a 20 percent improvement in tender or swollen joint counts as well as 20 percent improvement in three of the other five criteria set by the ARC.

Part B: In pair-wise comparisons, all 3 ofatumumab doses were found to be significantly better than placebo but the active doses did not differ significantly from one another. Within each subgroup population, higher response rates were observed for patients on active treatment vs. placebo and for patients using concomitant MTX. The subgroup of RF- patients was too small for a meaningful comparison between RF- and RF+ patients.

In general, anti-TNF-naïve patients and patients with few prior RA treatments obtained higher response rates.

ACR: The ACR50/ACR70 response rates at week 24 were 24%/6% in actively treated patients vs. 5%/0% in the placebo group. All 3 doses were significantly different from placebo for ACR50, but not for ACR70. The median maximum ACRn in actively treated patients at Week 24 was 43 (range -243 to 94)% versus 13 (range –100 to 57)% in the placebo group. There was a correlation between exposure and ACR20 response and the data indicated that the 700 mg and 1000 mg ofatumumab doses provided greater exposure than the 300 mg dose.

Change in DAS28: At Week 24, the median DAS28 change in actively treated patients was –1.73 (range – 5.48 to 2.19) versus –0.52 (range: –3.91 to 1.08) in the placebo group. In actively treated patients no subgroup difference was seen for the stratification variables MTX and RF. Anti-TNF-naïve patients and patients with few prior RA treatments obtained higher response rates.

DAS28 remission: Among the actively treated patients 7% obtained remission at Week 24 versus 0% in the placebo group.

B-cell depletion**:** Ofatumumab caused profound, selective, and sustained reductions in CD20+ cells within one week of the 1st infusion. Recovery started after approximately 18-24 weeks. By Week 24, CD20+ counts had normalised in 7% of patients.

Comment: Within the group of subjects who received ofatumumab in Part A of the study, there was no correlation between differences in ofatumumab exposure and clinical response; in the larger Part B of the study, subjects who responded as assessed by ACR20 and ACR50 scores at Week 24 as well as by EULAR[18] criteria at Week 24 had higher ofatumumab exposures.

Efficacy

Pivotal Study Hx-CD20-406

Efficacy Analyses

An Independent endpoints Review Committee (IRC) was created to evaluate overall response. For Investigator Assessment of Response Per protocol, investigators were instructed to determine an assessment of response at each clinical evaluation visit. However, investigators were not instructed to determine an overall objective response for each individual patient.

The IRC reviewed clinical data for each patient eligibility and determined the level of response or progression according to the 1996 NCI-WG criteria (see Table 8).

[18] The EULAR (European League against Rheumatism) response criteria are based on the assessment of disease activity using the Disease Activity Score (DAS), a statistically-derived index consisting of number of tender joints, number of swollen joints, erythrocyte sedimentation rate, and global disease activity.

Table 8: NCI-WG 1996 CLL Response Criteria

Parameter	Complete Remission	Partial Remission	Progressive Disease
Lymphocytes	<4.0x10^9/L	≥50% reduction from baseline	≥50% increase to at least 5.0 x10^9/L
Lymphadenopathy	Absence by physical exam	≥50% reduction	≥50% increase for at least 2 weeks or new palpable node ≥1cm
Organomegaly	Normal size spleen and liver by physical exam	≥50% reduction if abnormal at baseline	≥50% increase
Constitutional Symptoms	None	Not defined	Not defined
Neutrophils	≥1.5x10^9/L	≥1.5x10^9/L or 50% improvement from baseline	Not defined
Platelets	>100x10^9/L	>100x10^9/L or 50% improvement from baseline	Not defined
Hemoglobin	>11.0 g/dL (untransfused)	>11.0 g/dL or 50% improvement from baseline (untransfused)	Not defined
Bone Marrow	Normocellular for age, <30% lymphocytes, no B-lymphoid nodules.	If done, ≥30% lymphocytes and/or B-lymphoid nodules	Not defined
Response Definition	**All above met for at least two months. If persistent nodules in bone marrow =nPR**	**Meets criteria for first three for at least 2 months, and at least one other of above met**	**At least one of above met, or transformation to more aggressive histology**

Duration of response, progression-free survival (PFS), time to next CLL treatment, and overall survival (OS) were estimated using Kaplan-Meier estimates. Quartile and median survival times were derived and presented with corresponding two-sided 95% confidence intervals (CI). These endpoints were censored if the subject was lost to follow-up, and in the case of missing data, progression-free survival (PFS) and duration of response were also censored. A list of definitions of response criteria was provided. Briefly:

- Duration of response was defined as the time from the initial response (first visit when response is observed) to progression or death.
- Progression-free survival was defined as the time from allocation until progression or death.
- Time to next CLL treatment was defined as the time from allocation until the time of first administration of the next CLL treatment other than ofatumumab.
- Overall survival is defined as the time from allocation until death.

The efficacy results presented in this summary are based on the interim analysis triggered by the availability of primary endpoint data for the first estimated 66 DR subjects, which occurred on 19 May 2008. All DR and BFR subjects who have primary endpoint data as of 19 May 2008 are included in this interim analysis. Subjects who did not meet the criteria for assignment to the primary DR or BFR populations as determined by the IRC have been categorised as Other (intolerant/ineligible to fludarabine and /or intolerant to alemtuzumab).

Statistical Methodology and Protocol Amendments

The primary endpoint was the objective response as measured over a 24 week period from start of treatment. To maintain the type-1 error rate, the data were analysed using group sequential methods. Based on advice from clinical experts, it was estimated that the objective response rate on best supportive care in these patient populations was 15% and that an objective response rate of 30% on ofatumumab would be a clinically important improvement. Assuming that the response rate was 30%, the probability that the two-sided 99% confidence interval (CI) would exclude a response rate of 15% was 63%, based on data from 66 patients (primary endpoint interim analysis) and 92% based on data from 100 patients (primary endpoint analysis). This applied equally for both the double refractory and the bulky fludarabine refractory groups.

A primary endpoint interim analysis was instituted at the initial estimated cohort of 66 patients, which was the minimum number of patients that would enable a reasonable power to test the null hypothesis. The objective response rate with salvage chemotherapy is 20-25%, and 0% with monoclonal antibodies, so observing a 30% overall response rate that excludes a 15% overall response rate at the 1% significance level indicates meaningful efficacy in this refractory population.

Methods used to assess secondary endpoints were listed in the study report. The study protocol had five amendments which primarily resulted in changes to the inclusion and exclusion criteria and the number of subjects planned.

Amendment 1 modified the inclusion and exclusion criteria and clarified the study objectives. No subjects were enrolled prior to Amendment 1. Based on feedback from the Food and Drug Administration on 23 May 2006, Amendment 2 and 3 defined the subject eligibility definition consistent with the DR and BFR subject populations. The intent of these amendments was to ensure that a more homogeneous subject population would be included in the trial and that an adequate number of subjects would be enrolled into each of these groups to test for efficacy in these populations. The subject populations therefore represented populations with a clinically unmet need based on failure to respond to prior fludarabine or alemtuzumab therapy. As a result, 16 subjects who were intolerant/ineligible to fludarabine or intolerant to alemtuzumab and enrolled prior to Amendment 2 were included in the interim analysis, and are described and analysed separately as Other. These 16 subjects are excluded from the efficacy analyses because they do not represent the pre-specified primary patient populations; however their data contribute to the safety analysis.

Amendment 4 was the most significant amendment with regard to the analysis of efficacy; it increased the sample size from 66 subjects to 100 subjects (per subject group) and introduced a primary endpoint interim analysis at the original full study cohort of 66 subjects per group. A stopping rule for futility was also introduced. Amendment 5 was an administrative amendment that did not change the conduct of the study.

Analysis Populations

The trial population included 3 populations established by IRC review, which were analysed separately:

- Patients refractory to both fludarabine treatment and alemtuzumab treatment (DR group).
- Patients refractory to fludarabine treatment and were considered inappropriate to alemtuzumab treatment due to bulky lymphadenopathy (BFR group).

- Other, that is, patients who were intolerant/ineligible to fludarabine treatment and/or intolerant to alemtuzumab treatment and who were not included in either of the 2 groups above.

Patients who fulfilled the definition of both double refractory and bulky fludarabine refractory were assigned to the DR group. The IRC was responsible for the allocation of patients to population subgroups.

Except for the primary endpoint, the level of the corresponding two-sided confidence intervals is 95%.

The full analysis set (FAS) includes all patients who had been exposed to trial drug irrespective of their compliance to the planned course of treatment. This was the primary analysis population used for evaluation of all endpoints and all 3 population subgroups.

The per protocol (PP) analysis population included patients who had not deviated from the protocol in such a manner that the assessment of efficacy endpoints could be biased. Exclusions from the PP set were also considered on visit level, that is, a patient could be included in the PP population but the data from a certain visit excluded.

Efficacy Results

Primary Efficacy Endpoint: Response Rate

Response assessments of the 138 fludarabine-refractory subjects (DR, BFR, and combined group), was assessed by the IRC. The response rate as assessed by the IRC was 58% in the DR group, 47% in the BFR group, and 51% in the combined groups (FAS population). In all groups, the 99% confidence intervals demonstrated that the response rate exceeded the pre-planned null hypothesis response rate of 15%. The observed response rates in the combined group, DR and BFR groups all exceeded 30%, and were higher than the response rates of 23% (DR: 20%, BFR: 26%) seen in fludarabine-refractory patients reported in literature (Tam *et al*, 2007).

In the combined group, 70 of 71 responses were PR (58% in DR, 46% in BFR). CR was observed for one subject in the BFR group. Response rates were similar between groups. Stable disease was observed for 50 subjects (31% in DR, 41% in BFR). Subjects who were responders or who had stable disease accounted for nearly 90% of the combined group population. Only 10 subjects experienced progressive disease (3% in DR, 10% in BFR) as best response to ofatumumab treatment.

The response rate in the total study population (FAS), which includes DR, BFR and Other subjects, was 52% (80/154), with 78 PR, 1 nPR and 1 CR. In the Other group, the response rate was 56%, with 8 PR and 1 nPR response observed. The response rates in the per protocol (PP) population were higher than in the FAS population. The response rate was 73% in the DR group (n=41), 67% in the BFR group (n=54), and 69% in the combined group (n=95). The majority of subjects were PR, with 30 (73%) in the DR group and 35 (65%) in the BFR group.

The sponsor performed a sensitivity analysis of the IRC response assessment using an algorithm based on the response criteria in the NCI-WG 1996 guidelines to calculate the primary endpoint of response rate from the efficacy data as recorded in the electronic Case Report Form (eCRF). Overall, the algorithm defined non-response or progressive disease in clinical situations where there may be ambiguity as to whether the changes in the response parameters were consistent with disease or with response.

Investigator Assessment of Response

A summary of the IRC assessment, Investigator assessment and the Sponsor Calculated Assessment of response rate is provided in Table 9. A response assessment by each of the three methods confirmed that the response rate in each group exceeded the pre-specified 15% response rate (excluding 15% at the lower limit of the 99% confidence interval) and confirmed the efficacy of ofatumumab in these patient populations. The observed response rate reached or exceeded 30% for all groups by each method.

Table 9. Summary of Response Rates as Assessed by IRC, Investigator and Sponsor, Study Hx-CD20-406.

Response Rates	DR N=59	BFR N=79	Combined DR+BFR N=138
IRC Assessment			
Responders, n (%) 99% CI (%)	34 (58) (40, 74)	37 (47) (32, 62)	71 (51) (40, 63)
Investigator Assessment			
Responders, n (%) 99% CI (%)	25 (42) (26, 60)	27 (34) (21, 49)	52 (38) (27, 49)
Sponsor Calculated Assessment			
Responders, n (%) 99% CI (%)	22 (37) (22, 55)	24 (30) (18, 45)	46 (33) (23, 44)

Note: Investigator Assessment and Sponsor Assessment for Other was not conducted.

Investigators evaluated subjects for response at each visit and may not have referred to baseline measurements when determining response. In contrast, the IRC was provided all relevant data at the same time, including baseline measurements, for a more comprehensive assessment of overall response. This may explain the differences between investigator response rates and IRC response rates.

Overall, the conclusion of superiority to the pre-specified 15% response rate made by the IRC was validated by the sponsor sensitivity analysis and the investigator derived analysis. In addition, the IRC, investigator and sponsor response rates all exceeded 30%, and were higher than the response rates of 23% (DR: 20%, BFR: 26%) seen in fludarabine-refractory patients (Tam *et al*, 2007).

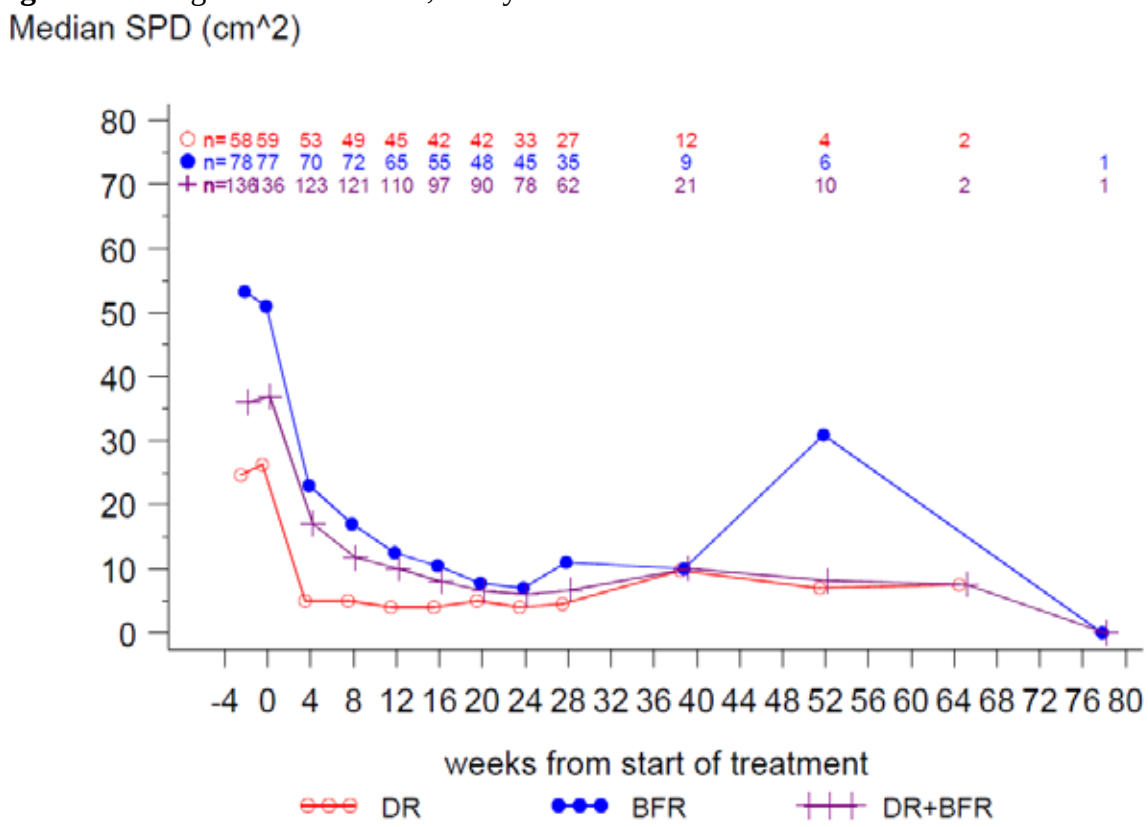
Secondary Efficacy Endpoints

Reduction in Lymph Node SPD

Lymph node size, as measured by physical exam and reported as the sum of products of greatest diameters (SPD) was assessed from baseline until Month 24. The changes in median SPD are shown in Figure 2. The figure shows the rapid and effective decrease in palpable lymph node size after initiation of treatment with ofatumumab. Within 4 weeks of ofatumumab treatment, median lymph node SPD decreased dramatically in the combined group from 36.9 cm^2 to 17.0 cm^2, from 26.3 cm^2 to 5.0 cm^2 in the DR group, and from 51.0 cm^2 to 23.0 cm^2 in the BFR group. This corresponds to an overall 60% decrease in median SPD over 4 weeks (DR: 71%, BFR: 51%). At Week 8, the overall median decrease in SPD versus baseline was 69% (DR: 76%, BFR: 63%). Reductions in median lymph node SPD continued during the treatment period; at Week 24, the reduction in median SPD versus baseline in the combined group was 81% (DR: 78%, BFR 83%). The rapid and sustained reduction of lymphadenopathy with ofatumumab is noteworthy in the light of the limited efficacy of alemtuzumab on bulky fludarabine-refractory CLL reported in the literature. After the 24 week treatment period ended, the median SPD did not increase over baseline values in

the DR group, while there was evidence of PD in the lymph nodes in the BFR group. Results should however be interpreted with caution given the small number of subjects evaluated during the Follow-up period.

Figure 2: Change in Median SPD, Study Hx-CD20-406. Trend over time: Median values.



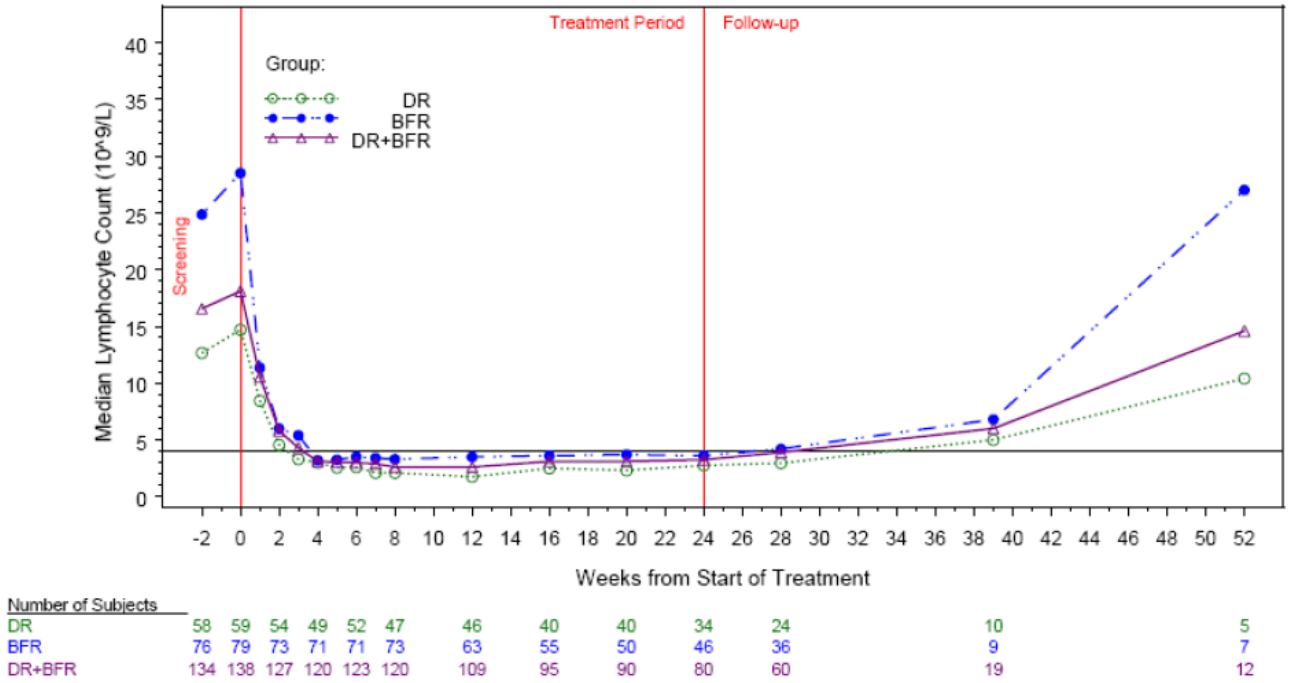
Reduction in Lymphocyte Count

Within 1 week of initiation of ofatumumab treatment, the combined group median lymphocyte count was decreased from 18.1 x 10^9 cells/L at baseline to 10.6 x 10^9 cells/L, with a reduction in the DR group from 14.7 x 10^9 cells/L to 8.5 x 10^9 cells/L, and from 28.5 x 10^9 cells/L to 11.4 x 10^9 cells/L in the BFR group. This corresponds to a 41% combined median reduction (DR: 42%, BFR: 60%). By Week 4, the combined group median lymphocyte count was 3.1 x 10^9 cells/L, with a reduction in the DR group to 3.0 x 10^9 cells/L, and 3.2 x 10^9 cells/L in the BFR group, an 83% combined group median reduction compared to baseline (DR: 81%, BFR: 89%). Figure 3 shows the median lymphocyte count over time for DR, BFR and combined groups.

Initiation of treatment with ofatumumab resulted in a rapid decrease in median lymphocyte counts to levels within the normal range that was sustained throughout the treatment period. After ofatumumab treatment ended, the median lymphocyte count remained within the normal range for several weeks, followed by a gradual increase in median lymphocyte count that remained below baseline.

Most subjects had a greater than 50% reduction in lymphocyte count during the treatment period, and for many of these subjects the lymphocyte count was reduced to normal. Reductions in lymphocyte count were not limited to subjects who achieved a PR or CR as best response to therapy. This treatment effect on median lymphocyte count was similar in the subjects who were responders and subjects who were non-responders, and only a few subjects had no decline in lymphocyte counts.

Figure 3: Median Lymphocyte Count, Study Hx-CD20-406



Malignant B Cells in Peripheral Blood

Malignant B cells are CD45+CD5+CD19+ or CD45+CD5+CD20+ cells. Ofatumumab binds to CD20 and could interfere with the CD45+CD5+CD20+ assay, therefore, the CD45+CD5+CD19+ assay was also used. Immunophenotyping was done at baseline and every 3 months thereafter.

After only 1 week of ofatumumab treatment, the combined group median CD45+CD5+CD19+ cells decreased, from 13.30 x 10^3 cells/mm^3 to 7.37 x 10^3 cells/mm^3, with a reduction in the DR group from 9.32 x 10^3 cells/mm^3 to 5.21 x 10^3 cells/mm^3, and 20.88 x 10^3 cells/mm^3 to 8.69 x 10^3 cells/mm^3 in the BFR group. This corresponds to a 23% overall median reduction (DR: 19%, BFR: 24%) By the next assessment at Week 7, CD45+CD5+CD19+ cells in all groups are reduced from baseline by more than 90%. The overall median CD45+CD5+CD19+ cell counts were 6.03 x 10^2 cells/mm^3, with a reduction in the DR group to 5.75 x 10^2 cells/mm^3, and 7.18 x 10^2 cells/mm^3 in the BFR group. This corresponds to a 92% overall median reduction (DR: 91%, BFR: 93%). The median levels appeared to increase after the treatment period ends, but the number of subjects was limited.

Similarly, after only 1 week of ofatumumab treatment, the median CD45+CD5+CD20+ cells decreased in the combined group from 12.01 x 10^3 cells/mm^3 to 2.12 x 10^3 cells/mm^3, with a reduction in the DR group from 5.41 x 10^3 cells/mm^3 to 1.88 x 10^3 cells/mm^3, and 17.47 x 10^3 cells/mm^3 to 3.71 x 10^3 cells/mm^3 in the BFR group. This corresponds to a 55% combined median reduction (DR: 65%, BFR: 54%).

By Week 7, the median levels of CD45+CD5+CD20+ cells in all groups were reduced to zero. This 100% reduction in CD45+CD5+CD20+ cells was maintained throughout the treatment period to Week 24.

In summary, treatment with ofatumumab was associated with a rapid and profound depletion of malignant B cells in peripheral blood. This effect was sustained throughout the treatment period, with a gradual increase in malignant B cells after discontinuation of therapy. This pattern of reductions in malignant B cells was consistent with the reductions observed in

lymphocyte counts, and supports that resistance to ofatumumab during treatment is likely to be uncommon.

Time to Event Endpoints

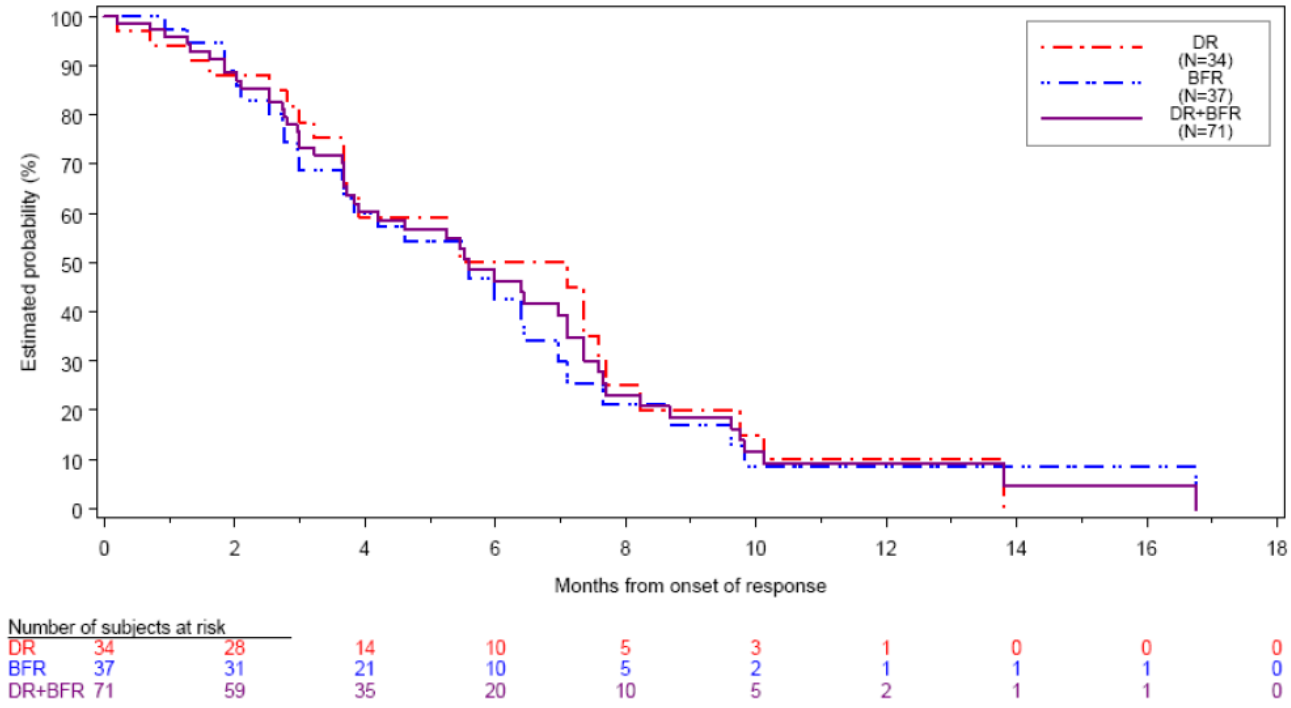
Duration of Response

The onset of response was rapid, with more than 40% responding by the first assessment at 4 weeks, and approximately 70% by the next assessment at 8 weeks. The median time to onset of response was 1.8 months overall and in each group.

Figure 4 shows the median duration of response in subjects who responded in each group, and combined. The median duration of response was 7.1 months in the DR group, and 5.6 months in the BFR and combined groups, indicating that the median duration of response was nearly as long as the intended treatment duration with ofatumumab (24 weeks or 6 months). By comparison, the time to treatment failure observed in fludarabine-refractory patients was 2-3 months (Tam *et al*, 2007).

When duration of response was measured from the time of the last infusion until progression of CLL or death, the median duration of response was 2.5 months in the DR group, 1.9 months in the BFR group, and 2.1 months combined. Response was maintained after last infusion for at least 2 months in more than 50% of subjects, and for up to 9 months in approximately 10% of subjects. The duration of response after last infusion was similar across groups.

Figure 4: Duration of Response, Study Hx-CD20-406



Progression-free Survival

The median PFS for the 102 subjects (DR: 40, BFR: 62) with an observed progression of CLL or death was 5.7 months, and was consistent between groups.

Time to Next CLL Treatment

Time to next CLL treatment was defined as the time from baseline (allocation of treatment) to the time of first administration of the next CLL treatment other than ofatumumab. A total

of 31 DR (53%) and 51 BFR subjects (65%) with disease progression during the study period received subsequent CLL therapy. The median time to next CLL treatment was similar across groups (DR: 9.0 months, BFR: 7.9 months). Responders had a longer time to next CLL treatment than non-responders.

Overall Survival

At the time of the interim analysis, 27 DR, 31 BFR subjects (58 combined group) had died. The median overall survival was similar across groups (DR: 13.7 months, BFR: 15.4 months) and compares favourably to the 9 month median survival (DR: 8 months, BFR: 14 months) seen in fludarabine-refractory patients (Tam *et al*, 2007).

Overall Survival by Response

There was a correlation between response and overall survival when tested with a post-hoc landmark analysis at Week 12. Landmark analyses of overall survival in responders vs. non-responders were performed to minimise bias in the evaluation of the relationship of response and overall survival. In landmark analyses, only subjects who survive until the analysis time-point are included. A direct comparison between responders and non-responders may be misleading since subjects that die shortly after the start of treatment do not have the opportunity to become responders and are by default allocated to the non-responder group. The landmark analysis should be conducted at a time point that maximises the number of responders and maximises the duration of follow-up. The landmark analysis at Week 12, is the earliest time-point at which a response identified at Week 4 could be confirmed, and satisfied both of these conditions.

At Week 12, 53 of 59 DR subjects (Figure 5) and 75 of 79 BFR subjects were included in the landmark analysis (Figure 6).

Figure 5: Overall Survival per Response in Week 12 Survivors, DR Group, Study Hx-CD20-406

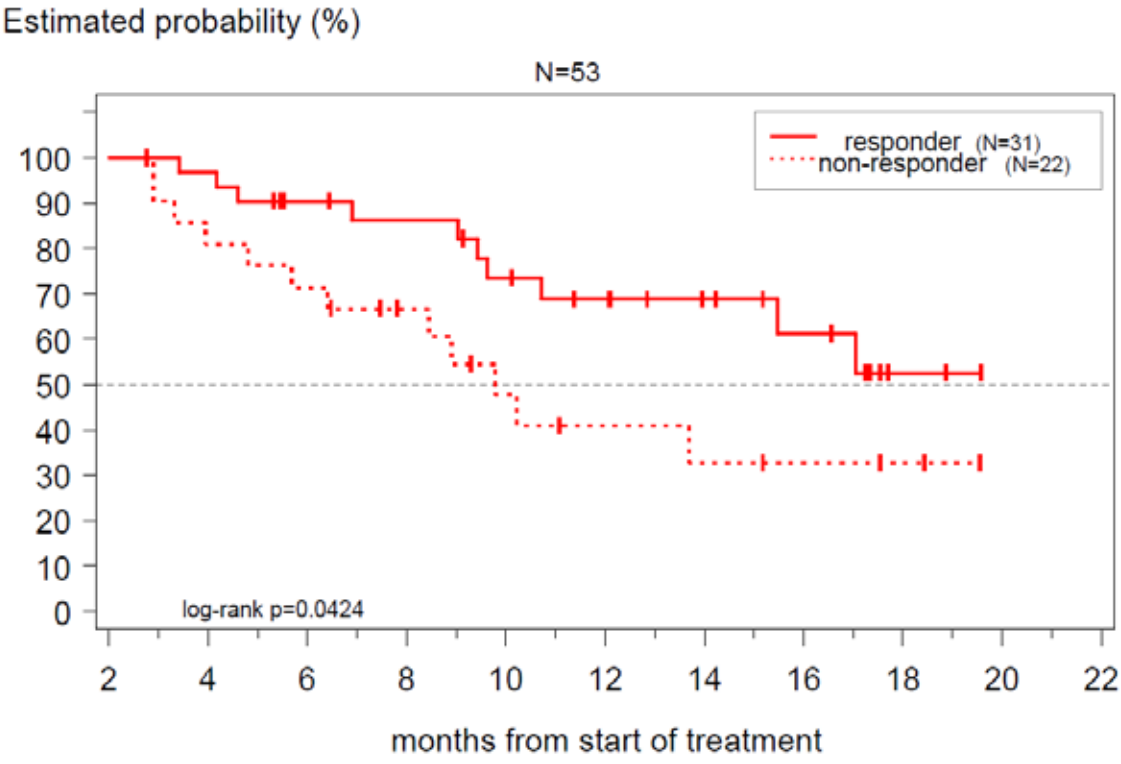
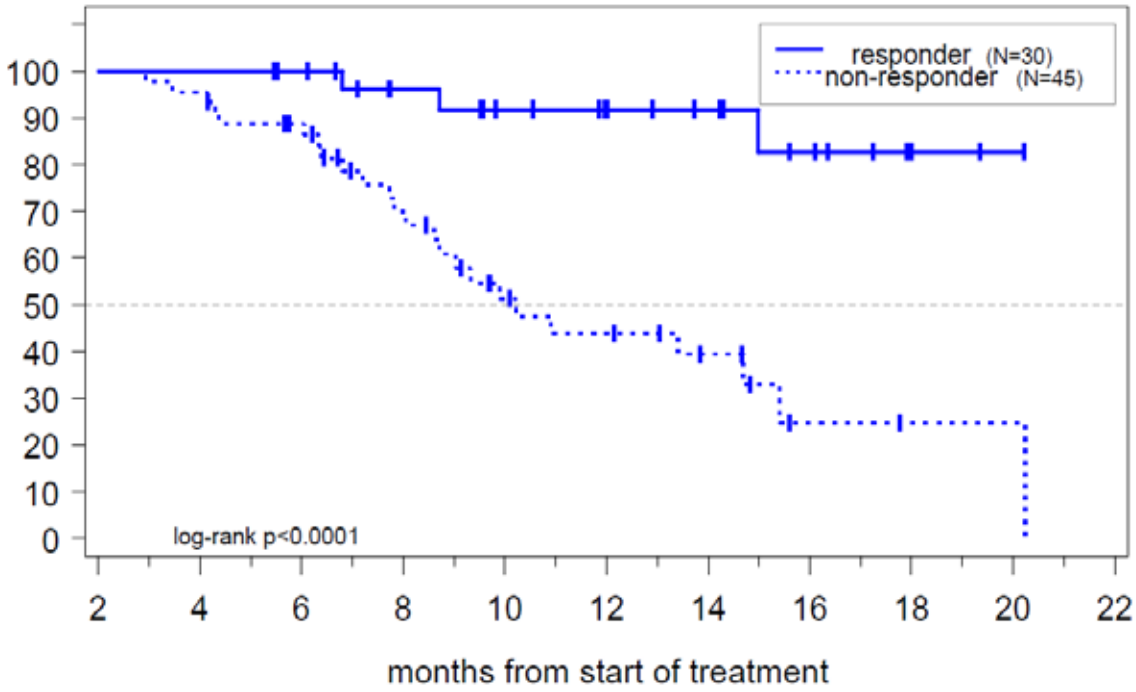


Figure 6: Overall Survival per Response in Week 12 Survivors, BFR Group, Study Hx-CD20-406.
Estimated probability (%). N=75.



Subjects responding to ofatumumab are likely to live longer than non-responders. In the DR group, response to ofatumumab was associated with at least a 10 month longer median overall survival (p=0.0424); the median overall survival was not reached for responders. In the BFR group, response to ofatumumab was associated with a greater than 10 month increase in median overall survival (p<0.0001); the median overall survival was not reached for responders.

Constitutional Symptoms

Night sweats, weight loss, fever, and extreme fatigue are debilitating constitutional symptoms commonly associated with active CLL. Resolution of constitutional symptoms improves the feeling of well-being providing a meaningful clinical benefit. Constitutional symptoms were reported by subjects and results captured by investigators every 4 weeks during the treatment period.

Complete resolution of all constitutional symptoms was analysed over time in the combined group and DR and BFR groups, and by response. Complete resolution of all constitutional symptoms was defined as presence of at least one symptom at baseline followed by the absence of all symptoms thereafter. Data was not included after initiation of next CLL therapy, study withdrawal or death.

At baseline (Week 0), 77 subjects suffered from constitutional symptoms (31 DR, 46 BFR), 60 subjects had no constitutional symptoms (28 DR, 32 BFR) and data was missing for one BFR subject. Post-baseline data was not available for 7 subjects (6 with baseline constitutional symptoms, one without baseline symptoms) in the analyses of the overall and during treatment time periods.

More than three-quarters of subjects with baseline constitutional symptoms experienced complete resolution of all symptoms at some point during the study (79%, 61/77). All but one of these subjects experienced complete resolution during the treatment period. Nearly all responders with baseline constitutional symptoms experienced complete resolution (93%,

40/43). In addition, all subjects without constitutional symptoms at baseline remained symptom-free during the study.

In each of the DR and BFR groups, the change in percentage of subjects with constitutional symptoms over time gave data that was limited by the declining number of evaluable subjects over time, and was too limited to be included beyond Week 52. Figure 7 presents the same data by response. Non-responders included subjects with stable disease, progressive disease or those who were non-evaluable.

Figure 7: Constitutional Symptoms Over Time by Response, in Subjects with at Least One Symptom Present at Baseline.

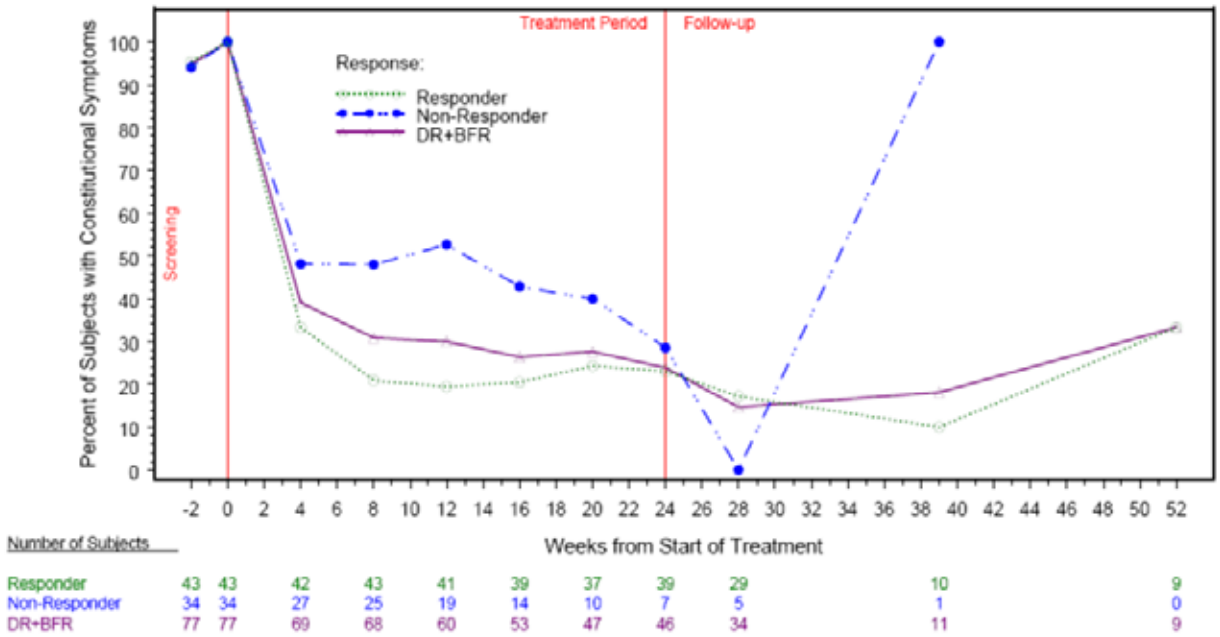


Table 10 provides further detail on the duration of the resolution of constitutional symptoms, summarising the consecutive number of months that subjects were symptom-free for each of the DR, BFR, and combined groups. The absence of constitutional symptoms for at least 2 consecutive months is a criterion of complete remission according to the NCI-WG 1996 guidelines. More than half of subjects in the combined group with baseline constitutional symptoms were symptom-free for at least 2 months, with some subjects symptom-free for at least 6 months.

Table 10: Duration of Constitutional Symptom-Free Period in Subjects with Symptoms at Baseline .

Duration of Symptom-Free Period	DR n=31	BFR n=46	Combined DR+BFR n=77
at least 2 months, n (%)	15 (48)	29 (63)	44 (57)
at least 4 months, n (%)	12 (39)	20 (43)	32 (42)
at least 6 months, n (%)	7 (23)	7 (15)	14 (18)

Data Source: ISE Table 20.1.3.2.1
Includes only subjects with baseline constitutional symptoms
Duration of time is in consecutive months

In summary, the percent of subjects with constitutional symptoms increased from screening to baseline, reflective of the aggressiveness of refractory CLL. With start of ofatumumab therapy, more than half of the subjects in each group with baseline constitutional symptoms

experienced complete resolution of symptoms regardless of response. The resolution was rapid, with more than half of subjects experiencing complete resolution by Week 4. The complete resolution was sustained through the treatment period, and remained below baseline after the end of treatment. The complete resolution was durable, with more than half of subjects, including both responders and non-responders, experiencing a symptom-free period of at least 2 consecutive months, and at least 6 consecutive months in some subjects.

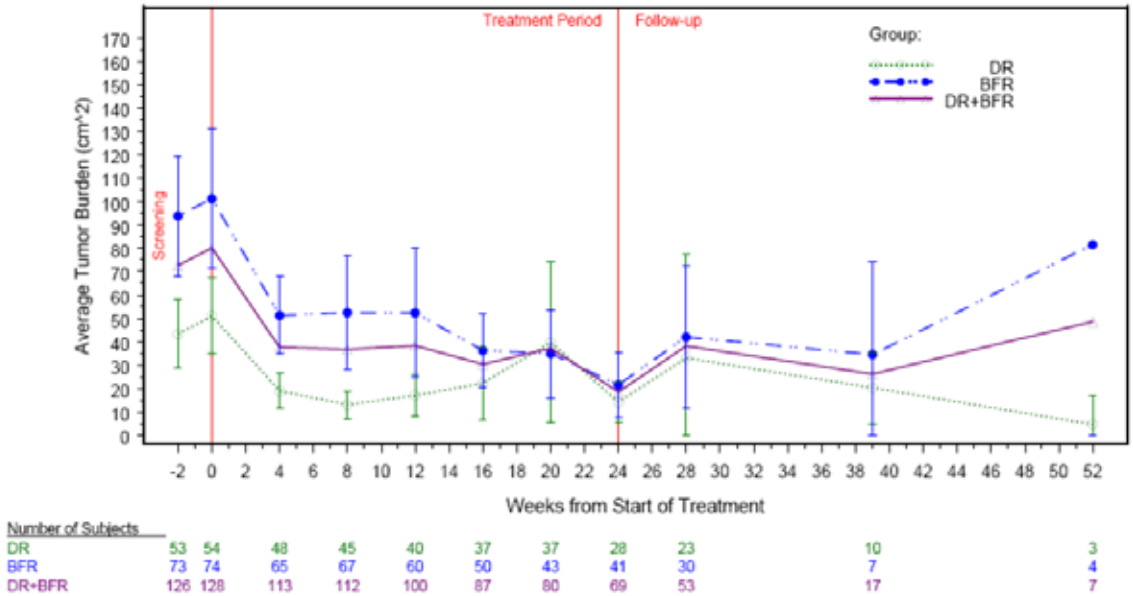
Resolution of Lymphadenopathy

Lymphadenopathy can cause physical discomfort in CLL subjects, particularly in those with bulky disease (lymph nodes >5 cm). Decrease in size or resolution of lymphadenopathy (all nodes <1 cm) can alleviate discomfort and improve a subject's cosmetic appearance. Lymphadenopathy was assessed by physical exam at each visit as part of the assessment of response. Complete resolution of lymphadenopathy, one of the parameters of CR, was analysed over time and by response in the combined group. Complete resolution of lymphadenopathy was defined as the presence of palpable lymph nodes ≥1 cm at baseline followed by palpable lymph nodes of normal size (<1 cm) at a later time.

At baseline, 128 subjects had palpable lymphadenopathy (54 DR, 74 BFR), 10 subjects had no palpable lymph nodes (5 DR, 5 BFR). Post-baseline data was not available for 7 subjects in the analyses of the overall and during treatment time periods. One-fifth of the combined group subjects with baseline lymphadenopathy had complete resolution at some point during the study (20%, 25/128); the majority had some persistent lymphadenopathy during study treatment. There were no subjects without baseline lymphadenopathy that developed new lymphadenopathy during the study.

The average tumour burden, represented by the sum of products of greatest diameters (SPD) was analysed over time as the average tumour burden in the DR, BFR and combined groups, and by response. The average tumour burden was used to adjust for the decreasing number of evaluable subjects over time. Data was excluded upon death, study withdrawal, or initiation of next CLL therapy. Figure 8 shows the change in average tumour burden (the sum total of SPD at each time-point divided by the number of evaluable subjects) during screening, during the treatment period, and during follow-up, stratified by group.

Figure 8: Average Tumour Burden (in cm^2) Over Time in Subjects with Lymphadenopathy at Baseline, Study Hx-CD20-406



Most subjects (82%, 99/121) experienced a reduction in SPD of at least 5 cm^2 during the study, with 18 subjects experiencing a decrease ≥100 cm^2. The decrease in SPD during treatment with ofatumumab was not only limited to responders, as subjects with SD or even PD also saw an impressive reduction in tumour load in the lymph node compartment.

The number of consecutive months that subjects experienced a >50% reduction or complete resolution of lymphadenopathy in the combined group was measured to determine the duration of clinically meaningful improvement in lymphadenopathy. A 50% or greater decrease for two months meets the criteria for a partial remission for this parameter, while complete resolution meets the criteria for a complete remission. Table 11 summarises the improvements and complete resolution of lymphadenopathy for subjects with baseline lymphadenopathy and for subjects with baseline palpable bulky lymphadenopathy (>5 cm).

Table 11: Duration of SPD Decrease in Combined Group (DR+BFR) Subjects with Lymphadenopathy at Baseline, Study Hx-CD20-406.

	Baseline Lymphadenopathy (n=129)		Baseline Bulky (>5 cm) Lymphadenopathy (n=47)	
Duration of SPD Decrease	>50% Decrease	100% Decrease	>50% Decrease	100% Decrease
at least 2 months, n (%)	70 (54)	17 (13)	20 (43)	1 (2)
at least 4 months, n (%)	47 (36)	8 (6)	14 (30)	0
at least 6 months, n (%)	13 (10)	2 (2)	3 (6)	0

Duration of time in consecutive months.

In summary, after initiation of treatment with ofatumumab, 25 subjects with baseline lymphadenopathy had complete resolution of lymphadenopathy at some time during the study, and this was more pronounced in responders than in non-responders. The decrease was rapid, with an approximate 50% decrease in average tumour burden in the palpable lymph nodes by Week 4. The decrease continued throughout the treatment period, and did not return to baseline after the end of treatment. The decrease in the lymph node SPD as best response exceeded 100 cm^2 in some subjects. The benefit was clinically meaningful and durable, with more than half of subjects, including both responders and non-responders, experiencing a period of reduction in lymphadenopathy lasting at least 2 consecutive months, and for at least 6 consecutive months in some subjects.

Resolution of Splenomegaly and Hepatomegaly (Organomegaly)

CLL subjects may experience abdominal discomfort, fullness, or early satiety resulting from hepatomegaly or splenomegaly. Hepatomegaly and splenomegaly were assessed by physical exam at each visit as part of the assessment of response. Complete resolution of hepatomegaly was defined as the presence of an enlarged palpable liver at baseline followed by absence of hepatomegaly post-baseline. Complete resolution of splenomegaly was defined as the presence of an enlarged palpable spleen at baseline followed by absence of splenomegaly post-baseline.

More than two-thirds of subjects in the DR and BFR groups experienced complete resolution of hepatomegaly for at least 2 months during the study (71%, 24/34), and all occurred during the treatment period. A total of 17 of 24 subjects experienced complete resolution of hepatomegaly during response. The absence of hepatomegaly was maintained in all subjects without baseline hepatomegaly and only one subject had new or worsening hepatomegaly as best response during the study period.

More than half of subjects in the DR and BFR groups experienced complete resolution of splenomegaly sometime during the study (60%, 42/70), and all occurred during the treatment period. A total of 34 of 42 subjects experienced complete resolution of splenomegaly. The absence of splenomegaly was maintained in the majority of subjects without baseline splenomegaly and only two subjects had worsening of splenomegaly as best response during the study period.

To provide further detail on the duration of reduction or complete resolution of organomegaly, the number of consecutive months that subjects experienced each type of reduction was analysed for the combined group. A 50% or greater decrease lasting at least 2 months met the criteria for partial remission for this splenomegaly and hepatomegaly, and complete resolution met the criteria for complete remission. Table 12 summarises the duration of resolution data for subjects with baseline splenomegaly and for the subset of subjects with baseline organomegaly >10 cm. Table 13 summarises the duration of resolution for subjects with baseline hepatomegaly and for the subset of subjects with baseline hepatomegaly >10 cm.

Table 12: Duration of Splenomegaly Decrease in Combined Group (DR+BFR) Subjects with Splenomegaly at Baseline, Study Hx-CD20-406.

	Baseline Splenomegaly n=76		Baseline >10 cm Splenomegaly n=13	
Duration of Splenomegaly Decrease	>50% Decrease	100% Decrease	>50% Decrease	100% Decrease
at least 2 months, n (%)	42 (55)	30 (39)	4 (31)	1 (8)
at least 4 months, n (%)	33 (43)	21 (28)	3 (23)	1 (8)
at least 6 months, n (%)	9 (12)	7 (9)	0	0

Includes only subjects with baseline splenomegaly.

Duration of time in consecutive months.

Table 13: Duration of Hepatomegaly Decrease in Combined Group (DR+BFR) Subjects with Hepatomegaly at Baseline, Study Hx-CD20-406.

	Baseline Hepatomegaly n=39		Baseline >10 cm Hepatomegaly n=2	
Duration of Hepatomegaly Decrease	>50% Decrease	100% Decrease	>50% Decrease	100% Decrease
at least 2 months, n (%)	24 (62)	20 (51)	1 (50)	0
at least 4 months, n (%)	15 (38)	14 (36)	0	0
at least 6 months, n (%)	5 (13)	4 (10)	0	0

Includes only subjects with baseline hepatomegaly.

Duration of time in consecutive months.

In summary, more than 50% of subjects with baseline organomegaly, including some with massive organomegaly (>10 cm), experienced clinically meaningful, durable reductions in organomegaly for at least 2 consecutive months after initiation of ofatumumab treatment. A decrease in organomegaly was observed throughout the treatment period, and did not return to baseline after the end of treatment. In responders the benefit lasted for up to a year. Complete resolution of organomegaly occurred in more than one-third of subjects with baseline organomegaly for at least 2 months (meeting the criteria of a complete remission for this parameter), this included two subjects with massive organomegaly >10 cm.

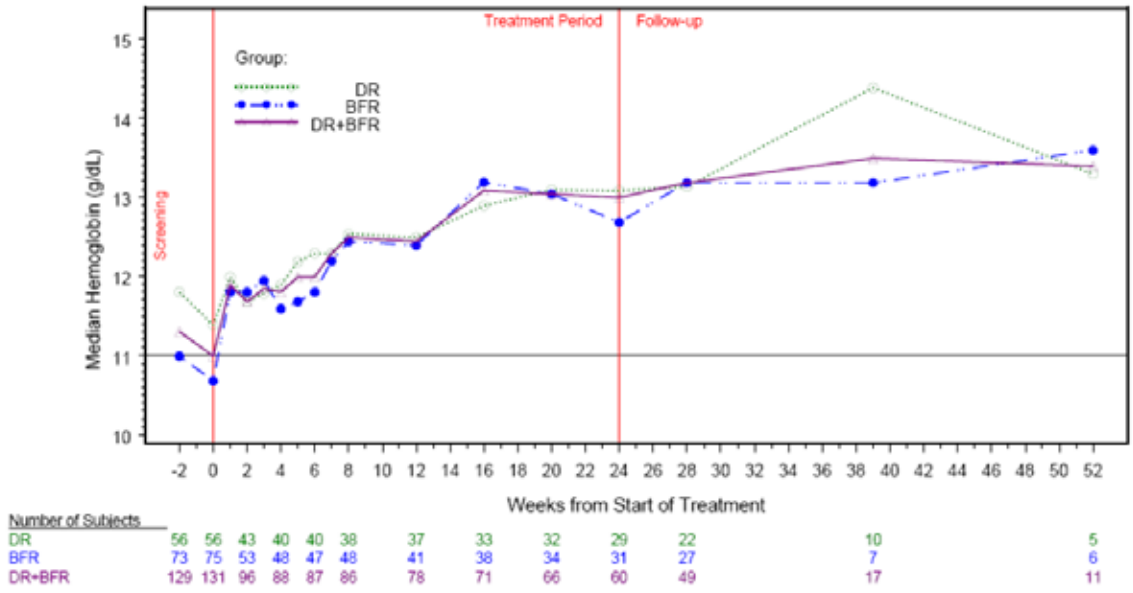
Improvement in Haemoglobin Values

Refractory CLL itself, the damage from prior treatments and advanced age can contribute to low haemoglobin values in patients with CLL. A normalisation, or clinically meaningful increase, in haemoglobin may relieve subjects of the signs and symptoms of anaemia. Haemoglobin values were therefore assessed at all visits by a central laboratory. The results show that median haemoglobin values increased steadily from baseline through the treatment period and into the Follow-up period.

Haemoglobin values were analysed over time in the DR and BFR groups and in the combined group, and by response status. Non-responders include subjects with stable disease, progressive disease or those who were non-evaluable. Subjects were excluded from the analysis once they received concomitant red cell transfusions or erythropoietin treatment. Data was excluded following initiation of next CLL therapy, and after study withdrawal or death.

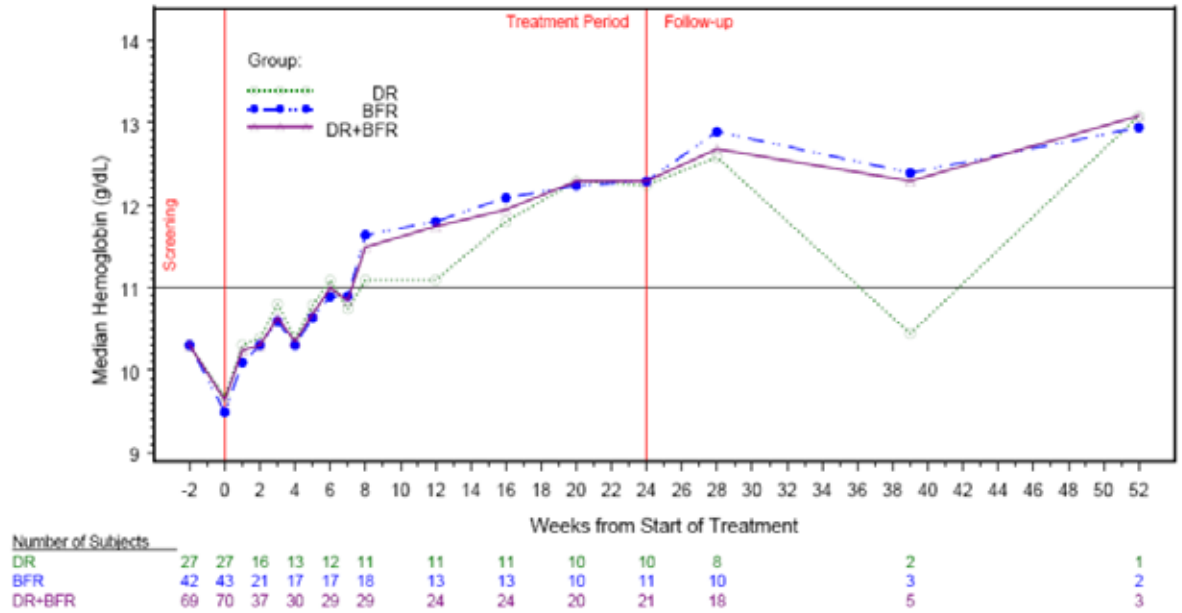
Figure 9 shows improvement in haemoglobin as median haemoglobin over time. After a decrease from screening to baseline, median haemoglobin values improved steadily after ofatumumab treatment began, and by Week 8 were above 12 g/dL. The improvement continued through Week 24 during the treatment period. During Follow-up period, median haemoglobin values remained above 12 g/dL through Week 52. The pattern of improvement was consistent in both the DR and BFR groups. Data was limited by the declining number of evaluable subjects over time, and was excluded beyond Week 52.

Figure 9: Median Haemoglobin over Time, Study Hx-CD20-406.



The NCI-WG 1996 response criteria defined haemoglobin levels >11.0 g/dL or a 50% improvement over baseline as a clinically beneficial response. Median haemoglobin values were also analysed in a subset of subjects with baseline haemoglobin below the normal value for CLL of 11 g/dL. At baseline (Week 0), 68 subjects were anaemic (26 DR, 42 BFR), with haemoglobin levels below the normal value for CLL of 11g/dL. Figure 10 shows the change in median haemoglobin value during screening, during the treatment period, and during follow-up, stratified by group. Data from the limited number of evaluable subjects beyond Week 52 was not included. For subjects with missing baseline data, latest screening or unscheduled data was carried forward to baseline.

Figure 10: Median Haemoglobin over Time in Subjects with Anaemia at Baseline Study Hx-CD20-406.



Median haemoglobin values improved steadily after ofatumumab treatment began, and by Week 8 were above 11 g/dL in the combined group. The improvement continued through Week 24 of the treatment period. Although the data is limited by the number of evaluable subjects during follow-up, median haemoglobin values remained normal through Week 52, with the exception of a transient decrease in the two evaluable DR subjects at Week 39. The pattern of improvement was consistent in both the DR and BFR groups regardless of response.

To provide further detail of the improvement in haemoglobin, the change in haemoglobin over the course of the study was analysed in the DR, BFR and combined groups (see Table 14).

Table 14: Change in Haemoglobin from Baseline, Study Hx-CD20-406.

Change in Hemoglobin Subjects improved/subjects at baseline (%)	DR N=59	BFR N=79	Combined DR+BFR N=138
≤11 g/dL at baseline and ≥2 g/dL increase post-baseline	7/26 (27)	10/42 (24)	17/68 (25)
<10 g/dL at baseline and >12 g/dL post-baseline	3/16 (19)	3/30 (10)	6/46 (13)
<11 g/dL at baseline and >11 g/dL post-baseline	10/26 (38)	15/42 (36)	25/68 (37)

Data Source: ISE Table 20.1.5.3
Excludes subject visits from the date of first transfusion or erythropoietin
For subjects with missing baseline data, latest screening/unscheduled data was carried forward to baseline.

A small number of subjects in the combined group experienced clinically meaningful increases in haemoglobin counts for at least 2 months, with some having durable improvements for 4 or 6 months. Table 15 summarises the duration of time in consecutive months that subjects in the combined group experienced improved haemoglobin counts.

Table 15: Duration of Change in Haemoglobin Count in Combined Group (DR+BFR) Subjects with Baseline Haemoglobin Count Less than 10 g/dL or Less than or Equal to 11 g/dL, Study Hx-CD20-406

Duration of Change in Hemoglobin Count	≤11 g/dL at baseline and ≥2 g/dL increase post-baseline n=68	<10 g/dL at baseline and >12 g/dL post-baseline n=46	<11 g/dL at baseline and >11 g/dL post-baseline n=68
at least 2 months, n (%)	14 (21)	2 (4)	19 (28)
at least 4 months, n (%)	4 (6)	1 (2)	13 (19)
at least 6 months, n (%)	1 (1)	0	4 (6)

Data Source: ISE Table 20.1.5.3.2.1
Excludes subject visits from the date of first time on growth factors
For subjects with missing baseline data, latest screening/unscheduled data was carried forward to baseline
Duration of time is in consecutive months

In summary, an increase in median haemoglobin values was observed in the combined group, regardless of response, and in subjects with baseline anaemia. It should be noted that the analysis over time is limited by survival bias, as patients who die or withdraw from the study no longer contribute to the dataset. For patients who remained on study, the improvement was sustained through the treatment period, and did not decline to baseline after the end of treatment. This benefit was achieved without transfusions or growth factor support, suggesting that ofatumumab treatment triggered a recovery of bone marrow function.

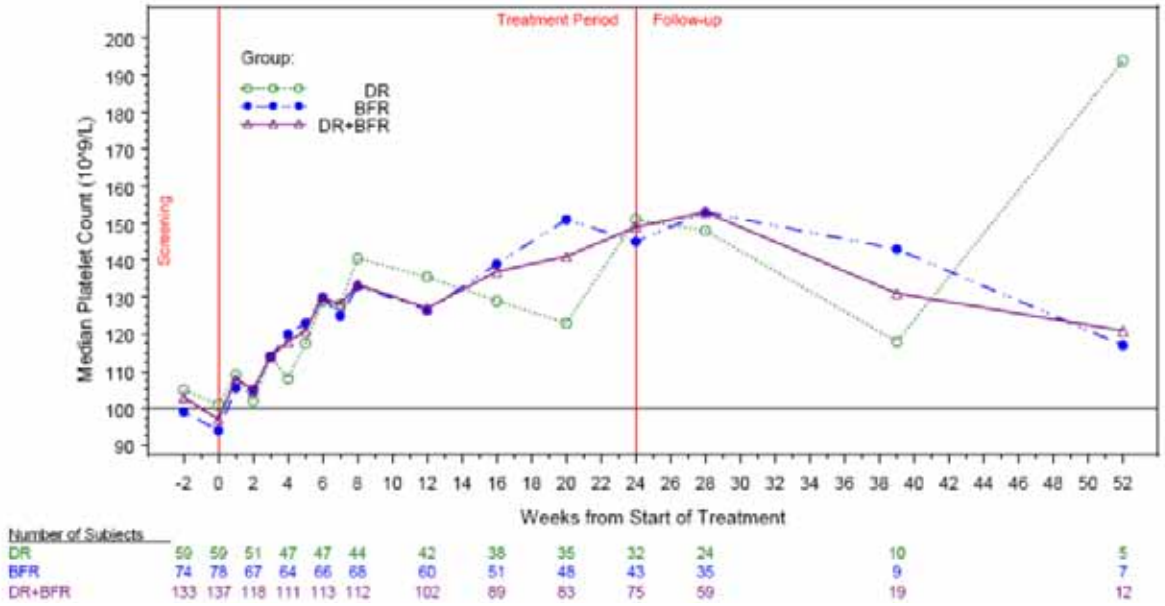
Improvement in Platelet Counts

Thrombocytopaenia is associated with severe CLL and may increase the risk of bleeding. In the combined group, median platelet counts increased steadily from baseline through the treatment period and into the Follow-up period. Normalisation of platelet counts was also observed in subjects with baseline thrombocytopaenia.

Increases in platelet counts were analysed over time in each of the DR, BFR and combined groups, and by response. Non-responders include subjects with stable disease, progressive disease or those who were non-evaluable. Subjects were excluded from the analysis once they received platelet transfusions.

Almost half of subjects with low platelets at baseline had documented improvement in platelet levels at some time during the study (46%, 46/100), with most of the improvements occurring during the treatment period. Nearly all of the subjects with normal or high platelet levels at baseline maintained their levels during the study (97%, 36/37). Results for median platelet count over time in each group are shown in Figure 11.

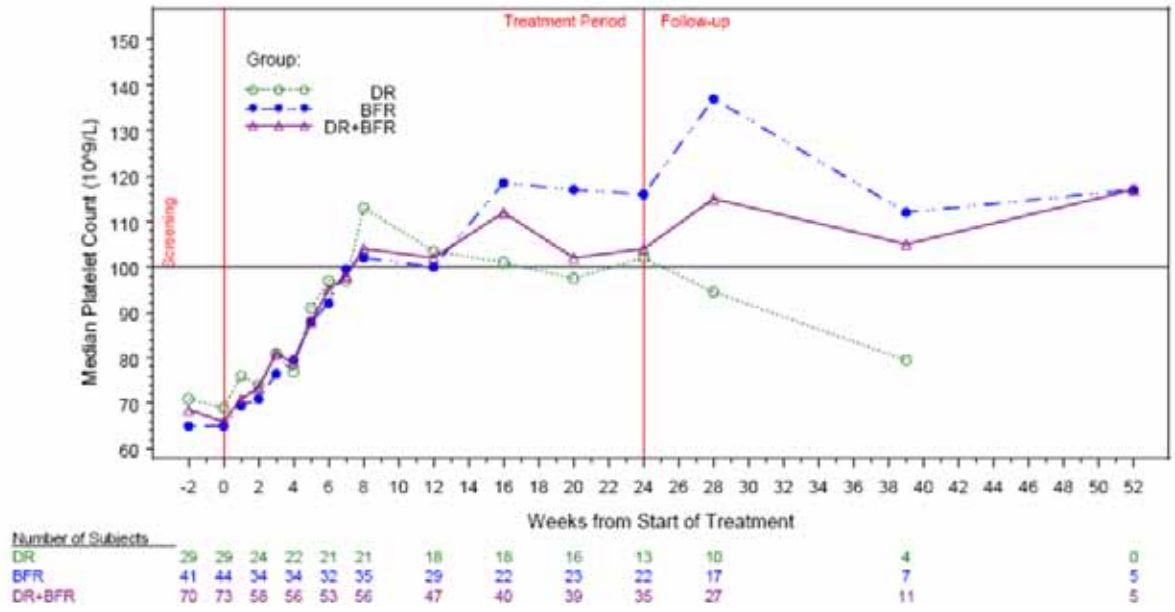
Figure 11: Median Platelet Count over Time, Study Hx-CD20-406.



Median platelet counts increased steadily after ofatumumab treatment from 97 x 10^9/L to more than 120 x 10^9/L within 8 weeks, continued to rise to levels above 140 x 10^9/L, and remained above baseline values during the follow-up, through Week 52. The pattern of improvement was consistent in both the DR and BFR groups.

Median platelet counts were also analysed in a subset of subjects with baseline thrombocytopaenia. At baseline, 73 subjects (29 DR, 44 BFR), had platelet counts below 100 x 10^9/L. Figure 12 presents the change in median platelet count during screening, during the treatment period, and during follow-up, stratified by group. Data beyond Week 52 was limited by the number of evaluable subjects and was excluded.

Figure 12: Median Platelet Count over Time in Subjects with Baseline Thrombocytopaenia, Study Hx-CD20-406.



To provide further detail of the improvement in platelet counts, the change in platelet counts over the course of the study was analysed in the DR, BFR and combined groups for two important threshold levels. The NCI-WG 1996 response criteria defined platelet levels >100

x 10^9/L or a 50% increase over baseline as a clinically beneficial response. The data is summarised in Table 16.

Table 16: Change in Platelet Counts from Baseline, Study Hx-CD20-406.

Change in Platelet Counts Subjects improved/subjects at baseline (%)	DR N=59	BFR N=79	Combined DR+BFR N=138
<100x10⁹/L at baseline to >50% increase or >100x10⁹/L post-baseline	17/29 (59)	31/44 (70)	48/73 (66)
<30 x10⁹/L at baseline to >30x10⁹/L post-baseline	1/4 (25)	2/9 (22)	3/13 (23)

Data Source: ISE Table 20.1.6.3
Excludes subject visits from the date of first transfusion
For subjects with missing baseline data, latest screening/unscheduled data was carried forward to baseline.

Table 17 summarises the duration of time in consecutive months that subjects in the combined group experienced improved platelet counts.

Table 17: Duration of Change in Platelet Count in Combined Group (DR+BFR) Subjects with Baseline Platelet Count Less than 100 x 10^9/L and Less than <30 x 10^9/L, Study Hx-CD20-406.

Duration of Change in Hemoglobin Count	<100x10⁹/L at baseline to >50% increase or >100x10⁹/L post-baseline n=73	<30 x10⁹/L at baseline to >30x10⁹/L post-baseline n=13
at least 2 months	29 (40)	3 (23)
at least 4 months	17 (23)	1 (8)
at least 6 months	6 (8)	0

Data Source: ISE Table 20.1.6.3.2.1
Excludes subject visits from the date of first time on growth factors
For subjects with missing baseline data, latest screening/unscheduled data was carried forward to baseline
Duration of time is in consecutive months

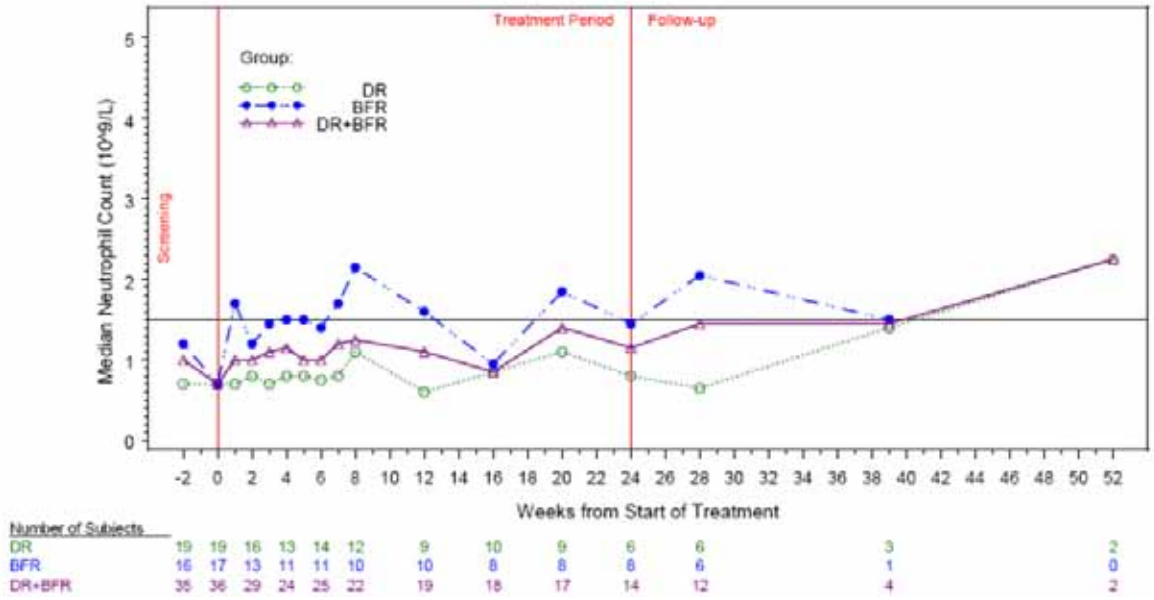
Improvement in Neutropaenia

Refractory CLL itself, damage from prior treatments, and advanced age can contribute to neutropaenia in this study population. Treatment-induced neutropaenia may increase the risk of developing serious and possibly life-threatening infections that are frequent complications and a major cause of death. Changes in neutrophil counts were analysed over time in the DR, BFR and combined group, and by response. Subjects were excluded from the analysis once they received concomitant growth factors for neutropaenia (granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF)).

In the combined group, median neutrophil counts at baseline were 2.3 x 10^9/L. The median counts fluctuated but remained above the normal threshold level for CLL of 1.5 x 10^9/L during the treatment period and during follow-up, regardless of group. This fluctuation may be a result of the difficulty of accurately measuring neutrophil counts in the presence of highly elevated lymphocyte levels.

Median neutrophil counts were also analysed in a subset of subjects with baseline neutropenia (<1.5 x 10^9/L). At baseline, 36 subjects were neutropaenic (19 DR, 17 BFR), with neutrophil counts below the normal value for CLL of 1.5 x 10^9/L. Figure 13 shows the change in median neutrophil count during screening, during the treatment period, and during follow-up, stratified by group. Data from the limited number of evaluable subjects beyond Week 52 was not included.

Figure 13: Median Neutrophil Count (10^9/L) over Time in Subjects with Baseline Neutropaenia, Study Hx-CD20-406



To provide further detail on the maintenance of neutrophil counts, Table 18 summarises the change in neutrophil counts over the course of the study in the DR, BFR and the combined groups. The NCI-WG 1996 guidelines define a clinically beneficial response as neutrophil levels $\geq$1.5 x 10^9/L or 50% improvement from baseline. Increases in neutrophil counts from <1 x 10^9/L to >1 x 10^9/L post-baseline, and an increase to normal (>1.5 x 10^9/L) post-baseline were observed in this study at some time point in a limited number of subjects. Increases from <1.5 x 10^9/L to >1.5 x 10^9/L post-baseline were also observed. Table 19 summarises the duration of time in consecutive months that subjects improved neutrophil counts to >1 x 10^9/L or >1.5 x 10^9/L in the combined group.

Table 18: Change in Neutrophil Count from Baseline in Combined Group (DR+BFR) Subjects with Neutropaenia at Baseline, Study Hx-CD20-406.

Change in Neutrophil Count Subjects improved/subjects at baseline (%)	DR n=59	BFR n=79	Combined DR+BFR n=138
<1x10^9/L at baseline to >1x10^9/L post-baseline	7/13 (54)	7/9 (78)	14/22 (64)
<1x10^9/L at baseline to >1.5x10^9/L post-baseline	5/13 (38)	6/9 (67)	11/22 (50)
<1.5x10^9/L at baseline to >1.5x10^9/L post-baseline	10/19 (53)	12/17 (71)	22/36 (61)

Data Source: ISE Table 20.1.7.3.1
Excludes subject visits from the date of first time on growth factors
For subjects with missing baseline data, latest screening/unscheduled data was carried forward to baseline.

Table 19: Duration of Change in Neutrophil Count in Combined Group (DR+BFR) Subjects with Baseline Neutrophil Count Less than 1 or 1.5 x 10^9/L, Study Hx-CD20-406.

Duration of Change in Neutrophil Count	<1x10^9/L at baseline to >1x10^9/L post-baseline n=22	<1x10^9/L at baseline to >1.5x10^9/L post-baseline n=22	<1.5x10^9/L at baseline to >1.5x10^9/L post-baseline n=36
at least 2 months, n (%)	5 (23)	3 (14)	6 (17)
at least 4 months, n (%)	4 (18)	1 (5)	2 (6)
at least 6 months, n (%)	1 (5)	0	0

Data Source: ISE Table 20.1.7.3.2.1
Excludes subject visits from the date of first time on growth factors
For subjects with missing baseline data, latest screening/unscheduled data was carried forward to baseline
Duration of time is in consecutive months

The effect of ofatumumab on neutrophil counts was less pronounced compared to the effects on haemoglobin and platelet counts. However, in a few subjects, an increase in neutrophil counts from less than 1 x 10^9/L to more than 1.5 x 10^9/L was observed. This increase can be clinically meaningful, as subjects with neutrophil counts less than 1 x 10^9/L are especially prone to developing infections, while subjects with neutrophil counts above 1.5 x 10^9/L have reached nearly normal neutrophil counts and thereby have less of an infection risk.

Comparison of Results in Sub-Populations for Study Hx-CD20- 406

Prior Therapy

Subgroup analyses were performed to determine the effect of prior therapy on response rates to ofatumumab. All subjects in this study were refractory to fludarabine as part of study entry criteria, and most subjects had received previous treatment with cyclophosphamide and rituximab. Prior Fludarabine + Cyclophosphamide CLL patients refractory to FC therapy usually respond poorly to subsequent CLL therapies. FC therapy was the qualifying criteria for 19 DR subjects and 32 BFR subjects. The impact of prior FC therapy on response to ofatumumab was evaluated (Table 20).

Table 20: Response Rates in Subjects with Prior FC Therapy, Study Hx-CD20- 406.

Prior FC Therapy	DR N=59	BFR N=79	Combined DR+BFR N=138
Prior FC as qualifying therapy, n	19	32	51
Responders, n (%)	14 (74)	18 (56)	32 (63)
No prior FC therapy, n	40	47	87
Responders, n (%)	20 (50)	19 (40)	39 (45)

The response rate in the combined group with prior FC was slightly higher than in subjects without prior FC (63% vs. 45%). Unlike other CLL treatments, subjects refractory to prior FC therapy in either group had similar responses to ofatumumab treatment compared to subjects who were refractory to other fludarabine-containing regimens.

Prior Rituximab

Rituximab monotherapy or combination therapy is used in CLL. Rituximab is a monoclonal antibody that binds to CD20, therefore it is important to determine if prior rituximab therapy has an influence on response to ofatumumab. There were 35 DR subjects and 43 BFR subjects who had prior rituximab therapy (monotherapy and/or combination). A comparison of response rates in subjects with prior rituximab and subjects without prior rituximab is presented in Table 21.

Subjects who had prior rituximab therapy, either as monotherapy or in combination with other medications, responded to treatment with ofatumumab at a similar rate as those who have not had prior rituximab therapy. Importantly, in this population of DR and BFR subjects with prior rituximab therapy, response rates to ofatumumab were similar to the overall ofatumumab treated population. Prior rituximab therapy did not influence or predict the response to ofatumumab in the combined group, in DR or BFR subjects.

Table 21: Response Rates in Subjects with Prior Rituximab Therapy, Study Hx-CD20-406.

Prior Rituximab Therapy	DR N=59	BFR N=79	Combined DR+BFR N=138
Prior rituximab[a], n	35	43	78
Responders, n (%)	19 (54)	19 (44)	38 (49)
No prior rituximab, n	24	36	60
Responders, n (%)	15 (63)	18 (50)	33 (55)

Data Source: ISE Table 110.13.5

a. Prior rituximab as monotherapy or in combination with other drugs.

Prior FR and FCR

Another common front-line and second-line treatment for CLL is fludarabine given in combination with rituximab and/or cyclophosphamide (FR and FCR). CLL patients refractory to FCR therapy respond poorly to subsequent CLL therapies. Response rates in subjects with prior FR and FCR were compared to those without prior FR or FCR therapy, and results are shown in Table 22. Response rates in subjects with prior FR, and with prior FCR therapy were similar to response rates in subjects without prior FR or FCR therapy; therefore prior FR and FCR therapy appears to have no effect on response to ofatumumab.

Table 22: Response Rates in Subjects with Prior FR and FCR Therapy, Study Hx-CD20-406.

Prior FR and FCR Therapy	DR N=59	BFR N=79	Combined DR+BFR N=138
Prior FR, n Responders, n (%)	18 9 (50)	27 14 (52)	45 23 (51)
No prior FR, n Responders, n (%)	41 25 (61)	52 23 (44)	93 48 (52)
Prior FCR, n Responders, n (%)	16 8 (50)	16 7 (44)	32 15 (47)
No prior FCR, n Responders, n (%)	43 26 (60)	63 30 (48)	106 56 (53)

Number of prior treatments for CLL

Most subjects (116/138, 84%) had more than 2 prior CLL therapies, including 88% of DR subjects and 81% of BFR subjects. The median number of prior CLL therapies was 5 in the DR group, and 4 in the BFR group. The response rate in subjects with more than 2 prior therapies was 51% in the combined group, 58% in the DR group, and 45% in the BFR group, which was similar to the RR for each group. Only 2 subjects in the DR group had 1 prior therapy (fludarabine + alemtuzumab), and both of these subjects were responders. There were 5 subjects in the DR group that had 2 prior therapies, and of these, 2 were responders. In the BFR group, 10 subjects had only 1 prior therapy, and 6 of these were responders. There were 5 subjects in the BFR group that had 2 prior therapies and of these, 2 were responders.

Subjects with one or two prior CLL treatments did not have a significantly different response rate than subjects with more than two prior CLL treatments. The number of prior CLL treatment regimens did not appear to influence response to treatment with ofatumumab overall, in DR or BFR subjects.

Steroid Use During Treatment

Steroids are used to prevent infusion reactions, but are also used to treat CLL. The impact of use of steroids for pre-medication during ofatumumab treatment on response to ofatumumab was therefore evaluated. A detailed comparison of steroid pre-treatment dose cannot be done because of the high number (nearly 80%) of subjects who received 100% of steroid pre-treatment. Therefore, only a comparison of 100% use of steroid pre-treatment to less than 100% use of steroid pre-treatment was conducted.

Subjects who received less than 100% of steroid pre-medications appeared to have higher response rates than subjects who received 100% of steroid pre-medications. There were few subjects who did not receive steroid pre-medication at every infusion of ofatumumab, but in those subjects, the response rate appeared higher (69% versus 47% in combined group). Use of steroid pre-medication during treatment with ofatumumab does not appear to have an additive effect on the response to ofatumumab in the combined group, in DR or BFR subjects.

Concomitant Glucocorticosteroid Medications During Study

Concomitant glucocorticosteroids use during the study did not appear to have an effect on response rate. There were 52 subjects who received concomitant glucocorticosteroids during the study for various reasons, and 24 were non-responders. Of the remaining 28 subjects who were responders, 7 subjects received concomitant glucocorticosteroids after the 24 week treatment period and therefore did not affect the assessment of the primary endpoint of response rate. The remaining 21 subjects who responded received concomitant glucocorticosteroids during the 24 week treatment period. Fourteen of the 21 subjects who

responded to ofatumumab during the 24 week treatment period received concomitant glucocorticosteroid medications at doses unlikely to affect response rates.

Baseline Demographic Characteristics

Subgroup analyses were performed to determine the effect of subject age, sex and race on response rates to ofatumumab.

Age

Response rates are usually lower in CLL subjects age 65 years or older. In the combined group, 60 subjects (43%) were age 65 or older, and 14 (23%) of those were age 75 or older (see Table 23). The response rates in both the DR and BFR subjects 65 years of age or older, and 70 years or older are similar to the response rate in younger subjects. Advanced age did not appear to significantly diminish the response to ofatumumab.

Table 23: Response Rates in Subjects by Age, Study Hx-CD20-406.

Age	DR N=59	BFR N=79	Combined DR+BFR N=138
Age <65 years, n	32	46	78
Responders, n (%)	20 (63)	22 (48)	42 (54)
Age ≥65 years, n	27	33	60
Responders, n (%)	14 (52)	15 (45)	29 (48)
Age ≥70 years, n	10	19	29
Responders, n (%)	6 (60)	8 (42)	14 (48)
Age ≥75 years, n	4	10	14
Responders, n (%)	2 (50)	3 (30)	5 (36)

Sex

The majority of subjects were male (72%, 111/154), with 75% male subjects in the DR group and 72% male subjects in the BFR group. Despite the imbalance in gender, the response rates in male and female subjects were similar to each other by group, and to the overall response rates by group. In the DR group, 67% of female subjects were responders, compared to 55% of male subjects. In the BFR group, 36% of female subjects were responders, compared to 51% of male subjects. In the combined group, the response rate was 49% in females, and 52% in males. There was no clear pattern of response with regard to subject sex.

Race

Overall, 97% of subjects were Caucasian, with only 1 Asian subject, 1 Hispanic or Latino and 1 'other race' subject in the DR group, and 1 Black or African-American subject in the BFR group. The numbers of non-Caucasian subjects are too small to make any meaningful comparison of efficacy between racial subgroups.

Rai Score at Screening

According to the Modified Rai staging at screening, most subjects were considered to be in the high-risk group (stage III and IV), including 54% of DR subjects and 70% of BFR subjects. The proportion of subjects in the intermediate-risk group (stage I and II) was 44% of DR subjects and 30% of BFR subjects. Only 1 DR subject was considered low risk (stage 0).

The response rates for DR and BFR subjects in the high-risk group were similar to those in the respective intermediate risk group and also similar to the response rate overall for each respective group. The combined response rate of high-risk DR subjects (stage III and IV) was 56% (18/32), and 58% (15/26) in the intermediate-risk (stage I and II) DR subjects. The

combined response rate of the high-risk BFR subjects was 44% (24/55) compared to 54% (13/24) in the intermediate-risk BFR subjects.

The combined group response rate was 48% (42/87) in the high-risk subjects and 56% (28/50) in the intermediate-risk subjects. The modified Rai score at screening did not appear to affect the response to ofatumumab in either the DR or BFR groups.

Binet Score at Screening

Subjects were also assessed at screening using the Binet staging system. The majority of subjects were classified as stage C, indicating the most advanced stage of CLL. The response rates for DR and BFR subjects who were classified as stage C were similar to those classified as stage B, indicating intermediate stage CLL, and also similar to the overall response rate for each respective group. Few subjects were classified as stage A.

The response rate for the combined group subjects classified as stage C or B were 51% (41/81) and 53% (25/47), respectively. The response rate for DR subjects classified as stage C or B were 57% (17/30) and 61% (14/23), respectively. The response rate for BFR subjects classified as stage C or B were 47% (24/51) and 46% (11/24), respectively. Advanced Binet score at screening did not appear to affect response to ofatumumab.

Bone Marrow Involvement at Baseline

There was no correlation between bone marrow involvement at baseline and response to ofatumumab since almost all subjects had nearly complete bone marrow involvement at baseline.

Enlarged Lymph Nodes at Baseline

Overall, there did not appear to be a clear correlation between largest lymph node size at baseline and response to ofatumumab in any group.

Chromosomal Abnormalities, CD38 Status and Fc Receptor Polymorphism

Chromosomal abnormalities

Subjects were assessed at baseline by the FISH (fluorescent in situ hybridization) assay for chromosomal abnormalities known or suspected to affect response to CLL treatment. Subjects were categorised into subgroups by the abnormality detected: 17p deletion, 11q deletion (but not 17p deletion), 12q trisomy (but not 17p or 11q deletion), 13q deletion only, and no chromosomal abnormalities found.

Most subjects had baseline chromosomal abnormalities. The response rates were similar in subjects with and without chromosomal abnormalities (52%). In the DR group, 57 subjects had this assessment, and most (49/57, 86%) had chromosomal abnormalities. The response rate in subjects with no chromosomal abnormalities was 75%, compared to 55% for subjects with chromosomal abnormalities In the BFR group, 78 subjects had this assessment, and most (59/78, 76%) had no chromosomal abnormalities. The response rate in subjects without chromosomal abnormalities was 42%, compared to 49% for the subjects with chromosomal abnormalities. Response rates for subjects with and without 17p deletions and 11q deletions, which are adverse prognostic indicators in CLL treatment, are shown in Table 24.

Table 24: Response Rates by Chromosomal Abnormality, Study Hx-CD20-406.

Chromosomal Abnormality	DR N=59	BFR N=79	Combined DR+BFR N=138
Subjects, n	57	76	133
17p deletion, n	17	14	31
Responders, n (%)	7 (41)	2 (14)	9 (29)
No 17p deletion, n	40	62	102
Responders, n (%)	26 (65)	34 (55)	60 (59)
Subjects, n	57	78	135
11q deletion, n	24	22	46
Responders, n (%)	15 (63)	14 (64)	29 (63)
No 11q deletion	33	56	89
Responders, n (%)	18 (55)	23 (41)	41 (46)

CD38+ Status

Over-expression of CD38+ is an adverse prognostic marker for CLL. Subjects were assessed at baseline for CD38 expression levels. Subjects were considered CD38+ if the percentage of CD38+ among CD5+CD19+ cells was greater than 20% as compared to isotope controls. CD38+ status appeared to be predictive of response in DR subjects, but not in BFR subjects. DR subjects who were CD38+ had a response rate of 41%, versus 80% in subjects who were CD38- (p=0.0036) although data is limited by the number of subjects evaluated.

Fc receptor polymorphism

Subjects were assessed at baseline for Fc receptor polymorphisms, and were classified by one of three phenotypes of FcγIIa (H/A, A/A, H/H), and by one of three phenotypes of FcγIIIa (V/P, P/P, V/V). The response rates were similar for all phenotypes within both the DR and BFR groups, suggesting that Fc receptor polymorphisms are not predictive of response to ofatumumab.

Comment: The efficacy results from pivotal Study Hx-CD20-406 demonstrate compelling efficacy of ofatumumab monotherapy in two fludarabine-refractory populations, with response rates of 47-58%. The responses occurred quickly, were durable, and were consistent across subgroups. Landmark analysis at 12 weeks showed that responders in both DR and BFR groups had markedly longer median survival than non-responders.

Subjects who were non-responders by NCI-WG *1996 CLL response criteria experienced improvement or resolution of clinical symptoms and haematological parameters of CLL. Overall, the efficacy data from the pre-planned interim analysis from pivotal Study Hx-CD20-406 support the clinical benefit for ofatumumab monotherapy in the treatment of subjects with fludarabine-refractory CLL.*

Supportive Study Hx-CD20-402

Efficacy Endpoints

The primary efficacy endpoint was response over the period from screening to Week 19, based on the NCI-WG 1996 guidelines for CLL. Response was evaluated by the international coordinating investigator for all subjects at all visits from Week 4 to Week 27. Subjects were classified as responders or non-responders as follows: complete remission (CR), nodular partial remission (nPR), and partial remission (PR) were classified as responders, while stable disease (SD) and progressive disease (PD) were classified as non-responders. Responses were required to be maintained for at least two months. The treatment groups are detailed in the footnote to Table 25.

The secondary efficacy endpoints were response during the study (from Week 4 to Week 27), CD5+ CD19+ cells in peripheral blood, CD5+CD20+ and CD5-CD20+ cells in peripheral blood, time to progression, duration of response, and time to next CLL therapy.

Response from Screening to Week 19

The primary endpoint of response from Screening to Week 19 is shown in Table 25. An overall response rate of 42% was observed, with a response rate of 48% in Group C. One subject in Group C was withdrawn from treatment after one infusion, and was therefore not evaluable. However, they were included in FAS. In Group C, the onset of response was early with 16 (59%) subjects achieving response at Week 4. Three subjects did not respond until Week 7 or Week 11. At Week 19, the number of subjects with sustained response was reduced to 9 (33%).

Table 25: Summary of Response from Screening to Week 19, Study Hx-CD20- 402.

Response	Group A N=3	Group B N=3	Group C N=27
Not Evaluable, n (%)	0	0	1 (4)
Responders, n (%)	1 (33)	0	13 (48)
95% CI	(1, 91)	0	(30, 70)
Response, n (%)			
CR	0	0	0
nPR	0	0	1 (4)
PR	1 (33)	0	12 (44)
SD	1 (33)	2 (67)	13 (48)
PD	1 (33)	1 (33)	0

Data Source: Hx-CD20-402 Study Report Table 9-1, Hx-CD20-402 Table 3.02.1
Group A: ofatumumab 500 mg
Group B: ofatumumab 1000 mg
Group C: ofatumumab 2000 mg

Response from Week 4 to Week 27

The responses observed from Week 4 to Week 27 were the same as the responses observed from screening to Week 19, due to the early onset of response. Responses were observed by Week 4 in 24 subjects (89%) in Group C. Two subjects (7%) in Group C maintained their response to Week 27.

Malignant Cells in Peripheral Blood

Overall, the median CD5+CD19+ cell count at screening was 47,713 x 10^6/L. Subjects in Group C had a 55% median reduction in CD5+CD19+ cell count at Week 1, and 97% median reduction at Week 4. The reduction in CD5+CD19+ cell count below baseline values was maintained in the majority of subjects for up to one year.

The overall median CD5+CD20+ cell count at screening was 47,742 x 10^6/L. Subjects in Group C had a 100% median reduction in CD5+CD20+ cell count at Week 1, which was maintained to Week 11. The reduction in CD5+CD20+ cell count was maintained in most subjects for up to one year.

In summary, treatment with ofatumumab 2000 mg resulted in rapid reductions in median malignant B cells CD5+CD19+ and CD5+CD20+ by Week 1. By Week 4, median malignant B cell counts were reduced by 97-100%, and maintained at this level in most subjects for up to one year.

Time to Progression

Time to progression was defined as the number of days from baseline/Day 0 to first disease progression or death due to CLL. The overall median time to progression (full analysis population) was 3.6 months, and 4.4 months in Group C. In the subgroup of responders, the median time to progression in all responders was 5.3 months, and 5.3 months in Group C.

Duration of Response

Duration of response was defined as the time from the initial response (first visit when response is observed) to progression or death due to CLL. Overall, the median duration of response was 4.3 months, and 4.4 months in Group C.

Time to Next CLL Treatment

Time to next CLL treatment was defined as the time from allocation until the time of first administration of the next CLL treatment other than ofatumumab. The overall median time to next CLL treatment was 12.0 months, and 12.1 months in Group C.

Summary of Efficacy.

Patients with CLL refractory to fludarabine often do not derive clinical benefit from alemtuzumab due to lack of response (DR) or presence of bulky lymphadenopathy that makes responses to alemtuzumab unlikely (BFR). In these patients there is a high unmet medical need as they are without approved or otherwise accepted standard therapies. Response rates with other therapies are low in this patient population (0-26%), and median survival is reported to be between 8-14 months (Tam *et al*, 2007). In the single arm, multi-centre, open-label pivotal Study Hx-CD20-406, subjects with fludarabine-refractory CLL received ofatumumab monotherapy (an initial dose of 300 mg, followed one week later by 2000 mg once weekly for seven infusions, followed 5 weeks later by 2000 mg once every 4 weeks for 4 infusions, for a total of 12 infusions).

In the pre-planned interim analysis of 154 subjects, 138 met the criteria defined for DR or BFR disease. The response rate was 51% (99% CI: 40-63%) in the combined group, 58% (99% CI: 40- 74%) in the DR group and 47% (99% CI: 32-62%) in the BFR group. There was 1 CR in the BFR group, all other responders were PR. The response rates support the results in the Phase II Study Hx-CD20-402 in relapsed or refractory CLL subjects (48% response rate in subjects who received 500 mg, followed one week later by three weekly 2000 mg doses). The response rates, and the results of other efficacy parameters, were consistent between the DR and BFR subject groups, providing independent corroboration of the treatment effect of ofatumumab.

Responses were achieved rapidly. The median time to response was 1.8 months in all groups (DR, BFR, combined). The median duration of response was 5.6 months in the combined group (7.1 months DR, 5.6 months BFR), and the duration of response after last infusion was 2.1 months in the combined group (2.5 months DR, 1.9 months BFR). The median progression-free survival was 5.7 months in the combined group (5.7 months DR, 5.9 months BFR). The median overall survival was 15.4 months in the combined group (13.7 months DR, 15.4 months BFR). The median time to next CLL therapy was 8.2 months in the combined group (9.0 months DR, 7.9 months BFR).

Improvements in the individual components of the response assessment were observed. There was a rapid and sustained depletion of lymphocytes and malignant B cells. In the combined group 54% of subjects experienced at least 50% resolution of lymphadenopathy for at least 2 months, and 13% of subjects experienced complete resolution of lymphadenopathy for at least 2 months. Together, this is evidence of the effect of ofatumumab on the target CD20+ cells in blood and lymph nodes.

Ofatumumab treatment was also associated with a complete resolution in constitutional symptoms for a minimum of 2 month for 57% of subjects in the combined group experiencing symptoms at baseline. Similar numbers of subjects with baseline splenomegaly and hepatomegaly had improvement or complete resolution for at least 2 months.

Improvements in haematologic values were also observed in subjects with abnormal baseline values, particularly for platelet counts and haemoglobin. The effect on neutrophils was less pronounced, nevertheless, 17% of subjects who were neutropaenic at baseline had an increase of neutrophils to $>1.5x10^9$/L for at least 2 months.

Subgroup analyses showed consistent responses across subgroups typically associated with poor outcomes, specifically subjects 65 years of age or older, subjects with several prior CLL treatments (median 5.0), and subjects with chromosomal abnormalities, including subjects with 17p and 11q deletions.

Overall, the pre-planned interim analysis from pivotal Study Hx-CD20-406 showed efficacy suggestive of clinical benefit for ofatumumab monotherapy in the treatment of subjects with fludarabine-refractory CLL. The compelling response rates, duration of response, and clinical improvements in the individual components of response were seen in both populations, demonstrating that ofatumumab addresses the unmet medical need in both the DR and BFR populations.

Safety

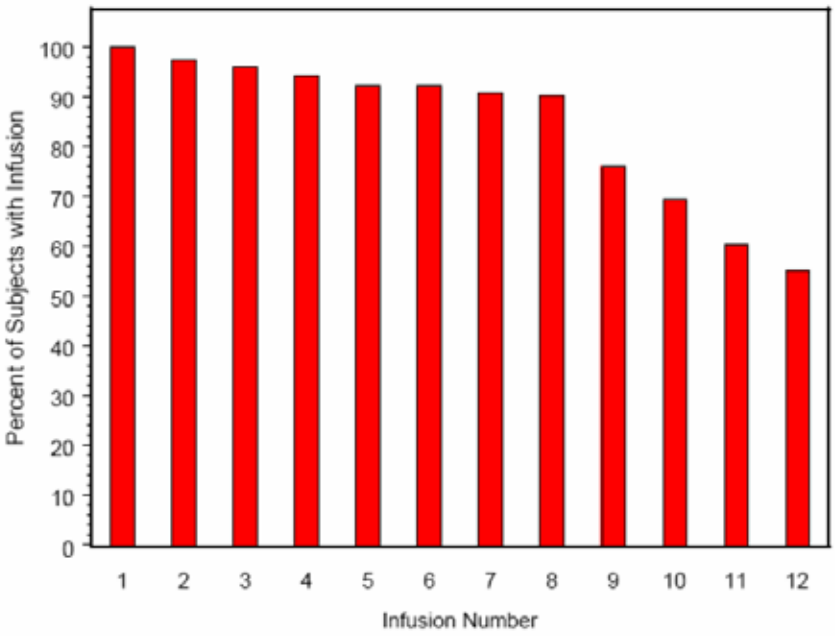
Safety data for ofatumumab was provided from 12 studies (completed or ongoing) in 648 subjects who have received at least one dose of ofatumumab. The primary safety data are provided from the pivotal Study Hx-CD20-406 in 154 fludarabine-refractory CLL subjects. Supportive studies will only be discussed briefly in this evaluation report.

Extent of Exposure to Ofatumumab

In Study Hx-CD20-406, the intended dosing regimen was 12 infusions of ofatumumab over duration of 24 weeks. The exposures for 154 subjects included in the interim analysis are discussed in this section, and the percent of subjects receiving each infusion is presented in Figure 14.

Most subjects (139/154; 90%) received all 8 weekly infusions, and 55% (85 subjects) received all 12 infusions (completed 24 weeks of treatment). The most common causes for withdrawal from treatment were infections (11 subjects) and progressive disease (4 subjects). The median dose per infusion was 300 mg for the first infusion, and 2000 mg for infusions 2-12. The median cumulative dose was 22,300 mg.

Figure 14: Percent of Subjects Receiving Infusions Over the Course of Treatment, Study Hx-CD20-406.



Number of Subjects												
n	154	154	154	154	154	154	154	154	154	154	154	154
Count	154	150	148	145	142	142	140	139	117	107	93	85
Percent	100%	97%	96%	94%	92%	92%	91%	90%	76%	69%	60%	55%

Note: Four subjects withdrew after first infusion: Subject 406167 and Subject 406110 withdrew due to refusal, Subject 406189 withdrew due to AE of herpes zoster and pneumonia, and Subject 406201 withdrew due to disease progression.

Adverse Events

The safety population for Study Hx-CD20-406 includes 154 subjects included in the planned interim analysis (cut-off date 19 May 2008). As per study protocol, deterioration of study disease was not to be reported as an AE unless it fulfilled the SAE criteria. An independent external Data Monitoring Committee (DMC) was appointed to conduct ongoing regular safety surveillance of the study. The DMC's safety reviews included evaluations of all SAEs, all non-serious AEs of Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 and 4, and all other relevant safety data.

As of the cut-off date for the interim analysis, 146 (95%) of the 154 subjects treated with ofatumumab had a total of 1209 AEs during treatment or in the Follow-up period. The majority of AEs (81%) occurred during the treatment period. A total of 98 (64%) subjects had 494 (41% of 1209) AEs considered by the investigator to be related to ofatumumab (see Table 26).

Table 26: Overview of AEs in Subjects in Study Hx-CD20-406 (Treatment or Follow-up).

Number of subjects, n (%)	DR (N=59)	BFR (N=79)	Other (N=16)	Total (N=154)
Any AE	54 (92)	76 (96)	16 (100)	146 (95)
Drug-related AEs	36 (61)	48 (61)	14 (88)	98 (64)
AEs ≥Grade 3	38 (64)	38 (48)	12 (75)	88 (57)
Infusion Reaction AEs	38 (64)	48 (61)	13 (81)	99 (64)
Infections	41 (69)	54 (68)	13 (81)	108 (70)
All AEs leading to withdrawal from treatment	12 (20)	8 (10)	2(13)	22 (14)[1]
All SAEs	32 (54)	38 (48)	12 (75)	82 (53)
Fatal (Grade 5) SAEs	12 (20)	10 (13)	2 (13)	24 (16)

[1]Five additional subjects had disease progression listed as the AE that resulted in discontinuation.

A total of 61 subjects died as of the cut-off date for safety. Some 24 fatal SAEs occurred during treatment or follow-up (DR: 12/59, 20%; BFR: 10/79, 13%; Other: 2/16, 13%). Early death, defined as death occurring within the first 8 weeks of treatment, occurred in 6 of the 24 subjects (5 due to infection, 1 due to myocardial infarction). The causes of death for the other 18 subjects were disease progression (6 subjects), infections (11 subjects), and cardiac failure (1 subject). Some 37 deaths occurred during the Extended Follow-up period. 7 fatal SAEs occurred before initiation of new CLL treatment, and 30 deaths occurred after the initiation of alternative CLL treatment and were therefore not reported as SAEs.

Common AEs

The most frequently reported AEs were pyrexia, cough, diarrhoea, pneumonia, neutropaenia, anaemia, fatigue and dyspnoea (see Table 27). Other AEs reported at incidences of >10% were rash, bronchitis, upper respiratory tract infection and nausea. No clinically relevant differences were observed among the subgroup populations with regard to types of AEs.

Table 27: AEs experienced by ≥10% of CLL Subjects in Any Group or Total in Study Hx-CD20-406

System Organ Class Preferred Term	DR (N=59)	BFR (N=79)	Other (N=16)	Total (N=154)
Any AEs, n (%)	54 (92)	76 (96)	16 (100)	146 (95)
General disorders and administration site conditions, n (%)				
Pyrexia	15 (25)	9 (11)	7 (44)	31 (20)
Fatigue	9 (15)	13 (16)	1 (6)	23 (15)
Edema peripheral	5 (8)	8 (10)	1 (6)	14 (9)
Chills	6 (10)	5 (6)	2 (13)	13 (8)
Disease progression	1 (2)	5 (6)	3 (19)	9 (6)
Respiratory, thoracic and mediastinal disorders, n (%)				
Cough	11 (19)	14 (18)	5 (31)	30 (19)
Dyspnea	11 (19)	8 (10)	3 (19)	22 (14)
Gastrointestinal disorders, n (%)				
Diarrhea	11 (19)	12 (15)	5 (31)	28 (18)
Nausea	7 (12)	9 (11)	1 (6)	17 (11)
Blood and lymphatic system disorders, n (%)				
Neutropenia	9 (15)	10 (13)	6 (38)	25 (16)
Anemia	10 (17)	13 (16)	2 (13)	25 (16)
Infections and infestations, n (%)				
Pneumonia	10 (17)	11 (14)	4 (25)	25 (16)
Bronchitis	11 (19)	6 (8)	0	17 (11)
Upper respiratory tract infection	2 (3)	13 (16)	2 (13)	17 (11)
Lower respiratory tract infection	1 (2)	3 (4)	3 (19)	7 (5)
Urinary tract infection	2 (3)	2 (3)	2 (13)	6 (4)
Skin and subcutaneous tissue disorders, n (%)				
Rash	8 (14)	6 (8)	5 (31)	19 (12)
Urticaria	3 (5)	8 (10)	1 (6)	12 (8)
Dry skin	0	1 (1)	2 (13)	3 (2)
Erythema	1 (2)	0	2 (13)	3 (2)
Musculoskeletal and connective tissue disorders, n (%)				
Back pain	7 (12)	3 (4)	2 (13)	12 (8)
Musculoskeletal pain	2 (3)	0	3 (19)	5 (3)
Psychiatric disorders, n (%)				
Insomnia	6 (10)	4 (5)	1 (6)	11 (7)
Nervous system disorders, n (%)				
Paresthesia	3 (5)	2 (3)	2 (13)	7 (5)
Dizziness	0	1 (1)	2 (13)	3 (2)

For the majority of system organ classes (SOCs), AEs were most frequently reported among subjects in the Other group than in the DR or BFR groups; however due to the small number of subjects in this subgroup (N=16), no firm conclusions could be drawn. It should be noted that these subjects were in the study for a longer period (median follow up of 269 days versus 195 days) than those in the other 2 groups, which may account for the higher rate of AEs reported.

AEs Related to Study Treatment

A total of 98 (64% of 154) subjects experienced 494 AEs (41% of all 1209 AEs) considered to be drug-related. With the exception of neutropaenia (21 subjects, 14%), individual AEs considered to be drug-related were reported by <10% of subjects (see Table 28). Other frequently reported drug-related AEs included rash, urticaria, fatigue, chill, pyrexia, pneumonia, dyspnoea, cough, diarrhoea, and nausea.

Table 28: Drug-related AEs experienced by ≥5% of CLL Subjects in Any Group or Total in Study Hx-CD20-406.

System Organ Class Preferred Term	DR (N=59)	BFR (N=79)	Other (N=16)	Total (N=154)
Any Event, n (%)	36 (61)	48 (61)	14 (88)	98 (64)
Blood and lymphatic system disorders, n (%)				
Neutropenia	9 (15)	6 (8)	6 (38)	21 (14)
Anemia	2 (3)	5 (6)	1 (6)	8 (5)
Skin and subcutaneous tissue disorders, n (%)				
Rash	5 (8)	2 (3)	5 (31)	12 (8)
Urticaria	3 (5)	7 (9)	1 (6)	11 (7)
Hyperhydrosis	3 (5)	4 (5)	1 (6)	8 (5)
Pruritus	3 (5)	4 (5)	0	7 (5)
General disorders and administration site conditions, n (%)				
Fatigue	3 (5)	7 (9)	1 (6)	11 (7)
Chills	3 (5)	5 (6)	2 (13)	10 (6)
Pyrexia	5 (8)	1 (1)	3 (19)	9 (6)
Infections and Infestations, n (%)				
Pneumonia	5 (8)	4 (5)	0	9 (6)
Respiratory, thoracic and mediastinal disorders, n (%)				
Dyspnea	5 (8)	3 (4)	1 (6)	9 (6)
Cough	5 (8)	4 (5)	0	9 (6)
Gastrointestinal disorders, n (%)				
Diarrhea	5 (8)	3 (4)	2 (13)	10 (6)
Nausea	3 (5)	5 (6)	1 (6)	9 (6)
Vascular disorders, n (%)				
Hypotension	2 (3)	4 (5)	1 (6)	7 (5)

Haematologic Adverse Events

A total of 29 subjects (19%) had 42 events associated with decreased neutrophil counts. The most common reported event was neutropaenia: 25 subjects (16%) had 35 events. 15 of the 29 subjects (52%) who had AEs associated with a decreased neutrophil count were neutropaenic at baseline, as defined by the CTCAE version 3 criteria (≥ Grade 1; <1.8 x 10^9/L). Of these, 11 subjects (73%) with baseline neutropaenia received G-CSF as concomitant medication during the course of the study. Of the 42 events associated with decreased neutrophil count, 1 event was fatal (neutropaenic sepsis), 10 events were Grade 4 (9 neutropaenia, 1 neutrophil count decreased), 21 events were Grade 3 (16 neutropaenia, 1 neutrophil count decreased, 2 neutropaenic sepsis and 2 febrile neutropaenia), and 10 events were Grade 1-2.

A total of 29 subjects (19%) had 39 events associated with decreased haemoglobin. The majority of these events were anaemia (25 subjects [16%], 33 events). Approximately one-third of these events (14/39) were considered by the investigator to be related to ofatumumab treatment. Four events were serious (1 anaemia, 1 autoimmune haemolytic anaemia, 2 haemolytic anaemia) and one of these 4 serious events (haemolytic anaemia) was considered by the investigator to be related to ofatumumab. None of the 39 AEs associated with decreased haemoglobin were fatal. A total of 3 events were Grade 4 (1 anaemia, 1 anaemia haemolytic autoimmune, and 1 haemolytic anaemia), 12 events were Grade 3 (10 anaemia, 1 haemoglobin decreased, 1 haemolytic anaemia), and 24 events were Grade 1-2 (22 anaemia, 2 haemoglobin decreased).

Four subjects (3%) had 5 events of decreased platelet count (3 events of thrombocytopaenia and 2 events of decreased platelet count). Four of these events were considered by the investigator to be related to ofatumumab. An SAE of thrombocytopenia was reported for 1 subject and the event was considered by the investigator not to be related to ofatumumab.

This hematologic profile compares favourably to the frequency and severity of hematologic adverse events that would be expected with cytotoxic therapy options in this clinical setting.

Biochemistry Adverse Events

Eight subjects (5%) had NCI-CTC[19] ≥Grade 3 uric acid elevations. 3 of these subjects had hyperuricemia reported as an AE of which one was considered by the investigator to be related to ofatumumab.

Serious Adverse Events

A total of 82 subjects (53%) had 152 SAEs, and 25 subjects (16%) had 39 SAEs that were considered by the investigator to be related to ofatumumab (see Table 29). The most common drug-related SAEs were infections (14 subjects, 9%), and neutropenia (8 subjects, 5%).

Overall, the SOC of 'infections and infestations' was the most common category of SAEs reported, and 51 (33%) subjects had at least 1 such event considered as SAEs. A total of 14 (9%) subjects had SAEs of infections considered to be related to the study drug. Of all SAEs reported, lower respiratory infections (pneumonia, bronchitis and bronchopneumonia) were the most common (24 subjects, 16%), followed by septic complications (sepsis, neutropaenic sepsis) (3 subjects, 2%). All 3 SAEs of septic complications were considered by the investigator to be drug-related. Eight subjects (5%) had SAEs of lower respiratory infections that were considered by the investigator to be drug-related.

Other common SAEs reported during treatment and in the Follow-up period were neutropaenia (6%), disease progression (6%), and pyrexia (5%). A total of 19 (12%) subjects discontinued due to their SAEs. The most common reason for discontinuation due to SAE was pneumonia (6 subjects) and sepsis (6 subjects). The majority of the SAEs (58%) occurred during treatment. A total of 39 SAEs (39/152, 26%) occurred within 30 days of the last infusion of ofatumumab. Infections were the most common SAEs, regardless of the time since last infusion, and there were no differences in the type of SAEs reported during treatment as compared to after completion of treatment.

Cardiac events were reported in 7 subjects (2 DR, 4 BFR and 1 Other). None of the 9 events were considered as related to ofatumumab by the investigator. Two subjects had cardiac failure, two subjects had myocardial infarction, two subjects had myocardial ischaemia, and one subject had perimyocarditis. Two subjects (1 DR, 1 BFR) were diagnosed with small bowel obstruction during the study. In both cases, the events resolved and were considered by the investigator to be unrelated to ofatumumab treatment. Five subjects had five SAEs of new or secondary neoplasms reported. One subject had Hodgkin's Lymphoma, which was considered related to ofatumumab. One subject had CLL transformation, one subject had Mantle Cell Lymphoma, one subject had breast cancer, and one subject had caecal adenocarcinoma; all were considered not to be related to ofatumumab treatment.

Of the 154 subjects, 111 entered extended follow-up after completion of treatment and the initial follow up period, or following withdrawal from treatment or follow-up. Nine of 111 subjects that entered the extended follow-up had 11 SAEs before initiation of new CLL treatment; however none of the SAEs reported in the 9 subjects were considered drug-related by the investigator.

[19] The National Cancer Institute Common Toxicity Criteria (NCI-CTC).

Table 29: Summary of SAEs experienced by More Than One Subject During Treatment or Follow-up (Excludes SAEs That Occurred During Extended Follow-up) – Study Hx-CD20-406.

System Organ Class Preferred Term	DR (N=59)	BFR (N=79)	Other (N=16)	Total (N=154)
Subjects with SAEs, n (%)	32 (54)	38 (48)	12 (75)	82 (53)
Infections and infestations, n (%)				
Pneumonia	8 (14)	9 (11)	2 (13)	19 (12)
Sepsis	3 (5)	4 (5)	0	7 (5)
Herpes zoster	2 (3)	1 (1)	0	3 (2)
Bronchopneumonia	2 (3)	1 (1)	0	3 (2)
Neutropenic sepsis	1 (2)	1 (1)	1 (6)	3 (2)
Sinusitis	1 (2)	2 (3)	0	3 (2)
Urinary tract infection	1 (2)	1 (1)	1 (6)	3 (2)
Bronchitis	2 (3)	0	0	2 (1)
Septic shock	2 (3)	0	0	2 (1)
Blood and lymphatic system disorders, n (%)				
Neutropenia	3 (5)	2 (3)	4 (25)	9 (6)
Febrile neutropenia	0	1 (1)	1 (6)	2 (1)
Hemolytic anemia	0	2 (3)	0	2 (1)
General disorders and administration site conditions, n (%)				
Disease progression	1 (2)	5 (6)	3 (19)	9 (6)
Pyrexia	4 (7)	3 (4)	0	7 (5)
Cardiac disorders, n (%)				
Myocardial infarction	1 (2)	2 (3)	0	3 (2)
Cardiac failure	1 (2)	0	1 (6)	2 (1)
Myocardial ischemia	0	2 (3)	0	2 (1)
Injury, poisoning and procedural complications, n (%)				
Fall	0	2 (3)	0	2 (1)
Gastrointestinal disorders, n (%)				
Small intestinal obstruction	1 (2)	1 (1)	0	2 (1)
Vascular disorders, n (%)				
Deep vein thrombosis	0	2 (3)	0	2 (1)
Eye disorders, n (%)				
Diplopia	1 (2)	1 (1)	0	2 (1)
Psychiatric disorders, n (%)				
Confusional state	2 (3)	0	0	2 (1)

AEs Leading to Withdrawal

In Study Hx-CD20-406, 27 (17%) of subjects had AEs that led to withdrawal from treatment (21 subjects) or follow-up (6 subjects) as of the data cut-off date. Of the 27 subjects, 5 subjects discontinued due to AEs considered to be disease progression by the investigators. Of the other 22 subjects, 14 subjects died due to infections. The most common AEs that resulted in withdrawal were pneumonia (6 subjects: 4 DR, 2 BFR) and sepsis (6 subjects: 4 DR, 2 BFR).

The proportion of subjects with AEs leading to withdrawal (excluding 5 subjects who discontinued due to disease progression but were listed as AEs) was numerically higher in the DR group (11 subjects) than in the BFR group (8 subjects). The majority of subjects had AEs leading to discontinuation that were not considered by the investigator to be related to study drug (23/27, 85%). Four subjects had AEs that were considered to be related to study medication; 2 in the DR group (pneumonia and hypersensitivity), 1 in the BFR group (pneumonia), and 1 in the Other group (neutropaenia).

Nineteen subjects had 20 SAEs resulting in withdrawal from treatment or follow-up and 11 subjects were withdrawn due to SAEs with fatal outcome. Four AEs leading to withdrawal of

4 subjects were judged by the investigator as drug-related (Grade 5 pneumonia, Grade 4 pneumonia, Grade 3 hypersensitivity, and Grade 2 neutropaenia).

An additional 45 (41%) subjects withdrew from all study activities due to SAEs in extended follow up. The reason for withdrawal of 43 of these 45 subjects was death. Fatal SAEs were reported as the cause of death of 37 subjects with the most common fatal SAE being disease progression in 10 subjects.

Deaths

A total of 61 subjects died during study as of 19 May 2008. Early death was defined as death occurring within 8 weeks of start of ofatumumab treatment. Six of 154 subjects (4%; 4 DR subjects and 2 BFR subjects) died within 8 weeks after the start of treatment, 5 were due to infection, and 1 due to myocardial infarction. Most subjects died >60 days after the last dose of ofatumumab. More subjects died after the start of new CLL treatment than prior to the start of new CLL treatment.

Of the total 61 deaths, 24 were reported during treatment or in the Follow-up period (the AE reporting period for the study) and 37 were reported during the Extended Follow-up period (7 before and 30 after initiation of new CLL treatment). Of the 24 deaths during this time period, 4 were considered related to ofatumumab, but only 1 occurred within 30 days of ofatumumab treatment: pneumonia in a DR subject 25 days after the 8th infusion.

Of the 24 deaths during treatment or follow up period, 4 subjects died during response to ofatumumab, defined as within 30 days of last ofatumumab dose and an investigator assessed response status of PR, nPR or CR at the time-point closest to the onset of the fatal SAE.

Sixteen of the 24 deaths during treatment and follow-up were due to infections: 10 (17%) of 59 DR subjects, 5 (6%) of 79 BFR subjects and 1 (6%) of 16 Other subjects. Disease progression, including CLL transformation and hemiparesis due to CLL CNS involvement, was the cause of death in 6 subjects during treatment or follow-up. One subject died due to cardiac failure and 1 subject (Other group) died due to myocardial infarction. Both were considered unrelated to ofatumumab treatment by the investigator.

Adverse Events of Special Interest

The following events of interest are generally known to be associated with anti-CD20 therapies:

- Infections
- Infusion reactions
- Autoimmune hematologic complications
- Tumour lysis syndrome
- Mucocutaneous reactions

Infections

Subjects with advanced, pre-treated CLL are prone to infections due to immune defects inherent to the primary disease as well as to therapy-related immunosuppression (Morrison, 2007). Infection-related AE preferred terms were grouped to better understand if the pattern of infection in the refractory CLL population could be explained by the underlying disease in this heavily pre-treated, immunocompromised subject population or if there was evidence that ofatumumab might have contributed to the infection rate in the study population.

Of the 154 subjects enrolled in the study, 108 subjects (70%) had infections of any severity grade reported as AEs (21% of 1209 AEs). Respiratory tract infections were the most common events. Infections of the lower respiratory tract (pneumonias) were more common

than upper respiratory tract infections. The second most frequently reported events were septic complications. The frequency of infections was similar between the DR and BFR subgroups (summarised Table 30).

The majority of infections were of Grade 1 or 2 in severity (91 subjects, 59%). Fatal infections occurred in 16 of 154 subjects (10%) during treatment or the Follow-up period. During extended follow-up, an additional 14 subjects died due to infections (6 pneumonia, 7 sepsis, 1 aspergillus infection). No cases of hepatitis B reactivation have been reported across the clinical program to date; however subjects with active hepatitis B were excluded from the studies.

Table 30: Summary of All Infections in Study Hx-CD20-406.

	DR (N=59)		BFR (N=79)		Other (N=16)		Total (N=154)	
	Events	n (%)	Events	n (%)	Events	n (%)	Events	n (%)
Any infections	104	41 (69)	111	54 (68)	35	13 (81)	250	108 (70)
All Respiratory Tract Infections[1]	67	31 (53)	67	38 (48)	17	8 (50)	151	77 (50)
Lower respiratory tract infections[2]	44	24 (41)	29	21 (27)	13	7 (44)	86	52 (34)
Pneumonias[3]	19	15 (25)	17	14 (18)	7	6 (38)	43	35 (23)
Bronchial infections[4]	16	11 (19)	8	6 (8)	0	0	24	17 (11)
Lung infections[5]	4	3 (5)	1	1 (1)	0	0	5	4 (3)
Upper respiratory tract infections[6]	23	15 (25)	38	24 (30)	4	3 (19)	65	42 (27)
Septic complications[7]	6	6 (10)	6	5 (6)	1	1 (6)	13	12 (8)
Other infections[8]	31	22 (37)	38	25 (32)	17	10 (63)	86	57 (37)

Data Source: Hx-CD20-406 ICTR In-text Table 11-22

1. **AE terms grouped under All respiratory tract infections:** Pneumonia, bronchitis, lower respiratory tract infection, bronchopneumonia, lung infection, lobar pneumonia, bronchitis bacterial, pneumocystis jiroveci pneumonia, pneumonia fungal, pneumonia streptococcal, respiratory syncytial virus infection, upper respiratory tract infection, nasopharyngitis, rhinitis, sinusitis, pharyngitis, acute tonsillitis, laryngitis, tracheitis, and upper respiratory tract infection bacterial.
2. **AE terms grouped under Lower respiratory tract infections:** Pneumonia, bronchitis, lower respiratory tract infection, bronchopneumonia, lung infection, lobar pneumonia, bronchitis bacterial, pneumocystis jiroveci pneumonia, pneumonia fungal, pneumonia streptococcal, and respiratory syncytial virus infection.
3. **AE terms grouped under Pneumonias:** Pneumonia, bronchopneumonia, lobar pneumonia, pneumocystis jiroveci pneumonia, pneumonia fungal, pneumonia streptococcal, and respiratory syncytial virus infection.
4. **AE terms grouped under Bronchial infections:** Bronchitis and bronchitis bacterial.
5. **AE terms grouped under Lung infection:** Lung infection.
6. **AE terms grouped under Upper respiratory tract infections:** Upper respiratory tract infection, nasopharyngitis, rhinitis, sinusitis, pharyngitis, acute tonsillitis, laryngitis, tracheitis, and upper respiratory tract infection bacterial.
7. **AE terms grouped under Septic complications:** Sepsis, neutropenic sepsis, and septic shock.
8. **AE terms grouped under Other infections:** Herpes zoster, urinary tract infection, infection, oral herpes, viral infection, ear infection, folliculitis, gastroenteritis, influenza, cellulitis, herpes simplex, oral fungal infection, otitis media, wound infection, cytomegalovirus infection, localized infection, tinea pedis, abscess, anal infection, appendicitis, aspergilloma, bacteremia, bacterial infection, bacterial pyelonephritis, Campylobacter intestinal infection, catheter related infection, clostridial infection, cystitis, enterocolitis infectious, eye infection, fungal infection , Fusarium infection, gastroenteritis salmonella, gastrointestinal infection, hordeolum, injection site infection, onycomycosis, oral candidiasis, paronychia, peritoneal infection, progressive multifocal leukoencephalopathy, Pseudomonas infection, tinea infection, tooth abscess, tooth infection, and vulvovaginal mycotic infection.

In 32 subjects (21%), the infections were considered related to ofatumumab treatment by the investigator (see Table 31).

Table 31: Summary of All Drug-Related Infections in Study Hx-CD20-406.

	DR (N=59)		BFR (N=79)		Other (N=16)		Total (N=154)	
	Events	n (%)	Events	n (%)	Events	n (%)	Events	n (%)
Any drug-related infections	20	12 (20)	29	17 (22)	5	3 (19)	54	32 (21)
All Respiratory Tract Infections	15	8 (14)	13	11 (14)	3	1 (6)	31	20 (13)
Lower respiratory tract infections	14	8 (14)	8	7 (9)	1	1 (6)	23	16 (10)
Pneumonias	8	6 (10)	5	5 (6)	0	0	13	11 (7)
Bronchial infections	1	1 (2)	2	2 (3)	0	0	3	3 (2)
Lung infections	2	1 (2)	0	0	0	0	2	1 (1)
Upper respiratory tract infections	1	1 (2)	5	4 (5)	2	1 (6)	8	6 (4)
Septic complications	0	0	3	3 (4)	0	0	3	3 (2)
Other infections	5	5 (8)	13	8 (10)	2	2 (13)	20	15 (10)

Infections Reported as SAEs

A total of 51 subjects (33%) had infections that were reported as SAEs. In 14 subjects (9%), these events were considered drug-related by the investigators. Subjects in the DR group had a higher frequency of drug-related infection SAEs compared to subjects in the BFR and Other group (see Table 32). Fatal infections occurred in 16 subjects (10%).

Table 32: Summary of Drug-Related Serious Infections in Study Hx-CD20-406.

	DR (N=59)		BFR (N=79)		Other (N=16)		Total (N=154)	
	Events	n (%)	Events	n (%)	Events	n (%)	Events	n (%)
All drug-related infection SAEs	11	9 (15)	6	4 (5)	1	1 (6)	18	14 (9)
All Respiratory Tract Infections	7	6 (10)	2	2 (3)	0	0	9	8 (5)
Lower respiratory tract infections	7	6 (10)	2	2 (3)	0	0	9	8 (5)
Pneumonias	7	6 (10)	2	2 (3)	0	0	9	8 (5)
Bronchial infections	0	0	0	0	0	0	0	0
Lung infections	0	0	0	0	0	0	0	0
Upper respiratory tract infections	0	0	0	0	0	0	0	0
Septic complications	0	0	3	3 (4)	0	0	3	3 (2)
Other infections	4	4 (7)	1	1 (1)	1	1 (6)	6	6 (4)

Grade 3 and Grade 4 Infections

A total of 31 subjects (20%) had 39 Grade 3 infections; in 27 subjects, these events were also reported as SAEs. The incidence of Grade 3 infections was similar among the three subgroups of subjects. In 8 subjects with Grade 3 infections, the events were considered drug-related by the investigator. Six of these infections were also reported as SAEs. Some 8 subjects (5%) had Grade 4 infections, all of which were also reported as SAEs. The majority of these infections (6 events in 6 subjects) were respiratory tract infections, with pneumonias being the most common events (4 subjects, 4 events). Grade 4 infections in 6 subjects (3%) were considered drug-related.

Grade 5 (Fatal) Infections

A total of 16 subjects (10%) had fatal infections during treatment and follow-up. The fatal infections in 4 of the 16 subjects were considered by the investigator to be related to study drug. The most common cause of death from infections during treatment and follow-up was sepsis (7 subjects), followed by pneumonia (6 subjects). The 3 other infections were one case each of progressive multifocal leukoencephalopathy (PML), fusarium infection, and peritoneal infection.

Of these 16 deaths, 9 (6 DR, 3 BFR) occurred within 30 days of the last dose of ofatumumab, 5 (3 DR, 1 BFR, 1 Other) occurred within 30 to 60 days after last dose of ofatumumab, and 2 (1 DR, 1BFR) occurred beyond 60 days after the last dose of ofatumumab. During extended follow-up, an additional 14 subjects died due to infections (6 pneumonia, 7 sepsis, and 1 aspergillus infection). Two of these 14 deaths occurred within 30 days of the last dose, 1 being categorized as an early death (within 8 weeks of starting treatment). Both deaths occurred after the start of new CLL therapy.

Analysis of Risk Factors for Infection

The potential for ofatumumab to increase the risk of infection was analysed by four different confounding risk factors related to aspects of disease status or to clinical characteristics that emerged during treatment: Rai Stage, number of prior CLL therapies, neutrophil counts at baseline, and infections over time. The data did not suggest that ofatumumab had altered or increased the risk of infection in this population in a clinically significant way.

Infusion Reactions

Infusion reactions are commonly associated with anti-CD20 antibody therapy. These reactions typically include a constellation of symptoms including rash, cough, pain, chills and rigors, pyrexia and fever, and dyspnoea. Infusion reactions were broadly defined as signs and symptoms that could be infusion related, occurred on infusion days and started after the beginning of the ofatumumab infusion. The events were usually mild, and generally allowed for the administration of the fully intended infusion dose.

Pre-medication consisting of paracetamol (1000 mg or equivalent) and an antihistamine (cetirizine 10 mg or equivalent) was to be administered before each ofatumumab infusion. In addition, administration of IV steroids (prednisolone, 100 mg or equivalent) was mandatory before the first 2 weekly and the first monthly infusion (infusion 9). For all other infusions, IV steroid administration was optional (3rd to 8th infusion) or could be administered at reduced doses (10th to 12th). During the study, more than 80% of subjects received IV steroids as pre-medication before ofatumumab infusion.

Dose interruptions as a means to treat infusion reactions were most frequent during the first dose (33 subjects, 21%), and decreased with subsequent doses. Despite the dose interruptions, there was only 1 subject who did not ultimately receive the full intended dose.

Overall, 64% of subjects had any kind of infusion reactions during or following any of the 12 scheduled infusions. The events were usually mild (≤Grade 2), most common with the first infusion and, with the exception of 1 subject, did not preclude the administration of the fully intended infusion dose. In this study, 41% of subjects had infusion reaction AEs following the first infusion declining to 25% with the second infusion, and to 6% with the last infusion. One subject stopped treatment due to an infusion reaction. A total of 5 subjects had infusion reactions classified as SAEs. One subject discontinued due to an infusion reaction and subsequently developed PML. No fatal infusion reactions occurred on any infusion day.

Although direct comparisons cannot be made due to differences in pre-medication schedules and subject populations, the frequency of these reactions appear to be lower than rates described with IV use of rituximab or alemtuzumab in the literature (Keating, 2002b; O'Brien, 2001a).

Autoimmune Haematologic Complications

Autoimmune haemolytic anaemia (AIHA), immune thrombocytopenia (ITP) and pure red cell aplasia (PRCA) are well-known complications that can occur in subjects with CLL; however, they were rarely observed with ofatumumab. In Study Hx-CD20-406, 3 of 154 subjects (2%) were diagnosed with AIHA (one in the DR group and 2 in the BFR group). All 3 events were reported as SAEs and considered by the investigator as unrelated to ofatumumab treatment. None of the subjects had a history of haemolytic anaemia; however haemolysis was evident in 2 out of 3 cases at baseline with positive Coombs test and low haptoglobin levels.

One case of Grade 2 PRCA was reported 46 weeks after the last dose of ofatumumab. The subject had a prior history of haemolytic anaemia (1 year prior to entry into the study following fludarabine therapy). The PRCA was considered as not related to study drug by the investigator and the subject was withdrawn from study. No cases of ITP were reported in this study.

Tumour Lysis Syndrome

No tumour lysis syndrome **(**TLS) events were reported as of the interim analysis cut-off date for Study Hx-CD20-406.

Mucocutaneous Reactions

Using the terms indicating severe mucocutaneous reactions (paraneoplastic pemphigus, Stevens-Johnson Syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis), a review of the entire AE database for the ofatumumab oncology studies included in the submission through the safety cut-off date did not reveal a single case of these events.

Safety in Other Studies

Data from 5 additional supportive studies (Hx-CD20-402, Hx-CD20-407, Hx-CD20-001, Hx-CD20-405, and Hx-CD20-409), both ongoing and completed, in subjects with CLL or FL were submitted for evaluation. The safety profile reported in those studies supported the safety profile of ofatumumab reported in Study Hx-CD20-406. These studies evaluated the safety and efficacy of ofatumumab as monotherapy in relapse/refractory CLL, relapsed/refractory FL, and as combination therapy with fludarabine and cyclophosphamide (FC) or with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) in the frontline CLL and FL settings, respectively, and included 208 subjects.

Supportive safety data (SAEs only) were also analysed from 286 subjects in studies of ofatumumab in diffuse large B cell lymphoma (DLBCL), rheumatoid arthritis (RA) and chronic obstructive pulmonary disease (COPD). No additional safety concerns emerged from these additional supportive studies.

Overdose, Withdrawal and Rebound

Overdose, withdrawal and rebound effects are not applicable to this submission.

Summary of Safety

The safety data from the Hx-CD20-406 studies demonstrated that treatment with ofatumumab was generally well tolerated in the study population with advanced, heavily pre-treated, highly refractory CLL. Adverse events were common and were predominantly mild to moderate infections, infusion reactions and haematologic abnormalities, side effects that were to be expected in this patient population for both frequency and severity. These events were mostly manageable. No unexpected adverse events were observed. SAEs were the minority of all AEs.

POST-MARKETING EXPERIENCE

No post-marketing data were provided for evaluation.

Clinical Summary and Conclusions

The efficacy and safety data in support of the application for registration of ofatumumab are primarily derived from the results of an interim analysis of an ongoing pivotal study (Study Hx- CD20-406). This study is a single arm, open-label, multicentre study of ofatumumab in subjects with CLL who were refractory to both fludarabine and alemtuzumab (double refractory, DR), or were fludarabine-refractory and considered inappropriate for alemtuzumab due to bulky lymphadenopathy (bulky fludarabine refractory, BFR).

Additional supportive evidence of safety and efficacy was provided by a Phase I/II study (Study Hx-CD20-402) of ofatumumab in subjects with relapsed/refractory CLL. The findings from this Phase I/II study served as the rationale for the ongoing pivotal study (Hx-CD20-406).

Patients with CLL refractory to fludarabine often do not derive clinical benefit from alemtuzumab due to lack of response (DR) or presence of bulky lymphadenopathy that makes responses to alemtuzumab unlikely (BFR). In these patients there is a high unmet medical need as they are without approved or otherwise accepted standard therapies. Response rates with other therapies are low in this patient population (0-26%), and median survival is reported to be between 8-14 months (Tam *et al*, 2007). In the single arm, multi-centre, open-label pivotal Study Hx-CD20-406, subjects with fludarabine-refractory CLL received ofatumumab monotherapy (an initial dose of 300 mg, followed one week later by 2000 mg once weekly for seven infusions, followed 5 weeks later by 2000 mg once every 4 weeks for 4 infusions, for a total of 12 infusions).

In the pre-planned interim analysis of 154 subjects, 138 met the criteria defined for DR or BFR disease. The response rate was 51% in the combined group, 58% in the DR group and 47% in the BFR group. There was 1 CR in the BFR group, all other responders were PR. The response rates, and the results of other efficacy parameters, were consistent between the DR and BFR subject groups, providing independent corroboration of the treatment effect of ofatumumab.

Responses were achieved rapidly. The median time to response was 1.8 months in all groups (DR, BFR, combined). The median duration of response was 5.6 months in the combined group (7.1 months DR, 5.6 months BFR), and the duration of response after last infusion was 2.1 months in the combined group (2.5 months DR, 1.9 months BFR). The median progression-free survival was 5.7 months in the combined group (5.7 months DR, 5.9 months BFR). The median overall survival was 15.4 months in the combined group (13.7 months DR, 15.4 months BFR). The median time to next CLL therapy was 8.2 months in the combined group (9.0 months DR, 7.9 months BFR). Improvements in the individual components of the response assessment were observed. There was a rapid and sustained depletion of lymphocytes and malignant B cells. Data supported the effect of ofatumumab on the target CD20+ cells in blood and lymph nodes.

Ofatumumab treatment was also associated with a complete resolution in constitutional symptoms for a minimum of 2 month for 57% of subjects in the combined group experiencing symptoms at baseline. Similar numbers of subjects with baseline splenomegaly and hepatomegaly had improvement or complete resolution for at least 2 months.

Improvements in haematologic values were also observed in subjects with abnormal baseline values, particularly for platelet counts and haemoglobin. The effect on neutrophils was less pronounced, nevertheless, 17% of subjects who were neutropaenic at baseline had an increase of neutrophils to $>1.5x10^9$/L for at least 2 months.

Subgroup analyses showed consistent responses across subgroups typically associated with poor outcomes, specifically subjects 65 years of age or older, subjects with several prior CLL treatments (median 5.0), and subjects with chromosomal abnormalities, including subjects with 17p and 11q deletions.

Overall, the pre-planned interim analysis from pivotal Study Hx-CD20-406 showed efficacy suggestive of clinical benefit for ofatumumab monotherapy in the treatment of subjects with fludarabine-refractory CLL.

The safety data from the Hx-CD20-406 studies demonstrated that treatment with ofatumumab was generally well tolerated in the study population with advanced, heavily pre-treated, highly refractory CLL. Adverse events were common and were predominantly mild to moderate infections, infusion reactions and haematologic abnormalities, side effects that were to be expected in this patient population for both frequency and severity. These events were mostly manageable. No unexpected adverse events were observed. SAEs were the minority of all AEs.

It is the opinion of this evaluator that the data presented in this application provide evidence of efficacy of Arzerra in treatment of patients with CLL. The patient population enrolled in Study Hx-CD20-406 was refractory to fludarabine and alemtuzumab and this should be reflected in the approved indication.

Recommendation: At present, and on the basis of the data evaluated, it is recommended that the application to register ofatumumab (Arzerra) ***should be approved.***

The approved indication should be similar to the US approved indication as follows:

"Arzerra (ofatumumab) is indicated for the treatment of patients with chronic lymphocytic leukaemia (CLL) refractory to fludarabine and alemtuzumab.

The effectiveness of Arzerra is based on the demonstration of durable objective responses [see Clinical Studies]. No data demonstrate an improvement in disease related symptoms or increased survival with Arzerra."

Sponsor's response:

Company's position

It is well recognised that CLL patients who become refractory to approved therapies like fludarabine and alemtuzumab have few, if any, therapeutic options, resulting in a median survival of approximately a year [Keating, 2002, Tam, 2007] and for patients who have bulky fludarabine refractory disease, alemtuzumab therapy is known to be associated with an 8-12% response rate and a median overall survival of 9-10 months [Keating 2002, Fiegl 2006, Moreton 2005], making alemtuzumab less effective in this population.

The pivotal study Hx-CD20-406 explored the efficacy of ofatumumab in patients with CLL who are either refractory to both fludarabine and alemtuzumab, or who are refractory to fludarabine and were considered inappropriate for alemtuzumab treatment due to bulky lymphadenopathy. Single agent ofatumumab was administered as 8 weekly infusions followed by 4 monthly infusions over 24 weeks. The primary endpoint was response rate over a 24 week period.

Adult subjects were eligible for participation in study Hx-CD20-406 if they had active CLL and were refractory to prior therapy defined as a minimum of 2 cycles of fludarabine and at least 12 administrations of alemtuzumab **(double refractory, DR).** Subjects were **also** eligible if they were refractory to prior therapy defined as a minimum of 2 cycles of fludarabine and were considered inappropriate candidates for alemtuzumab treatment due to the presence of bulky lymphadenopathy, defined as lymph node size of >5cm **(bulky fludarabine refractory, BFR).** The efficacy data from the pre-planned interim analysis was based on 59 subjects in the DR population and 79 subjects in the BFR population. .

Sub-group analyses were performed to determine the effect of prior therapy on response rates to ofatumumab as described on pages 35 and 36 of the clinical evaluation report. All subjects in this study were refractory to fludarabine as part of study entry criteria, and many (57%) of the subjects have had treatment with cyclophosphamide and rituximab. The response rates to ofatumumab were similar in DR and BFR subjects regardless of what prior fludarabine-containing regimens were used.

The clinical evaluator commented:

"The efficacy results from pivotal study Hx-CD20-406 demonstrate compelling efficacy of ofatumumab monotherapy in two fludarabine-refractory populations, with response rates of 47-58%. The responses occurred quickly, were durable, and were consistent across subgroups. Landmark analysis at 12 weeks showed that responders in both DR and BFR groups had markedly longer median survival than non-responders.

Subjects who were non-responders by NCIWG 1996 CLL response criteria experienced improvement of resolution of clinical symptoms and haematological parameters of CLL. Overall, the efficacy data from pre-planned interim analysis from pivotal study Hx-CD20-406 support the clinical benefit for ofatumumab monotherapy in the treatment of subjects with fludarabine-refractory CLL."

GSK agrees with the assessor's conclusions that both the DR and BFR populations represent an unmet medical need and that compelling efficacy have been demonstrated with ofatumumab in these populations. Similar to the DR population, the BFR population also has an unmet medical need due to lack of efficacy with standard therapies. Ofatumumab in the BFR population had a similarly compelling overall response rate (47%) and 5.9 month median progression free survival, along with an acceptable safety profile.

Thus, GSK proposes the following revised indication:

"*ARZERRA (ofatumumab) is indicated for the treatment of patients with chronic lymphocytic leukaemia (CLL) refractory to a fludarabine-containing regimen. The effectiveness of ARZERRA is based on the demonstration of durable objective responses [see Clincial Studies]. No data demonstrate an improvement in disease related symptoms or increased survival with ARZERRA.*"

The Company believes that this indication statement best reflects the results of pivotal study Hx-CD20-406, namely demonstrating the compelling efficacy of ofatumumab as monotherapy regardless of what prior fludarabine-containing regimen was used.

V. Pharmacovigilance Findings

Risk Management Plan

A risk management plan (RMP) was submitted by GlaxoSmithKline Australia Pty Ltd in support of such an application, and the following important safety concerns were identified by the sponsor (Table 33).

Table 33. Safety Concerns

Important identified risks	Infusion reactions Including Cytokine Release Syndrome Tumour Lysis Syndrome (TLS) Bowel Obstruction Cardiovascular
Important potential risks	Cytopenias Infections Progressive Multifocal Leukoencephalopathy (PML) Hepatitis B Virus (HBV) Reactivation Effects on Immunisations, Including Interactions with Live Vaccines Immunogenicity Effect of Concomitant HMG-CoA Reductase Inhibitors on Ofatumumab Response
Important missing information	Limited data in pregnant and lactating females Limited experience in patients with other relevant co-morbidities including cardiac disease, renal, hepatic, haematological, gastrointestinal, endocrine, pulmonary, neurological, cerebral or psychiatric diseases.

The proposed application of routine pharmacovigilance activities[20] for all safety concerns as identified by the sponsor and the application of additional pharmacovigilance activities for the specified safety concerns are generally acceptable.

In addition little detail has been provided regarding the 'targeted follow up questionnaire' to be employed for all reports of small bowel obstruction and PML. Therefore the sponsor was asked to provide copies of these documents to the TGA.

The sponsor provided a copy of this questionnaire in their Pre-Advisory Committee on Prescription Medicines (ACPM) response.

The ongoing studies identified in the pharmacovigilance plan are not considered to be part of the planned clinical studies in the pharmacovigilance plan. Nevertheless an update on the progress/results/analysis of these studies, according to the milestones presented, will be expected in future Periodic Safety Update Reports (PSURs) and at the foreshadowed milestones.

The sponsor has committed to supplying updates on on-going studies according to milestones in future PSURs.

[20] Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

The proposed application of routine risk minimisation activities to the safety concerns, as specified by the sponsor, is generally acceptable. Nevertheless it is recommended that the draft product information document be amended as follows:

- In regard to the identified risk: 'TLS', it is suggested that the associated risk factors be included to align the Australian PI with the currently proposed European SmPC.
- In regard to the potential risk: 'Infections', the following incidence of infections should be included to align the Australian PI with the currently proposed European Summary of Product Characteristics (SmPC):
    - "Infections and Infestations"
        - § Very common: Lower respiratory tract infection, including pneumonia, upper respiratory tract infection
        - § Common: Sepsis, including neutropenic sepsis and septic shock, herpes virus infection, urinary tract infection
- In regard to the potential risk: 'Hepatitis B Virus (HBV) Reactivation', it is suggested that the warning statements in the Australian PI be updated to the wording in the currently proposed European SmPC.
- In regard to the potential risk: 'Effects on Immunisations, Including Interactions with Live Vaccines', the warning statements in the currently proposed European SmPC should be included.
- In regard to the missing information relating to pregnant females, it is suggested that the period of adequate contraception after the last ofatumumab treatment be 12 months rather than 6 months to align the Australian PI with the currently proposed European SmPC.
- The draft consumer medicine information document should adequately reflect any changes made to the Australian PI as a result of the above recommendations.

The sponsor agreed to these changes and subsequently submitted draft PI and CMI documents reflecting these changes.

Finally the delivery of the recommended dose of 2,000 mg required the use of twenty vials and this raised concerns regarding the possibility of medication errors. However the American sponsor had committed to develop a more appropriate strength given the recommended dose. Consequently the Australian sponsor should also provide such a commitment and an assurance that once a more appropriate strength has been developed it will be submitted to the TGA for registration.

The sponsor gave a commitment that a larger vial size will be developed and submitted for registration.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There are no objections to registration on Quality grounds. The application was considered by the PSC at its March 2010 meeting and no objections to registration were raised.

Nonclinical

There are no nonclinical objections to registration. As ofatumumab was found not to bind to CD20 homologues of rodents, dogs or pigs, toxicity was studied in cynomolgus monkeys. The systemic exposures achieved in the monkey studies were only marginally above those seen in humans treated with the recommended dose. However, almost complete deletion of B cells was achieved at all doses studied.

The main toxicities observed were consistent with the mechanism of action of the drug (atrophy of lymphoid tissue, GIT infection). There was an increased incidence of haemolytic anaemia following long-term treatment with ofatumumab, which was considered to be the result of the formation of anti-ofatumumab antibodies. The formation of such antibodies was not observed in patients with CLL in the clinical studies.

Clinical

The clinical evaluator has recommended approval of the application, but with a more restricted indication than that being proposed by the sponsor. The indication proposed by the evaluator is "*treatment of patients with CLL refractory to a fludarabine and alemtuzumab*".

Pharmacodynamics

In the pivotal study included in the submission (Study Hx- CD20-406), administration of ofatumumab was associated with a 92% reduction in peripheral B-cells (CD19+) and B-CLL cells (CD19+, CD5+).

Pharmacokinetics

In an early dose-ranging study (Study Hx- CD20-402), PK were non-linear, with a greater than proportional increase in AUC/Cmax with increasing dose. Decreasing clearance with first versus subsequent doses was also noted. These findings would be consistent with saturation of available CD20 sites.

In the pivotal study, after repeated dosing, the drug was demonstrated to have a small volume of distribution (4 – 5 L), a low clearance (approximately 10 mLs / hr) and a half-life of approximately 14 – 16 days.

As with other therapeutic proteins with a large molecular weight, elimination would be expected to occur by catabolism through proteolysis. Studies in renal and hepatic impairment have therefore not been conducted.

Efficacy

Evidence for efficacy comes primarily from one pivotal, open, single-arm trial (Study Hx-CD20-406). The study has been published in the Journal of Clinical Oncology (2010[21]).

The trial enrolled subjects who:

- Had *B-cell* CLL (CD5+, CD20+, CD23+);
- Had *active* disease;
- Were refractory to fludarabine treatment, and:
- Were refractory to alemtuzumab treatment (double refractory – DR), or were considered unsuitable for alemtuzumab due to bulky disease (bulky, fludarabine refractory – BFR).

The trial enrolled 154 subjects, of whom 59 had DR disease and 79 had BFR disease. The population was a heavily pre-treated one with a median of 5.0 prior CLL regimens. The primary endpoint was response rate as defined by the 1996 NCI Working Group Guidelines and assessed by an independent review committee.

The response rate was 58% (99% CI: 40 to 74%) in the DR subgroup, with all responses being partial remissions. The response rate was 47% (99% CI: 32 to 62%) in the BFR

[21] Wierda W.G. *et al* 2010. Ofatumumab As Single-Agent CD20 Immunotherapy in Fludarabine-Refractory Chronic Lymphocytic Leukemia. *JCO* 28:1749-1755.

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subgroup with 46% partial remissions and 1% complete remission. Historical data (Tam *et al* 2007) suggest that response rates with other CLL therapies in this clinical situation are in the vicinity of 20 - 26%. Median duration of response was 7.1 months for the DR group and 5.6 months for the BFR group.

Findings on median overall survival are summarised in the following table:

Table 34.

Subgroup	Ofatumumab	Historical data [(1)]
DR	**13.7 m** (95% CI: 9.4 – NE)	**8 m** (95% CI: NS)
BFR	**15.4 m** (95% CI: 10.2 – 20.2)	**14 m** (95% CI: NS)

(1) – Tam *et al* 2007. NE = not estimable. NS = not stated

Multiple other secondary endpoints were studied. Ofatumumab treatment was associated with decreased lymphocyte counts, improvements in constitutional symptoms, lymphadenopathy, splenomegaly, hepatomegaly, haemoglobin and neutrophil and platelet counts.

Of note, the drug appeared to be equally effective in patients who had already received rituximab therapy.

The submission also included an earlier dose-ranging study (Study Hx- CD20-402) in patients with relapsed or refractory CLL. Treatment duration was limited to 4 weeks. The highest dose used (500 mg in Week 1, 2000 mg in Weeks 2, 3, 4) produced a response rate of 48%, which is comparable to that obtained in the pivotal study. Median duration of response was 4.4 months.

Safety

In the submitted studies a total of 648 subjects received at least one dose of ofatumumab. The most informative safety data come from the pivotal study where 154 CLL patients received the proposed dosage regimen. Of these, 85 completed the 12 infusions over 24 weeks.

The overall adverse event profile in the trial was summarised in the CER. There was a high incidence of adverse events (95%) with 64% of patients experiencing AEs that were considered drug-related. AEs of Grade 3 or greater severity occurred in 57% of subjects, and serious AEs in 53%. Due to the single-arm, non-comparative design of the study, it is impossible to determine whether the AEs seen in the trial were related to the drug or the disease.

The most common adverse events observed in the trial included the following:

- Hypersensitivity reactions – pyrexia, chills, cough, dyspnoea, rash, urticaria;
- Infections – pneumonia, respiratory tract infections;
- GIT events – diarrhoea, nausea.

In the pivotal study there were 4 deaths which were considered related to ofatumumab. All of these were related to infectious causes, including one case of PML.

The submission included one reasonably large (n=225), double-blind, placebo-controlled study in subjects with rheumatoid arthritis (Study Hx- CD20-406 Part B). Subjects received only two doses of ofatumumab. Hypersensitivity events were increased in the active groups compared to the placebo group (Table 35).

Table 35. Placebo-controlled dose-ranging study in rheumatoid arthritis (Study Hx- CD20-406 Part B).

MedDRA Preferred term	Placebo (N=56)		300 mg (N=58)		700 mg (N=57)		1000 mg (N=54)		Total Active (N=169)	
	n (%)	E	n (%)	E	n (%)	E	n (%)	E	n (%)	E
Total number of subjects with AEs	32 (57%)	135	47 (81%)	179	48 (84%)	207	46 (85%)	154	141 (83%)	540
Rash			6 (10%)	6	14 (25%)	15	10 (19%)	12	30 (18%)	33
Throat irritation			9 (16%)	10	5 (9%)	5	6 (11%)	7	20 (12%)	22
Dyspnoea	1 (2%)	2	3 (5%)	4	7 (12%)	8	8 (15%)	8	18 (11%)	20
Pharyngolaryng. pain	2 (4%)	2	5 (9%)	6	5 (9%)	6	5 (9%)	5	15 (9%)	17
Pruritus			3 (5%)	3	6 (11%)	13	4 (7%)	4	13 (8%)	20
Nausea	4 (7%)	9	4 (7%)	4	6 (11%)	6	4 (7%)	4	14 (8%)	14
Urticaria			3 (5%)	3	4 (7%)	5	5 (9%)	6	12 (7%)	14
Headache	4 (7%)	6	4 (7%)	4	4 (7%)	5	2 (4%)	3	10 (6%)	12
URTI	3 (5%)	3	3 (5%)	3	4 (7%)	4	3 (6%)	4	10 (6%)	11
Fatigue	2 (4%)	4	3 (5%)	3	4 (7%)	6	2 (4%)	2	9 (5%)	11
Cough	6 (11%)	9	5 (9%)	5	4 (7%)	4			9 (5%)	9
Rhinitis	2 (4%)	2	1 (2%)	1	2 (4%)	2	5 (9%)	5	8 (5%)	8
Hypertension	3 (5%)	3	2 (3%)	2	5 (9%)	6	2 (4%)	2	9 (5%)	10
Rheumatoid arthritis	5 (9%)	5	5 (9%)	6	1 (2%)	3	1 (2%)	1	7 (4%)	10
Dysphagia			2 (3%)	3	1 (2%)	1	4 (7%)	4	7 (4%)	8
Dry throat			3 (5%)	4			3 (6%)	3	6 (4%)	7
Throat tightness			1 (2%)	1	5 (9%)	5			6 (4%)	6
Infusion rel. react.	1 (2%)	1	2 (3%)	2	1 (2%)	1	3 (6%)	3	6 (4%)	6
Hypersensitivity					5 (9%)	5	1 (2%)	1	6 (4%)	6
Flushing	1 (2%)	2	3 (5%)	3	1 (2%)	1	2 (4%)	2	6 (4%)	6

N=Number of subjects exposed to trial drug
n=Number of subjects with Adverse Events (AEs)
%=proportion of patients reporting AE
E=Number of adverse events
URTI= upper respiratory tract infection
For rash, urticaria, hypertension and upper respiratory tract infection, the numbers include "NOS" although these are presented as separate terms in the statistical output. This was done in order to 1) not underestimate the prevalence and 2) maintain consistency with the interim analysis (in which these events were grouped as a result of the MedDRA version used)

Risk Management Plan

The sponsor's Risk Management Plan (RMP) was evaluated by the TGA's Office of Medicines Safety Monitoring (OMSM). The RMP was found to be acceptable.

Risk-Benefit Analysis

1. Lack of randomised controlled trial data

   The application is based on a Phase II trial with efficacy assessed using comparisons to historical data. The EMA guideline on anticancer agents which has been adopted by the TGA generally requires provision of Phase III data (comparing the drug to an established comparator) to obtain marketing approval.

   However, the Australian Drug Evaluation Committee (which has now been succeeded by ACPM) and the TGA have previously approved oncology applications based on Phase II data in situations where:

   a) the condition is rare; or

   b) the condition is a life-threatening one for which no other therapy is available, and the evidence for efficacy is convincing.

   CLL is not a rare disease and hence randomised controlled trials should be feasible. Refractory CLL is a life-threatening disease and the observed response rates in the pivotal study (47 – 58%) would appear to constitute convincing evidence of efficacy, especially when compared to historical data.

   The pivotal study enrolled two patient subgroups – DR and BFR disease. The FDA and the EMA have both approved the drug, but only for the DR subgroup. The grounds for rejecting the BFR subgroup appear to have been the same for both agencies – that established treatments for the BFR subgroup are available and it should therefore be possible to conduct a randomised controlled trial. Possible comparators for this subgroup could include rituximab with chemotherapy, or alemtuzumab monotherapy.

   The ACPM's advice is sought as to whether there are any established treatments for patients who have proven refractory to both fludarabine-based therapy and alemtuzumab. If not, the Delegate considered it would be reasonable to approve the product (for the DR population only) on the basis of Phase II data.

   The sponsor is conducting various Phase III randomised controlled trials of ofatumumab in CLL in the first and second-line setting. However, these will not provide further data on use in patients with disease that has proven refractory to fludarabine-based therapy and alemtuzumab.

   Previous approvals for cladribine (2nd line; 1999) and alemtuzumab (3rd line; 2006) in CLL were based on single-arm, non comparative trials.

2. Indication

   Data concerning the safety and efficacy of the drug when used in combination with chemotherapy for the treatment of refractory CLL have not been provided. If the application is to be approved, the Delegate proposed the following indication:

   > *"ARZERRA (ofatumumab), as a single agent, is indicated for the treatment of patients with B-cell chronic lymphocytic leukaemia (CLL) refractory to fludarabine and alemtuzumab."*

3. Proposed vial size of 100 mg
   Both the PSC and the OMSM evaluator have highlighted the issue of the proposed vial size of 100 mg. The recommended dosage regimen includes individual doses up to 2000 mg, requiring 20 vials. The sponsor has given a commitment that a larger vial size will be developed and submitted for registration.

Proposed action:

Subject to the ACPM's advice regarding appropriateness of using Phase II data as a reasonable basis for approval in the double refractory setting, the Delegate proposed to approve the application for the limited indication outlined above. The advice of the ACPM is requested.

Advisory Committee Considerations

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal.

ACPM recommended approval of the submission from GlaxoSmithKline Australia Pty Ltd to register the new chemical entity for Ofatumumab (Arzerra) concentrated solution for IV infusion 100 mg in 5 mL vials for the indication:

> "For the treatment, as a single agent, of patients with B-cell chronic lymphocytic leukaemia (CLL) refractory to fludarabine and alemtuzumab."

In making this recommendation, the ACPM considered that an overall positive risk benefit profile for the amended indication was demonstrated; however the safety issues associated with the very high infection risks remain of concern and therefore required careful management and monitoring.

The specific conditions of registration should include a requirement to submit the results of the ongoing phase three clinical trials in CLL.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of ARZERRA injection concentrate vial containing ofatumumab 100mg/5mL. The approved indication for this therapeutic good is as follows:

> *Arzerra, as a single agent, is indicated for the treatment of patients with B-cell chronic lymphocytic leukaemia (CLL) refractory to fludarabine and alemtuzumab.*

The following specific conditions apply to this therapeutic good:

1. The Risk Management Plan dated 19 January 2010 with further modifications on 29 March 2010, as agreed with the Office of Product Review, must be implemented.
2. Results of the ongoing phase three clinical trials in CLL must be submitted to the TGA for review when available.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published.

For the current Product Information please refer to the TGA website at www.tga.gov.au.

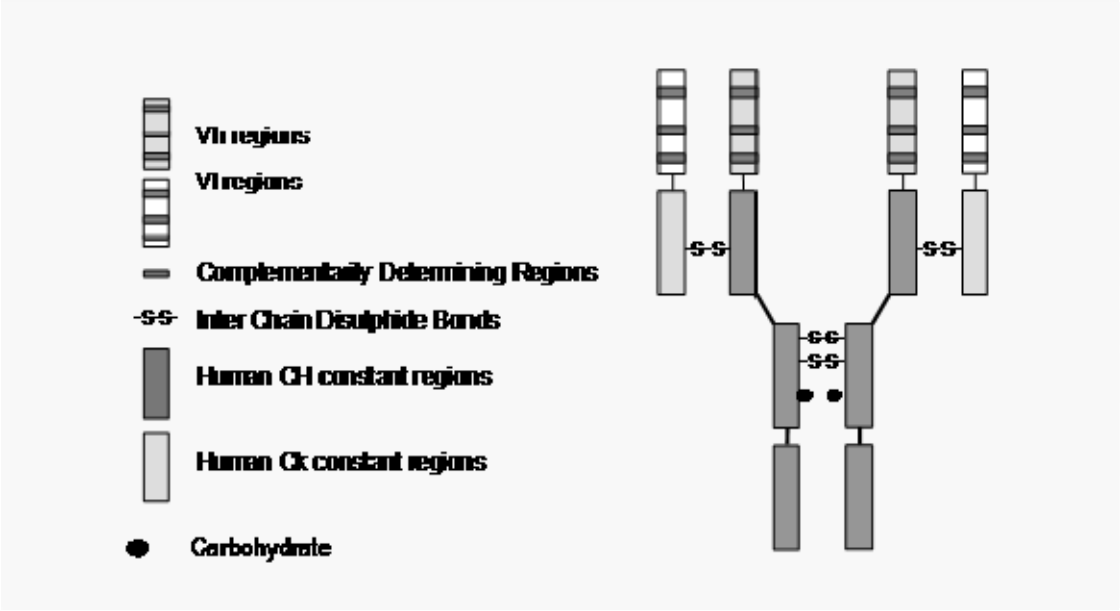
PRODUCT INFORMATION

ARZERRA® CONCENTRATED INJECTION

Ofatumumab (rmc) 100 mg/5mL Concentrated Injection)

NAME OF THE MEDICINE

ARZERRA® is the GlaxoSmithKline trade mark for ofatumumab (rmc).



ARZERRA (ofatumumab) is a human monoclonal antibody (IgG1κ) that binds specifically to both the small and large extracellular loops of the CD20 molecule epitopes on the human CD20 molecule on B cells. The antibody is generated via transgenic mouse and hybridoma technology and produced in a recombinant murine cell line (NS0) using standard mammalian cell cultivation and purification technologies.

The molecular weight is approximately 149 kDa.

CAS number: 679818-59-8

DESCRIPTION

ARZERRA is a sterile, clear, colourless, preservative-free, concentrated solution for intravenous infusion.

Each single-use vial of ARZERRA contains 100 mg of ofatumumab in 5mL (20 mg/mL). The product also contains 8.55 mg/mL sodium citrate, 195 micrograms/mL citric acid- monohydrate, 5.85 mg/mL sodium chloride and water for injections. The pH of the concentrated solution is 6.5.

PHARMACOLOGY

Mechanism of Action

Ofatumumab is a recombinant human monoclonal antibody (IgG1) that binds specifically to both the small and large extracellular loops of the CD20 molecule. The CD20 molecule is a transmembrane phosphoprotein expressed on B lymphocytes from the pre-B to mature B-lymphocyte stage on B-cell tumours. The B-cell tumours include chronic lymphocytic leukemia (CLL), that is generally associated with lower levels of CD20 expression, and non-Hodgkin's lymphomas (where >90% of tumours have high levels of CD20 expression).

The binding of ofatumumab to the membrane proximal epitope of the CD20 molecule induces recruitment and activation of the complement pathway at the cell surface, leading to complement-dependent cytotoxicity and resultant lysis of tumour cells. In addition, the binding of ofatumumab induces cell death through antibody-dependent cell-mediated cytotoxicity. Ofatumumab has been shown to induce lysis in cells both with high and low CD20 expression, including cells with high expression levels of complement defence molecules.

Pharmacodynamic effects

Peripheral B cell counts decreased after the first ofatumumab infusion in patients with haematologic malignancies. In patients with refractory CLL, the median decrease in B cell counts was 23% after the first infusion and 92% after the eighth infusion. Peripheral B cell counts remained low throughout the remainder of therapy in most patients, then gradually recovered (median decrease in B cell counts was 68% below baseline 3 months after the end of ofatumumab therapy).

Immunogenicity

There is a potential for immunogenicity with therapeutic proteins such as ARZERRA.

In the pivotal clinical study (Hx-CD20-406), serum samples from 154 CLL patients treated with ARZERRA were tested for anti-ofatumumab antibodies. Of these patients, 85 had completed the

full course of 12 infusions; including 33 patients in whom plasma ofatumumab concentrations had decreased sufficiently to allow detection of anti-ofatumumab antibodies were they to be present. All subjects tested negative for anti-ofatumumab antibodies.

Pharmacokinetics

Absorption

Ofatumumab is administered by intravenous infusion; therefore, absorption is not applicable. Maximum ofatumumab serum concentrations were generally observed at or shortly after the end of the infusion. Pharmacokinetic data were available from 146 patients with refractory CLL. The geometric mean C_{max} value was 63 µg/mL after the first infusion (300 mg); after the eighth weekly infusion (seventh infusion of 2000 mg), the geometric mean C_{max} value was 1482 µg/mL and geometric mean $AUC_{(0-\infty)}$ value was 674,463 µg.h/mL; after the twelfth infusion (fourth monthly infusion; 2000 mg), the geometric mean C_{max} value was 881 µg/mL and geometric mean $AUC_{(0-\infty)}$ was 265,707 µg.h/mL.

Distribution

Ofatumumab has a small volume of distribution, with mean Vss values ranging from 1.7 to 5.1 L across studies, dose levels, and infusion number.

Metabolism/Biotransformation

Ofatumumab is a protein for which the expected metabolic pathway is degradation to small peptides and individual amino acids by ubiquitous proteolytic enzymes. Classical biotransformation studies have not been performed.

Elimination

Ofatumumab is eliminated in two ways: a target-independent route like other IgG molecules and a target-mediated route which is related to binding to B cells. There was a rapid and sustained depletion of $CD20^+$ B cells after the first ofatumumab infusion, leaving a reduced number of $CD20^+$ cells available for the antibody to bind at subsequent infusions. As a result, ofatumumab clearance values were lower and $t_{½}$ values were significantly larger after later infusions than after the initial infusion; during repeated weekly infusions, ofatumumab AUC and C_{max} values increased more than the expected accumulation based on first infusion data.

Across the studies in patients with CLL, the mean values for CL and $t_{½}$ were 64 mL/h (range 4.3 - 1122 mL/h) and 1.3 days (range 0.2 - 6.0 days) after the first infusion, 8.5 mL/h (range 1.3 - 41.5 mL/h) and 11.5 days (range 2.3 - 30.6 days) after the fourth infusion, 9.5 mL/h (range 2.2 - 23.7 mL/h) and 15.8 days (range 8.8 - 61.5 days) after the eighth infusion, and 10.1 mL/h (range 3.3 - 23.6 mL/h) and 13.9 days (range 9.0 - 29.2 days) after the twelfth infusion.

Special Patient Populations

Elderly (greater than or equal to 65 years of age)
Age was not found to be a significant factor on ofatumumab pharmacokinetics in a cross-study population pharmacokinetic analysis of patients ranging in age from 21 to 86 years of age.

Children and Adolescents (up to 18 years of age)
No pharmacokinetic data are available in paediatric patients.

Gender
Gender had a modest effect (14 - 25% lower clearance and volume of distribution) on ofatumumab pharmacokinetics in a cross-study analysis, with higher C_{max} and AUC values observed in female patients (41% of the patients in this analysis were male and 59% were female); these effects are not considered clinically relevant, and no dose adjustment is recommended.

Renal Impairment
Baseline calculated creatinine clearance was not found to be a clinically significant factor on ofatumumab pharmacokinetics in a cross-study population analysis in patients with calculated creatinine clearance values ranging from 33 to 287 mL/min. No dose adjustment is recommended for mild to moderate renal impairment (creatinine clearance >30 mL/min). There are no pharmacokinetic data in patients with severe renal impairment (creatinine clearance <30 mL/min).

Hepatic Impairment
No pharmacokinetic data are available in patients with hepatic impairment. IgG1 molecules such as ofatumumab are catabolised by ubiquitous proteolytic enzymes, which are not restricted to hepatic tissue; therefore, changes in hepatic function are unlikely to have any effect on the elimination of ofatumumab.

CLINICAL TRIALS

The clinical efficacy of ARZERRA has been demonstrated in a planned interim analysis of an ongoing study Hx-CD20-406 (single-arm, open-label, multicentre), and one completed supportive study, Hx-CD20-402 (open-label, dose ranging, multicentre). The effectiveness of ARZERRA is based on the demonstration of durable objective responses. There are no data from controlled clinical trials demonstrating an improvement in disease-related symptoms or increased survival with ARZERRA.

Hx-CD20-406

ARZERRA was administered as a monotherapy to 154 patients with CLL. Patient median age was 63 years (range: 41 to 86 years), and the majority were male (72%) and white (97%). Patients received a median of 5 prior therapies, including rituximab (57%). Of these 154 patients, 59 patients were refractory to fludarabine and alemtuzumab therapy (defined as failure to achieve at least a partial response with fludarabine or alemtuzumab treatment or disease progression within 6 months of the last dose of fludarabine or alemtuzumab). Baseline cytogenetic (FISH) data were available for 151 patients. Chromosomal aberrations were detected in 118 patients; there were 33 patients with 17p deletion, 50 patients with 11q deletion, 16 patients with trisomy 12q, 30 patients with a normal karyotype and 19 patients with 13q deletion as the sole aberration.

The overall response rate was 58% in patients refractory to fludarabine and alemtuzumab (see Table 1 for a summary of the efficacy data from the study). Patients who had prior rituximab therapy, either as monotherapy or in combination with other medicinal products, responded to treatment with ofatumumab at a similar rate as those who had not had prior rituximab therapy.

Table 1. Summary of response to ARZERRA in patients with CLL

(Primary) endpoint [1]	Patients refractory to fludarabine and alemtuzumab n = 59
Overall response rate	
Responders, n (%)	34 (58)
99% CI (%)	40, 74
Response rate in patients with prior rituximab therapy	
Responders, n (%)	19/35 (54)
95% CI (%)	37, 71
Response rate in patients with chromosomal abnormality	
17p deletion	
Responders, n (%)	7/17 (41)
95% CI (%)	18, 67
11q deletion	
Responders, n (%)	15/24 (63)
95% CI (%)	41, 81
Median overall survival	
Months	13.7
95% CI	9.4, non-estimable
Progression-free survival	
Months	5.7
95% CI	4.5, 8.0
Median duration of response	
Months	7.1
95% CI	3.7, 7.6
Median time to next CLL therapy	
Months	9.0
95% CI	7.3, 10.7
[1] The overall response was assessed by an Independent Response Committee using the 1996 National Cancer Institute Working Group (NCIWG) guidelines for CLL.	

Improvements also were demonstrated in components of the NCIWG response criteria. These included improvements associated with constitutional symptoms, lymphadenopathy, organomegaly, or cytopenias (see Table 2).

Table 2. Summary of clinical improvement with a minimum duration of 2 months in subjects with abnormalities at baseline

Efficacy endpoint or haematological parameter[a]	Subjects with benefit/subjects with abnormality at baseline (%) Patients refractory to fludarabine and alemtuzumab
Lymphocyte count	
≥50% decrease	31/42 (74)
Normalisation (≤4x10^9/l)	20/42 (48)
Complete resolution of constitutional symptoms[b]	15/31 (48)
Lymphadenopathy[c]	
≥50% improvement	34/55 (62)
Complete resolution	9/55 (16)
Splenomegaly	
≥50% improvement	16/30 (53)
Complete resolution	14/30 (47)
Hepatomegaly	
≥50% improvement	11/18 (61)
Complete resolution	9/18 (50)
Haemoglobin <11 g/dl at baseline to >11 g/dl post baseline	8/26 (31)
Platelet counts <100x10^9/l at baseline to >50% increase or >100x10^9/l post baseline	12/29 (41)
Neutrophils <1x10^9/l at baseline to ≥1.5x10^9/l	1/19 (5)

[a] Excludes subject visits from date of first transfusion, treatment with erythropoietin, or treatment with growth factors. For subjects with missing baseline data, latest screening/unscheduled data was carried forward to baseline.

[b] Complete resolution of constitutional symptoms (fever, night sweats, fatigue, weight loss) defined as the presence of any symptoms at baseline, followed by no symptoms present.

[c] Lymphadenopathy measured by sum of the products of greatest diameters (SPD) as assessed by physical examination.

ARZERRA was also given to a group of patients (n=79) with bulky lymphadenopathy (defined as at least one lymph node > 5cm) who were also refractory to fludarabine. The overall response rate in this group was 47% (99% CI: 32%, 62%). The median progression-free survival was 5.9 months (95% CI: 4.9, 6.4) and the median overall survival was 15.4 months (95% CI: 10.2, 20.2). The response rate in patients with prior rituximab therapy was 44% (95% CI: 29, 60). These patients also experienced comparable clinical improvement, in terms of the efficacy endpoints and haematological parameters detailed above, to patients refractory to both fludarabine and alemtuzumab.

Additionally a group of patients (n=16) who were intolerant/ineligible for fludarabine treatment and/or intolerant to alemtuzumab treatment were treated with ARZERRA. The overall response rate in this group was 56% (99% CI: 24%, 85%).

Hx-CD20-402

A dose-ranging study was conducted in 33 patients with relapsed or refractory CLL. Patient median age was 61 years (range: 27 to 82 years), the majority were male (58%), and all were white. Treatment with ARZERRA (when given as 4 once weekly infusions), led to a 50% objective response rate in the highest dose group (1st dose: 500 mg; 2nd, 3rd and 4th dose: 2000 mg) and included 12 partial remissions and one nodular partial remission. For the highest dose group, the median time to progression was 15.6 weeks (95% CI: 15-22.6 weeks) in the full analysis population, and 23 weeks (CI: 20-31.4 weeks) in responders. The duration of response was 16 weeks (CI: 13.3 – 19.0 weeks) and the time to next CLL therapy was 52.4 weeks (CI: 36.9 – non-estimable).

INDICATIONS

ARZERRA (ofatumumab), as a single agent, is indicated for the treatment of patients with B-cell chronic lymphocytic leukaemia (CLL) refractory to fludarabine and alemtuzumab.

CONTRAINDICATIONS

ARZERRA is contraindicated in patients with hypersensitivity to the active substance ofatumumab or to any of the excipients *(see DESCRIPTION).*

PRECAUTIONS

Infusion Reactions

ARZERRA has been associated with infusion reactions leading to temporary interruption of treatment or withdrawal of treatment. Pre-medications attenuate infusion reactions but these may still occur, predominantly during the first infusion (see *Dosage and Administration)*. Infusion reactions may include anaphylactic reactions, cardiac events, chills/rigors, cough, cytokine release syndrome, diarrhoea, dyspnoea, fatigue, flushing, hypertension, hypotension, nausea, pain, pyrexia, rash, and urticaria. Even with pre-medication, severe reactions, including cytokine release syndrome, have been reported following ARZERRA use. In cases of severe infusion reaction, the infusion of ARZERRA must be interrupted immediately and symptomatic treatment instituted (see *Dosage and Administration* for changes to infusion rates following infusion reactions).

Infusion reactions occur more frequently on the first day of infusion and tend to decrease with subsequent infusions. Patients with a history of decreased pulmonary function may be at a greater risk for pulmonary complications from severe reactions and should be monitored closely during infusion of ARZERRA.

Cytopenias

Prolonged (≥1 week) severe neutropenia and thrombocytopenia can occur with ARZERRA. Monitor complete blood counts (CBC) and platelet counts at regular intervals during therapy, and increase the frequency of monitoring in patients who develop Grade 3 or 4 cytopenias.

Tumour Lysis Syndrome

In patients with CLL, tumour lysis syndrome (TLS) may occur with use of ARZERRA. Risk factors for TLS include a high tumour burden, high concentrations of circulating cells (≥ 25,000/mm^3), hypovolaemia, renal insufficiency, elevated pre-treatment uric acid levels and elevated lactate dehydrogenase levels. Management of TLS includes correction of electrolyte abnormalities, monitoring of renal function, maintenance of fluid balance and supportive care.

Infections

ARZERRA causes a marked reduction in B lymphocytes and therefore may increase the risk of infection. In the pivotal study in CLL patients, 14 of 154 patients (9%) had serious infections that were considered drug-related. Fatal infections occurred in 16 of 154 patients (10%). Of these, 4 (3%) were considered drug-related.

Progressive Multifocal Leukoencephalopathy (PML)

Progressive multifocal leukoencephalopathy (PML) and death has been reported in CLL patients receiving cytotoxic pharmacotherapy, including ARZERRA. A diagnosis of PML should be considered in any ARZERRA patient who reports the new onset of or changes in pre-existing neurologic signs and symptoms. If a diagnosis of PML is suspected ARZERRA should be discontinued and referral to a neurologist should be considered.

Hepatitis B Reactivation

Hepatitis B infection (HBV), including fatal infection, can occur in patients taking ARZERRA. Hepatitis B reactivation including fulminant hepatitis and death occurs with other monoclonal antibodies directed against CD20. Patients at high risk of HBV infection should be screened before initiation of ARZERRA. Carriers of hepatitis B should be closely monitored for clinical and laboratory signs of active HBV infection during treatment with ofatumumab and for 6-12 months following the last infusion of ARZERRA. ARZERRA should be discontinued in patients who develop viral hepatitis, and appropriate treatment should be instituted. Insufficient data exist regarding the safety of administration of ARZERRA in patients with active hepatitis.

Immunisations

The safety of, and ability to generate a primary or anamnestic response to, immunisation with live attenuated or inactivated vaccines during ARZERRA treatment has not been studied. The response to vaccination could be impaired when B cells are depleted. Due to the risk of infection, administration of live attenuated vaccines should be avoided during and after treatment with ARZERRA, until B cell counts are normalised. The risks and benefits of vaccinating patients during ARZERRA therapy should be considered.

Cardiovascular

Patients with a history of cardiac disease should be monitored closely. ARZERRA should be discontinued in patients who experience serious or life-threatening cardiac arrhythmias.

Bowel Obstruction

Bowel obstruction has been reported in patients receiving anti-CD20 monoclonal antibody therapy, including ARZERRA. Patients who present with abdominal pain, especially early in the course of ARZERRA therapy, should be evaluated and appropriate treatment instituted.

Laboratory Monitoring

Since ARZERRA binds to all CD-20-positive lymphocytes (malignant and non-malignant), complete blood counts and platelet counts should be obtained at regular intervals during ARZERRA therapy and more frequently in patients who develop cytopenias. Appropriate management should be considered should cytopenias occur.

Sodium content

ARZERRA contains 64.5 mg sodium per 300 mg dose and 430 mg sodium per 2000 mg dose. This should be taken into consideration by patients on a controlled sodium diet.

Effects on fertility

There are no data on the effects of ARZERRA on human fertility. Effects on male and female fertility have not been evaluated in animal studies.

Use in pregnancy (Category C)

There are no adequate and well controlled data for the use of ARZERRA in pregnant women. An embryofetal study in which cynomolgus monkeys were treated during the period of organogenesis revealed no evidence of external, visceral or skeletal defects of the fetus at exposures similar to the anticipated clinical AUC. However, ofatumumab could be detected in the fetal circulation 50 days after the final dose and exposed fetuses had lower spleen weights and depleted B cells. Precautions should be undertaken to avoid pregnancy and adequate contraception should be used while using ARZERRA and for at least 12 months after the last ARZERRA treatment. ARZERRA should not be administered to pregnant women unless the possible benefit to the mother outweighs the possible risk to the fetus.

Use in lactation

The safe use of ARZERRA in humans during lactation has not been established. It is unknown whether ofatumumab is excreted in human breast milk. The excretion of ofatumumab in milk has not been studied in animals. As maternal IgG is excreted in breast milk, it is recommended that breastfeeding should be discontinued for the entire duration of treatment with ARZERRA.

Paediatric use

The safety and effectiveness of ARZERRA have not been established in the paediatric age group.

Use in the elderly

No substantial differences were seen in safety and efficacy related to age (see *Dosage and Administration).*

Ability to perform tasks that require judgement, motor or cognitive skills

No studies on the effects of ARZERRA on the ability to drive and use machines have been performed. No detrimental effect on such activities are predicted from the pharmacology of ARZERRA. The clinical status of the subject and the adverse event profile of ARZERRA should be borne in mind when considering the patient's ability to perform tasks that require judgement, motor or cognitive skills.

Carcinogenicity

The carcinogenic potential of ofatumumab has not been investigated.

Genotoxicity

As ofatumumab is a monoclonal antibody, the genotoxic potential of ofatumumab has not been investigated.

Interactions with other medicines

Although no formal interaction studies have been performed with ARZERRA, there are no known clinically significant interactions with other medicinal products.

Live attenuated or inactivated vaccine efficacy may be impaired with ARZERRA. Therefore, the concomitant use of these agents with ARZERRA should be avoided. If the coadministration is judged unavoidable, the risks and benefits of vaccinating patients during therapy with ARZERRA should be considered.

ADVERSE EFFECTS

Clinical Trial Data

The safety of ARZERRA in patients with relapsed or refractory CLL has been evaluated in two open label studies. In study Hx-CD20-406, 154 patients were enrolled to receive 12 infusions of ARZERRA administered as 300 mg initial dose (Dose 1), followed 1 week later by 2,000 mg weekly for 7 doses (Doses 2 through 8), followed 4 weeks later by 2,000 mg every 4 weeks for 4 doses (Doses 9 through 12).The second study (Hx-CD20-402) was a dose-finding study and

patients in three cohorts (3 patients, 3 patients, 27 patients) received a starting dose of 100 mg, 300 mg or 500 mg, followed a week later with 3 consecutive weekly infusions of 500 mg, 1000 mg or 2000 mg of ARZERRA, respectively. The adverse events reported are from final data from the initial dose-range finding and a planned interim analysis of study Hx-CD20-406.

The data listed below are derived from 154 patients in study Hx-CD20-406. All patients received 2,000 mg weekly from the second dose onward. 90% of patients received at least 8 infusions of ARZERRA and 55% received all 12 infusions. The median age was 63 years (range: 41 to 86 years), 72% were male, and 97% were White.

Body System/Adverse Event	Total (n=154)		DR (n = 59)		BFR (n = 79)	
	All Grades %	Grade ≥3 %	All Grades %	Grade ≥3 %	All Grades %	Grade ≥3 %
Infections and infestations						
Pneumonia[a]	23	14	25	15	19	14
Upper respiratory tract infection	11	0	3	0	16	0
Bronchitis	11	<1	19	2	8	0
Sepsis[b]	8	8	10	10	8	6
Urinary tract infection [d]	5	1	3	2	5	1
Nasopharyngitis	8	0	8	0	9	0
Herpes zoster	6	1	7	2	6	1
Sinusitis	5	2	3	2	6	3
Blood and lymphatic system disorders						
Neutropenia	16	12	15	10	13	10
Anaemia	16	5	17	8	16	4
Febrile neutropenia	1	1	0	0	1	1
Thrombocytopenia	1	<1	3	2	0	0
Leukopenia	1	<1	2	0	0	0
Agranulocytosis	<1	<1	0	0	1	1
Coagulopathy	<1	0	0	0	0	0
Red cell aplasia	<1	0	2	0	0	0
Lymphopenia	<1	<1	0	0	1	1
Psychiatric disorders						
Insomnia	7	0	10	0	5	0
Nervous system disorders						
Headache	6	0	7	0	6	0
Cardiovascular disorders						
Hypertension	5	0	8	0	4	0
Hypotension	5	0	3	0	6	0
Tachycardia	5	<1	7	2	5	0
Flushing	3	0	2	0	5	0
Respiratory, thoracic and mediastinal disorders						
Cough	19	0	19	0	18	0
Dyspnea	14	2	19	5	10	0
Bronchospasm	3	<1	3	2	1	0
Hypoxia	2	0	5	0	0	0
Pharyngolaryngeal pain	4	0	3	0	4	0

Gastrointestinal disorders						
Diarrhoea	18	0	19	0	15	0
Nausea	11	0	12	0	11	0
Small bowel obstruction	1	1	2	2	1	1
Immune system disorders						
Anaphylactoid reactions[e]	1	0	0	0	3	0
Hypersensitivity[f]	3	<1	8	2	0	0
Metabolism and nutrition disorders	<1	<1	0	0	1	1
Tumor lysis syndrome						
Skin and subcutaneous tissue disorders						
Rash[c]	14	<1	17	2	8	0
Urticaria	8	0	5	0	10	0
Hyperhidrosis	5	0	5	0	5	0
Pruritus	5	0	5	0	5	0
Musculoskeletal and connective tissue disorders						
Back pain	8	1	12	2	4	0
Muscle spasms	5	0	3	0	6	0
General disorders and administration site conditions						
Pyrexia	20	3	25	5	11	1
Fatigue	15	0<1	15	0	16	0
Edema peripheral	9	0	8	2	10	0
Chills	8	<1	10	0	6	0
Cytokine release syndrome	3	0	5	0	3	1
Chest discomfort	3		5	0	1	0

[a] Pneumonia includes pneumonia, lung infection, lobar pneumonia, and bronchopneumonia.
[b] Sepsis includes sepsis, neutropenic sepsis, bacteremia, and septic shock.
[c] Rash includes rash, rash macular, and rash vesicular.
[d] Urinary tract infection includes urinary tract infection, bacterial pyelonephritis, cystitis
[e] Anaphylactoid reactions includes anaphylactic reaction and anaphylactoid reaction
[f] Hypersensitivity includes hypersensitivity and drug hypersensitivity

Infusion reactions: In the pivotal study (Hx-CD20-406), infusion reactions occurred in 44% of patients on the day of the first infusion (300 mg), 29% on the day of the second infusion (2,000 mg), and less frequently during subsequent infusions (see section 4.4).

Infections: In the pivotal study, a total of 108 patients (70%) experienced bacterial, viral, or fungal infections. A total of 45 patients (29%) experienced ≥ Grade 3 infections, of which 19 (12%) were fatal. The proportion of fatal infections in the indicated fludarabine- and alemtuzumab-refractory group was 17%.

Neutropenia: Of 108 patients with normal neutrophil counts at baseline who were part of the pivotal study, 45 (42%) developed ≥ Grade 3 neutropenia. Nineteen (18%) developed Grade 4 neutropenia. Some patients experienced new onset Grade 4 neutropenia > 2 weeks in duration.

Post marketing data

No data available.

DOSAGE AND ADMINISTRATION

Method of Administration

ARZERRA is for intravenous infusion and must be diluted prior to administration (see Use and Handling).

ARZERRA should be administered under the supervision of a physician experienced in the use of cancer therapy and in an environment where full resuscitation facilities are immediately available.

Premedication

Patients should be pre-medicated 30 minutes to 2 hours prior to ARZERRA infusion according to the following dosing schedule:

Infusion number (dose)	Intravenous corticosteroid dose	Analgesic dose	Antihistamine dose
1 (300 mg)	Equivalent to 100 mg prednisolone	Equivalent to 1,000 mg paracetamol	Equivalent to 10 mg cetirizine
2 (2,000 mg)	Equivalent to 100 mg prednisolone	Equivalent to 1,000 mg paracetamol	Equivalent to 10 mg cetirizine
3-8 (2,000 mg)	Equivalent to 0-100 mg prednisolone [a)]	Equivalent to 1,000 mg paracetamol	Equivalent to 10 mg cetirizine
9 (2,000 mg)	Equivalent to 100 mg prednisolone	Equivalent to 1,000 mg paracetamol	Equivalent to 10 mg cetirizine
10-12 (2,000 mg)	Equivalent to 50-100 mg prednisolone [b)]	Equivalent to 1,000 mg paracetamol	Equivalent to 10 mg cetirizine

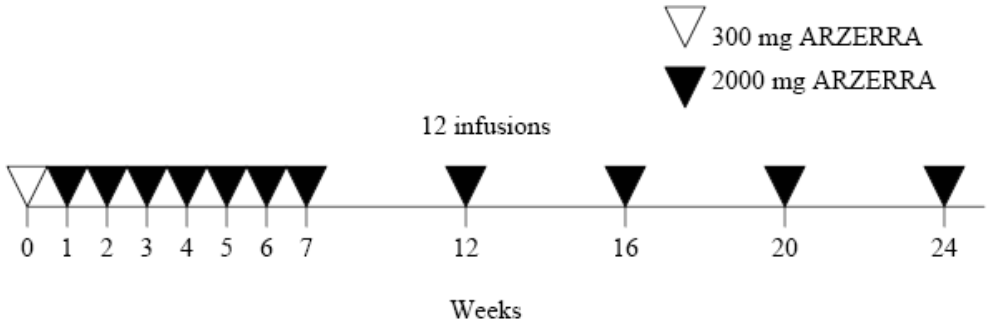
[a)] If the second infusion is completed without a severe adverse drug reaction, the dose may be reduced at the discretion of the physician.

[b)] If the ninth infusion is completed without a serious adverse drug reaction, the dose may be reduced at the discretion of the physician.

Dosage

The recommended dose is 300 mg ARZERRA for the first infusion and 2000 mg ARZERRA for all subsequent infusions. The infusion schedule is 8 consecutive weekly infusions, followed 4-5 weeks later by 4 consecutive monthly (i.e. every 4 weeks) infusions (See Figure 1 below).

Figure 1: Infusion schedule for ARZERRA



First and second infusions

The initial rate of the first and second infusion of ARZERRA diluted solution should be 12 mL/h (see Use and Handling). During infusion, the rate should be doubled every 30 minutes to a maximum of 200 mL/h (see Use and Handling).

Subsequent infusions

If the second infusion has been completed without severe infusion related adverse drug reactions (ADRs), the remaining infusions can start at a rate of 25 mL/h and should be doubled every 30 minutes up to a maximum of 400 mL/h (see Use and Handling).

Dose modification and reinitiation of therapy

Infusion related ADRs may lead to slower infusion rates.

- In case of a mild or moderate ADR, the infusion should be interrupted and restarted at half of the infusion rate at the time of interruption, when the patient's condition is stable. If the infusion rate had not been increased from the starting rate of 12 mL/hour prior to interrupting due to an ADR, the infusion should be restarted at 12 mL/hour, the standard starting infusion rate. The infusion rate can continue to be increased according to standard procedures, according to physician discretion and patient tolerance (not to exceed doubling the rate every 30 mins).

- In case of a severe ADR, the infusion should be interrupted and restarted at 12 mL/hour, when the patient's condition is stable. The infusion rate can continue to be increased according to standard procedures, according to physician discretion and patient tolerance (not to exceed doubling the rate every 30 mins).

- In case of a life-threatening ADR, do not resume the infusion.

Populations

Paediatrics

The safety and effectiveness of ARZERRA have not been established in the paediatric age group.

Elderly

No substantial differences were seen in safety and efficacy related to age. Based on available safety and efficacy data in the elderly, no dosage adjustment is required (see *Pharmacokinetics: Special patient populations*).

Renal Impairment

No formal studies of ARZERRA in patients with renal impairment have been performed. However, patients with renal impairment are unlikely to require dose modification (see Pharmacokinetics: Special patient populations).

Hepatic Impairment

No formal studies of ARZERRA in patients with hepatic impairment have been performed. However, patients with hepatic impairment are unlikely to require dose modification (see Pharmacokinetics: Special patient populations).

USE AND HANDLING

ARZERRA concentrate should be diluted using aseptic practices. ARZERRA does not contain a preservative and is for single use in one patient only. Therefore it is recommended that the diluted solution be used as soon as possible after preparation. The diluted solution for infusion must be stored at 2 to 8°C and used within 24 hours of preparation. Any unused solution remaining after this time should be discarded.

1) BEFORE DILUTING ARZERRA

Check the ARZERRA concentrate for particulate matter and discoloration prior to dilution. ARZERRA should be a colourless solution. **Do not use** the ARZERRA concentrate if there is discolouration.

Do not shake the ARZERRA vial for this inspection.

The concentrate may contain a small amount of visible translucent-to-white, amorphous, ofatumumab particles. The filters provided as part of the extension set will remove these particles.

2) How to dilute the solution for infusion

The ARZERRA concentrate must be diluted in saline prior to administration, using aseptic technique.

300 mg dose - Use 3 vials (15 mL total, 5 mL per vial):
• withdraw and discard 15 mL from a 1000 mL bag of 0.9% sodium chloride for infusion
• withdraw 5 mL of ARZERRA from each of 3 vials and inject into the 1000 mL bag
• **do not shake**, mix diluted solution **by gentle inversion.**

2000 mg dose – Use 20 vials (100 mL total, 5 mL per vial):
• withdraw and discard 100 mL from a 1000 mL bag of 0.9% sodium chloride for infusion
• withdraw 5 mL of ARZERRA from each of 20 vials and inject into the 1000 mL bag
• **do not shake**, mix diluted solution **by gentle inversion.**

3) How to administer the diluted solution

ARZERRA must not be administered as an i.v. push or bolus. Administer using an i.v. infusion pump, an i.v. administration set and using the in-line filter extension set provided.

Compatibility of ARZERRA has been established with the following dosing components:

1. Polyolefin saline bags
2. PVC and PVC lined with polyethylene administration sets
3. Provided filter set, filter membrane polyether sulfone.

ARZERRA must not be mixed with, or administered as an infusion with other medicinal products or intravenous solutions. Flush line before and after ARZERRA administration with 0.9% sodium chloride to avoid this.

For the first and second infusion, administer over 6.5 hours (see *Dosage and Administration*), through a peripheral line or indwelling catheter, according to the schedule below:

Infusion schedule for infusions 1 and 2

Time (minutes)	mL/hour
0 – 30	12
31 – 60	25
61 – 90	50
91 – 120	100
121 +	200

If the second infusion has been completed without a severe adverse reaction, the remaining infusions (3-12) should be administered over 4 hours (see *Dosage and Administration*), through a peripheral line or indwelling catheter, according to the schedule below:

Infusion schedule for infusions 3 to 12

Time (minutes)	mL/hour
0 – 30	25
31 – 60	50
61 – 90	100
91 – 120	200
121 +	400

If any adverse reactions are observed, infusion rates should be reduced (see *Dose modification and reinitiation of therapy).*

Any unused product or waste material should be disposed of in accordance with local requirements.

OVERDOSAGE

No case of overdose has been reported.

PRESENTATION AND STORAGE CONDITIONS

Shelf-Life

Vial 20 mg/mL concentrated injection for IV infusion
24 months.

Storage

Store at 2°C - 8°C. (Refrigerate. Do not freeze)
Protect from light.

Diluted Infusion Storage

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C.

Nature and Contents of Container

ARZERRA is presented in clear 10mL Type I glass vials with a latex-free rubber stopper and aluminium over-seal, containing 5mL of concentrated solution for infusion. The drug is supplied in a single use vial without a preservative. ARZERRA is available in packs of 3 or 10 vials*.

*not all pack sizes may be marketed.

ARZERRA is supplied with two SmartSite® Extension Sets comprising:
Low Sorbing Tubing
0.2 Micron low Protein Binding Filter
Needle-Free Valve Port

Incompatibilities

The concentrate for solution for infusion must only be mixed with 0.9% sodium chloride solution for infusion *(see Use and Handling)*. It is NOT RECOMMENDED that ARZERRA be mixed with any other drug in an infusion bag.

NAME AND ADDRESS OF THE SPONSOR:

GlaxoSmithKline Australia Pty Ltd
1061 Mountain Highway
Boronia Victoria 3155

POISON SCHEDULE OF THE MEDICINE - S4

This document was approved by the Therapeutic Goods Administration on: 15 December 2010

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Therapeutic Goods Administration

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