European Medicines Agency
Evaluation of Medicines for Human Use

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CHMP ASSESSMENT REPORT

FOR

Arzerra

International Nonproprietary Name: ofatumumab

Procedure No. EMEA/H/C/001131

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Glaxo Group Ltd submitted on 5 February 2009 an application for Marketing Authorisation to the European Medicines Agency (EMEA) through the centralised procedure for Arzerra, which was designated as an orphan medicinal product EU/3/08/581 on 7 November 2008. Arzerra was designated as an orphan medicinal product in the following indication: Treatment of chronic lymphocytic leukaemia. The calculated prevalence of this condition was 3.5 per 10,000 EU population.

The legal basis for this application refers to:

A - Centralised / Article 8(3) / New active substance.

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

The application submitted is a complete dossier composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

The applicant applied for the following indication: treatment of patients with chronic lymphocytic leukaemia (CLL) who have failed therapy with a fludarabine containing regimen and have failed therapy with, or are inappropriate for, an alemtuzumab containing regimen.

Information on Paediatric requirements
Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMEA Decision (P/47/2008) for the following condition:

- Treatment of chronic lymphocytic leukaemia

on the granting of a class waiver.

Protocol Assistance:
The applicant did not seek protocol assistance at the CHMP.

Licensing status:
Arzerra has been given a Marketing Authorisation in the USA on 26/10/2009.
A new application was filed in the following countries: Switzerland, Australia.

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: **Jens Ersbøll**	Co-Rapporteur: **Eva Skovlund**

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 5 February 2009.
- The procedure started on 25 February 2009.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 15 May 2009 . The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 15 May 2009

- During the CHMP meeting on 22-25 June 2009, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 26 June 2009
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 August 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 7 October 2009
- During the CHMP meeting on 19-22 October 2009, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant
- The applicant submitted the responses to the CHMP list of outstanding issues on 12 November 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 30 November 2009
- During a meeting of a SAG Oncology on 2 December 2009, experts were convened to address questions raised by the CHMP
- During a meeting of a Biologics Working Party on 7-9 December 2009 experts were convened to address questions raised by the CHMP.
- During the CHMP meeting on 16 December 2009, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- The Rapporteurs circulated an Updated Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 13 December 2009
- During the meeting on 18-20 January 2010, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a conditional Marketing Authorisation to Arzerra on 20 January 2010.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

B-cell chronic lymphocytic leukaemia (CLL) is a subtype of mature peripheral B-cell neoplasms, characterized by the accumulation of circulating malignant lymphocytes that typically express cell surface markers CD5, CD20, and CD23. It is the most common type of leukaemia in adults in Western Europe and in the US. The median age at diagnosis is 65-70 years, with a male to female ratio of 2:1. Initially, most patients present with asymptomatic lymphocytosis and do not need cytoreductive therapy [Kay, 2002]. Patients with active disease are characterized by a lymphocyte doubling time of less than 6 months, or progressive, even massive lymphadenopathy, hepatosplenomegaly, anaemia and thrombocytopenia. Constitutional symptoms such as fever, night sweats, unintended weight loss, and extreme fatigue are common in advanced disease and can significantly impact quality of life. CLL also causes relative immunosuppression that increases the risk of infections that are ultimately the major cause of death in this patient population. Median survival at diagnosis ranges from 5 to 20+ years depending on risk factors, but is only 6 to 14 months for patients with CLL refractory to available therapies [Tam, 2007].

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]. However, chlorambucil may still be a suitable first-line treatment for elderly patients with CLL [Rai 2000]. Alemtuzumab, a humanized monoclonal antibody directed against the CD52 antigen which is expressed on the cell surface of both B cells and T cells, has been approved for the treatment of patients with B-CLL for whom fludarabine combination chemotherapy is not appropriate. Recently, rituximab, an anti-CD20 monoclonal antibody, was approved for first-line treatment of patients with CLL in combination with chemotherapy (January 2009). Although most patients with CLL will achieve responses with initial therapy, nearly all patients relapse and require further treatments. Advanced age, more than 2 prior therapies [Wierda, 2005], and the presence of chromosomal abnormalities such as 17p and 11q deletions [Dohner, 2000] are associated with decreased response to therapy.

Therapy for second and subsequent lines depends on the response and the duration of response to prior therapy. If the duration of response is at least 12 to 18 months, the same regimen can be tried again. If the duration of response is short or lacking, a different therapeutic approach is needed.
For double-refractory patients (DR) who no longer respond to fludarabine and alemtuzumab, no established therapies are available. Patients with bulky (lymphadenopathy >5 cm) fludarabine-refractory CLL (BFR) also have a high unmet medical need because available treatment options appear to be less effective [Fiegl, 2006] and associated with increased toxicity [Perkins, 2002].

Ofatumumab is a human monoclonal antibody (IgG1) that 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.

Ofatumumab induces cross linking of CD20 molecules and relocation of these CD20 molecules to so-called lipid rafts considered important for induction of cell signalling and effective complement activation. The binding of ofatumumab induces cell death of CD20 positive cells, primarily through complement dependent cytotoxicity (CDC) and antibody dependent cell-mediated cytotoxicity (ADCC), and less by apoptosis. The resulting depletion of malignant B cells carrying the CD20 epitope by ofatumumab treatment is considered the main mechanism of action leading to clinical benefit to subjects with CD20-expressing cell tumours.

Glaxo Group Ltd applied for a marketing authorisation via the centralised procedure for ofatumumab with the invented name Arzerra. The application was made in accordance with Article 8(3) of Directive 2001/83/EC, as amended. The proposed indication was: 'treatment of patients with chronic lymphocytic leukaemia (CLL) who have failed therapy with a fludarabine containing regimen and have failed therapy with, or are inappropriate for, an alemtuzumab containing regimen'. The finally approved indication is: 'treatment of chronic lymphocytic leukaemia (CLL) in patients refractory to fludarabine and alemtuzumab'.
Ofatumumab is designated as an orphan medicinal product in the EU for the indication: "treatment of chronic lymphocytic leukaemia" (EU/3/08/581). The Committee for Orphan Medicinal Products (COMP) concluded that chronic lymphocytic leukaemia was estimated to be affecting approximately 3.5 in 10,000 persons in the Community, at the time the application was made (June 2008) and that the condition is chronically debilitating and life-threatening, in particular due to poor long-term survival in high-risk patients.
No paediatric investigation plan was submitted with the application, as ofatumumab is covered by a class waiver on the 'treatment of chronic lymphocytic leukaemia', a condition which is not applicable to children.

2.2 Quality aspects

Introduction

The active substance, Ofatumumab, is a fully human monoclonal antibody (mAb) directed against CD20 and binds specifically to epitopes which encompass the amino residues 163 and 166 in the small extracellular loop of the CD20 molecule epitopes on the human B cells.

Ofatumumab concentrated for solution for infusion, 20 mg/ml is clear, colourless solution filled into Type I clear glass vial sealed with bromobutyl rubber stoppers and aluminium overseals. Each vial contains 5 ml of ofatumumab.. The medicinal product may contain visible particles and the product is supplied with a commercially available polyether sulfone filter set. The filter set has a CE mark (CE 0086) in compliance with the Medical Device Directive 93/42/EEC.

Active Substance

The active substance is ofatumumab, an $IgG1_k$ human mAb which is produced from a recombinant murine cell line (NSO). The molecular weight (MW) of the antibody is approximately 149 kDa (25

kDa of the light chain and 50 kDa of the heavy chain). The antibody is N-linked glycosylated at ASN_{302} of the heavy chain with varying amounts of terminal galactose.

- Manufacture

The manufacturing process starts with the thawing of cells from the NSO working cell bank (WCB). During the cell culture stages, cells are progressively increased in number, prior to transfer into a production bioreactor with controls, which include pH, dissolved oxygen, temperature

When harvest criteria are achieved, the bioreactor contents are clarified prior to further purification. The different steps in the purification process include affinity and anion exchange chromtatography as well as robust viral clearance steps that are capable of removing adventitious agents and other contaminants. Following purification the active substance dispensed into sterile active substance containers prior to testing and release.

Control of materials

Comprehensive lists of all materials used during the fermentation and purification of the ofatumumab manufacturing process are given. Culture media are prepared from pre-formulated base powders supplemented with chemically defined components. The qualitative composition of the base powders is given.

The anti-CD20 antibody expressing murine cell line (SJT26) was generated via transgenic mouse and hybridoma technology. The information provided on generation of the cell substrate is considered to be adequate and sufficiently detailed.
Sufficient information is provided on the establishment and testing of MCB and WCB. Testing of the MCB and WCB is acceptable and in accordance with relevant guidelines.

MBC Testing – Characterisation test performed on the MCB includes: viability, sterility by direct inoculation, mycoplasma by agar and broth culture and Vero indicator cell procedures, Quantitative TEM of sections for the detection of viruses, fungi, yeasts, bacteria and mycoplasma.

No infections ecotropic or xenotropic retroviruses were detected. Retrovirus like particle A and C type have been detected. As is typical for NSO cell lines, a low level of murine leukaemia retrovirus capable of reproducing was detected in the *Mus dunni* assay, but it was demonstrated to be incapable of infecting the human cell line MRC-5 on co-cultivation with the SJT26 cell line.
No other viruses, virus like particles, mycoplasma, bacteria, fungi or yeasts were detected.

WCB Testing – WCB were tested for: viability, sterility by direct inoculation, mycoplasma by agar and broth culture and Vero indicator cell procedures. No adventitious viral contaminants were detected.

A limit of cell age of 50.0 generations beyond MCB is established. Genetic stability of the cell line has been demonstrated. Based on the results presented, this limit seems acceptable.

Process development and validation

In general, the ofatumumab active substance manufacturing process is considered well controlled and validated. The process development and establishment of process controls/test are built on the current understanding of the ICH, QbD concept. Information on the risk-matrix system has been provided and the establishment of critical/non-critical process parameters are carefully outlined. The quality system in place to evaluate derivations from Target Set Points/Acceptable range, Acceptance Criteria or a CCP value outside the acceptable range has been indicated. No design space is claimed.

The consistency study has demonstrated that the cell culture, harvest and purification process is routinely operated within predefined acceptance criteria.

Descriptions, supported with detailed tables, have been provided for all changes introduced over time in the ofatumumab active substance manufacturing process at the various process steps. In total three processes have been used, Process A, B and C. The changes introduced from Process A to Process B and Process C have been sufficiently described. Comparability with regard to characterization has overall been done by state-of the art methods and support that comparable ofatumumab active substance material has been used throughout the non-clinical and clinical studies, and that this material is comparable to the commercial material for the market.

Validation studies were performed for the active substance, ofatumumab, manufacturing process to define the quality attributes, operating parameters, control strategy, and to demonstrate process consistency. Following process development and scale up, the commercial process was established and a series of three batches (39575, 42873 and 45338) was run. Each batch was initiated from a separate vial thaw and carried through to active substance.

For each step of the manufacturing process, process parameters that could affect the critical quality attributes of active substance were evaluated and the range for these parameters during routine manufacturing was established. These ranges were monitored to confirm that they remained within the required limits.

An initial assessment of the applicability of the existing data (including experience with mAb production using murine cell lines) were done to support set point and ranges for each process parameter. Data were generated to justify process limits and evaluate the potential effect of each process parameter on the quality of the product.

A Critical Process Parameter (CPP) matrix is used to evaluate each parameter and categorize the magnitude of risk into three categories: high, medium and low, depending on whether the process parameter has a high risk of adversely affecting the product quality, if operated outside a defined acceptable range.

Process Limit Evaluation (PLE) studies were carried out for parameters where the CPP risk was assigned "high" and where sufficient data did not exist to support the process ranges; therefore, data from 4 to 6 commercial scale batches and 4 to 6 PLE studies, using small scale bioreactors, were analyzed to confirm the acceptable range of the parameter investigated. No CPPs were identified for the 4 steps of the cell culture and harvest process.

The consistency study data has demonstrated that the cell culture and harvest process is routinely operated within predefined acceptance criteria and that the three consistency lots had comparable cell growth kinetics, comparable ofatumumab concentrations and comparable purity.. From the study it can be concluded that the ofatumumab active substance batches from the process of consistency series are shown to be comparable to reference standard 31050/ARS. The data presented demonstrate that a consistent quality of ofatumumab active substance is manufactured.

Specific validation studies conducted following written protocols were used to validate the active substance manufacturing process. Validation studies were performed following production batch records and standard operating procedures as appropriate. Validation studies were performed using the commercial scale manufacture equipment, or where necessary, in small scale equipment designed to simulate the conditions used at commercial scale manufactures.

- Specification

The specification and limits proposed by the Applicant for release of ofatumumab active substance is based on data from the manufactured active substance lots and lots used in clinical trials.

Tests for purity, potency and identity are included, together with general tests such as appearance and pH and oligosaccharide mapping. All methods have been appropriately validated.

A shelf-life specification for ofatumumab has been accepted based on the justification and data given.

- Stability

The proposed shelf-life of 24 months for ofatumumab when is stored at 5 ± 3^{o}C protected from light, are acceptable as it is supported with full time; at scale and site, stability data for three batches from the commercial Process C. No significant changes were observed in any of the stability indicating parameters after storage at this condition, and all results met acceptance criteria.

The results obtained under accelerated (25^{o}C) conditions for up to 12 months, and under stress (40^{o}C) conditions for up to 6 months show that the active substance stability begins to decline at these

conditions. In addition, data generated following short term exposure to ICH photostability conditions indicates that ofatumumab requires protection from light during storage.

Medicinal Product

Arzerra (ofatumumab) Concentrate for Solution for Infusion 20 mg/ml is a clear, colourless, aqueous solution containing 20 mg/mL of ofatumumab in a 30 mM citrate buffer, pH 6.5 containing 100 mM sodium chloride. Prior to administration, the product is diluted into an infusion bag containing isotonic pyrogen free 0.9% Sodium Chloride Injection. Water for Injection is an inactive ingredient used as a solvent for the components of the buffer. During administration of the intravenous infusion the product solution is filtered through an in-line filter.

- Pharmaceutical Development

The development of the formulation and the DP manufacturing process is considered adequately described. Excipients and primary container components are considered standard for the product type. All excipients comply with Ph.Eur. and no animal/human on novel excipients are used. All analytical procedures used to control the excipients are in compliance with Ph.Eur.

Early formulation development work was performed by testing the quality and stability of ofatumumab in a variety of buffer systems over the pH range 4 to 8, suitable for intravenous infusion. The composition of these buffers was based on manufacturing experience of suitable formulation for biopharmaceuticals.

The formulations were stored at 5^{o}C, 25^{o}C, 40^{o}C and -20^{o}C. An aliquot of the samples stored at 5^{o}C was agitated for 24h on an end over end rotary mixer and tested for aggregate formation. Samples were also tested for purity and potency. Additionally, the formulation samples were checked for visual appearance and presence of particles.

The study demonstrated that the sodium citrate buffer was the buffer system that showed best stability of the ofatumumab molecule at 5^{o}C, 25^{o}C and 40^{o}C among the buffers tested. For the citrate buffer samples, pH 5.0 had elevated levels of fragments on accelerated stability compared to the citrate formulations at pH 5.5 or 6.5. For these reasons and because the 30 mM sodium citrate, 100 mM sodium chloride, pH 6.5 formulation met all of the design requirements that particular formulation was chosen. This formulation was used in all clinical trials for CLL and is proposed for commercial manufacture.

The formulation choice has also been validated by stability. The formulation maintains stability of ofatumumab when stored under the recommended condition. Besides biochemical stability, the potency of ofatumumab, as measured by the Potency assay is maintained throughout its shelf-life. The Potency assay has been shown to be very sensitive assay to detect changes in ofatumumab activity.

- Adventitious Agents

The cell banks (MCB and WCB) are sufficiently characterised and tested for adventitious agents.

Production bioreactor on day of harvest is routinely tested (in process control) for adventitious viruses.

Four viruses have been included in the virus validation study. A sufficient and acceptable rationale is given for the four viruses used in the virus validation study and virus reduction factor of at least Log_{10} > 11 is demonstrated for viruses.

Viral and microbiological safety of the ofatumumab active substance is considered assured.

- Manufacture of the Product

The proposed commercial manufacturing process employed comprises the following process steps: preparation of dilution buffer, preparation of bulk solution, filling, inspection and packaging. The filling overage has been justified and comparability has been adequately described.

The manufacturing process involves pooling active substance in an appropriate vessel and diluting to the target concentration with a matched buffer solution. After mixing, the solution is filtered through a 0.45 µm filter and a 0.2 µm sterile filter into a holding vessel and aseptically filled into vials.

The critical steps of the medicinal product manufacturing process are controlled by the in-process controls. These in-process controls are described and justified. There are no intermediate products in the manufacturing process.

The representative batch formula is provided for the medicinal product and also for the dilution buffer solution. Three commercial scale batches of medicinal product have been manufactured according to the proposed commercial manufacturing process at the proposed commercial site.

Validation of equipment sterilisation process, aseptic filling (media fill, Tryptone soya broth), container closure integrity (microbiological challenge study), filters, re-processing process hold time analysis, has also been performed. The hold time analysis provides a limit for holding product outside of cold storage for a cumulative time that should have no detrimental effect on quality.

- Product Specification

The proposed list of specifications is considered acceptable and in accordance with Ph.Eur. 01/2008:2013 "Monoclonal antibodies for human use" and relevant guidelines. No new impurities are formed during manufacture of the medicinal product and the purity/impurity profile for the medicinal product is comparable to active substance.

The endotoxin test and the sterility test have been qualified according to Ph.Eur.

The proposed specification for appearance is: "Clear, colourless liquid. Visible particles may be present". This is not fully in accordance with Ph.Eur. monograph 2031 "Monoclonal antibodies for human use", which states that the appearance should be "Without visible particles". However, according to Ph.Eur. monograph 0520 "Parenteral preparations", infusions should be "Practically free from particles". It has been demonstrated that the visible particles are product-related protein particles and there are no changes in protein content. As the product is dosed with an in-line filter, neither safety nor efficacy is affected by the presence of visible particles. The specification for appearance is therefore considered acceptable.

A shelf-life specification has been proposed for the medicinal product. The shelf-life specifications are identical to the release specification. This is considered acceptable as a commitment has been given by GSK to revise the specification 2 years post approval.

The medicinal product is supplied in Type I clear glass vials sealed with bromobutyl rubber stoppers and aluminium overseals. Each vial contains 5 ml of ofatumumab, 20 mg/ml. The vial and stopper are in compliance with Ph.Eur.

- Stability of the Product

The proposed shelf-life of 24 months at 2-8^{o}C, protect from light and do not freeze is based on 12 months stability data for the primary batches and 24 months data for the supportive batches. Comparability of DP manufactured at different sites during development is demonstrated by batch analyses data. The proposed medicinal product shelf-life is acceptable.

The results of accelerated and long-term stability studies for the primary stability batches demonstrate chemical and physical stability and equivalence to the supportive stability batches over the same 6 months span. Stability data form the supportive stability batches demonstrate the overall quality, purity and potency are retained over 24 months at the recommended storage temperature of 5±3^{o}C.

In the SPC it is stated that chemical and physical in-use stability has been demonstrated for 48 hours at ambient conditions (less than 25^{o}C). Based on data provided, this is considered acceptable.

GMP Status: The sites used for medicinal product and active substance manufacture, release and stability testing have been inspected and accepted.

2.3 Non-clinical aspects

Introduction

Primary pharmacology studies were conducted in immunodeficient mice and a secondary pharmacology study was conducted to examine the efficacy of ofatumumab in a mouse model of rheumatoid arthritis (RA). Based on cross-reactivity studies and cDNA analysis it was determined that cynomolgus monkey was suitable as test species in the nonclinical safety studies, but not mouse, rat or dog.
Preliminary toxicology and toxicokinetic studies were in general performed in accordance with the principles of Good Laboratory Practice (GLP). All definitive toxicology and toxicokinetic studies were performed in full compliance with GLP regulations.

Pharmacology

- Primary pharmacodynamics

Many of the primary pharmacology studies used the commercially available, type-I anti-CD20 antibody, rituximab (Mabthera), as a comparator.
Fluorescein isothiocyanate (FITC) labelled ofatumumab bound to human peripheral blood mononuclear cell CD20 (3 donors) with a mean EC_{50} value of 287±12.7 ng/mL. Similar numbers of iodinated ofatumumab and rituximab antibodies bound to CD20 on B-cell lymphoma cell lines, as shown by the similar levels of binding saturation. To exclude the possibility that the iodinated monoclonal antibodies bound via Fc-receptors, binding curves were confirmed using anti-CD20 F(ab')2 fragments (data not shown).
Epitope mapping studies using a mutagenesis approach have indicated that the amino acid residues alanine at position 170 (A170) and proline at position 172 (P172) in the second extracellular loop are critical for the recognition of human CD20 by known anti-CD20 antibodies, including rituximab [Polyak 2002]. To determine which amino acids are involved in ofatumumab binding to CD20, sequential single substitutions of human for mouse amino acids along the extracellular regions of CD20 have been conducted (site-directed mutagenesis). Replacement of the amino acid residues at positions 163 and 166 strongly reduced the binding of ofatumumab whereas binding of rituximab was unaffected. Mutating threonine to lysine at position 159 did not influence the binding of either antibody. However, triple mutations at positions 159, 163 and 166 completely abrogated the binding of ofatumumab and reduced the binding of rituximab (data not shown).
Ofatumumab and rituximab epitope mapping was also performed in a Pepscan-based ELISA using overlapping, mostly 15-mer synthesized peptides comprising the extracellular loops of CD20. In this study, ofatumumab bound to peptides N-terminal of A170/P172 in the second extracellular loop of CD20. It also bound to peptides derived from the small extracellular CD20 loop. Rituximab recognised peptides centred around A170/P172 but showed little or no reactivity with peptides located to the N-terminal side of A170/P172 on the large extracellular loop or the small loop of CD20 (data not shown).
Cells from different tumour B-cell lines (Daudi, ARH77, Raji, DOHH and Su-DHL-4) were pre-incubated with CD20-specific antibodies, before the addition of normal human serum, which induces CDC. Cell lysis was determined by measuring the number of propidium iodide positive cells by flow cytometry. Ofatumumab lysed >80% of cells in all tested cell lines. Rituximab lysed >80% Daudi and Su-DHL-4 cells and between 20-50% of cells in the remaining three cell lines (data not shown).
Complement inhibitors such as CD55 and CD59 appear to play an important role in the susceptibility to rituximab-induced CDC [Golay, 2001]. To study the role of CD55 and CD59 in anti-CD20 mediated CDC, both complement inhibitor molecules were blocked by specific antibodies prior to induction of CDC. Blocking of CD55 did not affect ofatumumab mediated CDC, while the addition of a CD59 antibody appeared to slightly increase the CDC-mediated lysis. Similarly, the results indicated that blocking of CD59 increased the cells susceptibility to rituximab, while no increase in efficacy was observed following CD55 blocking.
Flow cytometry analysis showed that FITC-conjugated anti-C1q antibody binds to ofatumumab-bound B-cells to a higher extent than rituximab-bound B-cells. However, in an ELISA assay, human C1q bound to immobilised ofatumumab and rituximab to the same extent. Moreover, fixation of C4c

(indicator of complement activation via classical route) after ofatumumab binding was higher than after rituximab binding. Similar binding of complement factor C3 to ofatumumab and rituximab was observed in an ELISA assay.

In order to investigate the impact of CD20 expression levels on ofatumumab-induced CDC, experiments were performed in CD20-transfected human CEM T cells, which lack endogenous CD20 expression. To this end, a panel of CD20-transfected human CEM T cell clones expressing different amounts of CD20 (4500 to 135,000 molecules/cell) was generated. Ofatumumab achieved complete lysis of any cell line expressing more than 60,000 molecules of CD20 and lysed approximately 18% of cells expressing as few as 4500 CD20 molecules/cell. Rituximab did not reach maximal lysis against clones expressing the highest levels of CD20 and showed CDC activity towards cells expressing at least 30,000 CD20 molecules/cell (data not shown).

^{51}Cr-labelled target cells, namely ARH-77 (a tumour B cell line), B cell acute lymphoblastic leukaemia (B ALL) cells after five rounds of subcloning, or fresh tumour B cells from various sources [B cell chronic lymphocytic leukaemia (CLL), hairy cell leukaemia, follicular lymphoma and primary mantle cell lymphoma], were incubated with ofatumumab or rituximab (0.01 to 10 µg/mL). Subsequently, effector cells in the form of polymorphonuclear cells, mononuclear cells or whole blood was added. ^{51}Cr release was measured using a gamma counter and used as an indicator of target cell lysis. In the presence of polymorphonuclear cells, minimal specific lysis was observed of ARH-77 cells and fresh tumour cells. However, in the presence of mononuclear cells, ofatumumab and rituximab mediated lysis of ARH-77 cells, CLL cells, B-ALL cells and hairy cell leukaemia cells to a similar extent, indicating that a similar fraction of cells was susceptible to ADCC by both antibodies. Neither antibody was able to induce ADCC-mediated lysis of follicular lymphoma or primary mantle cell lymphoma cells (data not shown).

It was further investigated how the cytotoxic effects of ofatumumab relate to the target occupancy. It was shown that ADCC induction reached its maximum level (51% lysis) at an ofatumumab concentration of about 0.1 µg/mL, which corresponds to the concentration at which half-maximal target occupancy was achieved. In contrast, maximum CDC (68% cell lysis) was only achieved at complete target occupancy (saturation).

Induction of apoptosis is an alternative mechanism by which anti-CD20 antibodies could kill tumour B cells [Johnson, 2003]. Therefore the ability of ofatumumab and rituximab (0.1-10 µg/mL) to induce apoptosis of Daudi or Raji cells was investigated in an Annexin-V apopotosis assay. Neither ofatumumab nor rituximab was able to induce significant apoptosis in Raji cells. Around 15% and 30% apoptotic Daudi cells was seen following incubation with ofatumumab and rituximab, respectively. In contrast, the positive control mouse anti-human CD20 antibody, B1, was a strong inducer of apoptosis in both cell lines (data not shown).

Homotypic aggregation correlates with the induction of apoptosis [Polyak, 2008], therefore, the ability of ofatumumab to induce homotypic aggregation of Daudi cells was investigated. Light microscopic evaluations showed that ofatumumab does not induce homotypic aggregation of Daudi cells, while rituximab induces minimal cell aggregation. The positive control antibody, B1, was a strong inducer of homotypic aggregation (data not shown).

Rapid complement activation has been suggested to underlie the first dose side effects of rituximab due to the release of inflammatory mediators such as the complement split products (anaphylotoxins) C4a, C3a and C5a [Van der Kolk 2001]. Analysis using C4a, C3a, and C5a antibody-coated cytometric beads and flow cytometry showed that ofatumumab had a tendency to induce higher levels of C4a, C3a and C5a during complement activation than rituximab (data not shown).

The induction of CD20 translocation into lipid rafts by anti-CD20 antibodies is considered to be an important mechanism for inducing cell signalling and complement activation [Deans, 1998; Teeling 2004]. It was shown that both ofatumumab and rituximab induce clustering of targeted CD20. Moreover, based on a series of *in vitro* assays, it was concluded that ofatumumab and rituximab treatment of Daudi lymphoma cells, induce the clustering of CD20 into lipid rafts to a similar extent (data not shown).

The potential therapeutic effects of ofatumumab *in vivo* were examined in severe combined immunodeficiency (SCID) mouse tumour xenograft models.

The first set of experiments assessed survival following a high dose of ofatumumab or rituximab. SCID mice (n=5/group) were IV inoculated with a human tumour B cell line (2.5 x 10^6 cells) and 7 days later given vehicle or 100 µg of ofatumumab or rituximab by IV bolus injection. Survival was recorded as the end-point of the study. Ofatumumab treatment of mice injected with one of the cell

lines resulted in 60% survival at the end of the experiment (100 days after the injection of tumour cells). Rituximab did not prevent death, with the mice dying between 50 to 83 days after tumour injection (data not shown).
To investigate the dose-effect relationship, groups of SCID mice (n=4 or 5/group) were injected with 2 x 10^6 cells of a second B cell line expressing higher levels of CD20 followed 7 days later by the vehicle or 0.1, 0.5, 2.0, 5.0 or 20 µg of ofatumumab or rituximab. A dose-dependent prolongation of survival was noted following treatment with ofatumumab at ≥2 µg per mouse (~80 µg/kg). Rituximab did not exert a dose-dependent effect on survival (data not shown).
Ofatumumab was subsequently evaluated in studies using a SCID mouse model in which disseminated outgrowth of human B cell tumours was followed by quantitative bioluminescence imaging. In these studies, 2 x 10^6 cells of a B-cell line transfected with firefly luciferase were injected IV into SCID mice. Several days after cell inoculation, the animals received ofatumumab, rituximab or the isotype control antibody, HuMab-KLH, by IP administration. In an experimental set up in which the animals (n=6/group) received a low dose of antibody (0.5 mg/kg) 8 days after cell inoculation, both ofatumumab and rituximab significantly inhibited tumour growth relative to the control (data not shown).
In another experimental set up in which mice (n=9/group) were treated much later (on Day 14), there was no difference in therapeutic efficacy between ofatumumab and rituximab (0.5 and 50 mg/kg). Ofatumumab and rituximab were also equally effective in mice (n=6/group) administered 0.5 mg/kg on Day 5 or Day 14 (n=6/group). Notably, both antibodies were more effective when administered early after cell inoculation (i.e. on Day 5) than when administered late after inoculation (i.e. on Day 14, data not shown).
Pharmacokinetic analyses indicated that differences in efficacy between ofatumumab and rituximab, where they occurred, could not be explained by differences in IgG plasma levels.
It was found that ofatumumab binding to CD20 expressing B-cell lymphoma cell lines was not affected by deglycosylation. However, N-linked glycosylation of ofatumumab was essential for binding of C1q to the Fc portion of the antibody and consequently for the ability to induce CDC. Hence, C4 deposition was eliminated following ofatumumab deglycosylation. Moreover, preliminary data suggested that deglycosylation decreased FcγRIIIa-158V binding to ofatumumab. Binding affinity of antibodies to Fcγ receptor IIIa has been shown to correlate with their potency to induce ADCC *in vitro* [Bleeker 2008; Carter 2006].
Similarly, changing the galactose content of ofatumumab did not affect its binding to CD20 expressing B-cell lymphoma cell lines. Changing the galactose content of ofatumumab reduced its ability to induce CDC in certain cell lines but not in others. Moreover, degalactosylation of ofatumumab reduced complement C1q binding and consequently C3 and C4 deposition (data not shown).
No difference in anti-tumour efficacy was observed in SCID xenograft mice IP treated with 500 µg/kg of ofatumumab or degalactosylated ofatumumab (n=9/group). Hence, the minor non-clinical effect of ofatumumab degalactosylation on CDC and FcγRIIIa-158V binding (ADCC) did not translate into an *in vivo* effect on treatment efficacy (data not shown).
Based on immunohistochemistry, ofatumumab and rituximab display similar cellular binding (B-cell follicles) in the tonsils of humans and cynomolgus monkeys. In contrast, ofatumumab did not bind to spleen sections obtained from mouse, rat, rabbit, pig and dog. Based on flow cytometry data, ofatumumab has a slightly higher affinity for cynomolgus monkey than human peripheral blood mononuclear cells (EC_{50} values of 139 and 287 ng/mL, respectively). In addition, the cDNA sequence of the second extracellular loop of cynomolgus monkey CD20 was determined and the amino sequence compared to that of human CD20. A single amino acid change was noted at position 158 (Ala_{human}-Val_{cyno}).

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

The obtained results are summarized in the following table 3:

Table 3: Summary of non-clinical primary pharmacology studies findings

Biological Activity	Ofatumumab	Rituximab

Apparent affinity (ng/ml)	EC_{50}: 287 ± 13 ng/ml	ND
Epitope	Discontinuous epitope Binding to small and large loop not containing $A_{170}xP_{172}$	Linear epitope Binding to large loop containing $A_{170}xP_{172}$
CDC	++	+
ADCC	+	+
Translocation into Lipid Rafts	+	+
Apoptosis	-	+/-
SCID mouse tumour model	++	+

ND = Not determined

- Secondary pharmacodynamics

In a secondary pharmacology study, the efficacy of ofatumumab in a mouse model of rheumatoid arthritis (RA) was examined. In patients with RA, large numbers of immune cells infiltrate the hyperplastic synovial tissue of the chronically inflamed joint, forming the so-called pannus, which erodes subjacent cartilage and bone. According to the applicant, the most important of the autoantibodies implicated in the condition are those against cyclic citrullinated proteins (anti-CCP antibodies), which are thought to play a role in the pathophysiology of the disease.
To evaluate the effectiveness of ofatumumab in the depletion of B cells and plasma cells responsible for the production of autoantibodies, SCID mice were implanted subcutaneously with human synovial tissue from patients with RA and intravenously administered 30 mg/kg of anti-KLH (control antibody) or ofatumumab between Days 7 and 9 after engraftment. Mice were implanted with synovium from anti-CCP^+ or anti-CCP^- RA patients. Grafts were explanted at various time points (Days 14, 22, 81 or 91) and stained by immunohistochemistry for B cells and other types of immune cells. Serum levels of human IgG and anti-CPP antibodies were measured by ELISA.
Only mice engrafted with tissue from anti-CCP^+ RA patients developed antibody titers against CCP. In general, there was no effect of ofatumumab on the human IgG titers. The applicant argued that the plasma cells, which are not affected by anti-CD20 antibodies, present at the time of treatment may be responsible for the majority of human antibody production in this model and concluded that assessing human antibody serum levels does not represent a sensitive measurement for B cell depletion in this model. However, ofatumumab efficiently depleted B cells in synovial tissue in one experiment, in which grafts were explanted early enough (after 14 days) to allow immunohistochemical analysis.

A large number of tissues from three unrelated patient donors were examined in a human cross-reactivity study. Sections of each sample of tissue from each donor were incubated with FITC-labelled ofatumumab at 0.5, 5.0 and 20.0 µg/ml. All tissue samples were treated with an antigen marker appropriate for each tissue in order to confirm the preservation of antigens in that tissue.
Specific, positive, membrane bound staining was recorded in lymphocytes of the lymph node, spleen, thymus and tonsil and also in the mucosa associated lymphoid tissue (MALT) of the small and large intestines in donors where lymphoid tissue had been sampled, at all concentrations of the test antibody. In addition there was positive membrane bound staining of lymphocytes scattered in the subepithelial tissue of at least one donor of cervix, endometrium, kidney, prostate, parotid salivary gland, skin, stomach, ureter and urinary bladder at all concentrations of the test antibody.

- Safety pharmacology programme

No specific safety pharmacology studies were submitted. However, some safety pharmacology end points, such as cardiovascular and renal parameters and body temperature, were evaluated as part of the pivotal 4 week and 7 month repeat dose toxicity studies in cynomolgus monkeys.
No changes in body temperature were observed in the 4 week repeat-dose toxicity study at doses up to 100 mg/kg. There were no treatment-related changes in heart rate or QT interval in either investigation at doses up to 100 mg/kg.
Urinalysis parameters (volume, specific gravity, pH, protein, blood pigments, glucose, ketones, urobilinogen and bilirubin; microscopic examination of the spun deposit) were evaluated at intervals throughout the 4 week and 7 month studies and showed no changes related to treatment with ofatumumab (see repeat dose toxicity studies).

- Pharmacodynamic drug interactions

No studies were submitted. Such investigations were considered by the Applicant as unnecessary, as ofatumumab is a biologic with high specificity and affinity for CD20, and it was felt very unlikely that it would affect other pharmacologically relevant targets.

Pharmacokinetics

Conventional pharmacokinetic studies are not applicable to monoclonal antibodies like ofatumumab in accordance with the ICH S6 guideline on preclinical safety evaluation of biotechnology-derived pharmaceuticals.
No specific pharmacokinetic studies were submitted by the applicant. All pharmacokinetic/ toxicokinetic parameters were obtained as part of repeat dose toxicology studies of up to 7 months duration in the cynomolgus monkey (Macaca fascicularis). The majority of studies were performed by the IV route (infusion over 30 minutes) as this is the clinical route of administration; however, the SC route of administration was also examined in a single study. The potential for the transfer of ofatumumab across the placenta was evaluated as part of an embryofetal development study.
In terms of analytical methods, different ELISA methods were developed to detect ofatumumab and rituximab in cynomolgus monkey plasma and serum as well as anti-ofatumumab antibodies (data not shown).
The pharmacokinetic data obtained during the repeat-dose toxicity studies conducted in cynomolgus monkeys are summarised in the following table 4.

Table 4: PK data obtained from toxicokinetic data in the toxicity studies

GLP status **Duration**	non-GLP 4 days	GLP 4 weeks	GLP 7-months	GLP 23-weeks	GLP 14-days	
N/sex	1/group/ either ♂ or ♀	2-3/sex/group	3-4/sex/ group	3/sex/group	6/♀/group	
Analysis	ELISA (colormetric)	ELISA (colormetric)	ELISA (colormetric)	ELISA (colormetric)	Immunoassay (not specified)	
Route	IV (infusion)	IV (infusion)	IV (infusion)	IV (infusion)	SC	IV (infusion)
Dose	1.25, 6.25, 12.5 mg/kg/day	20, 100 mg/kg/week	20, 100 mg/kg on Day 1, 8, 15, 22, 29, 36, 43, 50, 78, 106, 134, 162 and 190	20, 100 mg/kg on Day 1, 15, 148 and 162	20, 100 mg/kg given on Day 1 and Day 15	100 mg/kg given on Day 1 and Day 15
$T_{½}$ (h)	16-225	2-693	202-393	17-273	27-353	265-345
V_d (mL/kg)	30-223	15-134	34-52	29-119	-	-
Cl (mL/h/kg)	0.62-2.9	0.07-6.8	0.24-0.33	0.25-1.3	-	-
F (%)	-	-		-	9-110%	-

Since ofatumumab is an antibody, conventional absorption, distribution, metabolism and excretion studies as well as pharmacokinetic interaction studies were not submitted (see discussion on non-clinical aspects).

Toxicology

- Single dose toxicity

No single dose toxicity studies were submitted (see discussion on non-clinical aspects).

- Repeat dose toxicity (with toxicokinetics)

The design and results of the repeat-dose toxicity studies are summarized in the table below.

Table 5: Repeat dose toxicity studies

GLP status **Duration** **Species** **N/Sex/Group**	**Dose/Route**	**Major findings**
non-GLP 4-days + 130 days recovery Cynomolgus monkey/ 1/sex/group	Once daily IV infusion 1.25, 6.25, 12.5 mg/kg/day for 4 consec. days	**≥1.25 mg/kg/day:** Haematology: Changes in T-cell subsets in peripheral blood and in lymph nodes, ↓NK-cell counts Clinical chemistry: ↑ C-reactive protein (only on Day 2)
non-GLP 5-days Cynomolgus monkey/ 1/♂or♀/group	IV infusion 25, 50, 75, 100 mg/kg at Day 1 followed by 50, 75, 100, 150 mg/kg at Day 5	**100+150 mg/kg:** Organ weight: ↑ spleen, ↑ thyroid gland Macroscopic: Enlarged thyroid glands **NOAEL:** 75 mg/kg at Day 1 followed by 100 mg/kg at Day 5
GLP 4 weeks + 6 months recovery Cynomolgus monkey/ 2-3/sex/group	Once weekly IV infusion 20, 100 mg/kg/week	**≥20 mg/kg/day:** Histology: Minimal to moderate germinal centre or follicular atrophy in the mandibular and mesenteric lymph nodes, Peyer's patch and spleen **100 mg/kg/day:** Other tests: Inhibition of specific KLH antibodies **Recovery:** **≥20 mg/kg/day:** Histology: Minimal germinal centre atrophy in the spleen **100 mg/kg/day:** Other tests: Inhibition of specific KLH antibodies

GLP status Duration Species N/Sex/Group	Dose/Route	Major findings
GLP 7-months + 6 months recovery Cynomolgus monkey/ 3-4/sex/group	20, 100 mg/kg IV (infusion) on Day 1, 8, 15, 22, 29, 36, 43, 50, 78, 106, 134, 162 and 190	**≥20 mg/kg/day:** 2 deaths on Day 44 & 64 Haematology: ↓ Hb, ↓ RBC, ↓ Hct, ↑ reticulocyte, ↑ T cells (predominately $CD8^+$) in the lymph nodes, ↓ NK cells in the peripheral blood Clinical chemistry: ↑ lactate dehydrogenase (meanly ♂), ↑ total bilirubin Histology: Minimal to moderate lymphoid atrophy in submandibular and mesenteric lymph nodes, Peyer's patch in the ileum, and spleen, inflammation in the kidneys and perivascular inflammatory cell infiltration in the brain and sciatic nerve. Other tests: Positive Coombs test, inhibition of KLH **100 mg/kg/day:** 1 death on Day 139 Histology: Thymic atrophy, extramedullary haemopoiesis in the liver **Recovery:** **≥20 mg/kg/day:** 1 death on Day 268 Other tests: Inhibition of KLH **100 mg/kg/day:** 1 death on Day 276 Histology: Mild thymic atrophy, mild multifocal interstitial nephritis
GLP Cycled repeat dose (23-week) with a 4 month recovery period Cynomolgus monkey/ 3/sex/group	20, 100 mg/kg IV infusion on Day 1, 15, 148 and 162	**≥20 mg/kg:** Histopathology: Germinal centre atrophy in the spleen, tonsils, and the mandibular and mesenteric lymph nodes Other tests: Positive Coombs test, inhibition of KLH (only in the secondary response) **100 mg/kg:** Clinical signs: Swollen and scabbed scrotum and prepuce Haematology: ↑Reticulocytes (263%), ↓ Hb, ↓ erythrocyte count, ↓ Hct Clinical chemistry: ↑ Fe (up to 57%,♀), ↑ bilirubin (up to 128%) Macroscopic: Reddened medulla and pale cortex of the kidney (2/3♀) Histology: Haemorrhage in the kidney (correlating with the reddened medulla), hyperplastic dermatitis (correlating with scabbing) **Recovery:** **≥20 mg/kg:** Histopathology: Germinal centre atrophy of the spleen, and and the mandibular and mesenteric lymph nodes **100 mg/kg:** Clinical signs: Hair loss and extensive scab formation (♀) which in 1/3 female led to a opened and weeping wound Histology: hyperplastic dermatitis (1♂)
GLP 14-days + 33-weeks recovery Cynomolgus monkey/ 6/♀/group	20, 100 mg/kg SC or 100 mg/kg IV(infusion) given on Day 1 and Day 15	No treatment-related findings **NOAEL:** 100 mg/kg

Depletion of $CD20^+$ cells was not included in the table above as this finding was considered a pharmacological effect of ofatumumab. In general, depletion of CD20+ cells in the peripheral blood was detected already after the second administration and seemed to continue throughout the dosing period. In the recovery animals, the time needed before B-cell levels returned to baseline levels appeared to depend upon the dose, i.e. high dose animals recovered later than low dose animals. Depletion of $CD20^+$ cells in biopsies taken from the lymph nodes seemed to be consistent with those seen in peripheral blood. The depletion of $CD20^+$ cells occurred regardless of the route of administration (IV versus SC) and whether ofatumumab was administered daily, weekly, monthly or cyclically.
Ofatumumab treatment did not change the pool of other cell phenotypes, including T and NK cells, within the blood or lymph node compartments. In addition, there were no changes in neutrophil or monocyte populations. Immunisation of monkeys with keyhole limpet haemocyanin (KLH) following chronic IV infusion administration of ofatumumab resulted in detectable immune responses, although the magnitude of the IgG humoral immune response was reduced in monkeys dosed at 20 and 100 mg/kg. No effects on delayed type hypersensitivity reactions were noted at doses of ofatumumab up to and including 100 mg/kg (as assessed by immunisation with commercially available antigens, i.e., diphtheria toxoid, tetanus toxoid, Candida albicans and Trichophyton mix).
Increases in reticulocytes and lactate dehydrogenase, and decreases in haemoglobin concentration, haematocrit concentration and red blood cell count were indicative of haemolytic anaemia. A review of haemolytic events indicated that the majority of treated animals were experiencing a slowly developing haemolytic anaemia during both the dosing and recovery periods, and that this was associated with a progressive, dose-related increase in lactate dehydrogenase that was reversible. Furthermore, the direct Coombs' test results suggested that the monkeys probably developed antibodies to ofatumumab, which induced the formation of immune complexes and complement activation and was followed by binding of the complexes via the complement binding CR1 receptor to the surface of the red blood cells. This is likely to have resulted in sequestration in the spleen by macrophages leading to haemolytic anaemia. The cynomolgus monkey red blood cell surface contains approximately 7 times the number of CR1 epitopes found on human red blood cells [Edberg, 1992; Hebert, 1992], and according to the applicant this may have accentuated the observed haemolytic anaemia in the cynomolgus monkeys.
In the pivotal 7 month repeat-dose toxicity study (GLP), there were five monkeys that were either humanely sacrificed or found dead at both dose levels, none of these were attributable to direct toxicity of the test item. The reasons for animal withdrawal can be categorised into those which had a probable *Campylobacter jejuni* (*C. jejuni*) infection and those which showed signs of haemolytic anaemia.

- Genotoxicity

No studies were submitted (see discussion on non-clinical aspects).

- Carcinogenicity

No studies were submitted (see discussion on non-clinical aspects).

- Reproduction Toxicity

No studies on fertility and no peri- and post-natal toxicology studies were submitted (see discussion on non-clinical aspects).
In an embryofoetal development study, ofatumumab was administered iv to pregnant cynomolgus monkeys from day 20 to 50 of gestation (period of organogenesis). The animals received 0, 20 or 100 mg/kg once weekly (i.e. a total of 5 administrations). Foetuses were delivered via caesarean section and euthanized on day 100 ± 1 of gestation.
There were no unscheduled deaths during the study. The incidence of prenatal loss was also unaffected by treatment. No treatment-related effect was detected in pregnant females with respect to clinical observations, weight or haematology. A significant and almost complete depletion of peripheral CD20/CD40-positive B-cells was observed in all ofatumumab-treated dams at day 25 post coitum (the

earliest time point evaluated after dosing). Following the recovery period, the depletion of B-cells was still present.
There were no ofatumumab-related changes in fetal body weights or dimensions, placental weights, or foetal abnormalities. A reduction in spleen weights was observed for foetuses in the 100 mg/kg dose group, but no correlating microscopic changes were noted. A decrease in B cells was observed in foetal cord blood collected from the foetuses of animals in both dose groups, and B cell-depletion was noted in splenic tissue from the foetuses.
Ofatumumab was present in maternal plasma up to Gestation Day 100 and was also detectable in 17 of 20 umbilical cord blood samples from the foetuses, confirming exposure to ofatumumab during late pregnancy (GD100). The mean plasma AUC value for maternal ofatumumab exposure was 1646000 µg*h/mL. Antibodies against ofatumumab were detected in 3 of 24 female monkeys (2 of 12 animals dosed at 20 mg/kg and 1 of 12 animals dosed at 100 mg/kg). Moreover, anti-ofatumumab antibodies were detected in 3 of 24 dams and in 3 of 20 fetal cord blood samples.

- Toxicokinetic data

The systemic exposure ratios for ofatumumab in cynomolgus monkey and humans are presented in the following table.

Table 6: Systemic Exposure Ratios for Ofatumumab in Monkeys and Humans

Study Type Report No. (Study No.)	Dosage (mg/kg)	Sex	$AUC_{0-\infty}$ (µg.h/mL)		C_{max} (µg/mL)		Ratio of Animal to Human Exposure	
			Day 1[a,b]	End of Study[c]	Day 1[b]	End of Study[b]	$AUC_{0-\infty}$	C_{max}
Monkey 4 week IV	20	M	116657	336406	791	1031	0.50	0.70
		F	55707	249205	604	1246	0.37	0.84
	100	M	324771	1754363	4702	10595	2.6	7.1
		F	470349	2205818	5570	11535	3.3	7.8
Monkey 7 month IV	20	M	73950	202732	531	697	0.30	0.47
		F	62783	128482	462	567	0.19	0.38
	100	M	402347	903407	2699	3110	1.3	2.1
		F	423185	809700	2676	3460	1.2	2.3
Monkey cycled IV	20	M	20096	4144	481	504	0.006	0.34
		F	66864	134602	672	701	0.2	0.47
	100	M	462688	257645	9909	2812	0.38	1.9
		F	590493	273298	12363	4071	0.4	2.7
Monkey embryofetal development	20	F	107300	212800	628	760	0.3	0.51
	100	F	536600	1646000	3100	5680	2.4	3.8
Human (HuMax-CD20-406)	2000 mg		NA	674463[d]	NA	1482[d]	NA	NA

Notes:
a = Except for the monkey cycled study which used Day 15.
b = $AUC_{0-\infty}$ and C_{max} values based on mean of main study and recovery animals where applicable.
c = $AUC_{0-\infty}$ values based on mean of recovery animals where applicable.
d = $AUC_{0-\infty}$ and C_{max} are the highest mean values observed in the clinical programme and were obtained after the eighth weekly infusion in Study HuMax-CD20-406.
IV = Intravenous; NA =Not applicable

- Local tolerance

No separate studies assessing local tolerance to ofatumumab were submitted as macroscopic or microscopic examinations of the injection sites were conducted following intravenous and subcutaneous administration of up to 100 mg/kg of ofatumumab to cynomolgus monkeys as part of the repeat dose toxicology studies. No macroscopic of microscopic findings of local irritation were noted in any of these investigations.

- Other toxicity studies

Immunotoxicity. The activation and release of inflammatory and coagulation parameters was investigated following administration of ofatumumab to cynomolgus monkeys (GMB-3001-013). The blood samples used in this study were derived from the pilot dose-ranging toxicity study, in which cynomolgus monkeys (1 male or female per group) were given ofatumumab by intravenous infusion (30 minutes) at doses of 25, 50, 75 or 100 mg/kg on Day 1 (23315). Serum samples were taken prior to dosing and at 15 minutes, 30 minutes, 2 hours and 4 hours post-dose, and the levels of complement factors C3b/c and C4b/c, thrombin-anti-thrombin III complex (TAT), plasmin α2-anti-plasmin complex (PAP), interleukin-6 (IL-6), elastase-α1-antitrypsin complex (HNE/ATc, a marker for neutrophil degranulation), and tumour necrosis factor alpha (TNFα) were determined using ELISA assays.
An increase of C3b/c (activated form of C3) was noted in all monkeys at 15 minutes post-dose, but 2 to 4 hours later the level of C3b/c had decreased. C4b/c (activated form of C4) showed a similar increase following ofatumumab administration. TAT complex levels in the circulation increased in all monkeys at 15 minutes post-dose, but the increase was variable with the monkey treated at 50 mg/kg showing the greatest increase. PAP levels in the circulation increased in all animals but in 3 out of 4 animals, plasmin formation was transient. Neutrophil degranulation was observed in 3 of 4 animals, but the increase was very mild in the 25 mg/kg dose group. IL-6, one of the cytokines that increases most in humans under inflammatory conditions, appeared to follow a biphasic course, with the early increase possibly related to complement activation and the later increase to cellular activation. TNFα levels were measured but were below the limit of detection. These results suggest that administration of ofatumumab may be associated with cytokine release syndrome. However, the severity of this syndrome in the monkeys was limited and clinical manifestations were not observed.

Immunogenicity. The formation of anti-ofatumumab antibodies was investigated as part of the repeat dose toxicity studies and the embryofetal development study by the use of two ELISA assays. ADAs were detected in all of the studies where analyses were undertaken following both intravenous and subcutaneous dosing (data not shown, see discussion of non-clinical aspects).

Ecotoxicity/environmental risk assessment

No environmental risk assessment was submitted (see discussion of non-clinical aspects).

Discussion on the non-clinical aspects

In vitro binding studies indicated the specific binding of ofatumumab to CD20 and that ofatumumab binds to a CD20 epitope somewhat overlapping and somewhat distinct from that of rituximab.

Further in vitro experiments investigated the mechanisms of ofatumumab cytotoxicity and suggested that CDC and ADCC, but not apoptosis, mediate the cytotoxic effect. Generation of complement activation products (anaphylotoxins) and translocation of CD20 into lipid rafts, but not homotypic aggregation of B-cell line cells, were induced by ofatumumab. In vivo, ofatumumab was able to protect SCID mice from implanted B-cell line tumours.
Since ofatumumab is a biotechnology-derived product with highly specific receptor targeting, it was considered sufficient that safety pharmacology endpoints were evaluated as part of the toxicology studies.

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 ofatumumab (see Discussion on Clinical Safety).

It has been described in the literature that statin (HMGCoA reductase inhibitor) treatment decreases CD20 epitope accessibility due to cholesterol depletion and this can lead to reduced binding and activity of ofatumumab [Golab, 2007]. Monitoring of the potential for drug-drug interactions between ofatumumab and anti-hypercholesterolemic drugs such as statins is included in the Risk Management Plan (See section 3.5 Pharmacovigilance).

An ELISA was used for the quantification of ofatumumab in monkey serum and plasma. For the detection of anti-ofatumumab antibodies in monkeys administered with ofatumumab, several approaches were undertaken. Two ELISA methods were used in most studies; the F(ab')2 binding antibody preclinical assay and the whole ofatumumab binding antibody preclinical assay. For both assays several concerns were raised regarding the design and the validation of the methods, especially since the presence of ofatumumab seems to interfere with the detection of anti-ofatumumab antibodies even at low concentrations. The applicant did not provide adequate answers to these concerns. Thus, the results from the toxicity studies monitoring anti-ofatumumab antibodies and serum levels of ofatumumab should be interpreted with caution.

In accordance with the ICH S6 guideline, the lack of metabolism and excretion studies is acceptable. The lack of distribution studies is justified by 1) the fact that ofatumumab targets the CD20 molecule, whose tissue expression is characterized 2) the fact that toxicokinetic data indicate limited distribution beyond the plasma compartment and 3) the human cross-reactivity study indicates no potential for off-target binding.

The lack of single-dose toxicity studies is acceptable in accordance with the concept paper on single dose/acute toxicity (EMEA/CHMP/SWP/302413/2008).

In repeat-dose toxicity studies, haemolytic anaemia developed in cynomolgus monkeys, leading to unscheduled deaths. The Applicant ascribed the development of the haemolytic anaemia to formation of anti-ofatumumab antibodies, but this remains speculative and a potential clinical relevance cannot be excluded. Haemolytic anaemia has been included as a potential risk in the RMP.

Although no thromboembolic events have been reported in the monkey studies, increased thrombin-anti-thrombin / plasmin-anti-plasmin ratios were observed, indicating that ofatumumab may constitute a risk for thromboembolic complications. However, a plausible explanation for the observed effects is a mild, infusion related response without effects on the coagulation system, as apparent by unchanged platelet counts. The data presented do not indicate an increased risk of procoagulating events following the use of ofatumumab. Since thromboembolic events will be monitored through routine pharmacovigilance activities, and since cardiovascular effects are an identified risk of ofatumumab (included in the proposed Risk Management Plan), this is considered acceptable.

The lack of genotoxicity studies is considered justified according to ICH S6, while the Applicant justified the lack of carcinogenicity studies by claiming that 1) ofatumumab is not expected to interact directly with DNA or other chromosomal material, 2) ofatumumab is not pharmacologically active in rodents and so the standard carcinogenicity bioassays are unsuitable, 3) there is no scientific evidence to suggest that depletion of B cells by any other anti-CD20 therapeutics leads to cancer, and 4) populations of NK cells, which are central to immune surveillance, did not change during pivotal repeat dose studies of up to 7 months duration. The justification for not submitting carcinogenicity studies was considered acceptable and the lack of genotoxicity and carcinogenicity data is described in section 5.3 of the SPC.

Considering that the median survival of CLL patients is 10 years, an evaluation of fertility as well as pre- and post-natal development could theoretically be relevant. However, it was considered acceptable that fertility and pre- and post natal development studies were not submitted due to 1) the lack of ofatumumab off-target binding, 2) the lack of CD20 expression in reproductive tissues, 3) the

fact that antibodies does not appear to be able to cross the healthy blood-testis barrier, 4) the lack of a role for B-cells in organ system development, 5) the age of the patient population (median age of 65 to 70 years old), and 6) the lack of ofatumumab affinity for CD20 in rodents and rabbits. The lack of animal (and human) fertility data is reflected in section 4.6 of the SPC.

No maternal toxicity, developmental toxicity or teratogenicity was observed following IV administration of up to 100 mg/kg ofatumumab to pregnant cynomolgus monkeys once weekly from day 20 to 50 of gestation. The mean maternal plasma exposure corresponds to 2.4-fold the clinical exposure following administration of 2 gram ofatumumab. As expected, ofatumumab induced nearly complete B-cell depletion in the pregnant females. Moreover, a decrease in B cells was observed in foetal cord blood collected from the foetuses of animals in both dose groups, and B cell-depletion was noted in splenic tissue from the foetuses. These data and relevant warnings on pregnancy (and lactation) are included in sections 4.6 and 5.3 of the SPC.

The results of the immunogenicity analyses should be interpreted with caution due to limitations in the detection methods (ELISA assays). Moreover, it is agreed that formation of primate anti-human antibodies (PAHAs) is not predictive of the immunogenicity of the human antibody in patients. As mentioned above, the potential of PAHAs to have induced the haemolytic anaemia observed in the repeat-dose dose toxicity studies remains speculative, but monitoring of haemolytic anaemia has been included in the Risk Management Plan.

As a protein, ofatumumab is exempted under current guidance from the need for a detailed environmental assessment.

2.4 Clinical aspects

Introduction

The clinical documentation submitted in support of this application comprises primarily data from a pre-planned interim analysis of a single arm, open-label, multi-center ongoing pivotal study, Hx-CD20-406. Additional supportive evidence is provided by a phase I/II study, Hx-CD20-402.
The proposed indication was: 'treatment of patients with chronic lymphocytic leukaemia (CLL) who have failed therapy with a fludarabine containing regimen and have failed therapy with, or are inappropriate for, an alemtuzumab containing regimen'. The finally approved indication is: 'treatment of chronic lymphocytic leukaemia (CLL) in patients refractory to fludarabine and alemtuzumab'. 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. Dosing recommendations on first and second infusions, subsequent infusions, dose modification, reinitiation of therapy, and recommendations about special populations are described in the SPC (see Section 4.2).
A paediatric class waiver for CLL was issued on 14 July 2008 - confirmation number EMEA/18/2008
Arzerra is not recommended for use in children below 18 years due to insufficient data on safety and/or efficacy.
No studies in special populations, such as elderly, males/females or ethnic groups were submitted.

GCP

The pivotal study HX-CD20-406 and the supportive study HX-CD20-402 are stated to have been conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.

Pharmacokinetics

Pharmacokinetics were assessed in the course of the efficacy/safety studies supporting the current application as well as the development of ofatumumab in other indications. A total of six clinical studies with pharmacokinetics objectives and endpoints were submitted, with 433 subject receiving ofatumumab (Table 7). Moreover, a population pharmacokinetic/pharmacodynamic analysis and a

cross-study analysis of ofatumumab pharmacokinetics were made using data from studies 001, 402, 403 Part A and B and 406. In the former analysis, data from study 406 were only available for 53 patients, compared to 129 patients in the latter analysis.

Table 7: Listing of all clinical pharmacokinetic studies

Study ID	Objectives of the study	Study design	Dosage regimen	Number of subjects receiving ofatumumab	Diagnosis
Hx-CD20-001	Safety, efficacy, PK	Phase I/II, open-label, dose-escalating, multiple dose	Ofatumumab 300, 500, 700, or 1000 mg once weekly for four weeks	40	Follicular lymphoma (FL) grade I-II
Hx-CD20-402	Safety, efficacy, PK	Phase I/II, open-label, dose-escalating, multiple dose	A: Ofatumumab 100 mg first week, then 500 mg once weekly for four weeks B:300 mg/1000 mg C:500 mg/2000 mg	33	Relapsed or refractory CLL
Hx-CD20-403 Part A	Efficacy, safety, PK, host immune response	Phase I/II, double-blind, randomized, placebo-controlled, dose-escalating	Ofatumumab 300, 700, 1000 mg or placebo, two infusions two weeks apart	32	Rheumatoid arthritis (RA)
Hx-CD20-403 Part B (ongoing study)	Efficacy, PK, safety, host immune response	Phase II, double-blind, randomized, placebo-controlled, dose-escalating (interim analysis)	Ofatumumab 300, 700, 1000 mg or placebo, two infusions two weeks apart	169	RA
Hx-CD20-406 (ongoing study)	Efficacy, safety, host immune response, PK	Phase III, Open-label, single arm (interim analysis)	Ofatumumab 300 mg first week, then 2000 mg once weekly for seven weeks, then 2000 mg every four weeks for 16 weeks	154	CLL
Hx-CD20-408 (terminated prematurely due to SAEs)	Safety, efficacy, PK	Phase I/II, double-blind, randomized, placebo-controlled	Ofatumumab 100 mg day 0 (or 10 mg day 0 and 90 mg day 1) and 1000 mg week 3	5	Chronic obstructive pulmonary disease

An enzyme-linked immunosorbent assay (ELISA), a so called sandwich immuno-assay, was used for the quantification of ofatumumab in human serum. Several approaches were used to establish a method to monitor the development of anti-ofatumumab antibodies in patients, but only two ELISA assays were used to test samples from the clinical trials. The difference between the two is the specificity of the anti-ofatumubab antibody molecule detected. In the so called F(ab')2 binding antibody clinical assay, only antibodies against the antigen-binding region or F(ab')2 fragment of ofatumumab are detected, while the whole ofatumumab binding antibody clinical assay detects antibodies against any portion of the ofatumumab molecule. The latter was used in the pivotal efficacy study Hx-CD20-406.

- Absorption

Ofatumumab is administered by intravenous infusion. Maximum ofatumumab serum concentrations were generally observed at or shortly after the end of the infusion. In the pivotal efficacy trial (Study Hx-CD20-406), 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 had a small volume of distribution (geometric mean Vss values ranged from 1.7 to 5.1 L across studies, dose levels, and infusion number. This is consistent with distribution largely in the systemic circulation.

- Elimination

Ofatumumab is eliminated in two ways: a target-independent route as with 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 t½ values were significantly larger after later infusions than after the initial infusion.
Clearance and half-life values from the two studies in subjects with CLL are presented in Table 8. Half-life values increased from 1.3 days after the first infusion to 15.8 days after the eighth infusion and 13.9 days after the twelfth infusion.

Table 8: Clearance and Half-life Values for ofatumumab after infusion in subjects with CLL (Study Hx-CD20-402 and Study Hx-CD20-406)

Infusion Number	n	Clearance (mL/h)	Half-Life (h)
1[a] (500 mg)	27	63.7 (4.3-1122)	31.3 (3.8-143)
4[a] (2000 mg)	24	8.5 (1.8-41.5)	276 (55-735)
8[b] (2000 mg)	127	9.5 (2.2-23.7)	379 (212-1477)
12[b] (2000 mg)	77	10.1 (3.3-23.6)	334 (217-701)

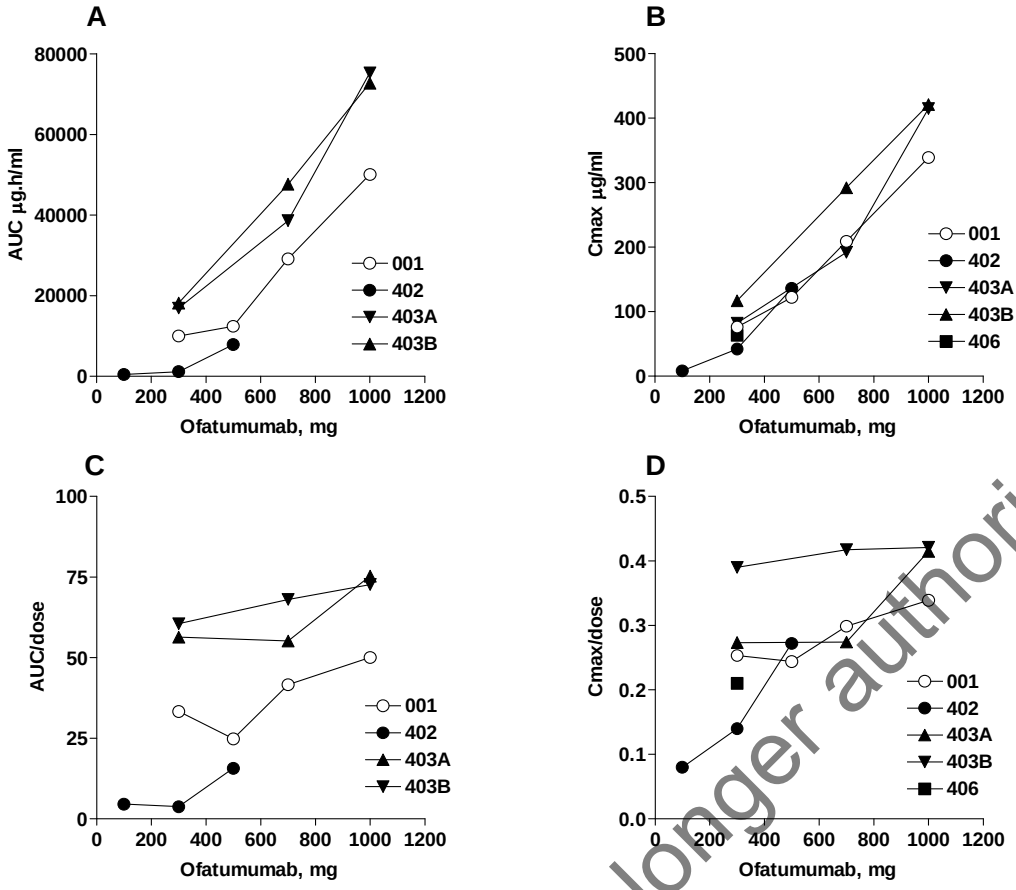
Data are presented as geometric mean (minimum-maximum).
a. Study Hx-CD20-402
b. Study Hx-CD20-406

Ofatumumab is a protein for which the expected metabolic pathway is degradation to small peptides and individual amino acids by ubiquitous proteolytic enzymes [Dempster, 2000]. The non-target mediated clearance of ofatumumab is likely to be largely mediated by proteolysis.

- Dose proportionality and time dependencies

Mean AUC(0-∞) and Cmax after the first dose of ofatumumab, as well as mean AUC(0-∞) /dose and mean Cmax/dose, plotted against dose, is presented in Figure 1. As seen in the figure, mean Cmax and AUC(0-∞) values for ofatumumab after the first dose seem to increase by dose more than expected in most studies.

Figure 1: Mean AUC0-∞ (A) and mean Cmax (B) of ofatumumab, and mean AUC0-∞/dose (C) and mean Cmax/dose (D), following first dose from studies 001, 402, 403A, 403B and 406



During repeated weekly infusions, ofatumumab AUC(0-∞) and Cmax values increased more than the expected accumulation based on first infusion data, as also described under 'Absorption' above.

- Special populations

No studies specifically addressing pharmacokinetics in special populations were submitted. However, pharmacokinetic differences in special populations were explored in the population pharmacokinetic/ pharmacodynamic analysis and in the cross-study analysis of ofatumumab pharmacokinetics based on data from studies 001, 402, 403 Part A and B and 406. In these analyses, the effect of body measures (weight, body surface area) on pharmacokinetic parameters was modest (data not shown).

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.

Gender had a modest effect (14-25%) 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.

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).

The potential influence of race was not assessed.

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.

- Pharmacokinetic interaction studies

No studies were submitted (see discussion on clinical pharmacology).

- Pharmacokinetics using human biomaterials

No studies were submitted.

Pharmacodynamics

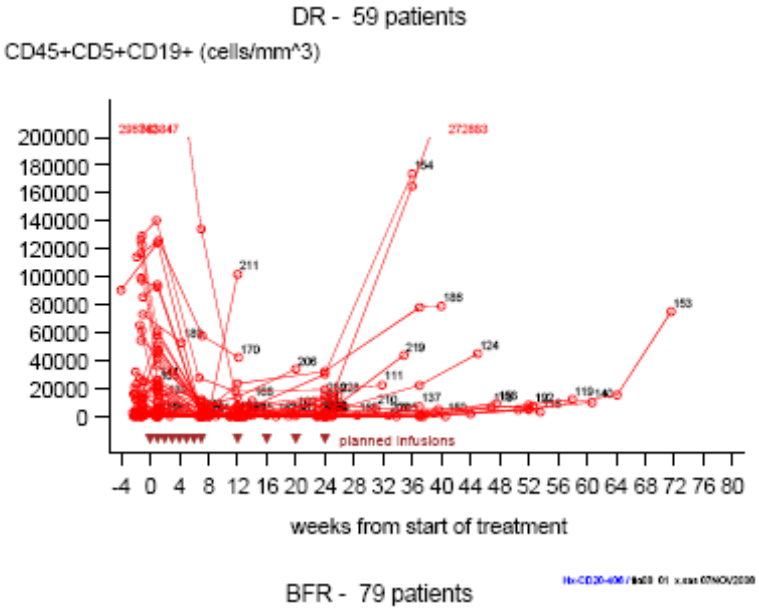
- Mechanism of action

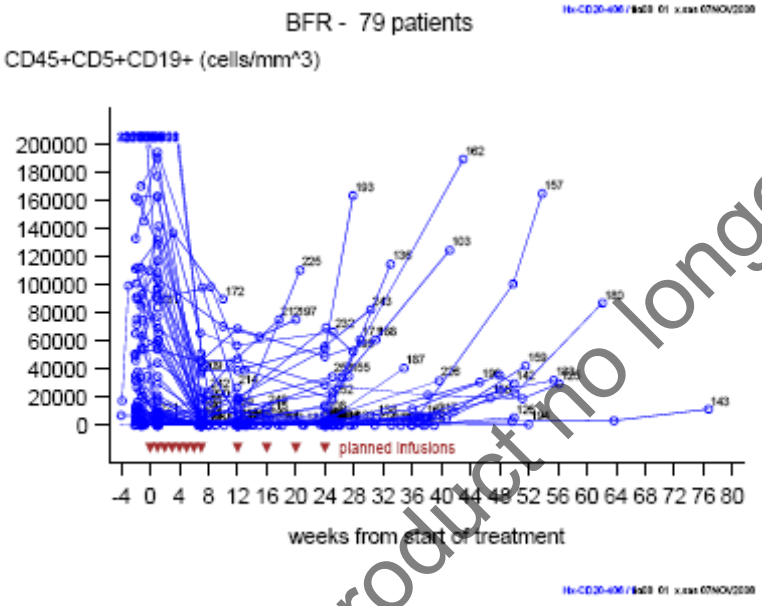
No clinical studies addressing the mechanism of ofatumumab action were submitted.

- Primary and Secondary pharmacology

Primary and secondary pharmacology parameters were measured in the course of the efficacy/safety/PK studies which are summarised in Table 7. In the following, results from the pivotal CLL study (Hx-CD20-406) are described, but references are also made to studies, 001, 402, 403A and 403B.
CD19+ B-cell counts were determined before, during, and after ofatumumab therapy to assess B-cell depletion. The B-cell surface antigen CD19 was used as a marker for CD20, because the two antigens have a similar expression profile on B cells and the presence of an anti-CD20 antibody binding to CD20+ cells can interfere with the flow cytometric measurement of CD20+ 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 (see Figure 2). 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.

Figure 2: $CD45^{+}CD5^{+}CD19^{+}$ cell counts over time in DR and BFR populations of pivotal study Hx-CD20-406





In general, serum IgG and IgA concentrations were stable during the studies, and serum IgM concentrations declined, consistent with long-term B-cell depletion; in Study Hx-CD20-406 (CLL), there appeared to be a modest decrease in mean IgG concentrations from baseline to Week 16. No clinically significant changes in serum complement levels, T-cell counts, or NK-cell counts were observed in the studies (data not shown).

There did not appear to be a relationship between ofatumumab dose and the incidence of infection across the studies. In the placebo-controlled studies of ofatumumab in subjects with RA (Study 403 Part A and Part B), similar infection rates were observed in placebo subjects and in subjects receiving ofatumumab at all three active dose levels. In subjects with CLL, no relationship was seen between ofatumumab pharmacokinetics and occurrence of infections in study 402. In study 406 (CLL) longer time to first major infection (defined as infections requiring at least 48 h hospitalization that occurred during or within four weeks of completing treatment) was correlated with higher AUC(0-∞) and Cmin values at the eighth infusion (data not shown).

Anti-ofatumumab antibodies were detected in only two samples out of the 274 subjects who received ofatumumab in studies 001, 402, 403 Part A and B. However, conclusions regarding these results are limited because the assay used to measure anti-ofatumumab antibodies was not capable of detecting antibodies to all ofatumumab domains (F(ab')2 binding antibody clinical assay). An assay which can detect antibodies to any epitope on ofatumumab was subsequently developed and is being used to test for anti-ofatumumab antibodies in ongoing study 406. In the 46 subjects who received at least eight infusions and for whom data have been generated at ofatumumab concentrations <500 ng/ml (33 of whom received all twelve infusions), there have been no positive samples (see SPC section 5.1). The

positive result in the subject in study 403 Part B was not confirmed using the whole ofatumumab binding antibody clinical assay.
In study 402 (CLL), statistically significant associations were seen between objective response and ofatumumab exposure after the fourth infusion (241% higher AUC, 43% higher Cmax, and 94% higher Cmin 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 (data not shown). In study 406 (CLL), ofatumumab exposure was higher at the eighth infusion (last weekly infusion) in subjects who responded (37% higher AUC, 23% higher Cmax, and 91% higher Cmin 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. Longer progression-free survival was associated with higher exposure (AUC, Cmax, and Cmin values) at both the eighth and twelfth infusions (data not shown). Finally, there was little apparent relationship between differences in ofatumumab exposure and clinical response in study 001 (FL) or study 403 Part A (RA). In study 403 Part B (RA), subjects who responded at Week 24 had higher ofatumumab exposures (data not shown).

Discussion on clinical pharmacological aspects

As also mentioned in the discussion of non-clinical aspects, several concerns were raised concerning the design and validation of the ELISA used to measure ofatumumab and the two ELISA methods used to detect and quantify anti-ofatumumab antibodies. These concerns have not been fully resolved by the applicant's responses. Anti-ofatumumab antibodies in ongoing and future studies should solely be monitored with the so called whole ofatumumab binding assay that seems capable of giving a more correct picture of the production of antibodies when patients are administered ofatumumab.

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.

No significant effect of impaired renal function, gender, age, and body measures (height, weight, body surface area) on pharmacokinetic parameters was found. The potential influence of impaired hepatic function and race was not assessed. Missing pharmacokinetic information in children and adolescents, in severe renal impairment and in hepatic impairment is reflected in the SPC.

No drug interaction studies were submitted. As stated in the EMEA 'Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins" (EMEA/CHMP/89249/2004): 'Interaction studies should be considered (…) when suppression of the immunological system is likely.' An example of the latter is methotrexate, which significantly decreases the clearance of co-administered antibodies.' The potential interaction with methotrexate will be investigated by the Applicant in ongoing clinical studies.

CD19+ B-cell counts were used to assess B-cell depletion, the B-cell surface antigen CD19 being considered as a marker for CD20. In the dose-finding study in patients with CLL (Hx-CD20-402), there were only three patients in each of the two lower dose groups, thus the evidence supporting the selected dose of the applied posology seems weak.

There was a significant drop in the IgM concentrations and a slight decrease in IgG concentrations after initiation of ofatumumab therapy. However, the changes did not result in increased risk of infections. The changes observed therefore do not give rise to immediate concern. However, these findings and plans to monitor this potential side effect prospectively have been included in the risk management plan.

The overall immunogenicity risk assessment for ofatumumab seems to be low. However, conclusions regarding these results are limited because the assay used to measure anti-ofatumumab antibodies in most studies was restricted to detection of antibodies of just one isotype (IgG1) and was not capable of detecting antibodies to CH2 and CH3 domains. Immunogenicity data from clinical trials are described in section 5.1 of the SPC. Immunogenicity is also listed as an identified risk in the Risk Management Plan and actions to monitor the risk of treatment failure and risk of adverse reactions (e.g. anaphylactic reactions) based on immunogenicity are described.

The relationship between plasma ofatumumab concentration and pharmacodynamic effect is complex and its interpretation is not straightforward. Higher exposures may result in more tumour reduction; however, lower or reduced tumour burden will result in reduced clearance and therefore higher exposures.

Clinical efficacy

The primary evidence of the efficacy of ofatumumab is provided by the results of the interim analysis of the ongoing pivotal study Hx-CD20-406. In addition, efficacy results from one completed supportive study, Hx-CD20-402 are provided. The number of subjects treated in these studies is summarized in the table below.

Table 9: Summary of ofatumumab efficacy studies

Study	Study Population Subjects Enrolled	Study Phase Design Status	Ofatumumab Dosage and Regimen
Hx-CD20-406	Subjects with CLL refractory to fludarabine and alemtuzumab, or refractory to fludarabine and inappropriate for alemtuzumab due to bulky lymphadenopathy N=154, as of Interim Analysis data cut-off 19 May 2008	Phase II Open-label Single arm Ongoing	All subjects: 300mg × 1 2000mg × 7 (weekly) 2000mg × 4 (every 4 weeks)
Hx-CD20-402	Relapsed/refractory CLL N=33	Phase I/II Open-label Dose-escalation Completed	Group A: 100mg×1 500mg×3 (weekly) Group B: 300mg×1 1000mg×3 (weekly) Group C: 500mg×1 2000mg×3 (weekly)

- Dose response study

Thirty-three subjects were enrolled into the Hx-CD20-402 dose-escalation study. Patients received 4 weekly infusions of ofatumumab:
Group A (n=3) received a first infusion of 100 mg, and 3 subsequent infusions of 500 mg
Group B (n=3) received a first infusion of 300 mg, and 3 subsequent infusions of 1000 mg
Group C (n=27) received a first infusion of 500 mg, and 3 subsequent infusions of 2000 mg.
The absolute doses applied in the current study were selected based on previous studies with rituximab in FL and CLL, and on previous experience with ofatumumab in FL patients. One subject in Group C was withdrawn from treatment after the first infusion due to an SAE of cytolytic hepatitis (elevation of transaminases, maximal CTC Grade 3), considered related to study medication. Subjects had a

median age of 61 years, ranging from 27 to 82 years, and 42% of subjects were female. All subjects were Caucasian. Most subjects were in the low or intermediate risk stage of their disease with Rai Stage I or II (39% and 45%), or Binet Stage A or B (21% and 67%), respectively. No subjects in Group A or Group B had constitutional symptoms. In Group C, 6% of subjects experienced extreme fatigue and 15% experienced night sweats. The median number of prior CLL therapies was 4 in Group A, 3 in Group B, and 2 in Group C.

Table 10: Summary of primary and secondary efficacy endpoints, study Hx-CD20-402

Efficacy Endpoint	Group A (n=3)	Group B (n=3)	Group C (n=27)
Primary Endpoint			
RR (%)by Week 24 (95% CI)	33 (1, 91)	0 (0)	48 (30, 70)
Secondary Endpoints	Median, months		
RR by Week 27, %	33	0	48
Duration of Response	3.4	n/a	4.4
Progression-free Survival	2.6	2.5	4.4
Time to Next CLL Treatment	5.3	3.2	12.1

Rapid, efficient, and sustained depletion of malignant and normal B cells was observed in all subjects in Group C during the study period. The median time to progression in Group C was 4.4 months in the full analysis population and 5.3 months in the subgroup of responders. The duration of response was 4.4 months, and the time to next CLL therapy was 12.1 months.
Based on the results of this study a dose of 2000 mg was chosen for the pivotal study. Higher doses of ofatumumab were not tested in this or any subsequent clinical study nor were any other phase I/II studies submitted in support of the choice of dose as well as the frequency and duration of treatment (see also section on supportive studies).

- Main study

Hx-CD20-406

This is an ongoing, single arm, open-label, multicentre (41 sites in 10 countries) 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.

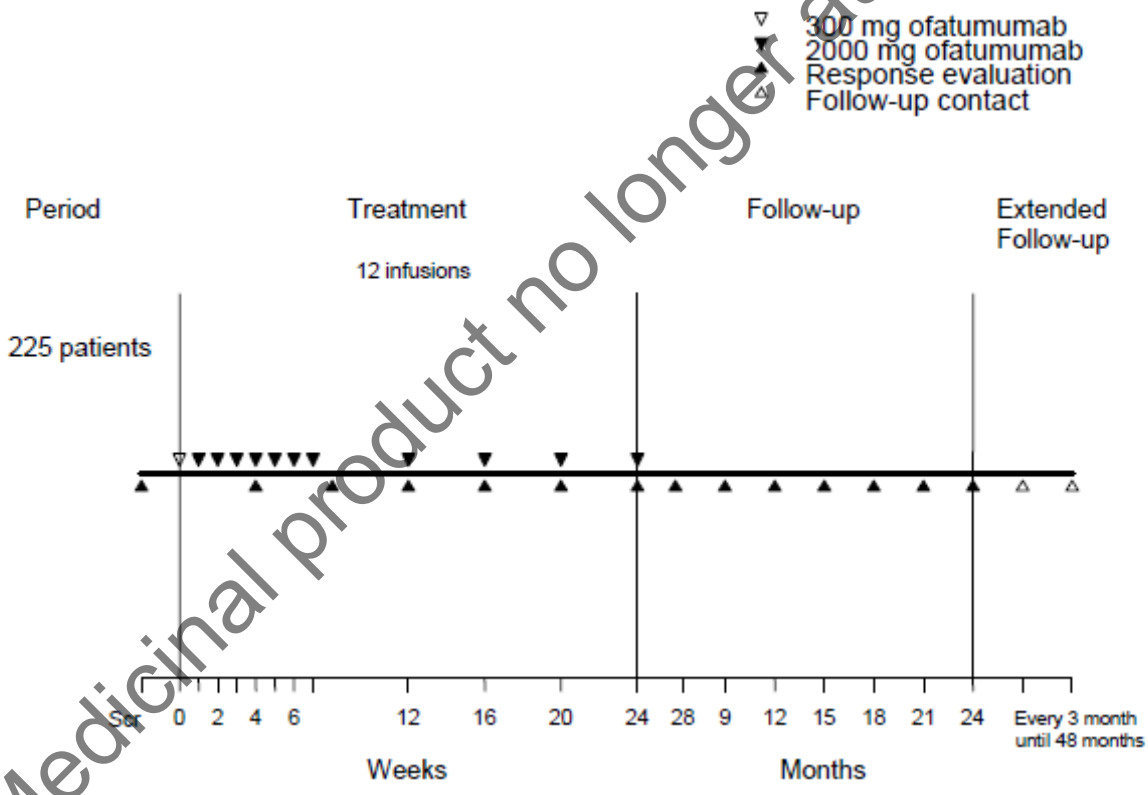
METHODS

Study Participants
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 (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 >5 cm (bulky fludarabine refractory, BFR).
Main inclusion criteria were: Tumour cell phenotype consistent with B-CLL (CD5+CD20+CD23+), patients with active B-CLL and with an indication for treatment defined as presenting one of the conditions defined by the NCIWG criteria (evidence of progressive marrow failure, massive or progressive splenomegaly or lymphadenopathy, progressive lymphocytosis, weight loss/fever/night sweats), refractory to one fludarabine-containing treatment regimen (failure to achieve at least PR or disease progression while on treatment or disease progression in responders within 6 months of treatment), failing at least one alemtuzumab-containing treatment regimen defined as either refractory to one alemtuzumab-containing treatment regimen (as above) or considered inappropriate for treatment with alemtuzumab due to lymphadenopathy with at least one lymph node >5 cm, ECOG Performance Status of 0-2, life expectancy of at least 6 months.

Main exclusion criteria included various concomitant or prior therapies, other malignancies or transformation of B-CLL to more aggressive malignancies, CNS involvement of B-CLL, other significant comorbidities, poor performance status or short life expectancy.
The trial population included 3 populations established by Independent Review Committee (IRC) review, which were analyzed 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, i.e. 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.

Treatments
The intended treatment consisted of 8 weekly infusions of ofatumumab (first dose: 300 mg; second – eighth dose: 2000 mg) followed by 4 monthly infusions of ofatumumab (ninth – 12th 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). The trial design is shown in Figure 3 below.

Figure 3: Ofatumumab treatment schedule, study Hx-CD20-406



Objectives
The primary objective of the pivotal trial was to evaluate the efficacy of ofatumumab in patients with B-cell chronic lymphocytic leukaemia (CLL) who had failed fludarabine and alemtuzumab. Secondary objectives were to determine the safety of ofatumumab, the host immune response to ofatumumab and the pharmacokinetic profile of ofatumumab.

Outcomes/endpoints
The primary efficacy endpoint of this study was response rate (RR) measured over a 24 week period from the start of treatment, as determined by the IRC. Clinical assessments were done by investigators, but response evaluations and classification of patients into DR, BFR and Other (the Other group did not meet either the DR or BFR classification criteria) were done centrally by an IRC based on evaluations of CRF data on lymph nodes and organomegaly (physical examination), relevant

laboratory data, constitutional symptoms, and medical history. In case of a possible CR, a CT scan and a bone marrow examination were to be performed 8 weeks after a patient fulfilled the NCIWG 1996 guidelines requirements of a CR for the first time. CT scans were required only for the documentation of suspected CR, otherwise, CT scans were not required nor done to confirm PR. Subjects not meeting the criteria for CR, PR or PD were considered to have Stable Disease (SD). Transformation to a more aggressive histology, including Richter's syndrome or prolymphocytic leukaemia with >55% prolymphocytes, was considered progressive disease.
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 (56 days). The definitions of each response category are shown in Table 11.

Table 11: Response criteria, NCIWG 1996 [Cheson, 1996]

Parameter	Complete Remission	Partial Remission	Progressive Disease
Lymphocytes	<4.0 x 10^9/L	≥50% reduction from baseline	≥50% increase to at least 5.0 x 10^9/L
Lymphadenopathy	Absence by physical exam	≥50% reduction (physical examination)	≥50% increase for at least 2 weeks of 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	≥1.5 x 10^9/L	≥1.5 x 10^9/L or 50% improvement from baseline	Not defined
Platelets	>100 x 10^9/L	>100 x 10^9/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 to be met for at least 2 months. If persistent nodules in bone marrow = nPR**	**Meets criteria for first 3 for at least 2 months, and at least 1 other of above to be met**	**At least 1 of above to be met, or transformation to more aggressive histology**

The secondary efficacy endpoints included: duration of response, progression-free survival, time to next CLL therapy, overall survival, reduction in tumour size, CD5+CD19+, CD5+CD20+ in peripheral blood, and expressions of CD19, CD20, CD55, and CD59 on CD45+CD5+ cells, progress of constitutional symptoms (night sweats, weight loss, fever and extreme fatigue), resolution of lymphadenopathy and organomegaly, improvement in ECOG Performance Status, haemoglobin, thrombocytopenia and neutropenia and number of blood transfusions. Another secondary endpoint was evaluation of the prognostic value of fluorescent in-situ hybridization (FISH) parameters, CD38+, VH mutational status, Fc receptor polymorphisms, β2 microglobulin, thymidine kinase, circulating CD20 and antigen density. At the time of the interim analysis, these results were not reported.

Sample size
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 [Tam, 2007], thus 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.

Randomisation
No randomisation was performed as this is an open-label trial.

Blinding (masking)
The pivotal study was a one-arm study with no control arm and blinding was not attempted.

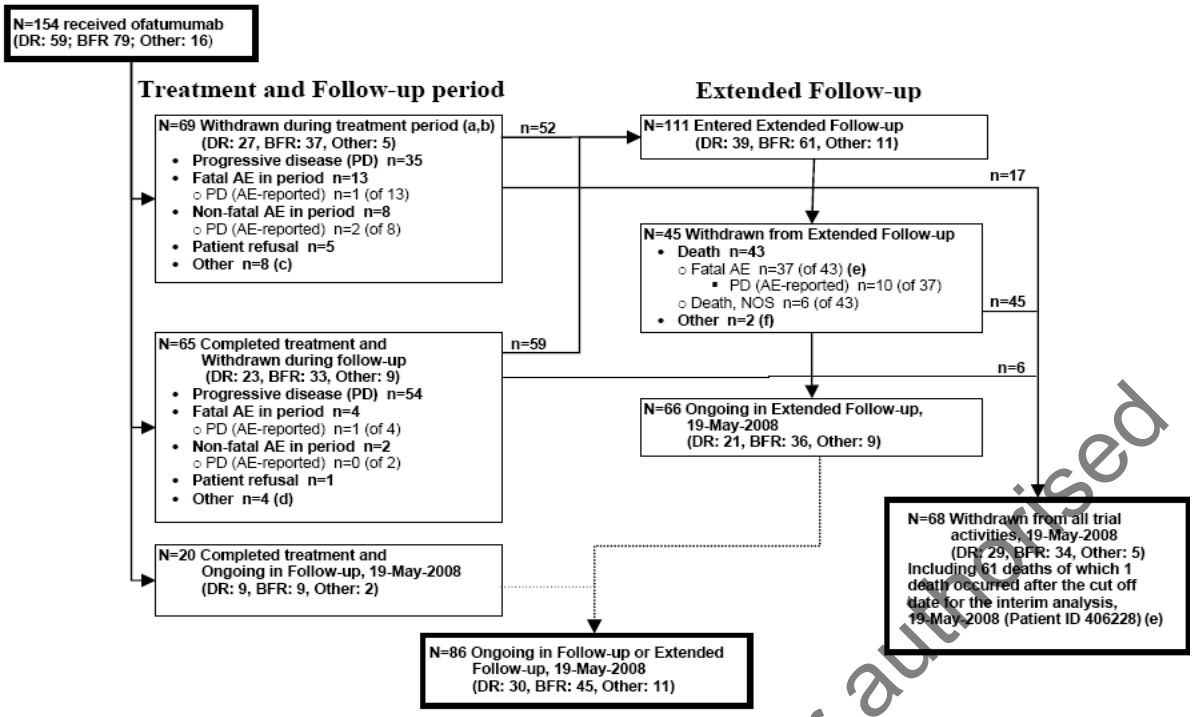
Statistical methods
The full analysis set (FAS) included all patients who had been exposed to trial drug irrespective of their compliance to the planned course of treatment. This was the primary analysis population used for evaluation of all endpoints and all 3 population subgroups. The per protocol (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, i.e. a patient could be included in the PP population but the data from a certain visit excluded.
Standard statistical analyses for each of the trial endpoints were used.
The patients still on trial at week 12 (landmark time) were separated into 2 response categories according to whether they responded before that time. An analysis was performed (landmark analysis) for which probability estimates and statistical tests were conditional on the response status of patients at the landmark time. The null hypothesis that 'survival from landmark does not depend on response status at landmark' versus the alternative that 'subsequent survival does depend on land-mark response status' was tested using the two-sided logrank test.

At the time that the primary efficacy endpoint data from the estimated 66 DR subjects were available, this triggered the pre-defined interim analysis of the IRC assessed response rates. The 66 DR subject trigger was based upon sponsor assessment of eligibility information and status. The IRC confirmed eligibility of 59 subjects in the DR group for this interim analysis, and ultimately reallocated 7 subjects from the DR to the BFR group. An independent data monitoring committee (DMC) reviewed the IRC assessed response rate analysis. In addition, sponsor generated data queries resulted in two reconsensus meetings of the IRC members to verify the final interim analysis response rates. The IRC was only instructed to downgrade responses to non-responses during this process, and non-responders were not re-evaluated.

RESULTS

Participant flow
Only patients with potential of having primary endpoint data at cut-off were evaluated (i.e. patients with planned or completed Visit 2). This included 198 screened patients of whom 154 were allocated and exposed to ofatumumab. Patient assignment based on the IRC assessment included 59 exposed DR patients, 79 exposed BFR patients, and 16 exposed CLL patients assigned as Other. The patient disposition is presented in Figure 4.

Figure 4: Patient disposition, study Hx-CD20-406



DR = Double-refractory; BFR = Bulky Fludarabine-refractory; PD = progressive disease; Death, NOS = death not otherwise specified (occurred after new CLL therapy; only date of death was to be recorded).

a. Action taken is "withdrawal" on AE page but "Progression of study disease" or "other" is stated as reason for withdrawal on Withdrawal From Treatment page. Here shown as AE withdrawals (fatal or non-fatal within treatment period).

b. If withdrawal reason stated on Withdrawal From Treatment page and End-of-study page differ, the treatment withdrawal reason is shown. For this reason one patient is shown as a non-fatal AE withdrawal (pneumonia) even though the patient died 3 months later (sepsis) without having been included in extended follow-up.

c. Due to bad general condition; prohibited therapy; new CLL treatment; no response (n=2); to disease progression and anxiety; to investigator's decision; disease transformation.

d. Due to bone marrow transplant; started new treatment; no response; allogeneic bone marrow transplant.

e. Seven patients died during extended follow-up due to SAEs with onset during treatment or follow-up phase.

f. Due to palliative care only; lost to follow-up.

Recruitment

The trial was initiated 13-Jun-2006 (first informed consent signed) and is still ongoing. The cut-off date for this protocol specified interim analysis was 19-May-2008.

Conduct of the study

The trial protocol underwent 5 amendments which primarily resulted in changes to the inclusion and exclusion criteria and the number of subjects planned. A summary of the major changes is given in the following table.

Table 12: Major amendments to the protocol

Amendment number and date	Key changes in the amendment
Amendment 1 27 February 2006	Updates on inclusion and exclusion criteria including: • Criteria for definition of refractoriness to alemtuzumab • Bulky lymphadenopathy (>5 cm lymph nodes) added as definition of ineligibility for alemtuzumab therapy No subjects were enrolled prior to the implementation of this amendment.
Amendment 2 26 September 2006	Clarification of primary study objective to include only efficacy. Updates on inclusion and exclusion criteria including: • Removal of inclusion criteria for intolerance and ineligibility to fludarabine therapy • Specification of minimum number of treatment cycles to define refractoriness to prior fludarabine and alemtuzumab Minimum Residual Disease (MRD) analysis was added to the secondary endpoints.
Amendment 3 16 April 2007	Definition of trial population to include two main groups to be analyzed separately: • Subjects refractory to fludarabine and alemtuzumab • Subjects refractory to fludarabine and considered inappropriate for alemtuzumab due to bulky lymphadenopathy The assumptions for the sample size calculations were updated, the maximum number of subjects to be enrolled in the trial was increased from 100 to 150 (target of 66 per group) and the Data Monitoring Committee stopping rules based on critical AEs were updated accordingly. Clarification of response evaluations: • Removal of the requirements of radiographic techniques from the CR definition • Addition of lymphocyte requirements to the CR definition • Lymphadenopathy was defined as lymph nodes with the largest diameter ≥1.0 cm
Amendment 4 31 October 2007	Increase in planned number of subjects to be enrolled from 66 subjects to 100 subjects in each subject group, to a maximum of approximately 225 subjects. Update to statistical analysis plan including testing for the primary endpoint to exclude a 15% response rate. Inclusion of interim analysis comprising superiority and futility analysis when primary endpoint data is available from 66 subjects in double-refractory group. Three secondary endpoints (early death, major infections and infections requiring hospitalization and IV antibiotics) were added.
Amendment 5 15 July 2008	Administrative changes in accordance with transfer of trial sponsorship from Genmab to GSK as of 28 April 2008

Amendments 2 and 3 defined the subject eligibility definition consistent with the DR and BFR subject populations and the study would no longer enrol subjects who had demonstrated lack of tolerability to fludarabine and alemtuzumab. 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 analyzed separately as "Other".

Baseline data

Baseline demographic characteristics of the patients in the pivotal study are presented in the following table.

Table 13: Baseline demographic characteristics

Demographic Characteristics	DR N=59	BFR N=79	Other N=16	Study Total N=154
Age, years				
Median	64	62	63	63
Min – Max	41-86	43-84	53-82	41-86
≥65 yrs, n (%)	27 (46)	33 (42)	6 (38)	66 (43)
≥75 yrs, n (%)	4 (7)	10 (13)	2 (13)	16 (10)
Sex, n (%)				
Female	15 (25)	22 (28)	6 (38)	43 (28)
Male	44 (75)	57 (72)	10 (63)	111 (72)
Race, n (%)				
White	56 (95)	78 (99)	15 (94)	149 (97)
Asian	1 (2)	0	1 (6)	2 (1)
Hispanic or Latino	1 (2)	0	0	1 (1)
African-American/African	0	1 (1)	0	1 (1)
Other	1 (2)	0	0	1 (1)

The disease characteristics at baseline were:

Disease Characteristics	DR N=59	BFR N=79	Other N=16	Study Total N=154
Duration of CLL in years, median (min, max)	6 (1, 19)	5.9 (1, 18)	7.5 (4, 17)	6.3 (1, 19)
Number of prior CLL regimens, median	5.0	4.0	6.5	5.0
ECOG performance status[a], n (%)				
0	27 (46)	25 (32)	3 (19)	55 (36)
1	19 (32)	40 (51)	9 (56)	69 (45)
2	12 (20)	13 (16)	4 (25)	29 (19)
3	1 (2)[b]	0	0	1 (1)
Rai at screening, n (%)				
0	1 (2)	0	0	1 (1)
I	11 (19)	7 (9)	2 (13)	20 (13)
II	15 (25)	17 (22)	4 (25)	36 (23)
III	10 (17)	11 (14)	4 (25)	25 (16)
IV	22 (37)	44 (56)	6 (38)	72 (47)
Binet at screening, n (%)				
A	6 (10	4 (5)	1 (6)	11 (7)
B	23 (39)	24 (30)	6 (38)	53 (34)
C	30 (51)	51 (65)	9 (56)	90 (58)
Chromosomal abnormalities, n (%)	n=57	n=78	n=16	n=151
17p deletion	17 (30)	14 (18)[c]	2 (13)[d]	33 (22)[e]
11q deletion	24 (42)	22 (28)	4 (25)	50 (33)
12q trisomy	3 (5)	8 (10)	5 (31)	16 (11)
13q deletion	5 (9)	13 (17)	1 (6)	19 (13)
No abnormalities found	8 (14)	19 (24)	3 (19)	30 (20)[f]
Median lymphocyte count at baseline (10^9/L)	14.7	28.5	72.4	19.7
Constitutional symptoms present at screening, n (%)	36 (61)	52 (66)	12 (75)	100 (65)
Bulky lymphadenopathy[g] present at baseline, n (%)	55 (93)	79 (100)	7 (44)	141 (92)
Organomegaly[h] present at baseline, n (%)	35 (59)	49 (62)	13 (81)	97 (63)

a. ECOG performance status at baseline; b. Subject 406102 was allowed to enroll in the study despite an ECOG performance status of 3, which due to an elbow surgery, and not related to CLL; c. BFR subjects with assessment of 17p = 76; d. Other subjects with assessment of 17p = 15; e. Total subjects with assessment of 17p = 148; f. Total subjects with assessment of no abnormalities = 150 ;g. Bulky lymphadenopathy defined as presence of at least one lymph node >5 cm by CT scan; h. Organomegaly defined as enlarged liver or spleen or both.

Nearly all subjects received more than two previous treatment regimens for CLL, most frequently alkylating agents (94%), purine analog combinations (81%), single agent cytotoxics (68%), and/or monoclonal antibodies (60%). Some subjects have been treated with investigational agents as well. The majority of subjects in all groups also received prior treatment with rituximab, either as monotherapy or as part of combination therapy.

Table 14: Prior CLL therapies, study Hx-CD20-406

Prior CLL Therapies	DR N=59	BFR N=79	Other N=16	Study Total N=154
Number of prior CLL Therapies, n (%)				
1	2 (3)	10 (13)	0	12 (8)
2	5 (8)	5 (6)	0	10 (6)
3	6 (10)	13 (16)	1 (6)	20 (13)
4	9 (15)	12 (15)	0	21 (14)
5	10 (17)	20 (25)	3 (19)	33 (21)
>5	27 (46)	19 (24)	12 (75)	58 (38)
Type of Prior CLL Therapy, n (%)				
Alkylating agents	55 (93)	73 (92)	16 (100)	144 (94)
Monoclonal antibodies[a]	55 (93)	27 (34)	11 (69)	93 (60)
Rituximab chemotherapy combinations	17 (29)	21 (27)	5 (31)	43 (28)
Single agent cytotoxics	40 (68)	52 (66)	13 (81)	105 (68)
Combination chemotherapy	22 (37)	28 (35)	13 (81)	63 (41)
Purine analog combinations[b]	50 (85)	65 (82)	10 (63)	125 (81)
Other therapy[c]	22 (37)	25 (32)	7 (44)	54 (35)

a. Monoclonal antibodies include rituximab monotherapy, alemtuzumab monotherapy, and alemtuzumab combination therapy except fludarabine combination therapy.
b. Purine analog combinations include all fludarabine combinations, including fludarabine + alemtuzumab combinations.
c. Other therapy includes investigational drugs and investigational or off-label use of approved drugs (i.e., lenalidomide, thalidomide).

All DR subjects had both prior fludarabine and alemtuzumab, either consecutively or as combination therapy. All BFR subjects had prior fludarabine treatment, either as monotherapy or as part of a combination therapy regimen.
The majority of subjects (57%) had prior treatment with one or more rituximab containing regimen. The most common regimen was FCR, particularly in the DR group.

Table 15: Prior Rituximab-containing CLL therapy, study Hx-CD20-406

Prior Rituximab-Containing CLL Therapy, n (%)	DR N=59	BFR N=79	Other N=16	Total N=154
Any rituximab[a]	35 (59)	43 (54)	10 (63)	88 (57)
Rituximab monotherapy	11 (19)	17 (22)	7 (44)	35 (23)
Fludarabine + rituximab[b] (FR)	5 (8)	19 (24)	3 (19)	27 (18)
Fludarabine + cyclophosphamide + rituximab[c] (FCR)	22 (37)	20 (25)	2 (13)	44 (29)

d. Subjects may have received more than one type of rituximab treatment regimen.
e. Any fludarabine + rituximab combination except FCR
f. Any fludarabine + cyclophosphamide + rituximab combination

Numbers analysed
Efficacy results for Study Hx-CD20-406 are presented for the DR, BFR and combined DR+BFR subjects (combined group), since these represent the fludarabine-refractory CLL population. The FAS population was the analysis population used throughout the presentation of results. Seven patients were screened and allocated to treatment, but were not treated with ofatumumab and they were therefore not included in the FAS. Among these, 4 patients were ineligible according to selection criteria at Visit 2 and 1 patient had progression of disease related symptoms prior to the first infusion. These 5 patients were considered as screening failures. Furthermore, prior to any ofatumumab exposure, one patient withdrew consent and one patient withdrawn due to deep vein thrombosis. The total number of patients analysed is thus 138, with 59 in the DR group and 79 in the BFR group. There were no major protocol deviations requiring exclusion of patients from the FAS or the PP population.

Outcomes and estimation

Primary Efficacy Endpoint: Response Rate
Response assessments of the 138 fludarabine-refractory subjects (DR, BFR, and combined group), as assessed by the IRC, are shown in the following table.

Table 16: Summary of response assessed by IRC, study Hx-CD20-406

Response	DR N=59	BFR N=79	Combined DR + BFR N=138
Response Rate			
Responders, n (%)	34 (58)	37 (47)	71 (51)
99% CI (%)	(40, 74)	(32, 62)	(40, 63)
Response			
CR, n (%)	0	1 (1)	1 (1)
nPR, n (%)	0	0	0
PR, n (%)	34 (58)	36 (46)	70 (51)
SD, n (%)	18 (31)	32 (41)	50 (36)
PD, n (%)	2 (3)	8 (10)	10 (7)
NE, n (%)	5 (8)	2 (3)	7 (5)

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 response for each individual subject. As a result, there was no overall response assessment for each subject determined by the investigator. An algorithm was applied to the individual investigator assessment of response at each visit to derive an overall response for each subject, from which an Investigator Assessment response rate was calculated. A summary of the IRC assessment, Investigator assessment and the Sponsor assessment of response rate is provided in the following table.

Table 17: Summary of Response Rates as Assessed by IRC, Investigator and Sponsor

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

An expert panel of IRC members applied the protocol specified method of response determination to assure an independent, consistent and medically appropriate application of this composite measure of response in CLL. Differences in the response rate assessment according to the three measures largely reflected differences in clinical assessment of transient changes that an expert would not interpret as evidence of disease progression. The algorithmic approach by the sponsor did not account for this, and so represented the most stringent test of the response rate. Nevertheless, the concordance rates between assessments by the IRC and Sponsor were 80% for the DR group and 84% for the BFR group. 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. This sensitivity analysis provided a range of possible response rate interpretations.

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. Within 4 weeks of ofatumumab treatment, median lymph node SPD decreased 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%).

Reduction in Lymphocyte Count. Lymphocyte counts were assessed from baseline to Week 24. Within 1 week of initiation of ofatumumab treatment, the combined group median lymphocyte count was decreased from $18.1x10^9$ cells/L at baseline to $10.6x10^9$ cells/L, with a reduction in the DR group from $14.7x10^9$ cells/L to $8.5x10^9$ cells/L, and from $28.5x10^9$ cells/L to $11.4x10^9$ 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 $3.1x10^9$ cells/L, with a reduction in the DR group to $3.0x10^9$ cells/L, and $3.2x10^9$ cells/L in the BFR group, an 83% combined group median reduction compared to baseline (DR: 81%, BFR: 89%).

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. Malignant B cells showed changes similar to those of total lymphocytes (data not shown).

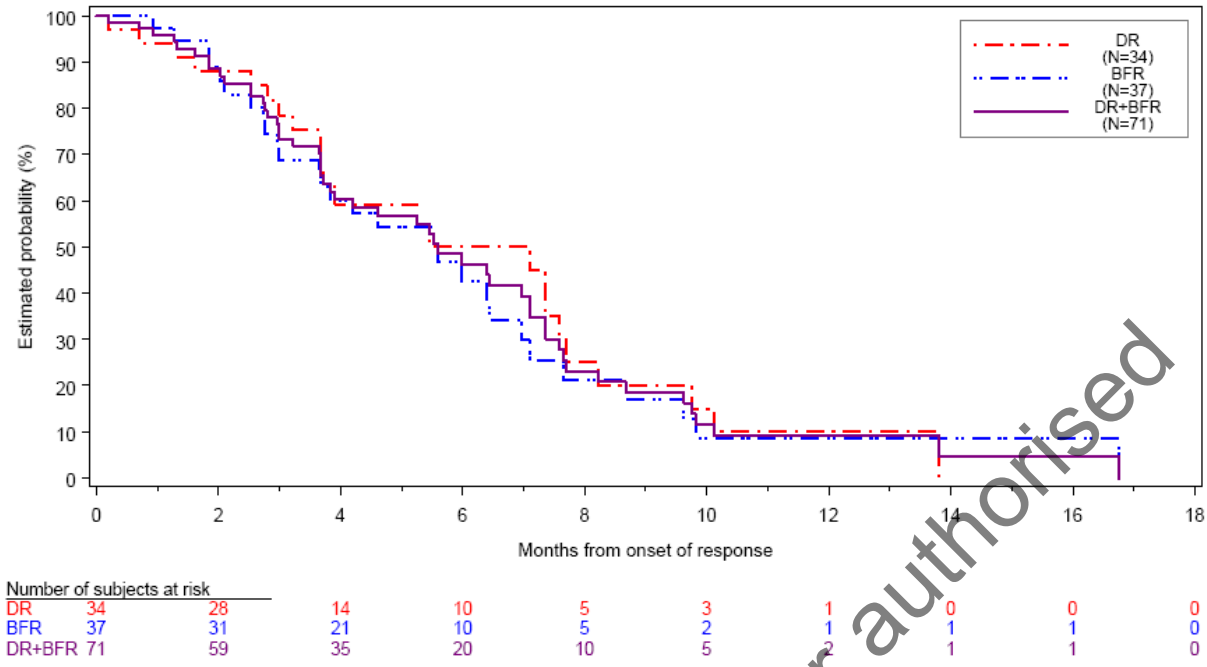
Duration of response. Duration of response was defined as the time from initial response to disease progression or death, and was defined only for subjects who responded (CR, nPR or PR) during the 24 week period from start of treatment. A sensitivity analysis of duration of response was also performed, which defined the duration of response as the time from initial response until progression reported by local investigator, or AE, or discontinuation of treatment for any reason including disease progression, new CLL treatment, treatment toxicity and death. The median time to onset of response, median duration of response, median duration of response sensitivity analysis, and the median duration of response after last infusion are shown in the following table.

Table 18: Summary of onset and duration of response (Responders only), study Hx-CD20-406

Onset and Duration of Response	DR N=34	BFR N=37	Combined DR+BFR N=71
Median time to onset of response (months)	1.8 95% CI: 1.0, 1.9	1.8 95% CI: 1.0, 1.9	1.8 95% CI: 1.0, 1.8
Median duration of response (months)	7.1 95% CI: 3.7, 7.6	5.6 95% CI: 3.6, 7.0	5.6 95% CI: 3.8, 7.1
Median duration of response, sensitivity analysis (months)	n=35 5.3 95% CI: 3.7, 7.1	n=38 5.5 95% CI: 3.2, 6.4	n=73 5.3 95% CI: 3.7, 6.4
Median duration of response after last infusion (months)	2.5 95% CI:0.9, 5.0	1.9 95% CI: 0.9, 2.8	2.1 95% CI: 1.1, 2.8

The figure below shows the median duration of response in subjects who responded in each group, and combined.

Figure 5: Duration of response



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).

Progression-free survival. Progression-free survival (PFS) was defined as the time from baseline (allocation to treatment) until progression of CLL or death. The progression events were defined in the protocol, and progression dates were verified by the IRC. PFS is presented in the table below for the 102 subjects (DR: 40, BFR: 62) with an observed progression of CLL or death.

Table 19: Summary of Progression-Free Survival, Study Hx-CD20-406

	DR N=40	BFR N=62	Combined DR+BFR N=102
Median PFS (months)	5.7 95% CI: 4.5, 8.0	5.9 95% CI: 4.9, 6.4	5.7 95% CI: 5.5, 6.4

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, see table below:

Table 20: Summary of Time to Next CLL Treatment

	DR n=31	BFR n=51	Combined DR + BFR n=82
Median time to next CLL treatment (months)	9.0	7.9	8.2
Median time to next CLL treatment in Responders (months)	9.3	9.5	9.3
Median time to next CLL treatment in Non-Responders (months)	8.5	5.9	5.9

Of the 154 patients, 88 patients (57%) had new subsequent CLL treatment following treatment with

ofatumumab in this trial. A total of 46 different treatment combinations were used as new CLL therapy that included chemotherapy, immunotherapy, chemo-immunotherapy, radiotherapy, allogeneic bone marrow transplantation and leukapheresis.

Overall Survival. At the time of the interim analysis, 27 DR and 31 BFR subjects (58 combined group) had died. The median overall survival was similar across groups.

Table 21: Summary of Overall Survival

	DR N=27	**BFR N=31**	**Combined DR+BFR N=58**
Median overall survival (months)	13.7 95% CI: 9.4, na	15.4 95% CI: 10.2, 20.2	15.4 95% CI: 10.2, 20.2

Constitutional symptoms. Constitutional symptoms were reported by subjects and results captured by investigators every 4 weeks during the treatment period (Week 0 to Week 24) and through the follow-up period (Week 28 to Month 24) as part of assessment of response. 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.

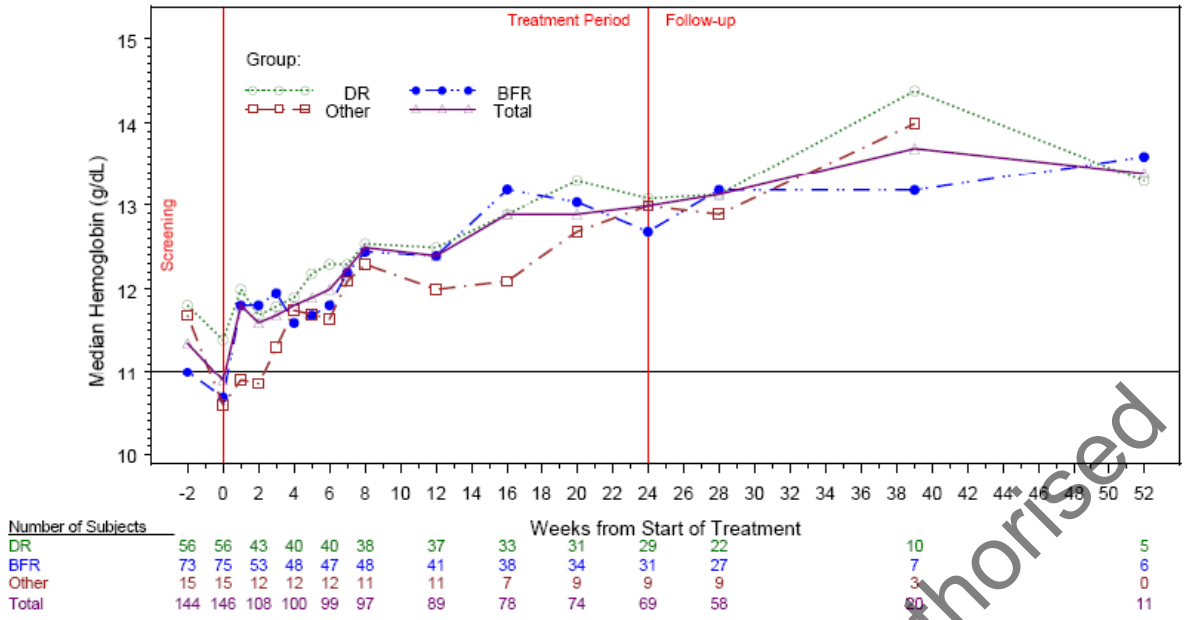
Resolution of lymphadenopathy. Complete resolution of lymphadenopathy was defined as the presence of palpable lymph nodes ≥1 cm at baseline followed by palpable lymph nodes of normal size (<1 cm) at a later time. One-fifth of the combined group subjects with baseline lymphadenopathy had complete resolution 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.

Resolution of splenomegaly and hepatomegaly. Complete resolution was defined as the presence of an enlarged palpable spleen or liver at baseline followed by absence of splenomegaly post-baseline. More than half of subjects in the combined group experienced complete resolution of splenomegaly some time during the study (60%, 42/70), and all occurred during the treatment period. Of these, 34 subjects experienced complete resolution of splenomegaly during response. More than two-thirds of subjects in the combined group experienced complete resolution of hepatomegaly some time during the study (71%, 24/34), and all occurred during the treatment period. Of these, 17 subjects experienced complete resolution of hepatomegaly during response. The absence of organomegaly was maintained in the majority of subjects without baseline organomegaly, two subjects had worsening of splenomegaly and one subject had worsening of hepatomegaly as best response during the study period.

Improvement in ECOG performance status. Nearly half of subjects with the opportunity to improve in ECOG performance status from baseline did improve (48%, 41/86), with the improvement occurring during the treatment period in 39 of 41 subjects. Most improvements in responders occurred during the time of response to ofatumumab (64%, 27/42). More than one-third of subjects with the opportunity to improve maintained their ECOG performance status (41%, 35/86), and very few subjects declined (5%, 4/86). Nearly all subjects with an ECOG performance status of 0 did not worsen during the study period (96%, 50/52).

Improvement in haemoglobin values. Haemoglobin values increased steadily from baseline through the treatment period and into the follow-up period, as shown in the following Figure 6.

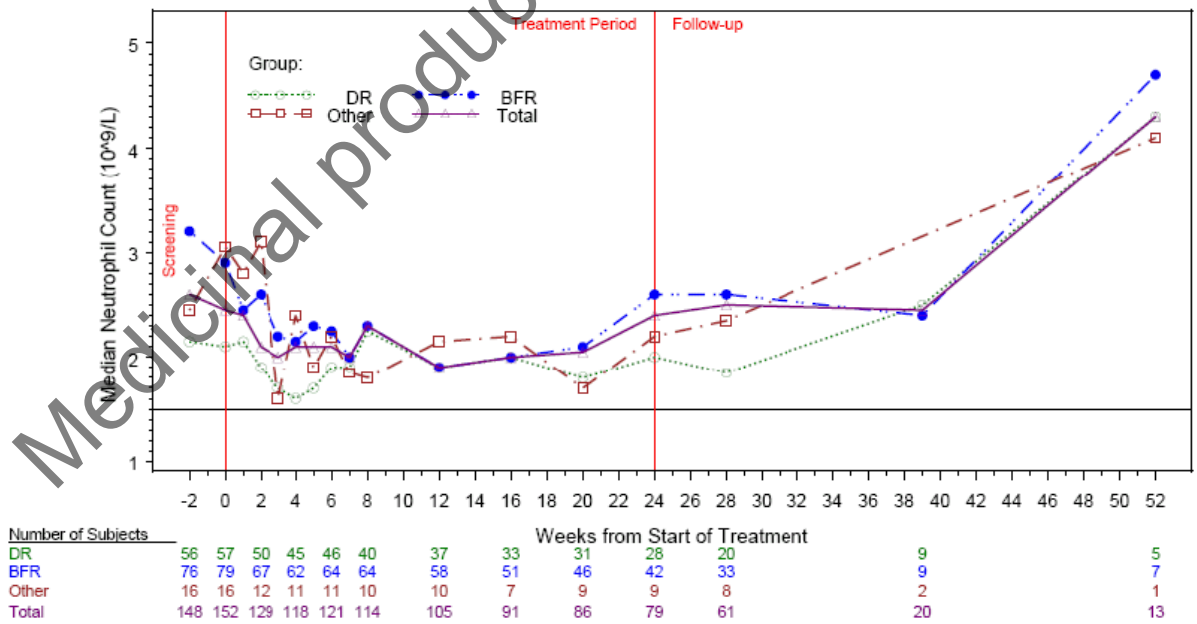
Figure 6: Median haemoglobin over time



Improvement in platelet counts. 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). Only one subject had a worsening of a normal platelet level during the study.

Improvement in neutropenia. Median neutrophil counts remained above the lower limit of normal from baseline through the treatment period and into the follow-up period, as shown in the following Figure 7.

Figure 7: Median neutrophil levels over time



Ancillary analyses

The Applicant submitted a number of ancillary analyses which indicated that the effect of ofatumumab was independent of prior cyclophosphamide, rituximab and FCR (fludarabine, cyclophosphamide and rituximab) treatment and independent of the number of prior CLL therapies employed (data not shown).

- Analysis performed across trials (pooled analyses and meta-analysis)

No analyses across trials were submitted.

- Clinical studies in special populations

Analyses in special populations of the pivotal study Hx-CD20-406 indicated that there was no difference in response to ofatumumab due to age, sex and geopraphic region. As very few patients were non-Caucasian, no race differences could not be assessed. Baseline disease characteristics, including bone marrow involvement and number and size of enlarged lymph nodes were not found to affect the response to ofatumumab. With regard to chromosomal abnormalities, 17q deletion, 11q deletion and 12q trisomy were not found to affect the response to ofatumumab, as opposed to 13q deletion, which seemed to favour the response.
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).
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.

- Supportive study

The only study in CLL apart from the pivotal Hx-CD20-406 study was the dose-finding Hx-CD20-402 study. A juxtaposition to the pivotal study Hx-CD20-402 is presented in the following table.

Table 22: Comparison of Study Hx-CD20-406 and Study Hx-CD20-402

Parameter	Study Hx-CD20-406	Study Hx-CD20-402
Study Design		
Study design and objectives	Open label, single arm study to evaluate efficacy	Open label, dose escalating study to evaluate safety, efficacy and pharmacokinetics
Ofatumumab treatment dose and duration of treatment	First dose 300 mg, then 2000 mg weekly for 7 weeks, monthly for 4 months Duration of treatment: 6 months	A: First dose 100 mg, then 500 mg weekly for 3 weeks (n=3) B: First dose 300 mg, then 1000 mg weekly for 3 weeks (n=3) C: First dose 500 mg, then 2000 mg weekly for 3 weeks (n=27) Duration of treatment: 4 weeks
Subject Disease Demographics		
Study population	Refractory to fludarabine and alemtuzumab, or fludarabine and ineligible for alemtuzumab Median age: 63 years Median number of prior therapies: 5	Relapsed or refractory to any CLL treatment Median age: 61 years Median number of prior therapies: 3
Disease stage	High risk Rai stage III and IV: 63% Binet stage C: 58% Intermediate risk Rai stage I and II: 36% Binet Stage B: 34%	High risk Rai stage III and IV: 12% Binet stage C: 12% Intermediate risk Rai stage I and II: 84% Binet Stage B: 67%
Efficacy Results		
Primary endpoint	Response by Week 24	Response by Week 19

	(NCIWG criteria,1996) RR in Combined group = 51% RR in DR group = 58% RR in BFR group = 47%	(NCIWG criteria,1996) RR = 42% overall RR in Group C = 48%
Secondary endpoints	92 - 100% median reduction of malignant cells in peripheral blood by Week 24 (end of treatment)	97-100% median reduction of malignant cells in peripheral blood (Group C) at Week 4 (end of treatment)
	Median Duration of response: Combined Group: 5.6 months DR: 7.1 months BFR: 5.6 months	Median Duration of response: 4.3 months (overall) 4.4 months (Group C)
	Median Progression-free survival[a]: Combined Group: 5.7 months DR: 5.7 months BFR: 5.9 months	Median Time to progression[b]: 3.6 months (overall) 4.4 months (Group C)
	Median Time to next CLL treatment: Combined Group: 8.2 months DR: 9.0 months BFR: 7.9 months	Median Time to next CLL treatment: 12.0 months (overall) 12.1 months (Group C)

- Discussion on clinical efficacy

The CHMP considered that the uncontrolled design of the pivotal trial Hx-CD20-406 was of major concern. Although ofatumumab showed activity in CLL, the lack of control group made it impossible to conclusively assess the efficacy of ofatumumab relative to other treatments in subjects with double refractory or fludarabine refractory-bulky lymphadnopathy CLL. The Applicant's view that it was not feasible to conduct a comparative study was questioned and the use of a historical comparison was not considered adequate. Similarly, the comparison of time-dependent endpoints in responding patients vs non-responders (landmark analysis) was questioned, as response could simply be a marker for patients with pretreatment characteristics that favour longer survival. Although no single therapy stands out as the treatment of choice for refractory patients, a comparison against "physician's choice" or standard of care was felt to have been an option. Mono- or combination therapies of alkylators, antimetabolites or monoclonal antibodies were proposed as potential comparators.

An Oncology Scientific Advisory Group (SAG-O) was convened to provide their clinical expert opinion on these issues. The SAG was asked to discuss potential acceptable active comparators for a confirmatory phase III trial in a comparable population to the one included in the pivotal phase II trial (patients refractory to fludarabine and alemtuzumab or refractory to fludarabine and ineligible for alemtuzumab due to bulky lymphadenopathy) also taking into account that 80% were deemed refractory to alkylating agents and that a substantial number of patients had progressed on chemotherapy with rituximab as add-on. They were also asked whether a comparison to physician's choice would be feasible. The SAG argued that it is important to distinguish two separate groups of patients, namely patients whose disease is refractory to at least two regimen including fludarabine and alemtuzumab ("double-refractory"), versus patients whose disease is refractory to fludarabine and ineligible for alemtuzumab due to bulky lymphadenopathy ("bulky fludarabine refractory"). These two groups differ significantly in terms of disease biology, number of therapies received, available treatment options.

For double-refractory disease, the SAG agreed that it was unfortunate that no comparative data were available, for example, to assess the effect of ofatumumab on overall survival, but also acknowledged that choice of comparator was very problematic. In this group, particular after disease progression after multiple regimens chemotherapy and monoclonal antibodies, performance status is often poor and there are no regimens with established efficacy and safety, according to scientific standards. Although in practice salvage chemotherapy is attempted when possible, such regimens are associated with significant toxicity including mortality. Therefore, their use as active controls could bias efficacy comparisons in favour of the less toxic treatments, regardless of efficacy. Thus, the SAG agreed that

although theoretically possible, the choice of an active and safe control in double-refractory disease was very difficult due to the lack of an established regimen. However, one SAG member disagreed arguing that even in this population it is feasible to conduct randomized controlled trials against physician best choice, and that in the absence of randomized trials the relative effects in terms of efficacy and safety cannot be established.

The SAG agreed that the situation is different in "bulky fludarabine-refractory" disease, where patients are less pre-treated and in a better condition to tolerate salvage therapies. In this second-line indication, acceptable comparators including salvage chemotherapy or chemotherapy and rituximab should be considered, although their activity is considered lower than for fludarabine-refractory patients. Indeed a number of patients had received such 2nd line regimen including rituximab. The SAG agreed that patients with "bulky fludarabine-refractory" disease that is refractory to at least two regimens (at least one of which included fludarabine), are considered to be in a similar situation as that of patients with "double-refractory" disease.

The SAG was also asked to discuss the acceptability and feasibility of a phase II trial with best supportive care as comparator. The SAG agreed that if the performance status allows it, best supportive care would not be an acceptable comparator due to the significant symptoms and rapid worsening of the disease. In patients when the performance status is poor and supportive care is the only available option, phase III trials would be difficult to conduct, due to the very poor prognosis and the limited chances for new treatments to change the course of the disease.

As an answer to the question whether an unmet medical need existed for the population in question, the SAG agreed that for patients with double-refractory disease there is clearly an unmet medical need. Available regimens have not been established according to scientific standards and are associated with significant toxicity including toxic deaths. The situation is different in "bulky fludarabine-refractory" disease, where patients are less pre-treated and in a better condition to tolerate salvage therapies; however following second line therapy no therapeutic option is available. Thus the unmet medical need for patients with "bulky fludarabine-refractory" disease that is refractory to at least two regimens (at least one of which included fludarabine), is similar to that of patients with "double-refractory" disease.

Finally, in response to the question whether the apparently high response rate observed in the pivotal trial is clinically relevant, the SAG agreed to the following: The population of patients whose disease is refractory to fludarabine and alemtuzumab was adequately represented in the pivotal Study Hx-CD20-406. In this subgroup, the median number of prior therapies was 5, 93% of patients received prior alkylating agents and 59% received prior rituximab. The SAG agreed that the ORR observed in this population was high, the onset of the response was rapid and the duration of response was long-lasting. The SAG agreed that it is reasonable to assume that this effect will lead to some improvement in disease related symptoms and that this is expected to be of clinical relevance. The clinical improvements may in principle allow further clinically relevant benefits, e.g., allowing further salvage treatments (or allogeneic stem cell transplantation) in general not doable in such patients.

Indeed, in the pivotal trial responses were associated with clinical improvement in disease-related symptoms and this would be of immediate clinical relevance to the patients. However, this is based on exploratory analyses of a single-arm trial and firm conclusions cannot be drawn.

The SAG agreed that further studies should address the basis for stopping treatment after 24 weeks, because treatment discontinuation was associated with loss of response.

The SAG agreed that drug refractoriness should be clearly defined in the prescribing information, in line with the definition used in the pivotal study, namely, 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.

The SAG agreed that similar considerations applied to patients with "bulky fludarabine-refractory" disease that is refractory to at least two regimens (at least one of which included fludarabine). These

patients were included in the study and similar response rates and durations were observed as for the double-refractory subgroup.

Clinical safety

The safety database included subjects who were exposed to at least one dose of ofatumumab. The studies contributing to the safety analysis are reported in Table 23. Because patients in other indications received significantly lower doses of ofatumumab in the course of their treatment, as detailed in Table 23, only CLL patients are considered in the following.

- Patient exposure

A total of 648 subjects were exposed to ofatumumab in 12 studies across oncology and non-oncology indications as of the cut-off date for this submission, 20 June 2008. The number of patients in each study and the doses of ofatumumab administered in these studies are summarised in the following Table 23.

Table 23: Overview of Subjects Contributing to the Safety Analysis of Ofatumumab

Study ID	**Ofatumumab Monotherapy**		**Ofatumumab in combination with other treatment**	**Ofatumumab in blinded treatment studies**
	Number of subjects receiving any dose	**Number of subjects receiving 2000 mg dose only**	**Number of subjects receiving 500 mg or 1000 mg dose**	**Number of subjects receiving placebo or 700 mg dose[1]**
Hx-CD20-406[2]	154	154	NA	NA
Hx-CD20-402[3]	33	27[14]	NA	NA
Hx-CD20-407[4]	NA	NA	28	NA
CLL Sub-totals	**187**	**181**	**28**	NA
FL studies				
Hx-CD20-001[5]	**CLL studies**	NA	NA	NA
Hx-CD20-405[6]	74[6]	NA	NA	NA
Hx-CD20-409[7]	NA	NA	33[7]	NA
FL Sub-totals	**114**	NA	**33**	NA
Clinical safety database	**362[8]**			
Other Oncology Indications				
GEN415/DLBCL	4	NA	NA	NA
Non-oncology Indications				
Hx-CD20-403[9] / RA	201	NA	NA	NA
GEN410[10] / RA	NA	NA	NA	54
GEN411[11] / RA	NA	NA	NA	12
GEN413[12] / RA	10	NA	NA	NA
Hx-CD20-408[13] / COPD	5	NA	NA	NA
Total of subjects in other indications	**286**			
Grand Total of Subjects who received at least one dose of ofatumumab	**648**			

1. In the blinded studies, subjects in the active arm received 700 mg ofatumumab.
2. Study Hx-CD20-406 (pivotal monotherapy CLL study) - subjects exposed to treatment up to 24 weeks (ongoing study). An additional 31 subjects were enrolled but not included in the interim analysis because primary endpoint data for interim analysis was not available at the time of the data cut-off. Only SAE data as of the cut-off date of 20 June 2008 is included for these 31 subjects.
3. Study Hx-CD20-402 (monotherapy dose escalation study) – subjects exposed to treatment up to 3 weeks (completed study).
4. Study Hx-CD20-407 - 14 subjects received 500 mg ofatumumab plus FC, and 14 subjects received 1000 mg ofatumumab plus FC - subjects exposed for up to 20 weeks (ongoing study).
5. Study Hx-CD20-001 (completed study) – subjects exposed to treatment up to 3 weeks.
6. Study Hx-CD20-405 (ongoing single-arm study) was a double-blind, two-dose study prior to a protocol

7. Study Hx-CD20-409 (ongoing study) - 17 subjects received 500 mg ofatumumab plus CHOP, and 16 subjects received 1000 mg ofatumumab plus CHOP.
8. Safety population consists of data from the three studies in CLL subjects (Hx-CD20-406, Hx-CD20-402, Hx-CD20-407) and three studies in FL subjects (Hx-CD20-001, Hx-CD20-405, Hx-CD20-409).
9. Study Hx-CD20-403 (completed study) - In part A of the study (sequential dose escalation), 12 subjects received 300 mg, 10 subjects received 700 mg, and 10 subjects received 1000 mg of ofatumumab. In part B of the study (parallel dose escalation), 58 subjects received 300 mg, 57 subjects received 700 mg, and 54 subjects received 1000 mg ofatumumab.
10. Study GEN410 (blinded ongoing study)- Subjects in the active arm received 700 mg ofatumumab in addition to methotrexate.
11. Study GEN411 (ongoing study) - Subjects received 700 mg ofatumumab or placebo plus methotrexate.
12. Study GEN413 - ongoing study.
13. Study Hx-CD20-408 - Study terminated.
14. One subject (402614) was allocated to 2000 mg dose group, but only received one infusion of 500 mg (priming dose).

The safety of Arzerra in patients with relapsed or refactory CLL was evaluated in two open label studies. In study Hx-CD20-406, 154 patients were enrolled to receive an initial dose of 300 mg followed by 7 consecutive weekly infusions of 2000 mg, followed five weeks later with 4 consecutive monthly infusions of 2000 mg. 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 reactions reported are from final data from the initial dose-range finding and a planned interim analysis of study Hx-CD20-406.
Most subjects in study 406 (90%, 139 subjects) received all 8 weekly infusions, 69% (107 subjects) received at least 10 infusions and 55% (85 subjects) received all 12 infusions (completed 24 weeks of treatment). In the supportive study 402, most subjects in the 2000 mg group received the intended 4 infusions (25/27).

- Adverse events

An overview of adverse events in the pivotal study Hx-CD20-406 as of the cut-off date for the interim analysis (19 May 2008) is given in Table 24.

Table 24: 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. 5 additional subjects had disease progression listed as the AE that resulted in discontinuation.

In addition to infections and infusion reactions, common adverse events (experienced by ≥10%) were: Pyrexia (31 subjects, 20%), cough (30 subjects, 19%), diarrhoea (28 subjects, 18%), pneumonia (25 subjects, 16%), neutropenia (25 subjects, 16%), anaemia (25 subjects, 16%), fatigue (23 subjects, 15%) and dyspnoea (22 subjects, 14%). Most of the adverse events were seen in subjects on treatment (81%). Infusion reactions occurred with the greatest incidence (44%) on the first infusion day (300 mg or 500 mg), decreased to 26% with the second infusion (2000 mg) and declined further during subsequent infusions (2000 mg).
In the supportive study Hx-CD20-402, 27 (82%) patients reported 246 AEs which predominantly (92%) were of CTC grade 1-2 intensity. A total of 23 of 33 (70%) subjects had infusion related events (i.e. events with onset on an infusion day). Of the 138 infusion related events 84 (61%) were reported

on the day of the first infusion. Sixteen of the 33 (48%) subjects had infections. The most common infections were of the respiratory tract (10 subjects, 30%). Eleven of the 33 subjects (33%) had ≥Grade 3 AEs. Thrombocytopenia (3 subjects, 9%), neutropenia (2 subjects, 6%), and pyrexia (2 subjects, 6%) were the most common ≥Grade 3 AEs.
Adverse events considered related to treatment by the investigator (adverse drug reactions) in both CLL studies (402 and 406) are shown in Table 25. A total of 21% of subjects in the study had an adverse event in the Infections and infestations SOC that was considered related to treatment. Symptoms that characterize infusion reactions were considered drug-related in 47% of the subjects.
Adverse drug reactions are listed below by MedDRA body system organ class and by frequency. Very common (≥ 1/10); Common (≥ 1/100 to < 1/10); Uncommon (≥ 1/1,000 to < 1/100); Rare (≥ 1/10,000 to < 1/1,000); Very rare (< 1/10,000), not known (cannot be estimated from available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 25: Adverse drug reactions in CLL studies Hx-CD20-402 and Hx-CD20-406

MedDRA System Organ Class	Very common	Common	Uncommon
Infections and Infestations	Lower respiratory tract infection, including pneumonia, upper respiratory tract infection	Sepsis, including neutropenic sepsis and septic shock, herpes virus infection, urinary tract infection	
Blood and lymphatic system disorders	Neutropenia, anaemia	Febrile neutropenia, thrombocytopenia, leukopenia	Agranulocytosis, coagulopathy, red cell aplasia, lymphopenia
Immune system disorders		Anaphylactoid reactions, hypersensitivity	
Metabolism and nutrition disorders			Tumour lysis syndrome
Cardiac disorders		Tachycardia	
Vascular disorders		Hypotension, hypertension	
Respiratory, thoracic and mediastinal disorders		Bronchospasm, hypoxia, dyspnoea, chest discomfort, pharyngolaryngeal pain, cough, nasal congestion	
Gastrointestinal disorders		Small bowel obstruction, diarrhoea, nausea	
Skin and subcutaneous tissue disorders	Rash	Urticaria, pruritus, flushing	
Musculoskeletal and connective tissue disorders		Back pain	
General disorders and administration site conditions		Cytokine release syndrome, pyrexia, rigors, chills, hyperhidrosis, fatigue	

Infections
Infections reported in the pivotal study Hx-CD20-406 were of Grade 1 or 2 in severity in 91 of 154 patients (59%).
A total of 31 (20%) subjects had 39 Grade 3 infections (in 27 subjects, these events were also reported as SAEs). In 8 subjects with Grade 3 infections, the events were considered drug-related by the investigator (pneumonias: 4 subjects; septic complication: 1 subject, other infections: 3 subjects). Six of these infections were also reported as SAEs.
Eight of 154 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 were considered drug-related (pneumonias: 3 subjects; septic complication: 1 subject, other infections: 2 subjects).
Grade 5 (fatal) infections occurred in 16 subjects (10%) during treatment or follow-up; 9 occurred within 30 days of the last dose of ofatumumab, 5 occurred within 30 to 60 days after last dose of ofatumumab, and 2 occurred beyond 60 days after the last dose of ofatumumab. During extended follow-up, an additional 14 subjects (9%) died due to infection (6 pneumonia, 7 sepsis, 1 aspergillus infection). Two of these 14 deaths occurred in close proximity (i.e., within 30 days) to last dose, one being categorized as an early death (defined as occurring within 8 weeks of starting treatment). Both deaths occurred after the start of new CLL therapy (one patient started on high dose steroids and died 38 days after the last dose, and the other started on high dose steroids and lenalidomide and died 32 days after the last dose.
A total of 40 (26% of 154) subjects had infections that required hospitalization and IV antibiotics.
A total of 24 of 154 subjects (16%) had 27 infections that were considered opportunistic based on clinical practice. All but one serious opportunistic infection occurred in non-responders. The opportunistic infections that were serious included herpes zoster, aspergilloma, fusarium infection, pneumocystis jiroveci pneumonia, fungal pneumonia and PML.
Factors associated with higher frequency and/or increased severity of infection included advanced stage of the disease, high number of prior treatments and baseline neutropenia (especially severe).
In the dose escalation supportive study Hx-CD20-402, 16 subjects (48%) had infections reported as AEs. Respiratory tract infections were the most common events, occurring in 10 of 33 subjects (30%). In contrast to the pivotal study, infections of the upper respiratory tract were more common (9 subjects, 27%) than lower respiratory tract infections (1 subject, 3%). The most common upper respiratory infection was nasopharyngitis occurring in 5 subjects (15%). Other infections occurred in 7 subjects (21%). There were no cases of sepsis reported.
A total of 3 subjects had 4 infections that were considered to be related to study treatment: one subject had herpes zoster and pustular rash, one subject had upper respiratory tract infection, and one had varicella. Three subjects reported infectious SAEs: Grade 3 herpes zoster, Grade 3 pneumonia, and Grade 2 event of sinusitis. Three subjects had Grade 5 (i.e., fatal) infections. One subject had ILD during the main study period and 2 subjects had pneumonia after completion of the study.

Infusion reactions
In the pivotal study, 41% of subjects had infusion reaction AEs following the first infusion declining to 6% for the last infusion. One subject stopped treatment due to an infusion reaction. The events were usually mild (≤Grade 2). Seven subjects had infusion reactions classified as SAEs. There were no deaths due to infusion reactions. Anaphylactoid events included 5 patients with cytokine release syndrome, all but one subject had cytokine release syndrome during their first infusion.

- Serious adverse event/deaths/other significant events

Pivotal Study HX-CD20-406
A summary of SAEs experienced by more than one subject during treatment or follow-up in study Hx-CD20-406 is shown in Table 26.

Table 26: Summary of SAEs experienced by More Than One Subject during Treatment or Follow-up (Excludes SAEs During Extended Follow-up) in 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)
Haemolytic anaemia	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)

Predominant SAEs reported during extended follow-up, i.e., after treatment withdrawal or withdrawal from follow-up, were infections (6 DR, 7 BFR, and 2 Other subjects) and disease progression/CLL (4 DR, 6 BFR, 0 Other subjects).
A total of 25 (16%) subjects had 39 SAEs that were considered by the investigator to be related to ofatumumab (11 subjects in the DR group, 8 in the BFR group, 6 in the Other group).

Supportive CLL Study (Hx-CD20-402) and CLL Combination Study (Hx-CD20-407)
Nine of 33 subjects (27%) had 10 SAEs during study Hx-CD20-402; the majority were in the 2000 mg group: neutropenia (2), haemolytic anaemia, carotid artery stenosis, angina pectoris, ILD, pneumonia, herpes zoster, sinusitis and cytolytic hepatitis. Five SAEs were considered drug-related: herpes zoster, 2 events of neutropenia, ILD and cytolytic hepatitis.
For the combination therapy study Hx-CD20-407, 12 subjects (43%) had 23 SAEs. The most common SAEs were neutropenia (5) and febrile neutropenia (3). Four of the subjects had drug-related SAEs: rhabdomyolysis, neutropenia, fungal pneumonia and decreased neutrophil count.

Deaths
A summary of all deaths observed in all ofatumumab studies is presented in the following Table 27.

Table 27: Number of deaths in all ofatumumab studies

Study ID	Number of patients	Number of deaths	Deaths during treatment	Deaths after withdrawal	Related (R) / Not related (NR)/ Not available (NA)
CLL studies					

Hx-CD20-406	154	61 (40 %)			4 R/ 19 NR/ 38 NA
Hx-CD20-402	33	3 (9 %)	1	2	1 R / 2 NR
Hx-CD20-407	28	0			
FL studies					
Hx-CD20-001	40	2 (5 %)		2	NR
Hx-CD20-405	76	5 (7 %)	3	2	3 R / 2 NR
Hx-CD20-409	33	0			
Other oncology Indications					
GEN415/DLBCL	4	0			
Non-oncology Indications					
Hx-CD20-403 / RA	201	0			
GEN410 / RA	54	0			
GEN411 / RA	12	0			
GEN413 / RA	10	0			
Hx-CD20-408 / COPD	5	0			

A total of 61 subjects (clinical cut-off 19 May 2008) died during the pivotal study Hx-CD20-406); 24 during treatment or follow-up and 37 during the extended follow-up (7 before and 30 after initiation of new CLL treatment). Most subjects died >60 days after the last dose of ofatumumab (Table 16) including 2 subjects who died >1 year after last dose of ofatumumab. In addition, four deaths (disease progression, pulmonary oedema, cardiac arrest and bladder cancer) occurred after the clinical cut-off date. Seven deaths occurred during the extended follow-up, with no specific diagnosis given as cause of death. Six subjects died within 8 weeks after the start of treatment (i.e., early death): 1 due to pneumonia (after initiation of new CLL therapy), 2 due to sepsis, 1 each due to fungal pneumonia, fusarium infection and myocardial infarction. None of these early deaths were considered related to treatment by the investigator.

Table 28: Summary of Deaths, Analyzed by Days after Last Infusion in Study Hx-CD20-406

Days From Last Infusion	DR (N=59)	BFR (N=79)	Other (N=16)	Total (N=154)
Number of deaths	n=27	n=31	n=3	n=61
Early deaths[1], n (%)	**4 (7)**	**2 (3)**	**0**	**6 (4)**
1 – 30 days, n (%)	**4 (7)**	**3 (4)**	**1 (6)**	**8 (5)**
>30 – 60 days, n (%)	**5 (8)**	**1 (1)**	**1 (6)**	**7 (5)**
>60 days, n (%)	**14 (24)**	**25 (32)**	**1 (6)**	**40 (26)**

1. Early death defined as occurring within 8 weeks of start of treatment.

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. The most common infections were septic complications (15 subjects) and pneumonia (10 subjects). Of all deaths in this study four cases were considered related to treatment by the investigator: sepsis, pneumocystis jiroveci pneumonia, pneumonia, PML.

The remaining eight deaths were caused by disease progression, including CLL transformation and hemiparesis in 6 subjects and cardiac events in 2 subjects during treatment or follow-up.

In the supportive CLL study Hx-CD20-402, there were 3 deaths, one during treatment and 2 after withdrawal from the study. One subject died of ILD 29 days after the last dose of ofatumumab; this fatal SAE was considered drug-related. This subject had a 10-year history of CLL, had 4 prior treatments for CLL, prior treatment for chronic hypogammaglobulinemia, and had several episodes of pneumonia (interstitial pneumopathy) prior to entry into the study. The investigator considered the event to be drug-related. Two subjects died after withdrawal from the study (pneumonia, disease progression). These events were not considered related to treatment.

There have been no deaths in the CLL combination study (Hx-CD20-407) or the FL combination study (Hx-CD20-409) as of the cut-off date of 14 April 2008. Seven deaths were reported in the FL monotherapy studies (Hx-CD20-001, Hx-CD20-405), none of which were considered related to treatment. Three deaths occurred on study and were caused by disease progression (2 cases, 63 days

and 6 months after last dose) and sepsis (37 days after last dose). Four cases occurred after withdrawal from study and were caused by sepsis, disease progression (2) and peritonitis.

Immunogenicity
Subjects were tested for Human anti-Human Antibodies (HAHA) at baseline, and at the indicated times over the course of the individual studies. A positive result was defined as an 8-fold increase over the baseline titre of HAHA.
There were no reports for the development of HAHA in any of the CLL studies. Of the 3 studies in Folicular Lymphoma (FL), one patient in one study was scored HAHA positive (8-fold increase in titre) in a single instance. In the Rheumatoid Arthritis (RA) study, one patient had a positive result (16-fold increase in titre) at a single instance, which was not confirmed using the whole ofatumumab binding antibody clinical assay.

- Laboratory findings

Haematologic Assessments
A decrease in the median neutrophil count within the first few weeks of ofatumumab treatment was evident. The neutrophil count in subjects with baseline neutropenia did not appear to worsen during the treatment period. Neutropenia, including Grade 3 or 4 neutropenia, was observed in subjects with baseline neutropenia as well as in some subjects with a normal neutrophil count at baseline. Decrease in the neutrophil count (including AEs with the preferred terms neutropenia, neutropenic sepsis, neutrophil count decreased, and febrile neutropenia) has been associated with anti-CD20 antibody therapy and it was reported in the pivotal study in 19% of subjects in at least one instance.
Anaemia was observed as an AE in 19% of subjects although many had anaemia at baseline. However, no decrease in median hemoglobin values and no clinically meaningful shifts to worse CTC grades were observed in the study population. On the contrary, there was evidence for an increase in median haemoglobin values during the 52 week observation period.
Thrombocytopenia was observed as an AE in 2 (1%) subjects and both were thrombocytopenic at baseline. However, no decrease in median platelet count and no clinically meaningful shifts to worse CTC grades were observed in the study population. On the contrary, there was evidence for an increase in median platelet counts during the 52 week observation period.

Biochemistry Assessments
Forty percent (40%) of patients had elevated values for uric acid of at least Grade 3 intensity, which is not unexpected due to the rapid cell destruction induced by ofatumumab. Three patients had hyperuricemia reported as an AE of which one was considered by the investigator to be related to ofatumumab. Despite these results, no AEs of tumour lysis syndrome were reported as of the cut-off date (19 May 2008).
Of the 6 patients who had AEs associated with potassium levels, none of these AEs were considered related to ofatumumab by the investigator. For the 5 patients that had laboratory transitions from Grade 0, 1 or 2 at baseline to Grade 3 or 4 on study, all normalized and none of these patients had concomitant AEs related to cardiac dysfunction.
A total of 3 patients had decreased laboratory values for sodium. Each of these patients had a single Grade 3 sodium value. One of these 3 abnormal sodium values was reported by the investigator as an AE considered by the investigator to be related to ofatumumab. The same patient also had arrhythmia reported on study day 86 during the dosing period, 5 days prior to laboratory assessment that revealed decreased sodium.
Three patients had creatinine abnormalities that were reported as adverse events. None of these abnormalities were >Grade 2 and patients recovered from each event.
Grade 3 hepatobiliary abnormalities were observed in 1% of the 154 subjects. There were no Grade 4 hepatobiliary abnormalities reported. No subject had concurrent elevation of GPT (ALT) and total bilirubin.

- Safety in special populations

Adverse events were analysed in the pivotal study by age. The incidence of AEs was higher in subjects ≥65 years of age compared with the younger subject population. Overall, the incidence of AEs was

92% in subjects <65 years of age, 98% in subjects ≥65 years of age, and 94% in subjects ≥75 years of age. There were few notable differences in the AE profile based upon age, though interpretation is limited by the small number of subjects in the oldest age group and the small number of subjects with AEs in each age (data not shown).
Among all subjects in the pivotal study, the overall incidence of AEs was similar in male subjects and female subjects. Male subjects had higher rates of respiratory tract infections and fatigue while female subjects had higher rates of anaemia (data not shown).
The majority (94-97%) of subjects in all studies were Caucasian. Therefore, no meaningful clinical conclusions can be drawn from analyses of AEs by race.
No specific studies of the effect of renal or hepatic impairment have been submitted with ofatumumab, nor has it been administered to subjects with significant hepatic or renal impairment.
No studies addressing the effect of ofatumumab on male and female fertility and on pregnant and lactating women were submitted. No information on the use of ofatumumab in children or adolescents was submitted.

- Safety related to drug-drug interactions and other interactions

No studies were submitted (see discussion on clinical safety).

- Discontinuation due to adverse events

In the pivotal Study Hx-CD20-406, 27 (17%) of 154 subjects had AEs that led to withdrawal from treatment (21 subjects) or follow-up (6 subjects) as of the data cut-off date of 19 May 2008. 14 subjects discontinued due to fatal infections (8 DR subjects, 5 BFR subjects, 1 Other subject). 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 higher in the DR group than in the BFR group (DR: 11/59 [19%]; BFR: 8/79 [10%], respectively). In the Other group, 3/16 subjects (19%) had an AE that led to withdrawal.
The majority of subjects had AEs leading to discontinuation that were considered by the investigator to be not 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 (neutropenia).
Nineteen subjects had 20 SAEs resulting in withdrawal from treatment or follow-up and 11 subjects were withdrawn due to SAEs with fatal outcome.

- Post marketing experience

Not applicable.

- Discussion on clinical safety

The CHMP considered that the safety profile of ofatumumab could not be sufficiently characterised due to the uncontrolled design of the pivotal trial. Particular concern was raised with regard to infections and deaths, the latter resulting primarily from infections. The SAG Oncology was consulted as to whether the safety profile was sufficiently evaluated. The SAG considered that this toxicity is not unacceptable compared to other salvage regimens that are commonly used in this setting, based on the literature. For instance, Tam et al reporting on 58 fludarabine and alemtuzumab refractory CLL patients treated at a single institution found that early deaths (defined as death within 8 weeks of starting therapy) occurred in 16% of patients and 60% of patients suffered major infections. The phase II study reported by Perkins et al (2002), although on 27 patients, reports 89% severe infections and 48% fatal infections. The SAG agreed by consensus that for patients with double-refractory disease, the toxicity profile has been sufficiently evaluated and is considered acceptable.

Ofatumumab was 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. Infusion reactions may include anaphylactoid events, 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, were reported. In cases of severe infusion reaction, the infusion must be interrupted immediately and symptomatic treatment instituted.

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 (see SPC section 4.2 and 4.4).

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 (see SPC section 4.2).

Patients should be premedicated prior to Arzerra infusion according to the dosing schedule described in the SPC (see SPC section 4.2).

Arzerra is contraindicated in case of hypersensitivity to ofatumumab or to any of the excipients (see SPC section 4.3).

In patients with CLL, tumour lysis syndrome (TLS) may occur with use of ofatumumab. Management of TLS includes correction of electrolyte abnormalities, monitoring of renal function, maintenance of fluid balance and supportive care (see SPC section 4.4).

Progressive multifocal leukoencephalopathy (PML) and death has been reported in CLL patients receiving cytotoxic pharmacotherapy, including ofatumumab. A diagnosis of PML should be considered in any patient who reports the new onset of or changes in pre-existing neurologic signs and symptoms. If a diagnosis of PML is suspected ofatumumab should be discontinued and referral to a neurologist should be considered (see SPC section 4.4).

The safety of, and ability to generate a primary or anamnestic response to, immunisation with live attenuated or inactivated vaccines during ofatumumab 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 ofatumumab, until B cell counts are normalized. The risks and benefits of vaccinating patients during ofatumumab therapy should be considered (SPC sections 4.4 and 4.5).

Hepatitis B infection (HBV), including fatal infection, can occur in patients taking ofatumumab. 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 treatment. Carriers of hepatitis B should be closely monitored for clinical and laboratory signs of active HBV infection during treatment with and for 6-12 months following the last infusion. Treatment should be discontinued in patients who develop viral hepatitis, and appropriate treatment should be instituted. Insufficient data exist regarding the safety of administration of ofatumumab in patients with active hepatitis (see SPC section 4.4).

Patients with a history of cardiac disease should be monitored closely. Ofatumumab should be discontinued in patients who experience serious or life-threatening cardiac arrhythmias (see SPC section 4.4).

Bowel obstruction was reported in patients receiving anti-CD20 monoclonal antibody therapy, including ofatumumab. Patients who present with abdominal pain, especially early in the course of therapy, should be evaluated and appropriate treatment instituted (see SPC section 4.4).

Since ofatumumab binds to all CD-20-positive lymphocytes (malignant and non-malignant), complete blood counts and platelet counts should be obtained at regular intervals during therapy and more frequently in patients who develop cytopenias (see SPC section 4.4).

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 (see SPC section 4.4).

There are no data from the use of ofatumumab in pregnant women. The effect on human pregnancy is unknown. Besides an expected pharmacological effect, i.e., depletion of B-cells, animal studies do not indicate direct or indirect harmful effects with respect to maternal toxicity, pregnancy or embryonal/foetal development (see section 5.3). Pre- and postnatal development studies have not been performed with ofatumumab. Ofatumumab should not be administered to pregnant women unless the possible benefit to the mother outweighs the possible risk to the foetus. Women of childbearing potential should use effective contraception during and for at least 6 months after the last ofatumumab treatment (see SPC section 4.6).

The safe use of ofatumumab in humans during lactation has not been established. The excretion of ofatumumab in milk has not been studied in animals. It is not known whether ofatumumab is secreted in human milk; however, human IgG is secreted in human milk. Published data suggest that neonatal and infant consumption of breast milk does not result in substantial absorption of these maternal antibodies into circulation. Breastfeeding should be discontinued for the duration of treatment with Arzerra unless the possible benefit outweighs the possible risk (see SPC section 4.6).

There are no data on the effects of ofatumumab on human fertility. Effects on male and female fertility have not been evaluated in animal studies (see SPC section 4.6).

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 ADR profile of Arzerra should be borne in mind when considering the patient's ability to perform tasks that require judgement, motor or cognitive skills (see SPC section 4.7).

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan

Table Summary of the risk management plan

Safety concern	**Proposed pharmacovigilance activities**	**Proposed risk minimisation activities**
Identified Risks		
Infusion Reactions Including Cytokine Release Syndrome	Routine pharmacovigilance Evaluation of data on infusion reactions and cytokine release syndrome reported from ongoing and	Warning statements on infusion reactions and cytokine release syndrome are included in Section 4.4 of the SmPC" "Arzerra has been associated with infusion reactions leading to temporary interruption of

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
	all other future clinical studies.	treatment or withdrawal of treatment. Pre-medications attenuate infusion reactions but these may still occur, predominantly during the first infusion. Infusion reactions may include anaphylactoid events, 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 Section 4.2 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." Statements on infusion reactions including cytokine release are included in Section 4.8 "undesirable effects' of the SmPC: "Infusion reactions occurred with the greatest incidence (44%) on the first infusion day (300 mg or 500 mg), decreased to 26% with the second infusion (2000 mg) and declined further during subsequent infusions (2000 mg)."
Tumour Lysis Syndrome (TLS)	Routine pharmacovigilance Evaluation of data on tumour lysis syndrome reported from ongoing and all other future clinical studies.	Warning statements on tumour lysis syndrome (TLS) are included in Section 4.4 of the SmPC: "In patients with CLL, tumour lysis syndrome (TLS) may occur with use of Arzerra. Risk factors for TLS include a high tumor burden, high concentrations of circulating cells ($\geq 25{,}000/mm^3$), hypovolemia, 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." In Section 4.8 'Undesirable effects' of the SmPC, tumour lysis syndrome is listed as an uncommon ($\geq$1/1000 to <1/100).
Bowel Obstruction	Routine pharmacovigilance Evaluation of data on bowel obstruction reported from	Warning statements on bowel obstruction are included in Section 4.4 of the SmPC: "Bowel obstruction has been reported in patients

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
	ongoing and all other future clinical studies. Targeted Follow Up Questionaire	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." In Section 4.8 'Undesirable effects' of the SmPC, small bowel obstruction is listed as common (≥1/100 to <1/10).
Cardiovascular Events	Routine pharmacovigilance Evaluation of data on cardiovascular events reported from ongoing and all other future clinical studies.	Warning statements on cardiovascular events are included in Section 4.4 of the SmPC: "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." In Section 4.8 'Undesirable effects' of the SmPC, tachycardia, hypertension and hypotension are listed as common (≥1/100 to <1/10).
Potential Risks		
Cytopenias	Routine pharmacovigilance Evaluation of data on haematologic parameters reported from ongoing and all other future clinical studies.	Warning statements on laboratory monitoring are included in Section 4.4 of the SmPC: "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."
Infections	Routine pharmacovigilance. Evaluation of all infectious adverse events reported from ongoing and all other future clinical studies.	Section 4.8 Undesirable Effects of the SmPC includes incidence of infections: "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
PML	Routine pharmacovigilance Evaluation of data on PML reported from ongoing and all other future clinical studies. Targeted Follow Up Questionaire	Warning statements on laboratory monitoring are included in Section 4.4 of the SmPC: "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."

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Hepatitis B Virus (HBV) Reactivation	Routine pharmacovigilance Evaluation of data on HBV reactivation reported from ongoing and all other future clinical studies.	Warning statements on laboratory monitoring are included in Section 4.4 of the SmPC: "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 Arzerra and for 6-12 months following the last infusion of Arzerra. Arzerra should be discontinued in patients who develop viral hepatitis, and institute appropriate treatment. Insufficient data exist regarding the safety of administration of Arzerra in patients with active hepatitis."
Effect on Immunisations, Including Interactions with Live Vaccines	Routine pharmacovigilance Evaluation of data on effect of ofatumumab on immunisations reported from ongoing and all other future clinical studies.	Warning statements on laboratory monitoring are included in Section 4.4 of the SmPC: "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. The risks and benefits of vaccinating patients during Arzerra therapy should be considered"
Immunogenicity	Routine pharmacovigilance Evaluation of data on immunogenicity reported from ongoing and all other future clinical studies.	Section 5.1 of the SmPC describes the potential for immunogenicity of ofatumumab. "There is a potential for immunogenicity with therapeutic proteins such as Arzerra; however the formation of anti-ofatumumab antibodies may be decreased because ofatumumab is a human antibody that depletes B cells in patients already immunocompromised by CLL. 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." GSK will continue to assess the incidence of formation of anti-ofatumumab antibodies using a bridging design ELISA assay in ongoing and future clinical studies. Immunogenicity risk will continue to be assessed to investigate possible relationships

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
		between antibody formation and treatment outcomes and adverse events.
Effect of HMG-CoA Reductase Inhibitors on Ofatumumab Response	Routine Pharmacovigilance Evaluation of data on ofatumumab response in patients receiving concomitant HMG-CoA reductase inhibitors from post-marketing reports upon completion of ongoing and future clinical trials	GSK will review reports of lack of effect in patients receiving concomitant HMG-CoA reductase inhibitors with ofatumumab reported spontaneously and examine response rates upon completion of ongoing and future clinical trials.
Important Missing Information		
Limited data in pregnant and lactating females	Routine pharmacovigilance Evaluation of data on any pregnancies or lactation reported from ongoing and all other future clinical studies.	Section 4.6 of the SmPC reviews the safety of ofatumumab in pregnancy and lactation. "Pregnancy There are no data from the use of ofatumumab in pregnant women. The effect on human pregnancy is unknown. Women of childbearing potential should use effective contraception during and for at least twelve months after the last ofatumumab treatment. Animal studies do not indicate direct or indirect harmful effects with respect to maternal toxicity, pregnancy or embryonal/foetal development (see Section 5.3). Lactation The safe use of ofatumumab in humans during lactation has not been established. The excretion of ofatumumab in milk has not been studied in animals. It is not known whether ofatumumab is secreted in human milk; however, human IgG is secreted in human milk. Published data suggest that neonatal and infant consumption of breast milk does not result in substantial absorption of these maternal antibodies into circulation. Breastfeeding should be discontinued for the duration of treatment with Arzerra unless the possible benefit outweighs the possible risk.
Limited experience in patients with relevant comorbidities	Routine pharmacovigilance Evaluation of data on comorbidities in patients from ongoing and future clinical studies and post marketing data	Section 4.2 of the SmPC describes the lack of formal studies in renal and hepatic impairment and Section 4.4 describes the warning on use in patients with cardiovascular disease. Posology and method of administration Renal impairment No formal studies of Arzerra in patients with renal impairment have been performed. No dose adjustment is recommended for mild to moderate renal impairment (creatinine clearance

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
		>30 ml/min). (see section 5.2). 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 section 5.2). Special warnings and precautions for use 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.

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of this product is considered to be acceptable when used in accordance with the defined conditions in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.
Commitments are made by the applicant to update some missing information, which does not impact on the risk benefit assessment of the mAb.

Non-clinical pharmacology and toxicology

Ofatumumab is a human monoclonal antibody (IgG1) that 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 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.

Preclinical data reveal no special hazards for humans.
Intravenous and subcutaneous administration to monkeys resulted in the expected depletion of peripheral and lymphoid tissue B cell counts with no associated toxicological findings. As anticipated, a reduction in the IgG humoral immune response to keyhole limpet haemocyanin was noted, but there were no effects on delayed-type hypersensitivity responses. In a few animals, increased red cell destruction occurred as a result of monkey anti-drug antibodies coating the red cells. A corresponding

increase in reticulocyte counts seen in these monkeys was indicative of a regenerative response in the bone marrow.

Intravenous administration of ofatumumab to pregnant cynomolgus monkeys at 100 mg/kg once weekly from days 20 to 50 of gestation did not elicit maternal or foetal toxicity or teratogenicity. At day 100 of gestation, as expected, B-cells were depleted in foetal cord blood and foetal splenic tissues.

As ofatumumab is a monoclonal antibody, genotoxicity and carcinogenicity studies have not been conducted with ofatumumab.

Efficacy

The planned interim analysis of an ongoing pivotal study Hx-CD20-406 (single-arm, open-label, multicentre), and one completed supportive study, Hx-CD20-402 (open-label, dose ranging, multicentre) supported the efficacy of ofatumumab in the treatment of CLL.

In the pivotal trial, ofatumumab was administered as a monotherapy to 154 patients with CLL. Of these 154 patients, 138 were refractory to fludarabine and alemtuzumab therapy (n=59), or were refractory to fludarabine and had bulky lymphadenopathy (defined as at least one lymph node > 5cm) and were inappropriate for alemtuzumab therapy (bulky fludarabine refractory, n=79). Patients received 300 mg Arzerra in the first infusion and 2000 mg Arzerra for all subsequent infusions. The infusion schedule was 8 consecutive weekly infusions, followed 5 weeks later by a single infusion for the following 4 consecutive months. The primary endpoint of this ongoing study was response rate over a 24 week period. The overall response rates were 58% in the fludarabine and alemtuzumab refractory group and 47% in the bulky fludarabine refractory group. All responses were partial remissions, with the exception of one patient in the bulky fludarabine refractory group who achieved a complete remission.

In the supportive trial, 33 patients with relapsed or refractory CLL received 4 weekly infusions of ofatumumab with 27/33 in the highest dose group (1st dose: 500 mg; 2nd, 3rd and 4th dose: 2000 mg). Treatment with ofatumumab led to a 50% objective response rate in the highest dose group and included 12 partial remissions and one nodular partial remission.

Safety

Infections and infusion reactions occurred in 70% and 64%, respectively, of ofatumumab treated CLL patients in the pivotal trial Hx-CD20-406. Other common adverse events were: pyrexia, cough, diarrhoea, neutropenia, anaemia, fatigue and dyspnoea. Infusion reactions occurred with the greatest incidence (44%) on the first infusion day (300 mg or 500 mg), decreased to 26% with the second infusion (2000 mg) and declined further during subsequent infusions (2000 mg). A total of 21% of subjects in the pivotal trial had an adverse event in the Infections and infestations SOC that was considered related to treatment. Symptoms that characterize infusion reactions were considered drug-related in 47% of the subjects.

The most common serious adverse events observed in CLL clinical trials with ofatumumab included infections, neutropenia and febrile neutropenia. The majority of deaths occurred in the course of infection, although it is noted that the disease also predisposes to infection and the minority of infections and infectious deaths were considered related to ofatumumab treatment.

From the safety database all the adverse reactions reported in CLL clinical trials have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

A User Testing Report was submitted. The results and user comments were incorporated in the finalisation of the Package Leaflet and the result is considered satisfactory.

Risk-benefit assessment

Ofatumumab treatment was accompanied by a high response rate in CLL patients refractory to fludarabine and alemtuzumab treatment (58%) and a slightly lower response rate (47%) in fludarabine refractory bulky lymphadenopathy patients for whom aletuzumab therapy is considered inappropriate. At the same time, the use of ofatumumab was accompanied by serious and life-threatening complications (infections and neutropenia), which, however, are also manifestations of the underlying disease, so that the safety profile does not cause particular concern overall. Having considered the argumentation put forward by the Applicant and the recommendation of the oncology Scientific Advisory group (SAG), the CHMP concluded that the benefit-risk of ofatumumab is positive for the double (fludarabine and alemtuzumab) refractory population but not for the fludarabine refractory, bulky lymphadenopathy population. However, there is a need to further confirm the positive benefit-risk in the double refractory population through the conduct of controlled trials in CLL disease settings in which such trials are feasible (fludarabine refractory, bulky lymphadenopathy population and earlier lines of therapy). Thus, the CHMP proposed a conditional marketing authorisation, after having consulted the applicant. The CHMP considered that ofatumumab is both a medicinal product which aims at the treatment of a life-threatening disease and an orphan medicinal product, and therefore falls within the scope of Regulation (EC) No 507/2006. Moreover, the CHMP considered that ofatumumab fulfils the requirements of Article 4 of Regulation (EC) No 507/2006 based on the following grounds:

(a) Efficacy in terms of response rate was demonstrated in a pivotal and a supportive open label, single arm trials conducted in fludarabine and alemtuzumab double-efractory patients. Overall, a response rate of 58% was observed. Treatment with ofatumumab was associated with adverse events indistinguishable from the underlying disease which don't give rise to particular concern. Therefore, the risk-benefit balance of the medicinal product, as defined in Article 1(28a) of Directive 2001/83/EC, is positive.

(b) There is a need to gain more understanding about the benefit-risk profile of ofatumumab. To this end, the applicant will provide comprehensive clinical data from ongoing Phase III randomised, controlled clinical studies in earlier disease settings. In addition, it is important to further confirm the high response rate and control of the disease in the refractory setting through controlled trials and extended ofatumumab treatment. The applicant will conduct a controlled trial comparing ofatumumab against physician's choice in fludarabine refractory, bulky lymphadenopathy patients. After 24 weeks of treatment, patients on the ofatumumab arm will be further randomised to either extended ofatumumab treatment or to observation alone. Finally, the applicant will conduct a Phase IV observational study. The applicant has provided draft proposals and estimated timelines as well as assurance about the feasibility of the last two studies. The timelines of these studies will be confirmed upon submission of the final study protocols within three months of the conditional marketing authorisation date. Thus, it is likely that the applicant will be in a position to provide the comprehensive clinical data.

(c) Currently there are no approved treatment options for fludarabine and alemtzumab refractory CLL patients. Ofatumumab has shown a high response rate and this effect was clinically significant in this patient population. In accordance with the definition of Article 4, paragraph 2, of Regulation (EC) No 507/2006, the medicinal product concerned will be of major therapeutic advantage to those affected. Therefore, unmet medical needs will be fulfilled.

(d) In view of the favourable benefit-risk profile, the immediate availability on the market outweighs the risk inherent in the fact that additional data are still required.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- routine pharmacovigilance was adequate to monitor the safety of the product

- no additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Arzerra in the treatment of Chronic Lymphocytic Leukaemia (CLL) in patients refractory to fludarabine and alemtuzumab was favourable and therefore recommended the granting of the conditional marketing authorisation.

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