European Medicines Agency

SCIENTIFIC DISCUSSION

Invented name/Name: MabCampath
International non-proprietary name/Common name: alemtuzumab

Extension of the indication: treatment of patients with B-cell chronic lymphocytic leukaemia (B-CLL) for whom fludarabine combination chemotherapy is not appropriate

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1. Introduction

Alemtuzumab is a recombinant DNA-derived humanized monoclonal antibody that is directed against the 21-28 kD cell surface glycoprotein, CD52. Alemtuzumab is produced in mammalian cell (Chinese hamster ovary) suspension culture in a medium containing neomycin. Neomycin is not detectable in the final product. Alemtuzumab is a sterile, clear, colourless, isotonic solution for injection.

Alemtuzumab exerts its therapeutic activity by initially binding to the CD52 antigen, which subsequently leads to lysis of target cells by antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-mediated cytotoxicity. Alemtuzumab is a genetically engineered humanized IgG1 kappa monoclonal antibody specific for the antigen CD52, a 21-28 kD lymphocyte cell surface glycosylphosphatidyl-inositol-linked glycoprotein comprised of 12 amino acids. The CD52 gene product is abundantly expressed at approximately 5×10^5 molecules/cell, making it a good target for complement-mediated attack on lymphocytes. It is thought that the efficiency of anti-CD52 antibodies in lympholysis may be due in part to the small size of the CD52 molecule and its lateral mobility due to its GPI-anchorage. The functions of the CD52 antigen are unknown, though it is not present on CD34+ haematopoietic stem cells. Since alemtuzumab does not deplete haematopoietic stem cells, immune system reconstitution follows therapy.

MabCampath (alemtuzumab) was granted a marketing authorisation at the 6th of July 2001 for the treatment of patients with chronic lymphocytic leukaemia (CLL) who have been treated with alkylating agents and who have failed to achieve a complete or partial response or achieved only a short remission (less than 6 months) following fludarabine phosphate therapy.

The Marketing Authorisation was granted "under exceptional circumstances" because it would be contrary to generally accepted principles of medicinal ethics to perform comparative Phase III trials in patients who have failed previous treatment therefore no alternative comparator exists. A comparison to best supportive care/placebo was not considered an option at the time of approval. The MAH agreed to provide, as requested by the CHMP, data that was to form the basis of a re-assessment of the benefit/risk ratio of MabCampath. The study, CAM307 a phase III study entitled “A Phase III study to evaluate the efficacy and safety of front-line therapy with alemtuzumab vs chlorambucil in patients with progressive B-cell chronic lymphocytic leukaemia”. Updates from the study have been submitted on a yearly basis as a part of the annual reassessment procedure. The study enrolled 297 patients by July 2004, when enrolment was stopped. Database lock occurred August 2006 and the final clinical study report has now been submitted for evaluation in order to get approval for a first-line indication in B-CLL.

2. Clinical aspects

Chronic Lymphocytic Leukaemia (CLL) is a neoplastic disorder characterized by increased numbers of clonal leukaemic cells that appear as mature lymphocytes. In most cases, these cells express B-cell markers, have prolonged cell survival, and accumulate in the blood, bone marrow, and lymphatic organs. As a result, patients with this disease commonly present with lymphocytosis, lymphadenopathy, splenomegaly and symptoms of fatigue, weight loss and malaise. As the disease progresses bone marrow replacement by the disease process leads to anaemia, neutropaenia and thrombocytopenia.

Patients with CLL are generally immunosuppressed due to both the underlying disease and the toxicity of prior chemotherapies. As a result of this immuosuppression, infection is a major cause of morbidity and mortality in CLL. Up to 80% of patients with CLL will experience an infection, ranging from moderate to life threatening, during the course of their disease and infection accounts for up to 60% of the deaths of these patients. The stage of disease (i.e. Rai or Binet stage) and intensity of previous therapy is clearly correlated with the incidence of infection and median survival in these patients. The survival of CLL patients greatly varies with the stage of their disease.

Treatment of chronic lymphocytic leukaemia (CLL) ranges from periodic observation with treatment of infectious, hemorrhagic, or immunologic complications to a variety of therapeutic options,

including steroids, alkylating agents (chlorambucil=CLB), purine analogues (fludarabine, cladribine or pentostatin), combination chemotherapy, monoclonal antibodies (alemtuzumab or rituximab), and transplant options. Because this disease is generally not curable, occurs in an elderly population, and often progresses slowly, it is most often treated in a conservative fashion. In asymptomatic patients, treatment may be deferred until the patient becomes symptomatic as the disease progresses.

A meta-analysis of randomised trials showed no survival benefit for immediate versus delayed therapy for patients with early stage disease, nor for the use of combination regimens incorporating an anthracycline compared with a single-agent alkylator for advanced stage disease. (J Natl Cancer Inst 91 (10): 861-8, 1999). However, most randomised studies including one from the French Cooperative Group on CLL have showed higher or equivalent response rates for fludarabine as compared to CLB or CAP (cyclophosphamide, doxorubicin, prednisone) and most showed an improvement in progression-free survival, though none showed an advantage in OS. Therefore, current first-line therapy includes fludarabine although it must be recognised that purine analogues are more toxic than CLB in terms of granulocytopenic infections, herpes infections, autoimmune haemolytic anaemia, and persistent thrombocytopenia. The increased risk of infection may persist for months or years after treatment with a purine analogue.

As stated previously, among large randomised prospective trials of untreated patients, almost all have demonstrated statistically significant improvements in response rates, event-free survival, and progression-free survival, but no trial has shown statistically significant improvement in OS.

Clinical studies
CAM307, A Phase III Study entitled, "A Phase III Study to Evaluate the Efficacy and Safety of Front-line Therapy with alemtuzumab (Campath®, MabCampath®) vs Chlorambucil in Patients with Progressive B-Cell Chronic Lymphocytic Leukaemia", was initiated to confirm the clinical benefit of alemtuzumab in the treatment of B-CLL and provide substantial evidence in support of the use of alemtuzumab as first-line therapy. The first patient was enrolled in December 2001, and enrolment was completed with a total of 297 patients in July 2004. The last study treatment was administered in May 2005.

The primary objective was to demonstrate that MabCampath is superior to chlorambucil as front-line therapy in patients with progressive B-CLL as measured by progression-free survival (PFS). Secondary objectives were to evaluate complete response (CR) and overall response rates (ORR), duration of response, time to alternative treatment, survival, safety, and time to treatment failure.
CAM307 was conducted in Croatia, Czech Republic, Estonia, France, Ireland, Italy, Lithuania, the Netherlands, Poland, Serbia, Slovakia, United Kingdom, and the United States, and met the ethical requirements of Directive 2001/20/EC.

In addition, two more sponsored studies are ongoing:
CAM314 study is a Phase III, prospective, multicenter, open-label, randomized, controlled study to evaluate and compare the efficacy and safety of fludarabine plus alemtuzumab vs fludarabine alone as second-line therapy in patients with B-CLL. An estimated 300 patients from investigational sites in the North America and Europe will be entered into the study. Patients will be randomized on a 1:1 basis to one of the two treatment arms.

CAM203 is a Phase II, open-label, prospective, multicenter study of subcutaneously (SC) administered alemtuzumab as therapy for B-CLL patients who have been previously treated. This ongoing study is designed to assess safety, efficacy, pharmacokinetics, and immunogenicity in previously treated B-CLL patients. At least 85 patients will be enrolled from investigational sites worldwide. This study is also designed to explore the requirement for dose escalation (3, 10, 30 mg) at the beginning of therapy.

2.1. Clinical pharmacology

The pharmacokinetic characteristics of alemtuzumab have been described based on data derived from studies conducted in B-CLL patients. Alemtuzumab pharmacokinetics were originally characterized in a study of 30 alemtuzumab-naïve patients with B-CLL who had failed previous therapy with purine analogues, in which alemtuzumab was administered as a 2-hour IV infusion, at the recommended dose and schedule, starting at 3 mg and increasing to 30 mg three times per week for up to 12 weeks. Alemtuzumab pharmacokinetics displayed nonlinear elimination kinetics. After the last 30 mg dose, the mean volume of distribution at steady-state was 0.1 to 0.4 L/kg. Systemic clearance decreased with repeated administration due to decreased receptor-mediated clearance (i.e., loss of CD52 receptors in the periphery). After 12 weeks of dosing, patients exhibited a seven-fold increase in mean AUC. The mean half-life was 2 to 32 hours after the first 30 mg dose and was 1 to 14 days after the last 30 mg dose.

While pharmacokinetic data were not collected in the submitted study CAM307, the expression of CD52, the target antigen on B-CLL cells recognized by alemtuzumab, following exposure of patients to alemtuzumab was assessed, as was the potential immunogenicity of alemtuzumab in patients randomized to the alemtuzumab arm of the trial. Following analyses were performed:

- Assessment of the incidence of loss of CD52 expression at the time of relapse or disease progression during or following alemtuzumab therapy.
- A quantitative analysis of the incidence and magnitude of HAHA and antiidiotypic antibodies at study entry and following exposure to alemtuzumab.

CD52 expression

The emergence of CD52-negative lymphocytes (note: not leukaemia cells) following alemtuzumab therapy has been reported in both RA patients and leukaemia (B cell NHL and B-CLL) patients. The primary intent of the assessment of the incidence of loss of CD52 expression at the time of relapse or disease progression during or following alemtuzumab therapy was to determine whether patients who recur have loss of CD52 expression on their malignant cells. These data are relevant to the consideration of patient populations who received alemtuzumab as the primary therapy and are candidates for re-treatment with alemtuzumab for second line therapy. Potential mechanisms for loss of CD52 expression, in vitro studies using the Wien 133 cell line were published by Rowan, et al. in 1998. Rowan, et al. concluded that the defect in the Wien 133 cells is reversible, with an unclear molecular mechanism.

The CAM307 protocol directed that flow cytometry evaluation of peripheral blood and bone marrow aspirate, when available, was to be done on study and during follow-up. This evaluation included markers to identify clonal tumour cells, including CD52 expression and CD3 subsets to analyze T-cell subpopulations. Follow-up flow cytometry performed after the end of study drug administration (at 1, 2 , 6 and 24 months post therapy) was also to be performed to assess the emergence of CD52 negative clones when patients relapse as well as recovery of T-cell populations. There was no protocol-mandated measurement of CD52 expression at the time of documented relapse or progression. However, analyses have been performed to evaluate whether there is any relationship between CD52 expression measured at the protocol specified time points (1, 2, 6 and 24 months) and patients' date of relapse or progression.

The loss of CD52 expression on tumour cells was assessed for any sample where at least 1% of the total cell population analyzed was comprised of B-CLL cells, defined by the cell population that co-expressed CD5 and CD19. For these samples, concomitant loss of CD52 expression (i.e. 0% expression of CD52) on the CD5+/CD19+ population defined "loss of CD52 expression". This definition applies stringent criteria to "loss of CD52 expression," and may not fully account for transient emergence of a CD52- negative clone(s) or clones that do not fully replace the entire B-CLL population.

However, given that the preponderance of values at or near the time of progression was at or near 100%, there is little evidence that such clones, even if they did transiently exist, succeeded in

emerging to any significance as assessed in this study population. Of the CD52 data available at any time point in patients who received alemtuzumab, loss of expression was observed in only 4 patients, two of which have progressed and this loss was observed only during active alemtuzumab therapy. However prior to progression, CD52 expression returned to essentially 100%.

With relevance to the intent of this analysis, CD52 expression had recovered in both of the patients who progressed prior to their relapse, and therefore, apparent loss of CD52 expression at or near the time of progression has not been observed in any patient. In patients treated with alemtuzumab for whom data are available at or near the time of progression (n=31), the median CD52 expression within ± 30 days of progression was the same, i.e. 100%, in both the alemtuzumab and chlorambucil arms. An expanded analysis of patients for whom CD52 expression data were available from 30 days prior to any time after progression yielded similar results; the median remained at 100%. Of these 44 patients, only 2 had CD52 expression ≤90%.
Five patients on the alemtuzumab arm appeared to be primary refractory to alemtuzumab therapy, i.e. their best response to treatment was progression. No loss of CD52 expression was observed in these patients.

Immunogenicity of alemtuzumab
The potential for immunogenicity of recombinant therapeutic proteins exists, with the underlying concern that development of antibodies may affect therapeutic outcomes. In trials supporting the original approvals, anti-alemtuzumab antibodies were measured in previously treated B-CLL patients and these data revealed minimal levels of immunogenicity (4 out of 211 (1.9%)) in this patient population. The levels of antibody measured in three of the four patients were low (164 to 262 U/mL; the limit of detection reported for the assay at that time was 160 U/mL). One patient was antibody negative up to one month post-treatment then developed a high concentration of anti-MabCampath antibody 5 months post-treatment, measured at a single time point.

As first line patients may be less immunocompromised than previously treated patients, there was a potential that these patients could have a greater risk of developing anti-MabCampath antibodies. To examine the potential for immunogenicity in the first line population with an expanded database, the incidence of anti-MabCampath antibodies was monitored in CAM307 by enzyme-linked immunosorbent assay (ELISA) and samples that tested positive by ELISA were further analyzed using an anti-MabCampath neutralizing antibody assay.

Patient samples from CAM307 were analyzed using a human anti-human antibody (HAHA) ELISA, wherein test samples are incubated in microtitre plates coated with alemtuzumab and bound antiglobulin is detected using biotin-labelled alemtuzumab and avidin-peroxidase. The ELISA response is standardized using an anti-idiotype monoclonal antiglobulin. Samples that tested positive by ELISA were further analyzed using an anti-MabCampath-neutralizing antibody assay. A total of 539 samples from 125 MabCampath-treated patients were analyzed. Overall, 13 samples from 11 patients in CAM307 tested positive (> 444 U/mL) for anti-MabCampath antibody. At baseline, anti-MabCampath antibody results were available for 125 patients; among them 1/125 patient (0.8%) tested positive. At the first and second month post-treatment evaluations, 3/117 patients (2.6%) and 3/112 patients (2.7%) tested positive, respectively. At the sixth month post-treatment evaluation, 6/102 patients (5.9%) tested positive. Overall, a total of 11 out of 133 patients tested (8.3%) had a positive anti-MabCampath antibody result during the follow up period. All of the 13 positive samples were tested using the neutralizing HUT-72 assay. Two of the 12 post-dose samples tested were weakly positive for neutralizing antibodies. These were found to have neutralizing titres of 1 (at 6 months follow-up) and 100 (at 2 months follow-up), respectively.

To assess whether development of anti-alemtuzumab antibodies had any effect on efficacy, patients who were anti-alemtuzumab antibody positive at any time point were evaluated for response outcomes. Based upon the IRRP assessment of response, only one (of 11) patient that tested positive for the anti-alemtuzumab antibody at the 2-month follow-up time did not respond to alemtuzumab therapy. This non-responder was non-evaluable; the patient was only on treatment for 11 days and refused further treatment due to adverse events. The remaining patients that tested positive for anti-

alemtuzumab antibodies during the follow-up period were all responders to alemtuzumab treatment (7 partial responses, 3 complete responses).
Ten of the eleven patients who were antibody-positive did have adverse events that were potentially infusion-related (e.g. fever, chills); most of these events were Grade 1 or 2. However, events in four patients were Grade 3: fever, hypertension, and dyspnea. In addition, there was a grade 4 event of a drug-related anaphylaxis that was considered potentially infusion-related.

2.2. Clinical Efficacy

The data presented in this application to support the first-line indication in B-CLL results from the clinical study **CAM307.** This was a Phase III, open-label, multicenter, randomized, comparative study of MabCampath versus chlorambucil as front line therapy in patients with progressive B-CLL. Eligible patients were to have previously untreated, Rai stage I-IV disease, and be experiencing progression of their B-CLL requiring treatment. Patients were randomized on a 1:1 basis to 1 of 2 treatment arms, Arm A for MabCampath and Arm B for chlorambucil. Patients enrolled in Arm A were treated to a maximum of 12 weeks with MabCampath. Patients enrolled in Arm B were treated to a maximum of 12 months with chlorambucil. Response to treatment was to be determined by the investigator based on the 1996 NCIWG criteria. The investigator was to determine the date of progression for each patient based on the definitions provided in the protocol. During the post-treatment follow-up period, all patients were to be evaluated for the assessment of disease status, safety, and survival.

Patients were to be randomly assigned on a 1:1 basis to one of two treatment arms. Treatment was to begin within 7 days following randomization.

- Treatment arm A: MabCampath 30 mg IV; three times per week, up to 12 total weeks, inclusive of any dose escalation periods
- Treatment arm B: Chlorambucil 40 mg/m2 PO once every 28 days, up to a maximum of 12 months

MabCampath was to be administered intravenously (IV) at a daily starting dose of 3 mg. The dose was to be increased to 10 mg when the dose was well tolerated; the same procedure was to be followed when the dose was increased from 10 mg to 30 mg. All subsequent doses of MabCampath were to be 30 mg administered three times per week for up to 12 weeks, inclusive of dose escalation period(s).

The primary objective of this study was to demonstrate that MabCampath is superior to chlorambucil as front-line therapy in patients with progressive B-CLL as measured by progression-free survival (PFS).
The secondary objectives of this study are to evaluate:
• Complete response (CR) and overall response rate (ORR) using the 1996 National Cancer Institute Working Group (NCIWG) criteria,
• duration of response,
• time to alternative treatment,
• survival,
• safety, and
• time to treatment failure.

The efficacy of study treatment was to be determined by assessing progression free survival (PFS), disease response using the NCIWG response criteria, overall survival, duration of response, time to treatment failure, and time to alternative therapy.
The safety of study treatment was to be assessed by monitoring the incidence, severity, and type of adverse events. The changes in physical examination results, incidence of infection, vital signs, bone marrow toxicity, and clinical laboratory results were to be evaluated. The NCI Common Toxicity Criteria (CTC) (version 2.0, 30 April 1999) was to be used by the investigator to grade adverse events.

The planned sample size of this study was 284 patients (142 per treatment arm). Patients were to be randomized on a 1:1 basis to receive either MabCampath (Arm A) or chlorambucil (Arm B). Total enrollment: 297 (213 male; 84 female); Arm A: 149 (50%) and Arm B: 148 (50%)

Patients were to be randomized to receive either MabCampath or chlorambucil as controlled by the IVRS for all study sites. Randomization was to be accomplished by utilizing the minimization (adaptive randomization) method described by Pocock and Simon using a randomization probability parameter of 0.80. Patients were to be allocated to a cohort group according to a set of predefined variables that would assure a balanced population between the 2 groups. The process of minimization is superior to conventional randomization in that balance can be achieved over a larger number of variables than can otherwise occur through conventional stratified randomization. The system was to be tested and validated according to standard life cycle development process guidelines.
This randomization methodology would ensure a balance between treatment arms by study centre, by Rai stage: (Rai I-II; Rai III-IV), by performance status (WHO = 0 or 1; WHO = 2) By age (<65; ≥65), by gender and by maximum lymph node size (none palpable or <5 cm; ≥5 cm)

All randomized patients were to be evaluated for efficacy on an intent-to-treat (ITT) basis. The primary efficacy endpoint in this study was PFS, defined as the time from randomization date to first objective documentation of disease progression or death due to any cause. This study was designed to detect a 50% improvement in PFS in either the MabCampath or chlorambucil treatment arm (80% power, α=0.05 two-sided). Differences in PFS in the MabCampath versus chlorambucil arm will be tested using the log-rank test, stratified by Rai stage. The primary analysis will be performed on an ITT basis for all randomized patients. The primary efficacy analysis was to be based on an independent response review panel's determination of eligibility (Rai stage and B-CLL diagnosis), response, and date of disease progression after response for all patients.

Summary statistics included sample size, mean, standard deviation, median, and range for continuous variables, where appropriate; number and percent were to be used for categorical variables. All confidence intervals for parameters to be estimated were constructed with a significance level of alpha = 0.05. Kaplan-Meier analyses of time-to-event variables were done using PROC LIFETEST in Statistical Application Software (SAS).

Toxicities, including laboratory results, were evaluated using the NCI Common Toxicity Criteria. Adverse events, serious adverse events, and infections were tabulated using the MedDRA coding system (version 9).

Results

Baseline data

Table 1 below summarizes the demographic characteristics across the two treatment arms for the ITT population, i.e., all patients who were randomized to a treatment arm.
Patients in each treatment arm were well balanced for pre-defined prognostic factors including Rai stage, performance status, age, sex, and maximum lymph node size. Overall, there were more male than female patients, 213/297 male (71.7%) and 84/297 female (28.3%), enrolled in the study; however, the treatment arms were balanced for males and females, 106/149 male (71.1%) and 43/149 female (28.9%) patients in the alemtuzumab arm and 107/148 male (72.3%) and 41/148 female (27.7%) patients in the chlorambucil arm. The majority of the study population was <65 years old, 64.6 % (192/297 patients) were <65 years old. The treatment arms were balanced for age ≥65 years old vs <65 years old, 96/149 patients (64.4%) in the alemtuzumab arm and 96/148 patients (64.9%) in the chlorambucil arm were <65 years old and 53/149 patients (35.6%) in the alemtuzumab arm and 52/148 patients (35.1%) in the chlorambucil arm were ≥65 years old. The median age overall was 60 years (range: 35 to 86 years). The majority of the study population was Rai stage I-II as assessed by both investigator and the IRRP. The study population was also well balanced by Rai stage by both methods of assessment.

Table 1: Summary of Patient Demographics (CAM307 ITT Population)

Variable	Alemtuzumab (N=149)	Chlorambucil (N=148)	Overall (N=297)
Race			
Caucasian	148 (99.3%)	147 (99.3%)	295 (99.3%)
Hispanic	.	.	.
Black	1 (0.7%)	1 (0.7%)	2 (0.7%)
Asian	.	.	.
Other	.	.	.
Sex			
Male	106 (71.1%)	107 (72.3%)	213 (71.7%)
Female	43 (28.9%)	41 (27.7%)	84 (28.3%)
Age Group			
< 65	96 (64.4%)	96 (64.9%)	192 (64.6%)
>= 65	53 (35.6%)	52 (35.1%)	105 (35.4%)
Age (Years)			
N	149	148	297
Mean (SD)	59.8 (9.92)	59.2 (10.70)	59.5 (10.30)
Median	59.0	60.0	60.0
Range	35, 86	36, 83	35, 86
Rai Stage (Investigator)			
0	.	2 (1.4%)	2 (0.7%)
I	37 (24.8%)	32 (21.6%)	69 (23.2%)
II	61 (40.9%)	63 (42.6%)	124 (41.8%)
III	23 (15.4%)	22 (14.9%)	45 (15.2%)
IV	28 (18.8%)	29 (19.6%)	57 (19.2%)
Rai Stage (IRRP)			
0	4 (2.7%)	1 (0.7%)	5 (1.7%)
I	50 (33.6%)	54 (36.5%)	104 (35.0%)
II	43 (28.9%)	42 (28.4%)	85 (28.6%)
III	24 (16.1%)	25 (16.9%)	49 (16.5%)
IV	26 (17.4%)	24 (16.2%)	50 (16.8%)
Missing	2 (1.3%)	2 (1.4%)	4 (1.3%)

- **Primary endpoint: PFS**

A total of 193 events of PD or deaths were identified, of which 191 events occurred in patients with Rai stage I-IV disease and 2 events occurred in patients who were either Rai stage 0 or had an unconfirmed B-CLL diagnosis by the IRRP. The primary analysis of PFS was based on the IRRP's assessment of eligibility (Rai stage and B-CLL diagnosis) and date of progression; the 191 events occurred in patients with Rai I-IV disease was used.

Table 2: Summary of Overall PFS by IRRP Assessment (CAM307)

Overall Statistic	Alemtuzumab (N=149)	Chlorambucil (N=148)	Unadjusted	Adjusted by Rai Group
N	149	148	.	.
KM Median (95% CI) in months	14.6 (12.3, 21.7)	11.7 (9.9, 13.2)	.	.
Min, Max	0.6, 25.1	0.3, 27.9	.	.
% Censored	45.0	26.4	.	.
p-value [a]	.	.	0.0002	0.0001
Hazard Ratio (95% CI) [b]	.	.	0.58 (0.435, 0.775)	0.58 (0.431, 0.768)

- [a] Comparisons between treatment groups are based on the log-rank test unadjusted or stratified for Rai stage, missing stratum is considered.
- [b] Hazard ratios are calculated using Cox model unadjusted or stratified for Rai stage, missing stratum is considered.

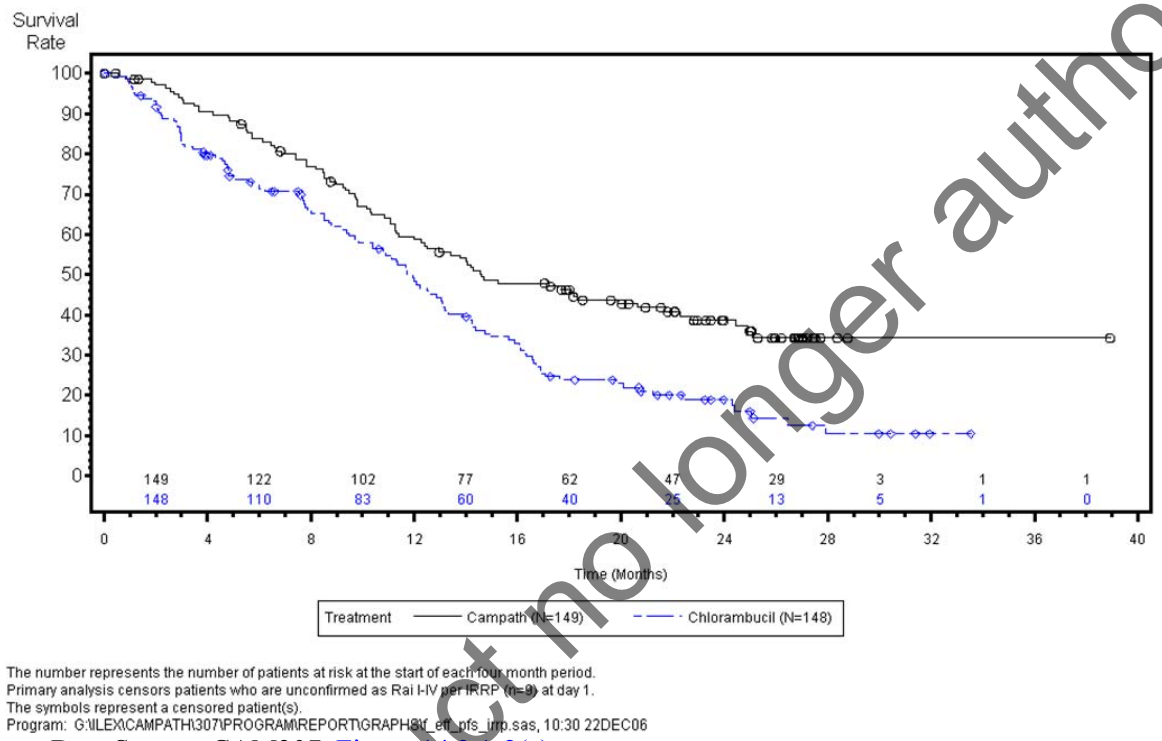
Table 2 summarizes the primary analysis of overall PFS for the ITT population (N=297). The difference in PFS was highly statistically significant (p=0.0001) with an estimated hazard ratio of 0.58

(95% confidence interval [CI]: 0.431, 0.768) after adjustment by Rai stage group (I-II vs III-IV), meaning that the risk of progression or death in treatment naïve B-CLL patients treated with alemtuzumab is 42% less than for those treated with chlorambucil.

The overall Kaplan-Meier median PFS was 14.6 months (95% CI: 12.3, 21.7 months) for patients in the alemtuzumab arm and 11.7 months (95% CI: 9.9, 13.2 months) for patients in the chlorambucil arm based on the IRRP determination of PD.

Figure 1 below shows two Kaplan-Meier curves as separating early and remaining separated with the difference increasing over time; the difference in treatment effect on PFS between alemtuzumab and chlorambucil was statistically significant (p=0.0001, stratified log-rank test).

Figure 1: Kaplan-Meier Curve for PFS by Treatment Arm based on IRRP Assessment



- Data Source: CAM307, Figure 14.2.1-2(a)

Table 3 presents the cumulative probability of PFS from the Kaplan-Meier analysis and an estimated hazard ratio calculated using the Life Table method at 6, 12, 18, and 24 months on-study time. The relative difference between the 2 arms increases at 18 and 24 months with the estimated hazard ratios generally smaller in the second year of the study suggesting a stronger benefit of alemtuzumab treatment with longer follow-up, despite the shorter duration of treatment (median of 11.7 weeks on alemtuzumab vs. 28.3 weeks on chlorambucil).

Table 3: Probability of PFS at Every 6-Month Intervals (CAM307 ITT Population)

Months On Study	Alemtuzumab [a] (N=149)	Chlorambucil [a] (N=148)	Estimated HR
6 Months	83.7% (77.5%, 89.9%)	72.2% (64.8%, 79.6%)	0.94
12 Months	58.7% (50.3%, 67.1%)	48.3% (39.8%, 56.9%)	0.69
18 Months	46.3% (37.8%, 54.8%)	23.8% (16.3%, 31.3%)	0.30
24 Month	38.6% (30.0%, 47.3%)	18.9% (11.8%, 26.0%)	0.54

- [a] Probability of progression-free survival is calculated using Kaplan-Meier methods.

- **Secondary endpoints**

Disease Response to treatment

Table 4 provides a summary of best response to treatment for the ITT population (N=297).

Table 4: Summary of Treatment Response by IRRP Assessment (CAM307)

	Alemtuzumab (N=149)		Chlorambucil (N=148)			
Response Category[a,b]	**n (%)**	**95% CI**[c]	**n (%)**	**95% CI**[c]	**p-value**[d]	**p-value**[e]
ORR	124 (83.2%)	(76.2%, 88.8%)	82 (55.4%)	(47.0%, 63.6%)	<.0001	<.0001
CR	36 (24.2%)	(17.5%, 31.8%)	3 (2.0%)	(0.4%, 5.8%)	<.0001	<.0001
PR	88 (59.1%)	.	79 (53.4%)	.		
SD	9 (6.0%)	.	42 (28.4%)	.		
PD	5 (3.4%)	.	18 (12.2%)	.		
NE	11 (7.4%)	.	6 (4.1%)	.		
Stage I-II[f]	93	.	96	.	.	
ORR	81 (87.1%)	(78.5%, 93.2%)	61 (63.5%)	(53.1%, 73.1%)	0.0002	.
CR	27 (29.0%)	(20.1%, 39.4%)	3 (3.1%)	(0.6%, 8.9%)	<.0001	.
PR	54 (58.1%)	.	58 (60.4%)	.		.
SD	4 (4.3%)	.	28 (29.2%)	.		.
PD	1 (1.1%)	.	6 (6.3%)	.		.
NE	7 (7.5%)	.	1 (1.0%)	.		.
Stage III-IV[f]	50	.	49	.	.	.
ORR	38 (76.0%)	(61.8%, 86.9%)	19 (38.8%)	(25.2%, 53.8%)	0.0002	.
CR	7 (14.0%)	(5.8%, 26.7%)	0 (0.0%)	(0.0%, 7.3%)	0.0125	.
PR	31 (62.0%)	.	19 (38.8%)	.		.
SD	4 (8.0%)	.	14 (28.6%)	.		.
PD	4 (8.0%)	.	12 (24.5%)	.		.
NE	4 (8.0%)	.	4 (8.2%)	.		.

- [a] ORR: Overall Response Rate=CR+PR, CR: Complete Response, PR: Partial Response, SD: Stable Disease, PD: Disease Progression, NE: not evaluable or not assessed.
- [b] Patients whose response cannot be evaluated will be treated as non-responders in order to run the Chi-Square test.
- [c] The 95% confidence interval is calculated using Exact method for binomial.
- [d] This p-value is based on the Pearson Chi-squared test for ORR or Fisher exact method for CR.
- [e] This p-value is based on the CMH method controlling for Rai stage (I-II vs III-IV), missing stratum is considered.
- [f] Denominators for the Rai group (I-II and III-IV) are based on the number of patients in that subgroup, which might differ between IRRP Assessment.
- Data Source: CAM307, Table 14.2.1-4
- Program: t_eff_resp.sas, 10:31 22DEC06

Per the IRRP-determined response, there was a slightly higher response rate for patients with Rai stage I-II disease compared to patients with Rai stage III-IV disease in both treatment arms as would be expected. The overall response rate for the Rai stage I-II patients was 81/93 patients (87.1%) compared to 38/50 patients (76.0%) with Rai stage III-IV disease in the alemtuzumab arm. The overall response rate for the Rai stage I-II patients was 61/96 patients (63.5%) compared to 19/49 patients (38.8%) with Rai stage III-IV disease in the chlorambucil arm. Among the patients that achieved a CR according to the IRRP assessment, there were more Rai stage I-II patients with a CR in the alemtuzumab arm compared to the chlorambucil arm; 27/93 patients (29.0%) were in the alemtuzumab arm and 3/96 patients (3.1%) were in the chlorambucil arm. Similarly, among the Rai stage III-IV patients that responded with a CR, 7/50 patients (14.0%) were in the alemtuzumab arm and no patients were in the chlorambucil arm. Confidence intervals were only calculated for ORR and CR. Differences in both ORR and CR rate were statistically significant in each Rai stage subgroup.

Table 5 below provides a summary of best response to treatment for the ITT population by IRRP assessment and investigator assessment of overall response. The investigator-determined ORR (CR + PR) was 115/149 patients (77.2%) in the alemtuzumab arm, which was slightly lower compared to the IRRP-determined ORR of 124/149 patients (83.2%). The investigator-determined ORR (CR+PR) was 60/148 patients (40.5%) in the chlorambucil arm, which was lower compared to the IRRP-determined ORR of 82/148 patients (55.4%). Per the investigators' assessment in the alemtuzumab arm, there were 46/149 patients (30.9%) with a CR and 69/149 patients (46.3%) with a PR; however, the IRRP determined there were 36/149 patients (24.2%) with a CR and 88/149 patients

(59.1%) with a PR. Per the investigators' assessment in the chlorambucil arm, there were 6/148 patients (4.1%) with a CR and 54/148 patients (36.5%) with a PR; however, the IRRP determined there were 3/148 patients (2.0%) with a CR and 79/148 patients (53.4%) with a PR. Although there was not full agreement between the IRRP and the investigator assessments, both assessments supported the result that alemtuzumab therapy produced a better ORR than chlorambucil therapy.

Table 5. IRRP vs Investigator Assessment of Response (CAM307 ITT Population)

		Alemtuzumab (N=149)		Chlorambucil (N=148)		
Assessment	**Response Category [a]**	**n (%)**	**(95% CI) [b]**	**n (%)**	**(95% CI) [b]**	**p-value [c]**
IRRP	ORR	124 (83.2%)	(76.2%, 88.8%)	82 (55.4%)	(47.0%, 63.6%)	<.0001
	CR	36 (24.2%)	(17.5%, 31.8%)	3 (2.0%)	(0.4%, 5.8%)	<.0001
	PR	88 (59.1%)	.	79 (53.4%)	.	
Investigator	ORR	115 (77.2%)	(69.6%, 83.7%)	60 (40.5%)	(32.6%, 48.9%)	<.0001
	CR	46 (30.9%)	(23.6%, 39.0%)	6 (4.1%)	(1.5%, 8.6%)	<.0001
	PR	69 (46.3%)	.	54 (36.5%)	.	.

- [a] ORR: Overall Response Rate=CR+PR, CR: Complete Response, PR: Partial Response.
- [b] The 95% confidence interval is calculated using Exact method for binomial.
- [c] This p-value is based on the Pearson Chi-squared test for ORR or Fisher's exact method for CR.
- Data Source: CAM307, Table 14.2.1-4
- Program: t_eff_resp.sas, 10:31 22DEC06

Duration of Response

The duration of response was defined in the protocol as the interval between the date of the first documented objective response (CR or PR) to the date of documentation of disease progression or death due to any cause. However the IRRP determined the date of best response (not the date of first response); therefore, in this section the duration of response is the time from best response to disease progression or death due to any cause.

The table below summarizes the duration of response for patients by overall response (CR+PR), CR alone, and by Rai stage using the IRRP date. For the overall response patients, the Kaplan-Meier median duration of response was 16.2 months (95% CI: 11.5, 23.0 months) for patients in the alemtuzumab arm and 12.7 months (95% CI: 10.2, 14.3months) for patients in the chlorambucil arm.

Table 6: Summary of Duration of Response per IRRP Assessment (CAM307)

IRRP Assessment	**Response Category [a]**	**Statistic**	**Alemtuzumab (N=149)**	**Chlorambucil (N=148)**
Overall [b]	CR+PR	N	124	82
		KM Median (95% CI)	16.2 (11.5, 23.0)	12.7 (10.2, 14.3)
		Min, Max	0.7, 23.7	3.7, 48.9
		% Censored	46.0	34.1
Overall [b]	CR	N	36	3
		KM Median (95% CI)	n/e (17.4, n/e)	n/e (n/e, n/e)
		Min, Max	4.6, 23.7	
		% Censored	69.4	100.0

- [a] Duration of response in months = (date of first objective measure of disease progression or death – IRRP reported date of best response [CR or PR]+1)/30.4375.
- [b] Primary analysis censors patients who are unconfirmed as Rai I-IV per IRRP (n=7 [2 CR+5 PR]) at day 1.
- n/e: not estimated
- Data Source: CAM307, Table 14.2.1-5
- Program: t_eff_dr.sas, 10:32 22DEC06

Overall Survival

Overall survival is defined as the time from randomization to date of death due to any cause. CAM307 was not designed or powered to detect differences in overall survival.

There was no overall difference in survival with a total of 24 deaths in the alemtuzumab arm (83.9% censored), and 24 deaths in the chlorambucil arm (83.8% censored). There were not enough events or long enough follow-up data to expect to detect a difference in the overall survival.

Time to treatment failure

The time to treatment failure is defined as the time from date of randomization to the earliest date of disease progression, death due to any cause, or discontinued from study treatment due to an AE. Treatment interruption due to an adverse event resulted in treatment delay over 4 weeks (i.e., 9 weeks [8 weeks + 1 week window]) since the last dose for chlorambucil, or 4 weeks since the last scheduled dose for alemtuzumab) are considered discontinuation of treatment for the purpose of comparing time to treatment failure between treatment arms. The date of treatment failure is taken as the earliest date of the documented disease progression, death, or the start date of the AE that resulted in treatment discontinuation.

Table 7 summarizes the time to treatment failure for all patients. These results showed no statistically significant difference between the treatment arms for time to treatment failure. It is a composite endpoint of discontinuations or delays >4 weeks due to adverse events (favouring chlorambucil) and PFS (favouring alemtuzumab). The overall Kaplan-Meier median time to treatment failure was 9.8 months (95% CI: 7.8, 13.4 months) for patients in the alemtuzumab arm and 11.3 months (95% CI: 9.3, 12.9 months) for patients in the chlorambucil arm based on the IRRP determination of PD with a non-significant hazard ratio of 0.82 (95% CI: 0.624, 1.077) benefiting the alemtuzumab arm. No statistically significant difference between the treatment arms for TTF was observed.

Table 7: Summary of Overall Time to Treatment Failure by IRRP Assessment (CAM307 ITT Population)

Time to Treatment Failure Statistic [a]	Alemtuzumab (N=149)	Chlorambucil (N=148)	Statistic [b, c]	Unadjusted	Adjusted by RAI Group
N	149	148	p-value	0.1551	0.1542
KM Median (95% CI)	9.8 (7.8, 13.4)	11.3 (9.3, 12.9)	Hazard Ratio (95% CI)	0.82 (0.625, 1.079)	0.82 (0.624, 1.077)
Min, Max	0.3, 22.3	0.2, 27.9	.	.	.
% Censored	35.6	22.3	.	.	.

- [a] Time to treatment failure in months = (date of treatment failure – date of randomization +1)/30.4375 [b] Comparisons between treatment groups are based on the log-rank test unadjusted or stratified for Rai stage, missing stratum is considered. [c] Hazard ratios are calculated using the Cox model unadjusted or stratified for Rai stage, missing stratum is considered.

Time to alternative treatment

During the follow-up period, 59/149 patients (39.6%) in the alemtuzumab arm and 86/148 patients (58.1%) in the chlorambucil arm had been treated with an alternative or subsequent therapy after discontinuing study treatment. Table 8 and Figure 2 present the time to alternative treatment results for the ITT patients. The overall Kaplan-Meier median time to alternative treatment was 23.3 months (95% CI: 20.7, 31.0 months) for patients in the alemtuzumab arm and 14.7 months (95% CI: 12.6, 16.8 months) for patients in the chlorambucil arm, which was highly significant (p=0.0001). Note that the time to alternative treatment does not adjust for the difference in duration of therapy, which is important because patients were generally treated for a maximum of 12 weeks with alemtuzumab vs up to 12 months with chlorambucil. Thus, with a median duration on treatment of 11.7 weeks for alemtuzumab and 28.3 weeks for chlorambucil, the difference in time off active treatment is even greater for the alemtuzumab-treated patients.

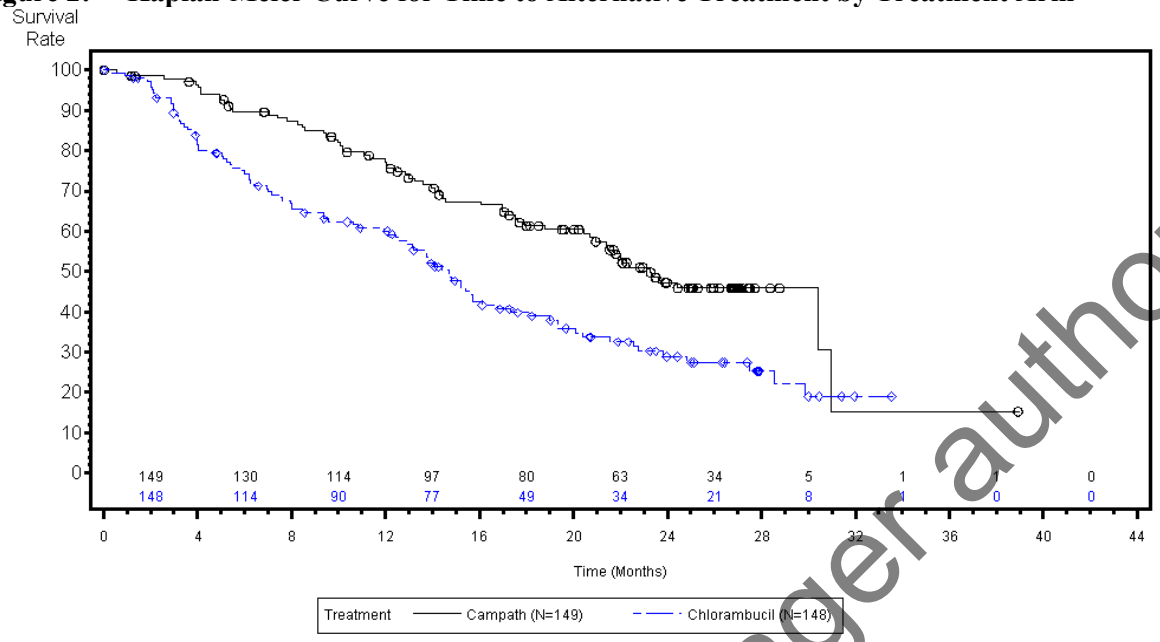
Table 8: Summary of Time to Alternative Treatment (CAM307 ITT Population)

Statistic [a] (months)	Alemtuzumab (N=149)	Chlorambucil (N=148)	Statistic [b, c, d]	Unadjusted	Adjusted by Rai Group (IRRP)
N	149	148	p-value	0.0002	0.0001
KM Median (95% CI)	23.3 (20.7, 31.0)	14.7 (12.6, 16.8)	Hazard Ratio (95% CI)	0.55 (0.398, 0.753)	0.54 (0.391, 0.742)
Min, Max	0.6, 31.0	0.4, 29.9			
% Censored	56.4	37.2			

- [a] Time to alternative treatment in months = (start date of alternative treatment or death – date of randomization +1)/30.4375.
- [b] Primary analysis censors patients who are unconfirmed as Rai I-IV per IRRP (n=9, 5 Rai 0 and 4 unconfirmed for B-CLL diagnosis) at day 1.

- [c] Comparisons between treatment groups are based on the log-rank test unadjusted or stratified for Rai stage, missing stratum is considered.
- [d] Hazard ratios are calculated using Cox model unadjusted or stratified for Rai stage, missing stratum is considered.

Figure 2: Kaplan-Meier Curve for Time to Alternative Treatment by Treatment Arm



The number represents the number of patients at risk at the start of each four month period.
Primary analysis censors patients who are unconfirmed as Rai I-IV per IRRP (n=9) at day 1.
The symbols represent a censored patient(s).
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Subgroup analyses

Patients were randomized at enrollment in order to ensure a balance between treatment arms with respect to the following prognostic factors: Rai stage (Rai stage I-II vs Rai stage III-IV), age (<65 vs ≥65), gender, performance status (WHO = 0 or 1 vs WHO = 2), and maximum lymph node size (none palpable or <5 cm vs ≥5 cm). An examination of these subgroups in relation to treatment outcomes of PFS and response rate was conducted.

The exploratory analysis of PFS by the prognostic factors that were used to randomize and stratify patients at enrollment generally showed a consistent effect across subgroups with a statistically significant difference in outcome in favour of alemtuzumab for patients <65 years old, for patients with maximum lymph node size <5cm, male, female, and for patients with performance status <2 although the study was not powered to detect differences in each of these subgroups.

Discussion on clinical efficacy

The data from CAM307 demonstrate superiority of alemtuzumab compared to chlorambucil as assessed by PFS, response rate, and time to alternative therapy in the intent to treat study population of previously untreated patients with progressive B-CLL requiring first-line therapy. Duration of response was also longer in the alemtuzumab treated patients. The hazard ratio for PFS is 0.58 (p=0.0001, stratified log rank test) after adjustment by Rai stage group, meaning that the risk of progression or death in treatment naïve B-CLL patients treated with alemtuzumab is 42% less than for those treated with chlorambucil. In terms of median PFS this improvement is almost 3 months (14.6 months vs. 11.7 months). As expected no clear PFS plateau emerges after 26-30 months on study. The ORR (CR or PR) was also significantly higher in alemtuzumab treated patients (83.2% versus 55.4%; p < 0,0001), and in absolute values alemtuzumab seems to be very effective in high-tumour burden CLL. Also for the duration of CR+PR endpoint alemtuzumab was superior to chlorambucil. There was a significantly higher percentage of CR patients in the alemtuzumab arm compared to the chlorambucil arm; 24.2% vs 2.0%, respectively; p<0.0001. The overall median time to alternative treatment was 23.3 months for patients in the alemtuzumab arm and 14.7 months for patients in the chlorambucil arm (p=0.0001, stratified log-rank test).

As stated previously, all larger randomised clinical trials in CLL for the past two decades have failed to show superiority with regards to overall survival even if the test regimen often was superior for the ORR endpoint and produced a higher CR rate.
Therefore, clinical benefit in CLL has to be demonstrated on the basis of PFS and ORR and the relation between a decrease in tumour load and improvement in haemoglobin levels and constitutional symptoms.

2. 3. Clinical Safety

Alemtuzumab has been marketed for the treatment of B-CLL since 2001, and the predominant safety concerns are reasonably well understood. The approach to monitoring and management of safety in CAM307 was based on prior experience with alemtuzumab in previously treated B-CLL patients. CAM307 was a multicenter, 2-arm, randomized, phase III open-label study designed to compare alemtuzumab (escalation from 3 mg to 30 mg 3 times a week administered intravenously (IV) for up to 12 weeks) to chlorambucil (40 mg/m^2 per os (PO) once every 28 days, for up to 12 months) in patients with previously untreated progressive B-CLL (i.e. "first-line patients"). The safety of alemtuzumab and chlorambucil was assessed by monitoring the incidence, severity, seriousness and relationship of AEs on the basis of clinical laboratory evaluations, physical examinations, and vital signs. Adverse events were quantified by the investigators using NCI CTC grades and laboratory toxicities were quantified using NCI CTCAE grades. In addition, a Data and Safety Monitoring Board (DSMB) was convened to formally review the safety and efficacy of study treatment.

Exposure to 30 mg of alemtuzumab in 147 first-line patients (CAM307) was as follows: 75 patients (51%) received >30 doses, 30 patients (20%) received between 21 to 30 doses, 24 (16%) patients received between 10 to 20 doses, 14 (10%) patients received between 1-9 doses and four patients (3%) did not receive a single dose of alemtuzumab. The median cumulative dose was 956 mg. Median duration of therapy, including treatment delays and interruptions, was 11.7 weeks. Nearly all patients were able to be treated with the target dose of 30 mg and for almost all patients the 30 mg dose was reached within 5 calendar days. The median number of weeks of chlorambucil exposure was 28.3 weeks. The median cumulative dose of chlorambucil was 515 mg and the median number of cycles administered was 7.

The protocol for CAM307 provided for patients in the alemtuzumab arm to receive a second course of alemtuzumab if they had progressive disease (PD) >6 months after achieving a complete response (CR) or partial response (PR). Although there were patients in the alemtuzumab arm that had PD after achieving a CR or PR, the investigator(s) did not re-treat these patients with alemtuzumab on this protocol.
During the follow-up period of CAM307, there were reports of patients that were subsequently treated with alemtuzumab alone or in combination, as an alternative therapy.

The number of patients with dose modifications or dose delays in CAM307 were 17/147 patients (11.6%) in the alemtuzumab arm that were dose reduced and 4/147 patients (2.7%) in the chlorambucil arm that were dose reduced. There were 80/147 patients (54.4%) in the alemtuzumab arm that had a dose delayed, and 40/147 patients (27.2%) in the chlorambucil arm that had a dose delayed. In the alemtuzumab arm, 36/147 patients (24.5%) had a drug infusion interrupted. According to protocol, patients in the alemtuzumab arm were to be discontinued from study treatment if the dose was delayed for >4 weeks. Ten of 147 patients (6.8%) in the alemtuzumab arm were delayed >4 weeks; all 10 patients were dose delayed due to AEs. One of 147 patients (1/147, 0.7%) in the chlorambucil arm was delayed >4 weeks (i.e., >8 weeks elapsed from date of previous drug administration until treatment resumed.)

Adverse Events
Overall, the incidence of reported AEs on study (overall study period), on treatment and post treatment was higher for patients in the alemtuzumab arm than for patients in the chlorambucil arm. At least one AE was reported for 91.2% of patients, 98.6% in the alemtuzumab arm and 83.7% in the chlorambucil arm. Furthermore, more patients were discontinued from study treatment due to an AE regardless of

causality in the alemtuzumab arm (n=33) than in the chlorambucil arm (n=17). The AEs presented below reflect the drug related events that occurred during the on treatment period (during treatment or within 30 days of last dose) with the exception of particular AEs of interest for alemtuzumab where the events are discussed regardless of causality, namely the infusion-related events, haematologic toxicities, and infections, including CMV, and SAEs.

In first-line patients, during the overall study period at least 1 AE was reported for 268/294 patients (91.2%); 145/147 patients (98.6%) in the alemtuzumab arm and 123/147 patients (83.7%) in the chlorambucil arm. Table 9 summarizes the MedDRA SOC for all AEs regardless of causality reported for >5% of all patients during the overall study period for CAM307

Table 9: MedDRA SOC for all AEs Regardless of Causality for >5% of Either Arm in Patients Treated with First-Line Therapy During the Overall Study Period (CAM307, Safety Population)

MedDRA System Organ Class [a]	Alemtuzumab (N=147)	Chlorambucil (N=147)	Overall (N=294)
Patients Experiencing At Least One Adverse Event [b]	*145 (98.6%)*	*123 (83.7%)*	*268 (91.2%)*
Infections and Infestations	118 (80.3%)	80 (54.4%)	198 (67.3%)
General Disorders and Administration Site Conditions	123 (83.7%)	40 (27.2%)	163 (55.4%)
Gastrointestinal Disorders	54 (36.7%)	74 (50.3%)	128 (43.5%)
Skin and Subcutaneous Tissue Disorders	53 (36.1%)	25 (17.0%)	78 (26.5%)
Blood and Lymphatic System Disorders	35 (23.8%)	29 (19.7%)	64 (21.8%)
Nervous System Disorders	36 (24.5%)	27 (18.4%)	63 (21.4%)
Respiratory, Thoracic and Mediastinal Disorders	38 (25.9%)	24 (16.3%)	62 (21.1%)
Vascular Disorders	46 (31.3%)	5 (3.4%)	51 (17.3%)
Cardiac Disorders	33 (22.4%)	10 (6.8%)	43 (14.6%)
Musculoskeletal and Connective Tissue Disorders	17 (11.6%)	26 (17.7%)	43 (14.6%)
Psychiatric Disorders	22 (15.0%)	11 (7.5%)	33 (11.2%)
Metabolism and Nutrition Disorders	12 (8.2%)	14 (9.5%)	26 (8.8%)
Injury, Poisoning and Procedural Complications	1 (0.7%)	8 (5.4%)	9 (3.1%)

- [a] Patients may have more than 1 occurrence of the same AE, but only 1 incidence at the highest grade is counted for each patient.
- [b] Includes all AEs reported on study (i.e., during both on-treatment and post-treatment periods).

Table 10 summarizes the drug related AEs grade 3 or higher (by NCI CTC grade) by MedDRA preferred term as reported during the on treatment period for ≥3% of patients in at least one of the treatment arms. (CAM307).

Table 10: All Drug Related, Grade 3 or Higher AEs by MedDRA Preferred Term and NCI CTC Grade for ≥3% of Patients in at Least One Treatment Arm in the On Treatment Period (CAM307)

	Alemtuzumab [a]				Chlorambucil [a]			
MedDRA Preferred Term	(N=147) n (%)	Maximum Grade 3	4	5	(N=147) n (%)	Maximum Grade 3	4	5
Thrombocytopenia	8 (5.4%)	5	3	.	6 (4.1%)	4	2	.
Neutropenia	11 (7.5%)	3	8	.	2 (1.4%)	.	2	.
Pyrexia	12 (8.2%)	11	1	.	.	.	.	.
Anaemia	3 (2.0%)	3	.	.	5 (3.4%)	4	1	.
CMV infection	6 (4.1%)	6	.	.	.	.	.	.
CMV viraemia	6 (4.1%)	6	.	.	.	.	.	.
Chills	5 (3.4%)	5	.	.	.	.	.	.

- [a] Patients may have more than one occurrence of the same adverse event, but only one incidence, at the highest grade, is counted for each patient. Data Source: CAM307, Table 14.3.1-11

Many of the events reported in the alemtuzumab arm were consistent with infusion-related events. All patients were to be premedicated per protocol with diphenhydramine and acetaminophen (or paracetamol) to limit the incidence and severity of infusion-related events. Thus, for the most part these were mild or moderate in severity, and decreased in frequency with subsequent doses. An additional contributory factor may have been the more frequently scheduled visits in the alemtuzumab arm (3 times per week whilst receiving study treatment) compared to in the chlorambucil arm (monthly for the whole of the study).

Infusion-Related Adverse Events
Alemtuzumab has been associated with infusion-related events including fever, chills/rigors, nausea, hypotension, urticaria, dyspnea, rash, vomiting, diarrhoea, and bronchospasm. Although the study was not explicitly designed to capture AEs as infusion-related and infusion-related AEs were not predefined in the protocol, there is a general recognition that these types of events occur as a consequence of alemtuzumab administration and decrease in frequency and severity over time. As such, the most conservative approach for safety reporting was to include all events regardless of temporal relationship to study drug administration. Therefore, the more appropriate term to describe these events may be "infusion-associated" as opposed to "infusion-related".

For first-line patients (CAM307), infusion-related AEs were divided into 2 groups: non-cardiopulmonary events (i.e., pyrexia, chills, nausea, vomiting, urticaria and rash) and cardiopulmonary events (i.e., hypotension, dyspnea and bronchospasm). All of these representative adverse events were most common in the first week of therapy, and generally declined in the second and third weeks of treatment. The only exception to this trend of decreasing AEs during the second and third weeks of treatment was urticaria, which increased slightly from Week 1 to Week 2 (from 6.8% to 7.1%) then decreased (to 3.7%) by Week 3.

Infections
As a consequence of the mechanism of action of alemtuzumab, profound lymphopenia can develop and persist throughout the on treatment period. Patients with B-CLL suffer from infectious complications as a result of their underlying disease, other co-morbidities, and therapies used to treat the malignancy. The infectious complications reported herein represent the investigators assessment of causality and, excluding CMV events, are representative of patients suffering from B-CLL.

Infections reported in ≥2 patients overall: Among the patients in the alemtuzumab arm, regardless of causality, the infections experienced in ≥3% (i.e., ≥5/147 patients) were CMV viremia (81/147 patients, 52.4%), CMV infection (23/147 patients, 15.6%), pharyngitis (8/147 patients, 5.4%), rhinitis (6/147 patients, 4.1%), and bronchitis (6/147 patients, 4.1%) while on-treatment or within 30 days of last administration of study drug. Among the patients in the chlorambucil arm, regardless of causality, the infections experienced in ≥3% (i.e., ≥5/147 patients) were CMV viremia (11/147 patients, 7.5%), pharyngitis (14/147 patients, 9.5%), rhinitis (8/147 patients, 5.4%), bronchitis (7/147 patients, 4.8%), pneumonia (6/147 patients, 4.1%), urinary tract infection (5/147 patients, 3.4%) and *Herpes simplex* (5/147 patients, 3.4%) while on treatment or within 30 days of last administration of study drug.

Regarding other opportunistic infections, the very low incidence of non-CMV opportunistic infections reported in the alemtuzumab arm was most likely due to the protocol-specified administration of prophylactic antibiotic and antiviral therapies.

In this randomized first-line study, the rate of infections excluding CMV was similar between the two treatment groups (45.6% of alemtuzumab patients and 50.3% of chlorambucil patients). Although there are distinct differences between the 2 treatment arms in the rate of infections when one considers CMV events, there is no evidence of important differences in the occurrence of drug-related febrile neutropenia (4.8% vs 2.7%) or bacteraemia/sepsis (3% vs 1.4%) events between alemtuzumab and chlorambucil, respectively.

CMV Events
The following MedDRA coding convention was used to distinguish between 2 distinct categories of CMV events: (i) CMV Viremia: a report of a positive CMV by PCR laboratory result for patients who

were without any evidence of symptomatic CMV infection. These events are referred to in the draft label as "asymptomatic PCR positive CMV" and (ii) CMV Infection: a report of a positive CMV by PCR laboratory result for patients who had 1 or more symptoms consistent with a CMV infection, e.g., fever. These events are referred to in the draft label as "symptomatic PCR positive CMV infection". During the process of reconciling the database, by convention an AE was added to the database for any patient with a single positive PCR assay result and coded as 'CMV viremia' although the protocol required independent confirmation prior to study drug interruption and institution of anti-viral therapy.

The difference in the monitoring schedules for CMV by PCR may have contributed to the higher incidence of CMV positivity in the alemtuzumab arm of CAM307 (first-line patients). Because of the frequent monitoring for CMV by PCR (weekly for alemtuzumab and monthly for chlorambucil while on treatment), CMV viremia was identified in 52.4% of the patients in the alemtuzumab arm during the on-treatment period. Only 15.6% of the patients developed CMV infections in the on-treatment period. The majority of CMV viremia/infection events were mild to moderate in severity and were readily managed by anti-viral therapy. None of the clinical cases of CMV infection was above grade 3. Although CMV viremia occurred commonly among patients in the alemtuzumab arm, it was managed in most cases without permanently disrupting therapy.

Asymptomatic laboratory positive CMV (i.e., CMV viremia) should not necessarily be considered a serious infection requiring interruption of alemtuzumab therapy, as was specified in CAM307. The CMV management guidelines recommended by experts in the field have matured since the design of CAM307 (O'Brien, 2006, Clin Lymphoma Myeloma; Keating, 2004, Clin Lymphoma).

Deaths on Treatment

Four patients (one in the alemtuzumab arm and 3 in the chlorambucil arm) died during treatment or within 30 days of the last dose of study drug. The one death in the alemtuzumab arm was attributed by the investigator to the underlying disease. The causes of death for the three patients in the chlorambucil arm were *Listeria monocytogenes* encephalitis, cardiac insufficiency, and sudden death (cause unknown). The only death considered by the investigator to be likely related to study drug was the patient with the *Listeria monocytogenes* encephalitis infection in the chlorambucil arm.

Eight patients died during the post-treatment period, ie, more than 30 days but within 6 months after last drug administration. Two patients were in the alemtuzumab arm and 6 patients were in the chlorambucil arm. None of these deaths were associated with a study drug-related AE. During the extended follow-up period of first-line patients (i.e., >6 months after the last administration of study drug), deaths were reported for an additional 34 patients (19 patients in alemtuzumab arm, and 15 patients in chlorambucil arm). None of these deaths were associated with a study drug-related AE.

Serious Adverse Events

The overall incidence of SAEs was also higher in the alemtuzumab arm than in the chlorambucil arm. When considering drug related SAEs, the only event that was more common in alemtuzumab patients was CMV events. The serious adverse events during the on treatment period are discussed regardless of relationship to study drug, either alemtuzumab or chlorambucil, in decreasing frequency. Among the patients in the alemtuzumab arm, the SAEs regardless of causality experienced in ≥3% (i.e., ≥5/147 patients) were CMV viremia, pneumonia, pyrexia, and CMV infection. Among the patients in the chlorambucil arm, the only SAE regardless of causality experienced in ≥3% (i.e., ≥5/147 patients) was pneumonia. Table 11 summarizes the SAEs experienced in ≥3% of patients per treatment arm regardless of causality as reported during the on treatment period in order of overall descending frequency, including the NCI CTC grades for these events.

Table 11: Summary of SAEs Experienced in ≥3% of Patients per Treatment Arm and Overall Regardless of Causality with NCI CTC Grade During the On Treatment Period (CAM307)

MedDRA Preferred Term	Alemtuzumab [a] (N=147) n (%)	Maximum Grade 1	2	3	4	5	Chlorambucil [a] (N=147) n (%)	Maximum Grade 1	2	3	4	5	Overall (N=294) n (%)
CMV viraemia	16 (10.9%)	7	3	6	.	.	.	.	.	.	.	.	16 (5.4%)
CMV infection	8 (5.4%)	1	3	4	.	.	.	.	.	.	.	.	8 (2.7%)
Pneumonia	2 (1.4%)	.	.	2	.	.	5 (3.4%)	.	1	4	.	.	7 (2.4%)
Pyrexia	5 (3.4%)	1	3	1	.	.	2 (1.4%)	1	.	1	.	.	7 (2.4%)

- [a] Patients may have more than one occurrence of the same SAE, but only one incidence at the highest grade is counted for each patient.

In particular, the incidence of SAE infections was higher in the alemtuzumab arm than in the chlorambucil arm. This can be attributed to the incidence of CMV viremia/infection SAEs, which was higher for the alemtuzumab arm than for the chlorambucil arm. Apart from this difference, there was no other apparent difference in the infection SAEs in particular nor in SAEs in general that were reported for the two treatment arms.

The most frequently reported SAE in the alemtuzumab arm was CMV viremia. Treatment of CMV viremia/infection with IV ganciclovir required hospitalization in many European countries. These hospitalizations, by definition an SAE, contributed to the increase in the overall incidence of SAEs in the alemtuzumab arm. An exploratory analysis for PFS in patients treated with alemtuzumab who experienced a CMV event during therapy revealed that efficacy was not compromised.

Clinical Laboratory Evaluations

- Haematologic Toxicity

Abnormal laboratory findings were not defined as AEs for the purpose of CAM307 (first-line patients). Clinical syndromes associated with laboratory abnormalities were to be recorded as appropriate (e.g., diabetes mellitus instead of hyperglycaemia). As a result, the haematologic toxicities reported are lab shift data from baseline to worst grade regardless of relatedness.

The table below summarizes the number of first-line patients that had a shift from low at baseline to a maximum CTC grade 3 or greater post-baseline for the haematology parameters, for both the overall (all values reported) and the on treatment periods in CAM307.

Table 12: Shift from Low Baseline Grade to Maximum Post-Baseline Grade ≥3 for Haematology Parameters in First-Line Patients (CAM307, Safety Population)

		Alemtuzumab		Chlorambucil		
Toxicity [a]	Study Period	Evaluable [b]	n (%)	Evaluable [b]	n (%)	P-value [c]
ALC	Overall [d]	145	142 (97.93)	144	4 (2.78)	<0.0001
	On Treatment [e]	145	142 (97.93)	144	2 (1.39)	<0.0001
ANC	Overall [d]	146	65 (44.52)	144	38 (26.39)	0.0014
	On Treatment [e]	146	60 (41.10)	144	36 (25.00)	0.0041
Hemoglobin	Overall [d]	146	18 (12.33)	145	27 (18.62)	0.1477
	On Treatment [e]	146	16 (10.96)	145	26 (17.93)	0.0978
Platelets	Overall [d]	147	24 (16.33)	147	18 (12.24)	0.4049
	On Treatment [e]	147	18 (12.24)	147	17 (11.56)	1.0000
WBC	Overall [d]	147	91 (61.90)	146	2 (1.37)	<0.0001

		Alemtuzumab		Chlorambucil		
Toxicity [a]	**Study Period**	**Evaluable [b]**	**n (%)**	**Evaluable [b]**	**n (%)**	**P-value [c]**
	On Treatment [e]	147	91 (61.90)	146	2 (1.37)	<0.0001

- [a] Toxicity is defined as lab grade shift from low baseline grade to a maximum post-baseline grade ≥3.
- [b] Number of patients with evaluable lab test both baseline and post-baseline overall or on-treatment period.
- [c] Fisher's exact method
- [d] Overall study period includes on-treatment period and post-treatment period.
- [e] On-Treatment study period includes treatment period through 30 days after last dose administration
- Denominators for the percentages are based on the number of patients with evaluable shifts

Haematologic toxicity was common in both treatment arms. Except for neutropenia, the incidence of treatment-emergent grade 3 and 4 haematologic toxicities including anaemia and thrombocytopenia were similar between the two treatment arms. The observed events in both treatment arms are consistent with recognized complications of B-CLL.

Pancytopenia/Marrow Hypoplasia:
With the exception of one case of pure red cell aplasia that occurred approximately 6 months after completion of treatment with alemtuzumab, no adverse events of pancytopenia/marrow hypoplasia were observed in first line patients treated with alemtuzumab.

Anaemia:
For patients who had baseline and post-baseline data, 11% of patients treated with alemtuzumab and 18% of patients treated with chlorambucil had one or more episodes of new onset NCI CTC Grade 3 or 4 anaemia during the on-treatment period. The median time to onset of treatment emergent Grade 3 or 4 anaemia was 4.4 weeks for patients treated with alemtuzumab and 8.1 weeks for patients treated with chlorambucil. The median haemoglobin recovered to a level greater than baseline by month 1 post-treatment for both study arms. Transfusions and/or erythropoietin were required in 61/93 patients (65.6%) during the overall study period.
One patient in the alemtuzumab arm developed haemolytic anaemia four months (related to malignancy) after the last dose of study drug and two patients in the chlorambucil arm developed haemolytic anaemia (one related to treatment and one related to malignancy) while on study drug.

Neutropenia:
For patients who had baseline and post-baseline data, 41.1% (60/146) of patients treated with alemtuzumab and 25% of patients treated with chlorambucil had one or more episodes of new onset NCI CTC Grade 3 or 4 neutropenia during the on-treatment period. The median time to onset of treatment emergent Grade 3 or Grade 4 neutropenia was 4.35 weeks for patients treated with alemtuzumab and 3.65 weeks for patients treated with chlorambucil. The median ANC results for all patients stayed within normal limits post-treatment for both study arms. Colony-stimulating factors were required for 33/93 patients (35.5%) during the study.
Although the incidence of grade 3 and 4 treatment-emergent neutropenia was higher in the alemtuzumab arm, the incidence of infection adverse events (excluding CMV events) was similar.

Thrombocytopenia:
For patients who had baseline and post-baseline data, 12.2% (18/147) of patients treated with alemtuzumab and 11.6 % (17/147) of patients treated with chlorambucil had one or more episodes of new onset NCI CTC Grade 3 or 4 thrombocytopenia during the on-treatment period. The median time to onset of treatment emergent Grade 3 or 4 thrombocytopenia was 1.3 weeks for patients treated with alemtuzumab and 7.9 weeks for patients treated with chlorambucil. No patients in the alemtuzumab arm and two patients in the chlorambucil arm developed autoimmune thrombocytopenia (related to treatment) while on study drug. Both chlorambucil patients were discontinued from the study. The median platelet count results recovered to baseline or above by week 3 of alemtuzumab treatment, but did not recover to baseline during treatment or during the post-treatment period. Platelet transfusions were required by 34/93 patients (36.6%) during the overall study period.

Blood Product Use

Overall, of the 140 patients in the alemtuzumab arm who had not received blood products at baseline (i.e., within 1 month prior to study enrollment), 19/140 patients (13.6%) received blood product support post baseline. Of the 141 patients in the alemtuzumab arm who had not received packed RBCs at baseline (i.e., within 1 month prior to study enrollment), 19/141 patients (13.5%) received packed RBCs post baseline. Overall, of the 142 patients in the chlorambucil arm who had not received blood products at baseline (i.e., within 1 month prior to study enrollment), 21/142 patients (14.8%) received blood product support post-baseline. Of the 142 patients in the chlorambucil arm who had not received packed RBCs at baseline (i.e., within 1 month prior to study enrollment), 21/142 patients (14.8%) received packed RBCs post baseline. Only a few patients in either treatment arm received platelet transfusions. One patient in the alemtuzumab arm received standard unit platelets and 2 patients received apheresis unit platelets. Three patients in the chlorambucil arm received standard unit platelets and 2 patients received apheresis unit platelets.

Lymphopenia:

In first-line patients receiving alemtuzumab, the median time to recovery of CD4+ counts to ≥200 cells/μL occurred by 6 months post-treatment; however the median at 2 months post-treatment was 183 cells/μL. Patients in CAM307 did not have baseline samples available for comparison to full recovery.

Subgroup analyses

Analyses of adverse events in subgroups (age group ≥65, <65 years old, and gender) were performed and revealed no substantial differences. A summary of AEs by race is not provided because only 2/297 first-line patients (0.7%) enrolled in CAM307 were non-Caucasian; 1 Black patient in the alemtuzumab arm and 1 Black patient in the chlorambucil arm.

Post marketing experience

The eighth PSUR for alemtuzumab has been provided as supportive evidence summarising the safety data received by Schering Global Medical Safety Surveillance from worldwide sources between 08-NOV-2005 and 07-MAY-2006.

Discussion on clinical safety

CAM307 confirms the safety profile of previously reported studies utilizing alemtuzumab in the treatment of first-line B-CLL patients. The previously reported studies were conducted with SC alemtuzumab and therefore direct comparison of infusion-related events is not appropriate. However, haematologic toxicities and infectious complications are similar.

The most important difference between alemtuzumab and chlorambucil is the frequency of CMV events. Although the incidence of CMV viremia/infection is greater in the alemtuzumab arm than in the chlorambucil arm, the data from CAM307 show that CMV events were easily managed and resulted primarily in only the temporary interruption of alemtuzumab therapy, without apparently compromising efficacy.

There is little doubt that alemtuzumab is more toxic than chlorambucil but this toxicity is not associated with a higher mortality supporting the applicant's claim that the toxicity can be managed.

There have been two other clinical studies which have utilized single agent alemtuzumab as first-line therapy, a study conducted by Österborg, et al and a second study conducted by Lundin, et al. Österborg treated nine patients with alemtuzumab administered either intravenously (N=5) or subcutaneously (N=4) thrice weekly for up to 18 weeks in a pilot study. Adverse events were consistent with the alemtuzumab safety profile, the most common being fever (8/9 patients), rigors (8/9 patients), nausea (3/9 patients) and rash (3/9 patients). All patients developed lymphopenia; however there was only one serious infectious event (CMV pneumonitis). Grade 3 neutropenia occurred in one patient, two patients had grade 2 and one patient had grade 1 (WHO grade). One patient developed transient grade 1 thrombocytopenia. In the Lundin study, alemtuzumab was administered subcutaneously (SC) for up to 18 weeks. Adverse events associated with the route of administration (i.e., infusion-related events) when alemtuzumab is administered IV are uncommon

when it is administered SC; however, "first dose" reactions, such as injection site reactions and fever, do occur. In fact, transient rigors were noted in 17%, but rash/urticaria, bronchospasm, hypotension and nausea were not reported. Twenty one percent of patients experienced grade 4 neutropenia; however, there were no events of febrile neutropenia. Symptomatic CMV (fever without pneumonia) occurred in only 4/41 patients and one patient developed PCP. Among the patients for whom long-term follow-up data were available, there were no opportunistic or other major infections recorded. The median time to both CD4+ and CD8+ recovery to >100 cells/µL was 4 months. The safety profile of subcutaneous alemtuzumab thus is confirmed with CAM307, the largest study treating B-CLL patients in the first-line setting.

The 8th PSUR has been assessed and adopted by the CHMP. In the 8th PSUR the MAH was asked to continue to keep "cardiac disorders" and "autoimmune phenomena" (including autoimmune thyroid dysfunction) under close surveillance. Some minor additional points were also raised. In addition this product was renewed in 2006 with the conclusion to stay under exceptional circumstances due to the outstanding specific obligation which now is addressed with this application.

Pharmacovigilance and Risk Management Plan

The applicant has provided documents that set out a detailed description of the system of pharmacovigilance. A statement signed by the applicant and the qualified person for pharmacovigilance, indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided.
The MAA submitted a risk management plan, which included a risk minimisation plan

Table 13: Summary of the risk management plan

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation (routine and additional)
Infusion-related events	Routine Pharmacovigilance	Warning in SmPC section 4.4: The frequency of infusion-related reactions was highest in the first week of therapy, and declined in the second or third week of treatment, in patients treated with MabCampath both as first line therapy and in previously treated patients. SmPC section 4.8 of the SmPC updated: 'Fever, chills, nausea, vomiting, hypotension, urticaria, dyspnoea, rash, bronchospasm, infusion site erythema & infusion site oedema'. • Educational Material.
Opportunistic infections	Routine Pharmacovigilance	All events listed below in bold can be described as '**opportunistic infections**': Warnings in SmPC section 4.4: Cytomegalovirus (**CMV**) viraemia should not necessarily be considered a serious infection requiring interruption of therapy. Ongoing clinical assessment should be performed for symptomatic CMV infection during MabCampath treatment and for at least 2 months following completion of treatment. SmPC section 4.8 updated to include infections and infestations in the table of 'undesirable effects in first-line patients': Very Common adverse events: **cytomegalovirus viraemia**,

		cytomegalovirus infection Common adverse events: **oral candidiasis** Uncommon adverse events: **tuberculosis**, **herpes ophthalmicus**, **candidiasis** SmPC section 5.1 updated to include wording on assessment of **CMV**. • Educational Material.
Haematologic toxicity	Routine Pharmacovigilance	Guidance in SmPC section 4.2 updated: 'For a decrease of ANC and/or platelet count to ≤ 50% of the baseline value in patients initiating therapy with a baseline ANC ≤ 500/µl and/or a baseline platelet count ≤ 25,000/µl: Withhold MabCampath therapy. When ANC and/or platelet count return to baseline value(s), resume Campath therapy.* Guidance in SmPC section 4.2 updated: There are no dose modifications recommended for severe lymphopenia given the mechanism of action of MabCampath. Warning in SmPC section 4.4: 'If a severe haematological toxicity develops, MabCampath treatment should be interrupted until the event resolves. SmPC section 4.8: Include the following adverse reactions occurring in first-line patients: Blood and lymphatic system disorder Common adverse events: febrile neutropenia, neutropenia, leukopenia, thrombocytopenia, anaemia Uncommon adverse events: agranulocytosis, lymphopenia, lymphadenopathy, epistaxis

The CHMP, having considered the data submitted in the application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product:

- The MAH shall agree to the details of an educational brochure with the National Competent Authorities.
- The MAH shall ensure that all doctors who prescribe MabCampath are provided with a healthcare professional information pack containing the following:
  - Educational brochure
  - Summary of Product Characteristics (SPC) and Package Leaflet and Labelling

<u>Key elements to be included in the educational brochure</u>

- The risk of opportunistic infections, in particular CMV viraemia
- Recommendation to avoid vaccination with live vaccines for at least 12 months following MabCampath therapy
- The risk of infusion reactions
  - Need for premedication
  - That treatment for hypersensitivity reactions, including measures for resuscitation should be available during administration
  - That the risk of infusion reactions is highest in first week of therapy

- That if the reaction is moderate or severe dosing should continue at the same level (ie no dose escalation) until each dose is well tolerated
- That if therapy is withheld for more than 7 days then MabCampath should be reinstituted with gradual dose escalation

3. OVERALL DISCUSSION AND BENEFIT-RISK ASSESSMENT

B-cell chronic lymphocytic leukaemia is one of the most common malignant lymphoid neoplasms in adult populations worldwide. Because the disease is generally not curable, occurs in an elderly population, and often progresses slowly, it is most often treated in a conservative fashion. In asymptomatic patients, treatment may be deferred until the patient becomes symptomatic as the disease progresses.

Treatment of chronic lymphocytic leukaemia (CLL) ranges from periodic observation with treatment of infectious, haemorrhagic, or immunologic complications to a variety of therapeutic options, including steroids, alkylating agents (chlorambucil=CLB), purine analogues (fludarabine, cladribine or pentostatin), combination chemotherapy, monoclonal antibodies (alemtuzumab, rituximab), and transplant options.

Most recent randomised studies including one from the French Cooperative Group on CLL have showed higher or equivalent response rates for fludarabine as compared to CLB or CAP (cyclophosphamide, doxorubicin, prednisone) and most showed an improvement in progression-free survival, though none showed an advantage in OS. Therefore, current first-line therapy includes fludarabine although it must be recognised that purine analogues are more toxic than CLB in terms especially granulocytopenic infections, herpes infections, autoimmune haemolytic anaemia, and persistent thrombocytopenia. The increased risk of infection may persist for months or years after treatment with a purine analogue.

The CAM307 study initiated at the request of the CPMP in 2001 compares alemtuzumab IV with a conventional scheme of chlorambucil in a randomised phase III design in treatment naïve patients with B-CLL. The data from CAM307 demonstrate superiority of alemtuzumab compared to chlorambucil as assessed by PFS, response rate, and time to alternative therapy in the intent to treat study population of previously untreated patients with progressive B-CLL requiring first-line therapy. Duration of response was also longer in the alemtuzumab treated patients. The hazard ratio for PFS is 0.58 ($p=0.0001$, stratified log rank test) after adjustment by Rai stage group. The ORR (CR or PR) was also significantly higher in alemtuzumab treated patients (83.2% versus 55.4%; $p < 0.0001$). There was a significantly higher percentage of CR patients in the alemtuzumab arm compared to the chlorambucil arm; 24.2% vs 2.0%, respectively; $p<0.0001$. The overall median time to alternative treatment was 23.3 months for patients in the alemtuzumab arm and 14.7 months for patients in the chlorambucil arm ($p=0.0001$, stratified log-rank test). It should be stressed that response rate in CLL is a valid surrogate endpoint since it is closely associated with increasing haemoglobin levels and decrease in constitutional symptoms. The trial was not designed to show overall survival benefit and such data are not required in this indication because no single agent or combination has so far demonstrated prolonged survival for patients with CLL

CAM307 confirms the safety profile of previously reported studies utilizing alemtuzumab in the treatment of first-line B-CLL patients. The previously reported studies were conducted with SC alemtuzumab and therefore direct comparison of infusion-related events is not appropriate. However, haematologic toxicities and infectious complications are similar.

As expected treatment with alemtuzumab is associated with more toxicity than the older conventional chlorambucil scheme. Alemtuzumab is associated with infusion-related events including fever, chills/rigors, nausea, hypotension, urticaria, dyspnea, rash, vomiting, diarrhoea, and bronchospasm. The infusion-related events are most common during the first infusions. The high frequency of CMV viraemia irrespective of clinical signs of CMV-disease resulting from the severe lymphopenia is of concern. Infections per se are not rare events among patients with B-CLL. Clinical CMV infection was observed in 2.7% of the patients, none of the cases exceeded Grade 3. Although the incidence of CMV

viremia/infection is greater in the alemtuzumab arm than in the chlorambucil arm, the data from CAM307 show that CMV events were easily managed and resulted primarily in only the temporary interruption of alemtuzumab therapy, without apparently compromising efficacy. The toxicity of MabCampath is not associated with a higher mortality supporting the claim that the toxicity can be managed.

Overall, no new clinical laboratory safety concerns were detected. Cases of ITP (a known manifestation of B-CLL) were not seen in the alemtuzumab group and there is no mentioning of thyroid abnormalities (seen in clinical trials in MS patients treated with alemtuzumab). One case of pure red cell aplasia in the alemtuzumab group 6 months after exposure should be noted. Lymphopenia seems to be the only specific laboratory finding in this comparative trial against chlorambucil.

At the time when CAM307 was initiated chlorambucil was a valid comparator since this alkylating agent has been the backbone of therapy for CLL for 40 years. Since 2000 fludarabine containing regimens have become more widely used as first-line therapy because of higher response rates and prolongation of PFS observed in randomised studies including one from the French Cooperative Group on CLL. However, an advantage in OS has not been observed.
Alemtuzumab is clearly superior to chlorambucil in terms of efficacy. The main problem while assessing this application was the lack of knowledge on how alemtuzumab performs in a head-to-head comparison against current state-of-the art first-line therapy; fludarabine containing chemotherapy. The only efficacy comparison is with literature data but such data were not sufficient for the approval of a wide first-line indication. The therapeutic indication was to be defined as fludarabine based regimens currently are viewed as the most appropriate first-line therapy for patients with B-CLL who can tolerate this treatment.

However, as pointed out by the applicant and supported by both a recent ESMO CLL Guideline (2007) and a market survey, chlorambucil is not an obsolete first-line agent since its known activity and better safety profile (as compared to fludarabine) makes it a suitable therapy for elderly patients with CLL.

The way alemtuzumab would perform in a head-to-head comparison against other treatment standards than chlorambucil in patients with CLL is a meaningful clinical research question, as are others, such as its role in consolidation or in combination with other active agents in the disease. The CAM307 data support consideration of such additional questions given MabCampath has been demonstrated to be among the most active agents, including the most active immunotherapeutic, in this disease. The heterogeneity of the disease necessitates the availability of alternative treatment options, the comparator is not obsolete in the front-line treatment of the disease, the clinical trial results of CAM307 are statistically significant and robust, and the safety profile of MabCampath is demonstrated to be predictable, manageable, and in line with other treatment regimens tested in the patient population under study.

Though chronic lymphocytic leukaemia is one of the most common malignant lymphoid diseases in non-Asian populations, with 15,340 new cases estimated in the United States in 2007 and similar incidences expected across Europe (Jemal, *CA Cancer J Clin*, 2007), the annual incidence is several fold lower than many other cancers, creating challenges in the development of new therapies. Significant advances in diagnosis, identification of prognostic factors, and treatment options have recently occurred, allowing previous paradigms with respect to disease management to undergo re-examination. Taking these factors into consideration, heterogeneity in both natural history and outcomes in individual patients, as well as response to alternative therapies, becomes apparent. This heterogeneity is characterized by a variable clinical course, such that the overall median survival for patients with the disease ranges from a few months to the same survival as that observed in age-matched normal populations (Catovsky, *Eur J Cancer*, 1995). Due to the limited number of patients with CLL, particularly those requiring therapy, controlled clinical trials such as CAM307, however, are performed in a relatively broad patient population. Evidence from CAM307 demonstrates the clinical benefit of MabCampath relative to chlorambucil in the overall patient population, while subgroup analyses suggest that benefit is also likely in certain subpopulations.

The above referenced published guidelines advocate the availability of a number of treatment options for the prescribing clinician so that factors such as the patient's overall health status can be taken into consideration when making treatment choices. In the 2007 ESMO clinical guidelines for the first-line treatment of CLL, there is a variety of suggested options including fludarabine monotherapy or in combination, chlorambucil monotherapy and MabCampath monotherapy or in combination. While the ESMO guidelines suggest that the more myelotoxic FC regimens be reserved for more "physically fit" patients, they also recognize that randomized trials have not demonstrated a survival benefit for purine analogues (e.g. fludarabine, cladribine) either alone or in combination with cyclophosphamide, versus chlorambucil (ESMO, 2007, *Annals of Oncology).*

The results from CAM307 demonstrate that the patients enrolled into this study reflect the heterogeneity of the patients who present with CLL and that alemtuzumab represents a significant advance in the treatment of these patients based on superior PFS (the primary endpoint), overall response rate, complete response rate, and time to alternative treatment in the overall study population compared to chlorambucil, with a predictable and manageable safety profile. In an attempt to provide greater context for these data, comparisons of results across studies, particularly with respect to time-to-event endpoints such as PFS, are fraught with the potential for misinterpretation due to differences in patient population characteristics, study design (including methodological differences in the determination of endpoints, e.g., the independence and/or frequency and rigor of response and disease progression assessments), and other factors. Moreover MabCampath is recognized as the single most effective agent in treating specific CLL subpopulations, e.g. patients with del 17p or p53 mutations, as these patients respond poorly to fludarabine, or fludarabine-based combination therapies.

The CHMP therefore considered that the benefit risk of MabCampath is positive in the indication:

- treatment of patients with B-cell chronic lymphocytic leukaemia (B-CLL) for whom fludarabine combination chemotherapy is not appropriate

A risk minimisation plan focusing on opportunistic infections, infusion-related reactions and haematologic toxicities has been agreed with the CHMP.