SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion and scientific discussion on procedures, which have been finalised before 1 December 2004. For scientific information on procedures after this date please refer to module 8B.

1. Introduction

MabCampath (alemtuzumab) is a humanised monoclonal antibody that recognises the human CD52 antigen, a membrane glycoprotein expressed in virtually all cases of chronic lymphocytic leukaemia (CLL) and in the majority of cases of non-Hodgkin's lymphoma (NHL), and present on at least 95% of all peripheral blood lymphocytes and monocytes/macrophages. This antigen has also been found in a subpopulation (<5%) of granulocytes but not on erythrocytes, platelets, or bone marrow stem cells. By binding to the CD-52, alemtuzumab causes lysis of lymphocytes through complement fixation and antibody-dependent cell-mediated cytotoxicity mechanisms.

Chronic lymphocytic leukaemia (CLL) is the most frequent form of leukaemia in Western countries, affecting 1.8 to 3 patients per 100,000 populations. CLL is marked by clonal proliferation and accumulation of neoplastic B-lymphocytes in the blood, bone marrow, lymph nodes, and spleen. Patients present 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, neutropenia and thrombocytopenia. Alkylating agents such chlorambucil are the standard chemotherapy, although they achieve few complete remissions. Combinations of alkylating agents with corticosteroids, anthracyclines or other compounds do not appear to prolong survival compared with alkylators alone. Fludarabine in resistant forms of CLL may achieve higher remission rates (approximately 30 %) but its impact on survival has not been demonstrated.

MabCampath is indicated as a third-line treatment of patients with chronic lymphocytic leukaemia (CLL) who have been treated with alkylating agents and who have failed fludarabine phosphate therapy.

It is a colourless concentrated solution for dilution with 0.9% sodium chloride solution or 5% glucose solution, for administration by IV infusion over approximately 2 hours.

2. Chemical, pharmaceutical and biological aspects

Composition

MabCampath is a buffered, isotonic, non-preserved solution, containing the active substance, alemtuzumab in a concentration 10 mg/ml, filled in ampoules as 30-mg/3 ml. The formulation also contains: disodium edetate (EDTA), polysorbate 80 and phosphate buffered saline (PBS) consisting of: potassium chloride, potassium dihydrogen orthophosphate, sodium chloride, dibasic sodium phosphate and water for injections.

Fill volume is 3.3 ml including an overfill of 0.3 ml.

The container is a 5 ml ampoule with white score ring composed of Type I clear tubing glass, which complies with Ph Eur and USP.

Product development and finished product

The active substance, alemtuzumab (INN) (previously known as CAMPATH-1H), is defined as the formulated product pool containing alemtuzumab, EDTA, polysorbate and PBS.

Manufacture of the active substance and the finished product is conducted at Boehringer Ingelheim Pharma KG, Germany (BI). Labelling and packaging is conducted at Schering AG, Berlin, Germany.

The CPMP did not require GMP inspections in relation to the manufacture of MabCampath.

Method of preparation

The final dosage form is produced by terminal sterilisation of the alemtuzumab bulk active substance via 0.22 µm sterile filter followed by filling into 5 ml glass ampoules to a volume of 3.3 ml.

Batch definition

A production batch is defined as the harvest from a single production vessel during and after purification to active substance.

Validation of the manufacturing process

The manufacturing process is fully validated for fermentation, purification, filling, visual inspection, intermediate hold times and media fills.

In process controls during fermentation monitor cell density, cell viability, microbial content, pH, product content and a variety of metabolic parameters.

In-process controls during filling include membrane integrity testing, bubble point tests, fill weight, fill volume, nitrogen purge flow rate, ampoule seal and automatic visual inspection.

A sterility test is performed on the sterile-filtered bulk active substance and on the filled vials.

Production and control of the starting materials

The active substance, alemtuzumab, is a humanised monoclonal antibody directed against the human CD52 antigen. It is a glycosylated immunoglobulin of the IgG_1 subclass.

Description of the molecule

The alemtuzumab molecule is a genetically engineered human IgG1 kappa monoclonal antibody with a molecular weight of approximately 150 kD. The humanised antibody was made by the insertion of six complementarity-determining regions (CDRs) from an IgG2a rat monoclonal antibody into a human IgG1 immunoglobulin molecule. The alemtuzumab molecule consists of two light chains of ~ 24 kD (214 amino acids) and two heavy chains (450 amino acids) linked together by two intra (light chain - heavy chain) disulphide bridges and two inter (heavy chain - heavy chain) disulphide bridges to form the typical Y-shaped IgG1 molecule. Each molecule also contains a total of 12 intra-chain disulphide bridges and an asparagine residue (301) in each heavy chain, which is glycosylated.

Developmental genetics

The product intended for commercialisation is an evolutive antibody obtained by a series of somatic cell and genetic manipulations. A rat hybridoma specific for human CD52 was genetically manipulated to enhance its affinity for the CD52 antigen expressed on lymphoid cells. In order to reduce the immunogenicity of rat immunoglobulins in patients, the CDR regions of this hybridoma were cloned and expressed with a human IgG1 framework. Details of the preparation, storage and distribution of the master and working cell banks have been provided.

The virological safety, genetic stability and equivalence of the extended production and limit of cell age cells with the MCB2 and WCB100 have been demonstrated in accordance with the CPMP Scientific Advice on Quality obtained in February and September 1998. No concerns relating to TSE compliance have been raised during the evaluation.

Production of bulk antibody

Alemtuzumab is produced by fermentation. The descriptions of the production process in relation to the facilities in which the various steps take place indicate that appropriate measures appear to be in place to minimise the risk of contamination.

All the materials used are sufficiently described. A list of suppliers has been given together with the specifications and the methods used to evaluate non-pharmacopoeial raw material. Composition of media has been given, as well as in process controls adopted to approve their use.

Purification of bulk antibody

The downstream processing of the active substance is a sequence of validated steps including affinity, cation exchange and size exclusion chromatography and two robust viral removal steps. The product is then formulated by the addition of polysorbate 80 and diluted to a final bulk concentration of 10 mg/ml.

The process has been demonstrated to adequately clear viruses, DNA and host cell proteins. Satisfactory rabbit pyrogen and general safety testing were performed on the three validation batches produced at the 12,000 l scale and on three batches produced at the 2,000 l scale. In process controls are adequate to control the quality and consistency of the production.

Characterisation

The primary, secondary, tertiary and quaternary structures of the active substance have been characterised using a combination of protein and carbohydrate analytical tools and physicochemical techniques. The primary structure has been confirmed by mass spectrometry analyses of proteolytic digests. The carbohydrate moieties are linked to the C_H2 domain at a single N-linked site ($asparagine_{301}$) and consist predominately of core-fucosylated biantennary structures containing, one or zero galactose residues.

Assessing the binding to the CD52 antigen performs biological characterisation. Batch analysis data on three commercial scale and three pilot scale batches demonstrate consistent production of the active substance.

Control tests

The active substance and the finished product are adequately controlled by a combination of validated physico-chemical, immunological and biological methods. Trending of batch analysis data demonstrates consistent production of both the active substance and the finished product.

Release tests include tests at the end of fermentation in addition to sterility, endotoxin, potency, appearance, pH and biochemical tests on bulk drug substance and final product to assess the quality of the desired product and verify removal of impurities.

All excipients and immediate packaging materials meet accepted pharmacopoeial requirements.

Stability

Stability assessment of the active substance shows that the material is stable for 18 months at 2-8°C and 14 days at 30°C. A shelf life of 6 months at 2-8°C has been assigned.
The available stability data justify a finished product shelf life of 36 months when stored 2-8°C (in a refrigerator) and protected from light.

Viral safety

Model viruses used for the clearance testing included SV-40, Reo-3, MulV and PRV. The viral safety of the product has been documented satisfactorily.
No concerns relating to TSE compliance have been raised during the evaluation. The Ph Eur Certificate of Suitability will be submitted to the EMEA when available.

Discussion on chemical, pharmaceutical and biological aspects

The applicant had sought CPMP Scientific Advice with regard to the potency assay, safety and characterisation data on genetic stability of limit for cell age (LCA) cells and microbial safety on end-of-production cells and product comparability between batches produced at different manufacturing sites. The documentation provided by the company had been reviewed by the Biotechnology Working Party. The applicant has complied with the advice given in February and in September 1998.

In general, the Part II of the dossier is of good quality; the Notice to Applicants has been followed and the EU guidelines have been fulfilled. A number of points related to stability of MCB and WCB after storage, shelf life of columns, stability of the finished product for the full-scale production, viral validation, will be answered on an on-going basis.

3. Toxico-pharmacological aspects

Alemtuzumab is a humanised monoclonal antibody that binds and mediates the lysis of the human CD52 antigen. CD52 is a membrane glycoprotein predominantly expressed on T- and B-lymphocytes, monocytes and macrophages in humans. It is present in virtually all cases of chronic lymphocytic leukaemia (CLL) and in the majority of cases of non-Hodgkin's lymphoma (NHL), and in at least 95% of all peripheral blood lymphocytes and monocytes/macrophages, in a subpopulation (<5%) of granulocytes but not on erythrocytes, platelets, or bone marrow stem cells.

Choice of animal model

A number of animals have analogues of the human CD52, but alemtuzumab only cross-reacts with old world monkeys as baboons and macaques. However, since the antibody also recognises erythrocytes in baboons and rhesus monkeys, the only possible animal model is the cynomolgus monkey, but even this model presents limitations. A single autosomal dominant gene is responsible for a heterogenous expression and these animals are therefore either all CD52 positive in the erythrocytes or all negative. Only the negatives are then selected for the trials. In addition, due to an amino acid deletion there is only 85% homology to the human CD52 molecule, which results in a 16 fold lower affinity of the cynomolgus CD52 vs the human antigen. Another restrictive factor is the development of neutralising anti-MabCampath antibodies after a few days treatment, which limits the extent of repeated dose studies. Also, the tissue distribution of the cynomolgus CD52 antigen is not sufficiently known.

For these reasons the *in vivo* preclinical studies are limited and pharmacodynamics, pharmacokinetics and toxicology data are derived from the same set of studies in cynomolgous monkeys. The CPMP, through their scientific advice review, approved this approach.

Pharmacodynamics

***In vitro* studies**

Alemtuzumab is a strongly lytic human IgG1, it cause lysis by three primary mechanisms: complement activation (CMC) and by antibody-dependent cell-mediated cytotoxicity (ADCC) and apoptosis. Secondary pathways include cytokine release, T-cell activation and non-specific activation of complement.

The affinity of alemtuzumab binding to CD52 was studied in a human T-cell line from a Sézary patient, a human Burkitt lymphoma B-cell line and a hamster fibroblast line transfected with a human CD52 antigen. The affinity constants were found to be $0.31x10^8$, $1.01x10^8$, and $0.74x10^8$ x M^{-1} and the half maximal binding of the CD52 antigen to be achieved at concentrations of 4.72, 1.47 and 2.00 μg/ml respectively.

Alemtuzumab binding to its target tissues (peripheral blood and bone marrow) as well as to other normal and malignant human cells is satisfactorily documented. It binds through its Fab to essentially all B and T normal lymphocytes as well as to monocytes, thymocytes and macrophages. In the bone marrow the lymphoid progenitors stain strongly with alemtuzumab while non-committed progenitors or myeloid committed progenitors stain very weakly. Furthermore more than half of NK cells and monocytes and a small fraction of less than 20 % of granulocytes were positive. There was no binding to erythrocytes or platelets. Alemtuzumab does not alter the ability of CD34 positive cells to repopulate bone marrow cultures *in vitro.*

With regard to other non-haematopoietic tissues, alemtuzumab specifically binds few cells of T-lymphocyte origin and some dendritic cells in the skin. CD52 antigen is expressed on 100% B and T CLL, 94% NHL, 79% ALL, 32% AML, in human epididymus, sperm, seminal vesicles and seminal plasma.

Apart from the specific Fab-binding present in the haemopoietic system, in lymphoid tissues, in the mononuclear phagocyte system and in the male reproductive tract, a nonspecific Fc-binding, which was found in a large number of organs and tissues, was seen in immunocytochemical studies. The specific binding in the haemopoietic and lymphoid system followed the pattern already described and lymph nodes, spleen, thymus, tonsils were all markedly stained. In lymph nodes the germinal centres stained comparatively weakly.

***In vivo* studies**

Based on *in vitro* data, antibody-dependent cell mediated cytotoxicity (ADCC) is thought to play the major role. Apoptosis was demonstrated *in vitro* with T- and B-cell lines, but its role in the *in vivo* lytic effect of alemtuzumab is uncertain. The exact mechanism of action of alemtuzumab *in vivo* is not completely understood.

Only one acceptable model for the *in vivo* lymphocytolytic effect of alemtuzumab has been found, the cynomolgus monkey, and it is not ideal, since the CD52 affinity for the antibody is 16 fold lower than in human cells. Experiments were carried out using single and repeated IV and SC doses for up to 30 days.

In all studies the treatment with 1 mg/kg and above led to a dose-related, profound and reversible lymphocytopenia, while a reversible neutropenia was only seen after prolonged treatment and at the high doses.

Single dose SC at doses 1 - 3 mg/kg produced the same magnitude of lymphocyte depletion as comparable doses IV, but with a trend towards later occurring nadirs.

Repeated IV or SC for up to 30 days led to very deep nadirs of 0 - 9 % of pre-treatment values, but the nadirs occurred late and the recovery seemed also delayed.

In a separate study of human B lymphoma transplanted into SCID mice, a marked lymphocytolytic effect of Campath-1G on the tumour cells was seen as a support to the *in vivo* effect.

Pharmacokinetics

Effects of single and repeated doses of alemtuzumab (given by IV infusion or SC bolus) were studied in cynomolgus monkeys. Cynomolgus monkeys were given 0.1, 1 and 3 mg/kg of alemtuzumab as a 40-min IV infusion. Pharmacokinetic parameters were calculated assuming a two-compartment model

excluding samples with antiglobulin response. The compound reached maximum serum concentrations (C_{max}) immediately after infusion, of 3.2 and 36.1 µg/ml at 0.1 and 1 mg/kg, 108.1 and 100.1 at 3 mg/kg. The exposure, in terms of area under the curve (AUC), increased from 541 µg/ml.h at 0.1 mg/kg to 11263 µg/ml.h at 3 mg/kg in one monkey (a 21 to 30-fold dose increment), and from 3976 µg/ml.h at 1 mg/kg to 9904 µg/ml.h at 3 mg/kg in a second one (a 2.5 to 3-fold dose increment). The volume of distribution (Vd) was low (0.09±0.02 and 0.13±0.05 l/kg), and so was the clearance (Cl) (0.25 ± 0.05 and 0.58 ± 0.22 ml/h/kg), resulting in a mean elimination $t_{1/2\beta}$ of more than 200 h (range 220-254 h). In other studies in monkeys given 3, 10 and 30 mg/kg IV as a 40-min infusion, the mean observed C_{max} were 72.1, 275.7 and 1036.1 g/ml respectively. AUC were 429, 1822 and 5396 g/ml/h. The distribution $t_{1/2\alpha}$ was 12-18 h, similar to that (12-15 h) found at 3 mg/kg in another study.

SC doses of 1, 2 and 3 mg/kg were slowly absorbed from the site of injection. The time (t_{max}) to reach maximum concentrations (C_{max}) was generally about 48 h. C_{max} increased with the dose, but due to the small number of animals (only one each for the 1 and 2 mg/kg doses) and the significant inter-animal variability at 3 mg/kg, it was not possible to establish whether the increase was dose-proportional. After the peak, mean plasma concentrations declined but then remained raised. The bioavailability of SC alemtuzumab was approximately 47%.

Tissue distribution was only studied in CD-1 nude mice bearing a CD52- transfected CHO tumour. Alemtuzumab binds to mouse Fcγ receptors but not to mouse CD52 antigen. Following injection of ^{35}S-labelled alemtuzumab the tissue radiolocalisation was at 7 and 24 hours mainly localised to spleen (32 and 18% respectively) and liver (20 and 14%), while it dropped to 6 -8% after 48 hours. In the tumour, the radioactivity increased from initially 5.8- 20.7 % at 48 hours. All mice produced measurable antibody titres after two injections.

Placental transfer and milk excretion of alemtuzumab were not investigated.

The repeated dose study evaluated five groups of monkeys: two groups received daily 40-minute IV infusions of alemtuzumab for either 14 or 30 days; two other groups received daily SC doses for either 14 or 30 days. The dosing schedule was as follows: 1.0 on days 1-7, 1.5 on days 8-10, 2.0 on days 11-14 and 3.0 mg/kg on days 15-30. As in the single dose studies, antiglobulin responses complicated the determination of alemtuzumab concentrations. At the end of treatment, the alemtuzumab concentrations were expected to decrease but instead an unexpected rise in alemtuzumab concentrations was observed. However, the C_{max} of alemtuzumab measured during dosing was in line with the values predicted from single dose studies, suggesting that there was no unexpected accumulation after IV or SC dosing in monkeys.

Toxicology

Studies in cynomolgus monkeys, including a single dose IV infusion study and a repeated dose SC injection and IV infusion study up to 30 days, are the same as those discussed above. The Applicant did not consider it ethical or necessary to conduct further pre-clinical toxicology or pharmacokinetic studies. The CPMP approved this approach through their scientific advice.

In view of the antiglobulin response the animals were treated for 30 days and not for 12 weeks as proposed for man. The highest daily dose given to cynomolgus monkeys was 30 mg/kg and the highest cumulative dose was 64.5 mg/kg. These doses were 50 times and 3 times the proposed single and cumulative patient doses (30 mg/patient - approximately 0.6 mg/kg - IV 3 x weekly, and 1033 mg, approximately 21 mg/kg).

No mortality, adverse clinical effects or macro- or microscopic treatment-related findings were observed after single doses of 0.1, 1 and 3 mg/kg by IV infusion, or after 1, 2 and 3 mg/kg SC. The cardiovascular and respiratory effects of alemtuzumab were evaluated in anaesthetised cynomolgus monkeys given IV administration. Slight to moderate changes in blood pressure were noted in monkeys treated with 3-30 mg/kg; male monkeys were less susceptible than females.
With the exception of a female that died after the 30-mg/kg doses, no important effect on echocardiographic patterns or myocardial conduction was seen.

A number of biochemical markers appeared to be influenced by high alemtuzumab doses. Urea, lactate dehydrogenase, glutamic oxaloacetic transaminase and α-hydroxybutyrate dehydrogenase were elevated at the 10 and 30 mg/kg doses. Cholesterol was reduced at 30 mg/kg these changes might largely reflect cardiac and renal changes.

Respiratory minute volume (rate and/or tidal volume) increased slightly to moderately in all groups. The effect was not dose-related.

No significant effect was seen on arterial blood PO_2 and PCO_2 or acid/base status. However the female monkey that died after a dose of 30 mg/kg experienced clinical deterioration that was highlighted by increasing metabolic acidosis. A post-mortem examination revealed "pale-coloured" kidneys, signs of necrosis in the liver, suggestive of hypoxia probably related to the hypotension, moderate alveolar haemorrhages and slight oedema in the lung. The latter was possibly a consequence of thrombosis, shocked lung syndrome, or altered pulmonary vascular haemodynamics.

Toxicity studies did not indicate any damage to central nervous, renal, and gastrointestinal system.

In the repeated dose toxicity study no mortalities, adverse clinical signs, nor macro- or microscopic histopathological treatment-related findings were observed in cynomolgus monkeys administered with 1.0, 1.5 and 2.0 mg/kg/day of alemtuzumab for up to 14 days and 3 mg/kg/day from day 15 to 30 by IV infusion or SC injection. Clinical observations did not show any drug-related changes in clinical health/behaviour. Repeated treatment did not cause any pathology other than exaggerated pharmacodynamic effects, which might be expected in patients.

Alemtuzumab reduced lymphocyte counts in proportion to the dose in all toxicity studies, independently of the administration route and frequency. Given IV or SC to monkeys for 30 days the drug provoked an absolute neutropenia, reversible during recovery. No important treatment-related changes in biochemical parameters were observed in either the IV or SC single dose studies, but in the repeated dose study, it lowered the concentrations of serum total protein and albumin.

No treatment-related adverse physical signs were observed after a single IV or SC dose (0.1-3.0 mg/kg) in the cynomolgus monkey. Transient mild to moderate fever was observed in one monkey in the repeated dose study and was probably due to haematological changes.

The potential immunosuppressive effect was investigated in cynomolgus monkeys vaccinated with live attenuated Simian immunodeficiency virus (SIV). About 14 months later, these animals and non-vaccinated controls received alemtuzumab (cumulative dose 23 mg/kg in 7 days) and on the next day were challenged with wild-type SIV. Despite the profound lymphopenia (99 % depletion of T lymphocytes), the vaccinated animals did not develop viraemia. The non-vaccinated alemtuzumab treated monkeys had the same antibody response as non-treated controls. Lymphoid reserves in extravascular tissues were still sufficient to preserve humoral and cellular memory responses in the vaccinated monkeys and to mount a primary response in the native animals.

Alemtuzumab seems to act on epithelial cells of the male reproductive tract, their secretions and mature sperm. The possibility that it might damage spermatogenesis was also considered. However, it is not clear whether effective concentrations of alemtuzumab are reached in the seminal fluid at therapeutic doses. The possibility of long-lasting damage to the male sex organs because of inflammatory reactions was also raised. During the repeated dose toxicology studies, male sex organs (testes, epididymis, prostate) were examined macro- and microscopically after histological staining. There were no remarkable observations.

The development of anti-alemtuzumab antibodies did not cause any noteworthy antigen-antibody reactions in cynomolgus monkeys.

Since alemtuzumab should not be given to women with childbearing potential, reproductive and developmental toxicity, including teratogenicity, have not been studied.

Mutagenicity of alemtuzumab was not studied. In general, it is accepted that such studies are not useful for biotechnology products, including monoclonal antibodies. Likewise, since alemtuzumab is not intended for prolonged treatment, carcinogenicity studies have not been conducted.

Local tolerance

SC and IV administration of alemtuzumab did not cause injection site reactions in cynomolgus monkeys. In clinical trials, after SC treatment, local injection site reactions were noted after the first dose, but soon disappeared.

- **Discussion on toxico-pharmacological aspects.**

Overall, the primary pharmacodynamic studies provided adequate information on the affinity and the binding to human cells and tissues, normal as neoplastic and on the *in vivo* lymphocytolytic effect in cynomolgous monkey which was the most relevant species for preclinical efficacy and safety studies, because of the lack of expression of the CD52 antigen on non-primate species.

Lymphocytopenia was the most common treatment-related effect in this species. A slight cumulative effect on the degree of lymphocyte depletion was seen in repeated dose studies and was rapidly reversible after cessation of dosing. Reversible neutropenia was seen following daily intravenous or SC dosing for 30 days, but not following single doses or daily dosing for 14 days. Histopathology results from bone marrow samples revealed no remarkable changes attributable to treatment. Single IV doses of 10 and 30 mg/kg produced moderate to severe dose related hypotension accompanied by a slight tachycardia.

Alemtuzumab binding was observed in lymphoid tissues and the mononuclear phagocyte system. Significant binding was also observed in the male reproductive tract (epididymis, sperm, seminal vesicle) and the skin. This information has been included in the SPC. No other findings, in the above toxicity studies, provide information of significant relevance to clinical use.

Overall, the toxicology programme was limited, however this was due to the recognised difficulties with the availability of a suitable animal model. This same problem probably contributed to the restriction in the number of *in vivo* studies. In view of the accumulated knowledge on pharmacology, safety and efficacy in the clinical testing, further preclinical animal testing is considered to be unnecessary.

4. Clinical aspects

MabCampath (alemtuzumab) is a humanised monoclonal antibody that recognises the human CD52 antigen, a membrane glycoprotein expressed in virtually all cases of CLL and in the majority of cases of non-Hodgkin's lymphoma (NHL), and present on at least 95% of all peripheral blood lymphocytes and monocytes/macrophages. By fixing to the highly expressed CD52 antigen on the cell surface it causes lysis of lymphocytes.

CLL is a neoplastic disease characterised by an accumulation of a population of monoclonal, small, mature appearing CD5 and CD52 positive lymphocytes either of B-type (95%) or T-type (5%). The incidence is 1.8 - 3.0 cases per 100.000 populations. The diagnosis depends on the detection of lymphocytosis in blood and marrow. Immunophenotyping is a necessary diagnostic tool for differential diagnosis and for characterisation of the tumour cells as being of the B- or T-cell line.

The course of CLL is highly variable with indolent disease without survival affection at one end of the spectrum and aggressive leukaemia with large tumour burden, B-symptoms, bone marrow insufficiency and a survival from diagnosis in the order of few months at the other end. Prognostic subgrouping of patients are therefore important and are being applied in various ways. The presence of lymphadenopathy, organomegaly and signs of bone marrow affection (thrombocytopenia, anaemia) are used in various combinations to delineate stages A, B or C in the Binet staging system or stages 0,

I, II, III or IV in the Rai staging system. Other important prognostic factors are age and the cytogenetic changes, most frequently trisomy 12 or deletions of 13q, and also cellular phenotype.

Treatment with chemotherapy is reserved for intermediate and advanced stages. The NCI guidelines for initiating treatment comprise: constitutional symptoms, symptomatic lymphadenopathy and/or hepato-splenomegaly, anaemia, thrombocytopenia (below 100 x 10^9/l), possibly leukocyte counts over 300x 10^9/l and possibly CLL related refractory autoimmune disease. The primary treatment in these cases has been the alkylating agent chlorambucil with or without prednisolone, which can induce complete remissions (CR) in about 25% plus partial remissions (PR) in about 50%. For patients almost refractory to alkylating agents a median survival of 15 months or below has been shown. This situation has changed somewhat with the introduction of the purine analogues, especially fludarabine, but also pentostatin (2 DCF) and cladribine (2 CDA), which induces remissions in a relative large proportion of alkylator-resistant patients. There is usually cross-resistance among purine analogues as is the case among various alkylating agents. In such double resistant patients no standard chemotherapy exists and the median survival is only in the order of 6 - 9 months. For these patients alemtuzumab could be an option, since it has a completely different mechanism of action.

MabCampath is indicated 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.

(a) Clinical trials

A total of 21 clinical studies with alemtuzumab were carried out, but only 7 CLL studies are relevant to the applied indication (see Table 1). The other 14 included 6 studies in lymphoma and other types of leukaemia, 3 compassionate use studies, 4 studies in rheumatoid arthritis and one kidney transplant study.

Pharmacology and dose-finding data were obtained from 4 studies: 125-001-C-91, 125-002-C-91, 125-003-C-91, 125-005-C-92.

Efficacy data were obtained mainly from 3 studies including 157 previously treated B-CLL patients: CAM211 (pivotal study), 125-005-C-92 (005) and 125-009-C-92 (009). Study 005 included 40 patients of whom 8 may have had a diagnosis of B-PLL rather than B-CLL. Thus, the majority of data for efficacy and safety assessment was based on a total of 149 B-CLL patients

Safety datawere primarily obtained from the treatment of the 149 previously treated B-CLL patients mentioned above, but supplemented by data from 36 additional CLL and 139 other patients treated in the Phase II studies and from more than 200 patients treated in oncology and polyarthritis studies.

TABLE 1: STUDIES CONDUCTED

Study No.	Phase/Design	No of Patients	Diagnosis	Duration of Treatment
125-001-C-91	I/II Dose ranging Multi-centre Open	All:68 CLL:23	B-CLL, NHL	4-12 weeks
125-002-C-91	I/II Dose ranging Multi-centre Open	All: 71 CLL: 8	B-CLL, NHL	4-12 weeks
125-003-C-91	I/II Dose ranging Multi-centre Open	All: 36 CLL: 5	B-CLL, NHL	4-12 weeks
125-004-C-91	Follow-up on studies 125-001,2,3	All: 55 CLL: 14	B-CLL, NHL Pts failed MabCampath or might benefit from retreatment	12 weeks or more at investigator's discretion
125-005-C-92	I/II Multi-centre Open	All: 125 CLL: 32	B-CLL, NHL Histological confirmation Pts failed 1st line fludarabine and other chemotherapy	12 weeks max
125-009-C-92	II Multi-centre Open	All: 24 CLL:24	CLL Histological confirmation Pts failed 1st line fludarabine and other chemotherapy or 2nd or 3rd line fludarabine	8-16 weeks
CAM211 (Pivotal)	II Multi-centre open	All: 93 CLL: 93	B-CLL, NHL Confirmation by lymphocyte counts/ CD type Pts who have received alkylators and failed fludarabine	4-12 weeks

Clinical pharmacology

Pharmacokinetic and pharmacodynamic studies are limited. Two additional studies are ongoing: CAM213, a Phase II study on pharmacokinetics and efficacy taking place at one centre in the UK and CAM002, a randomised cross-over pharmacokinetic and pharmacodynamic study investigating the IV and SC route of administration in the US. The results will be reported to the CPMP on an ongoing basis.

Pharmacodynamics

Specific pharmacodynamic studies were not performed. The effects on the major target, the lymphocyte, were described briefly in relation to dose and administration in the Phase I/II dose-finding studies.

In study 125-002, lymphocytolysis and a temporary decrease in peripheral lymphocyte counts began to occurr within a few hours following single weekly doses between 7.5 - 240 mg. However, at all doses there was a quick rebound and no consistent suppression of lymphocytes was seen. This is related to the lack of antineoplastic efficacy of this dose schedule.

The therapeutically recommended schedule, 3 x weekly, with a dose escalation 3 mg to 10 mg to 30 mg was used in study 125-005. The median time to a reporting of a lymphocyte count below 1.0 x 10^9 was 12 days, but with considerable interpatient variability and also with a trend towards longer time for patients with high pre-treatment counts. In two patients, who failed to dose escalate above 3 -10 mg, a fall down to the 1.0 x 109 count was not accomplished. Twenty previously treated CLL patients did dose escalate to 30 mg and did stay on study a reasonable time.

Studies exploring the cellular level of expression of CD52 its relation to MabCampath sensitivity and its relation to other prognostic factors are needed and such studies are undergoing at the M.D. Anderson Cancer Center in Texas, USA. The results should be reported to the CPMP.

(b) Dose finding studies

The 3 Phase I/II dose-ranging studies, 125-001-C-91, 125-002-C-91 and 125-003-C-91, are described in Table 2 below. In all 3 studies, MabCampath was administered as a 2 hour IV infusion.

TABLE 2: DOSE RAGING STUDIES

Study No.	Phase	Unit Dose (mg)	Dosing Frequency/Route/Duration
125-001-C-91	I/II	2.5, 8.0, 25, 80	3 x weekly / IV / 4-12 weeks
125-002-C-91	I/II	7.5, 24, 75, 240	1 x weekly / IV / 4-12 weeks
125-003-C-91	I/II	0.5, 5, 50	5 x weekly / IV / 4-12 weeks

Response rates to either 25 mg or 80 mg given 3 x weekly appear to be similar though there is a suggestion that the higher dose is associated with more adverse events. Thus, a dose of approximately 25 mg 3 x weekly appears to have the best risk-to-benefit ratio. The subsequent Phase II studies all used 30 mg 3 x weekly and this dose appears to be effective with acceptable toxicity.

II Pharmacokinetics

Four open-label, multicentre, Phase I/II studies were performed, (125-001-C-91, 125-002-C-91, 125-003-C-91 and 125-005-C-92) all in previously treated patients and all included both patients with CLL and NHL. A total of 76 patients with CLL and 139 with NHL participated. All patients received the drug by 2 hour IV infusion except for 7 CLL patients who received MabCampath by SC injection. Among the studies performed only 125-002-C-91 comprised collection of a full pharmacokinetic blood sample profile following infusions 1 and 4 (see Table 3), while in the other studies only pre- and post-dose samples were obtained for analysis.

TABLE 3: PHARMACOKINETIC PARAMETERS BY MAXIMUM DOSE LEVEL (POPULATION: ALL PATIENTS IN THE EVALUABLE PK POPULATION)

Dose	Statistic	C_{max} (µg/ml)	$t_{1/2}$ (hours)	$AUC_{0-\infty}$ (µg × hrs/l)
7.5 mg	Mean ± SD	1.23 ± 0.78	29.48 ± 19.67	40.54 ± 49.53
n=8	Median	1.01	23.57	30.55
24 mg	Mean ± SD	5.11 ± 2.84	47.28 ± 68.08	183.73 ± 165.1
n=9	Median	6.25	27.54	135.57
75 mg	Mean ± SD	11.93 ± 5.92	43.95 ± 34.16	386.6 ± 398.29
n=17	Median	11.55	30.35	244.55
240 mg	Mean ± SD	54.38 ± 27.78	97.36 ± 79.06	4131.39 ± 3052.94
n=7	Median	46.75	75.26	4655.12

Clinical efficacy

Efficacy and safety of MabCampath have been evaluated in 3 Phase II, non-comparative, open studies (005-; 009; CAM211) which included 157 B-CLL patients, treated with an intravenous (IV) or subcutaneous (SC) dose regimen of 30 mg daily 3 x weekly up to a maximum of 12 weeks. Basic elements of the studies are presented below.

TABLE 4: OVERVIEW OF STUDY DESIGNS

Evaluation/Criteria	Study CAM211	Study 005	Study 009
Patient Population:	B-CLL pts who had received an alkylating agent and had failed fludarabine	Pts with NHL including CLL who failed to respond or relapsed following treatment with conventional chemotherapy	CLL pts who had failed to respond to or had relapsed following treatment with fludarabine
Treatment regimen:			
Initial dosing regimen	gradual escalation from 3 to 10 to 30 mg	gradual escalation from 3 or 10 to 30 mg	gradual escalation from 10 to 30 mg
Final dosing regimen	30 mg IV 3 x weekly	30 mg IV (or SC) 3 x weekly	30 mg IV 3 x weekly
Maximum dose allowed	30 mg	80 mg[a]	80 mg[a]
Duration of infusion	2 hours	2 hours: could be reduced to 30 minutes[b]	2 hours: could be reduced to 30 minutes[b]
Duration of treatment	Tied to response; maximum of 12 weeks	12 weeks	16 weeks
Prophylactic antibiotics	From Day 8 to at least 2 months post-treatment	Optional	Optional

[a] Only two patients, one in Study 005 and one in Study 009 were escalated to 80 mg.
[b] Reduced at weekly intervals in the absence of acute-infusion related events.

70 - 75% of the patients were in Rai stage III-IV. The majority had lymph node involvement, about half had splenomegaly and 17 - 37% had B-symptoms.

About 80% had lymphocytosis in peripheral blood, and more than 50% had anaemia or thrombocytopenia.

The degree of bone marrow infiltration was also comparable among the studies. The percentages with more than 50% involvement of the marrow were 78.5, 75.0 and 87.5% in study CAM211, 005 and 009 respectively.

98.7% had received at least one prior regimen containing an alkylating agent and 85.9% had previously been treated with fludarabine (study 005 was initiated prior to the approval of fludarabine). 67% had received 3 or more prior regimens.

CPMP scientific advice

The pivotal CAM211 study was based on data from the previous 125-005 and 125-009 studies and was discussed with the EMEA (CPMP Scientific Advice of September 1998) and the FDA. It was designed as a non-comparative multicentre study in US and Europe with patients who had failed fludarabine, in order to confirm and extend results of previous studies. The duration would be 4-12 weeks therapy based upon response. It was then considered by the CPMP that a comparative Phase III prior to approval was not feasible or necessary since an acceptable comparator cannot be identified in this population and best supportive care is considered unethical.

The EMEA Clinical Scientific Advice indicated that NCI criteria had to be used for appropriate assessment of response and an overall response rate between 20 and 30% for > 6 months would be considered of true clinical significance for patients who relapsed after alkylating agents and/or fludarabine. The applicant has complied with the CPMP advice.

Evaluation of response

The investigators primarily evaluated the patients and the responses were classified. For each study an independent review-panel of haematology/oncology experts was formed. This panel reviewed the patient data and reclassified the response, using the classification of response recommended internationally and by the NCI 1996 workshop (Table 4). In this *Complete Response (CR)* means complete disappearance of detectable disease, absence of constitutional symptoms and normalisation of abnormal blood parameters. A *Partial Response (PR)* needs at least a 50% decrease in lymphocyte counts, lymphadenopathy, hepato-splenomegaly and one of three, defined haematological improvements. *Progressive Disease (PD)* denotes the situation with a 50% increase in lymphadenopathy, hepato-splenomegaly and lymphocyte count.

The response rate was considered, as an adequate surrogate parameter for patient benefit in CLL, since an improvement in haemoglobin and platelet counts is part of the response criteria. A decreasing tumour burden is correlated to a decrease in constitutional symptoms.

TABLE 5: 1996 NCIWG RESPONSE CRITERIA

COMPLETE RESPONSE (Duration ≥ 2 months)
• Normal physical examination (including nodes, liver, spleen) and by X-ray • No constitutional symptoms • Lymphocytes ≤ 4,000/µl • Neutrophils ≥ 1,500/µl • Platelets > 100,000/µl • Haemoglobin > 11.0 g/dl (untransfused) • Marrow normocellular for age, lymphs < 30%, no nodules; if hypocellular marrow, repeat in 4 weeks
PARTIAL RESPONSE (Duration ≥ 2 months)
• Lymphocytes ≥ 50% decrease from baseline, and • Lymphadenopathy ≥ 50% decrease from baseline, and/or • Liver/spleen ≥ 50% decrease from baseline, plus ≥ 1 of: • Neutrophils ≥ 1,500/µl or 50% increase over baseline • Platelets > 100,000/lL or 50% increase over baseline • Haemoglobin > 11.0 g/dl or 50% increase over baseline (untransfused) • Otherwise CR with persistent nodules classed as nodular PR • Otherwise CR with persistent anaemia or thrombocytopenia due to drug toxicity classed as PR and monitored prospectively.
PROGRESSIVE DISEASE
• ≥ 50% increase in sum of products of at least two nodes on two consecutive exams 2 weeks apart (at least one node must be ≥ 2 cm); new nodes • Liver/spleen ≥ 50% increase or new palpable organomegaly • Lymphocytes ≥ 50% increase to ≥ 5,000/µl • Transformation to more aggressive histology (eg Richter's syndrome or PLL with > 55% prolymphocytes
STABLE DISEASE
• All others

Efficacy

Major response rates

The CR+PR rate considered for efficacy was **33.3**% in the pivotal study CAM211, and **28.1** and **33.3**% in the two other studies, 005 and 009. With a large overlap in the confidence limits, there is no statistical difference among these results.

Data were presented for study CAM211 from a cut-off date in February 2000 and for studies 005 and 009 from their completion dates in 1995.

TABLE 6: SUMMARY OF DISEASE RESPONSE BY INDEPENDENT PANEL IN STUDIES CAM211, 005, AND 009 (n (%))

Response	Study CAM211 n = 93	Study 005 n = 32	Study 009 n = 24
Complete response (CR)	2 (2.2)	0	0
Partial Response (PR)	29 (31.2)	9 (28.1)	8 (33.3)
CR with persistent anaemia/ thrombocytopenia (PR)[a]	6 (6.5)	NR	NR
CR with persistent nodules[b]	5 (5.4)	NR	NR
Stable disease (SD)	50 (53.8)	14 (43.8)	6 (25.0)
Progressive disease (PD)	8 (8.6)	8 (25.0)	6 (25.0)
Not assessed	4 (4.3)	1 (3.1)	4 (16.7)
Responders (CR+PR)	31 (33.3)	9 (28.1)	8 (33.3)
95% CI on Percent Response	(24 - 44)	(14 - 47)	(16 - 55)

[a] Patients who fulfilled criteria for CR but who had persistent anaemia or thrombocytopenia were considered to have PR.
[b] CR with persistent bone marrow nodules.
NR denotes a category not recorded.

The response rate was independent of age (above or below 65 years) and gender (although there are reservations from the statistical point of view due the small numbers in the female group).

The response rate was higher in Rai stages 0-II (17/38 or 44.7%) than in stages III-IV (31/111 or 27.9%

The influence of previous resistance pattern was examined in study CAM211. 13/45 patients, who never responded to prior purine analogue-based regimens and thus were primary resistant had a response to MabCampath of 28.9%. In 18/48 patients, who previously had responded to at least one regimen, the MabCampath response was similar, 37.5%.

Time to event variables - response, progression, survival

Time to event variables are given in the Table 7 below:

TABLE 7: SUMMARY OF TIME TO EVENT VARIABLES IN STUDIES CAM211, 005 AND 009

Response (Months)	Study CAM211 n = 93	Study 005 n = 32	Study 009 n = 24
Median time to response	1.5	3.8	3.9
Duration of response	8.7	7.1	15.4
Median time to progression, alternate therapy or death - responders	9.5 *	10.3	19.6
Median time to survival - responders	Not reached **	44.3	35.8

* 3/31 responders were still in remission and therefore censored for analysis.
** Median survival for the 31 responders had not yet been reached with 21 (67.7%) of 93 patients still alive at February 2000. Overall, the 18-month survival rate was 45% (42/93 patients).

A part of the difference between the median times to response (from first dose to first evidence of CR/PR) across the 3 studies was explained by differences in the disease assessment time points (4 vs. 6 vs. 8 weeks).

Response at each major disease site

TABLE 8: SUMMARY OF COMPLETE OR ≥ 50% RESOLUTION IN DISEASE AT EACH MAJOR DISEASE SITE (n = 149)

Disease Sites	Study CAM211 (%)			Studies 005 + 009 (%)		
	All Patients	Responders	Stable Disease	All Patients	Responders	Stable Disease
Lymphocytosis	100	100	100	97.8	100	94.4
Bone Marrow	61.3	71.0	51.9	55.1	87.5	45.0
Lymphadenopathy	74.2	95.7	60.0	39.5	76.9	29.4
Hepatomegaly	74.2	88.9	78.9	40.0	66.7	33.3
Splenomegaly	82.6	100	73.1	46.7	75.0	38.5

In study CAM211, the response of the malignant lymphocytes in blood and marrow was assessed with flow-cytometry. In the bone marrow, the median % fell from a pre-treatment value of 81.8% to 10% by study week 4 and 0.8% by week 8. In blood, a median pre-treatment count of 33.61 x 10^9/l fell to 0.003 by week 4 and 0.001 x 109/l by week 8.

An analysis of the effect on other abnormal blood parameters in the pivotal study demonstrated that at the evaluation 2 months post-treatment 43.9% of 57 anaemic patients (and 73.3% of responders) met the criteria for haemoglobin response. Over all 3 studies, 24/34 (71%) patients with baseline grade 2-4 anaemia improved at least one grade at the 2-month follow-up.

At the same time-point 50.0% of 24 neutropenic patients (< 1500 cells/µl) had a 50% ANC improvement (60.0% in responders). Over all 3 studies, 12/15 (80%) of patients with a baseline neutropenia of grade 3 or 4 improved to grade 2 or better at the 2-month follow-up and therefore came into a lower category of risk of infection.

A platelet response was seen in 38.9% of 54 thrombocytopenic patients (platelets < 100.000) in the pivotal study, but in 53.8% among responders. In the 17 patients over all 3 studies with grade 3 or 4 thrombocytopenia at baseline, 11 (or 65%) improved to grade 2 or better at the 2-month follow-up and thus came into a lower category of risk for bleeding.

Improvement in disease related symptoms

In study CAM211, 63 patients had disease related symptoms at baseline. 28/63 (44.4%) had complete resolution of the symptoms following MabCampath treatment. A more specific analysis was made in CAM211: B-symptoms (fever, night sweats, weight loss) resolved in 29/39 (74.4%) of patients. Asthenia resolved in 10/32 patients and pain in 4/9 patients. Other types of disease related symptoms resolved in 7/19 patients. Over all three studies 59 patients had B-symptoms at baseline or fatigue and 31 (52.5%) had resolution of their symptoms?

Response according to previous treatment

The relevant response parameters for patients treated in the pivotal and supportive studies (CAM211, 005 and 009) are summarised below, according to response to prior therapy.

TABLE 9: RESPONSE PARAMETERS IN MABCAMPATH STUDIES, CAM211, 005 AND 009 BY RESPONSE TO PREVIOUS THERAPY (n = 157)

Patient Subgroup	No. of Patients	Median Duration of Response (months)	95% CI*	Median Survival (months)	95% CI
Failed Alkylating Agents					
All Patients	109	NA	NA	18.8	13.7 - 28.4
CR+ PR**	37	9.1	6.1 - 12.5	35.8	28.4 - 44.3
Failed Alkylating Agents and Fludarabine					
All Patients	84	NA	NA	16.1	11.3 - 30.3
CR+PR	27	8.3	5.3 - 12.5	35.8	18.8 - 35.3
Received Alkylating Agents and failed Fludarabine					
All Patients	110	NA	NA	14.2	11.3 - 30.3
CR+PR	35	8.7	5.9 - 11.5	35.8	35.8 - not reached

* CI = confidence interval
**CR = complete response; PR = partial response (intent-to-treat; independently assessed per 1996 NCI criteria)

Discussion on clinical efficacy

The claim for a marketing authorisation is based on one pivotal Phase II study (CAM211) with an objective response rate of 33% and duration of response in excess of 6 months along with supporting data from two other Phase II studies, 005 and 009.

It was considered at the time of the review of the applicant's request for Scientific Advice that a comparative Phase III prior to approval was not feasible or necessary since an acceptable comparator cannot be identified in this population and best supportive care is considered unethical. The applicant has complied fully with the CPMP advice.

The response rate was considered, as an adequate surrogate parameter for patient benefit in CLL, since an improvement in haemoglobin and platelet counts is part of the response criteria. A decreasing tumour burden is correlated to a decrease in constitutional symptoms. In this population of heavily pre-treated patients with CLL, MabCampath has shown outstanding anti-leukaemia activity.

Results of response in the 5 major disease sites showed a remarkable effect on the circulating lymphocyte mass, while the response at the other sites are still significant: improvement of bone marrow infiltrates, major resolution in lymphadenopathy, splenomegaly or hepatomegaly.

All disease-related symptoms resolved in 44% of the patients with such baseline characteristics in the pivotal study and the specific B-symptoms resolved in 74%. Haemoglobin improvement by at least one grade occurred across the protocols in 63% of the patients with baseline grade 2-4 anaemia. Improvement in thrombocytopenia to grade 2 or better occurred in 65% of the patients with grade 3 or 4 at baseline and improvement in neutropenia to grade 2 or better occurred in 80% of the patients with grade 3-4 at baseline. Another clinical benefit was the prolongation of the length of the chemotherapy-free period (related to the duration of remission), which was 4.0 months in the last series before MabCampath and 11.7 months in median following MabCampath treatment.

The applicant has committed to further development of MabCampath and has presented a clinical programme that includes 3 studies.

CAM307 is a randomised Phase III trial investigating MabCampath efficacy versus chlorambucil as front-line therapy in patients with progressive B-CLL as measured by progression-free survival (PFS).

CAM213 is an ongoing Phase II pharmacokinetic and efficacy study, which will be provided to the CPMP within one year post-authorisation.

CAM002 is an ongoing randomised crossover study to evaluate IVand SC administration.

Clinical safety

The primary studies used for assessment are the same three efficacy studies: CAM211, 125-005 and 125-009, which included 149 previously treated B-CLL patients. In addition, data are presented from 36 CLL patients plus further 139 other patients in the Phase I/II studies 125-001, 125-002 and 125-003. Furthermore data are available from 55 patients in the follow-up study 125-004, from 177 patients in compassionate need programmes and 7 other oncology studies and finally there are data from 140 patients in three studies of rheumatoid arthritis. Thus, at least 700 patients have been exposed to MabCampath.

The data presented below are based on the three B-CLL studies.

Discontinuations

The occurrence of adverse events was the major factor contributing to patient discontinuation of treatment: 26.9% of patients in study CAM211, 31.3% in study 005 and 37.5% in study 009. The majority of events were most commonly due to infections.

Adverse events,serious adverse events and deaths

Overall adverse events

148/149 CLL patients had at least one adverse event on study. The maximum severity was grade 1-2 in 50 patients, grade 3 in 50 and grade 4 in 48. The most frequently reported adverse events were the infusion-related events of fever (85.2%), rigor (85.9%), nausea (53.7%), vomiting (40.9%), rash (32.2%) and hypotension (31.5%). Frequently occurring infections include: pneumonia (16.1%), sepsis (14.8%) and herpes simplex infection (11.4%).

The very common (>10%), common (>1-10%) and uncommon (>0.1-1%) drug-related adverse reactions are reported in full in the SPC, Section 4.8.

Infusion-related reactions

Acute infusion-related reactions usually occur during the first week of therapy and substantially decline thereafter.

Very commonly reported reactions have been acute infusion-related reactions including fever, rigors, nausea, vomiting, hypotension, fatigue, rash, urticaria, dyspnoea, headache, pruritus and diarrhoea.

The majority of these reactions are mild to moderate in severity. Grade 3 or 4 infusion-related reactions are uncommon after the first week of therapy. Appropriate recommendations on premedication and dose escalation in order to avoid or ameliorate these events, are included in the SPC.

Haematological reactions

Severe bleeding reactions have been reported. One patient developed fatal idiopathic thrombocytopenic purpura (ITP) following MabCampath therapy. Pancytopenia has been reported commonly and may be grade 3 or 4 in severity or serious in nature. A positive Coombs test is also a common event; clinically apparent haemolysis has not been reported in patients treated to date.

Cardiovascular reactions

Decrease in blood pressure (BP) was most common in week one, where 19% had systolic values below 90 mm Hg and 60.0% diastolic values below 60 mm. The corresponding values for week 2 were 9.2% and 52.9%. For all subsequent weeks the proportion of patients, who had at least one reading below these limits were 13.5% for systolic BP and 57.3% for diastolic BP.

Infections

CLL is accompanied by a general immunosuppression inherent in the disease and worsened by the cytostatic treatment. Both bacterial and viral infections are therefore common, affecting about 80% of the patients and infection is the cause of death in up to 60% of the cases.

59% the 149 previously treated patients experienced at least one infection while on study medication, which in 42/88 was of grade 3 or 4. Most of these last patients (82%) had Rai stage III/IV disease and most were non-responders to MabCampath. Thus, only 6/48 patients with a major response had a grade 3-4 infection against 36/101 non-responders. Pneumonia was the most frequent infection. Pneumocystis carinii pneumonia (PCP) occurred in 5 patients, none of who had received effective prophylaxis. The on-study infections contributed to death in 8 patients.

Among the 15 blood borne infections 8 appeared related to indwelling catheters.

Opportunistic infections were seen on study in 21 patients and included PCP 5, CMV 8, aspergillus 3, herpes zoster 3, candidiasis 1, mucomycosis 1).

In the interval from 1 to 6 months after last treatment, 12 patients were found to have pneumonia, including 2 PCP (none received prophylaxis) and 2 aspergillus. 8 patients had sepsis, 6 patients had herpes zoster and 1 patient had a Listeria meningitis.

Serious reactions and all serious infections:

The following table summarises the on study serious drug-related reactions and all serious infections, which occurred in more than 1% of patients:

TABLE 10 : SUMMARY OF ON-STUDY DRUG-RELATED SERIOUS ADVERSE REACTIONS AND ALL SERIOUS INFECTIONS IN STUDIES CAM211, 005, AND 009 BY MAXIMUM NCI/WHO GRADE (POPULATION: B-CLL PATIENTS (n = 149)

WHO Preferred Term	No. of Patients	% of Patients	Maximum NCI/WHO Grade				
			1	2	3	4	NR
Total Pts with related SAEs[a]	73	49.0	--	13	24	33	3
Fever	29	19.5	1	19	6	1	2
Pneumonia	20	13.4	1	2	6	9	2
Sepsis	18	12.1	1	3	5	9	--
Granulocytopenia	10	6.7	--	1	2	5	2
Cytomegalovirus infection	8	5.4	--	3	4	1	--
Dyspnoea	7	4.7	--	1	1	5	--
Neutropenic fever	7	4.7	--	5	2	--	--
Thrombocytopenia	7	4.0	--	--	1	5	--
Rigors	5	3.4	--	4	1	--	--
Hypotension	5	3.4	1	--	3	1	--
Pneumonitis	5	3.4	--	--	3	2	--
Anaemia	4	2.7	--	--	2	2	--
Asthaenia	3	2.0	--	3	--	--	--
Abdominal pain	3	2.0	--	1	1	1	--
Pneumocystis carinii infection	3	2.0	--	--	2	1	--
Pancytopenia	3	2.0	--	1	--	2	--
Dehydration	2	1.3	--	--	2	--	--
Confusion	2	1.3	--	1	--	1	--
Moniliasis	2	1.3	1	--	1	--	--
Sinusitis	2	1.3	--	1	--	1	--
GI haemorhage	2	1.3	--	1	--	1	--
Leucopenia	2	1.3	--	--	--	2	--

Deaths

15 (10.1%) of the 149 B-CLL patients died during or within 30 days of treatment with MabCampath. None of these patients had had an objective response to treatment. The causes of death were:disease progression (5 patients), pneumonia (4), sepsis (2), pulmonary embolism (1), cerebral haemorrhage (1), suicide (1) and rhinocerebral mucormycosis. Eight of the deaths, including 7 infection-associated, were considered related to the treatment with MabCampath. In the follow-up period starting 30 days post-treatment 7 deaths were reported that were assessed as possibly related to treatment with MabCampath. 6 patients died from infection and one patient from idiopathic thrombocytopenic purpura (bleeding). 6/7 patients had not responded to MabCampath treatment.

Anti-MabCampath antibodies

In studies 005 and 009, 80 serum samples from 19 patients with CLL were analysed for the presence of anti-MAbCampath antibodies. 79/80 samples were negative and one sample had a low concentration of antibody.

In 7 other studies, including both CLL and NHL, 192 patients were examined. Three positive samples were found, two in very low titres and one with a high concentration in a sample obtained 5 months after the treatment, where the sample one-month post treatment had been negative.

Haematological changes

The haemoglobin concentration initially decreased slightly, but then increased to values above the baseline.
The absolute neutrophil count (ANC) demonstrated the same development. If only grade 3-4 neutropenia is considered the percentage changed from 18.9% at baseline to 37.4% in week 1-2 and to about 50% in the following weeks and then at the 2 month interval a decrease to about 22.5%. These numbers are for all patients, but neutropenia is most pronounced in non-responders.

The platelet count also showed an initial decrease and thereafter a constant improvement. At baseline 24.2% of patients had grade 3-4 thrombocytopenia, but this reduced to 9.9% at the 2-month point only 11/17 patients (64.7%) had improved from grade 3-4 to grade 2 or better.

The median values for lymphocyte counts reflect the expected pharmacologic, lymphocytolytic effect of alemtuzumab with a decrease down to 0.1 x 10^9/l at week 4.

In CAM211, flow cytometry was used to follow the recovery of the normal T- helper and T-suppressor cells (CD4+ and CD8+ respectively). Both decreased to very low values in week 4, but then gradually recovered and by month 6 they had returned to about 80% of the baseline values.

Safety information from other studies

Detailed presentation of safety data from studies 125-001,125-002, 125-003 and 125-004 with a total of 230 patients with CLL and NHL demonstrated a pattern similar to that described above.

Safety data were also collected from 120 patients in compassionate use programmes, from 57 patients in other oncology studies and from 140 patients in rheumatoid arthritis studies, but were not reported in detail. In the rheumatoid arthritis studies, 5 patients developed malignancies, but an analysis with comparison to a control group concluded that the incidence was not increased.

Discussion on clinical safety

Although there is no apparent significant increase in the risk of severe infections following sequential therapy with fludarabine and MabCampath, the analyses presented do not rule out the possibility of cumulative immunosuppression. The issue is addressed in the SPC, Section 4.4, but this potential risk needs close monitoring in future clinical trials. The programme of monitoring CD4+ and CD8+ lymphocytes and the planned pharmacovigilance programme with respect to infections has been presented.

Although there is no evidence of a HAMA response, the sample size was small. Further data will be forthcoming from the ongoing study CAM213.

5. Overall conclusion and benefit/risk assessment

The quality of MabCampath is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the clinical performance of the product have been investigated and are controlled in a satisfactory way.

Viral safety and batch-to-batch consistency has been documented and the relevant tests will be performed according to the agreed specifications. The applicant has made a commitment to provide additional information on an ongoing basis.

Overall, the primary pharmacodynamic studies provided adequate information on the affinity and the binding to human cells and tissues, normal as neoplastic and on the *in vivo* lymphocytolytic effect in cynomolgous monkey which was the most relevant species for pre-clinical efficacy and safety studies because of the lack of expression of the CD52 antigen on non-primate species.

Lymphocytopenia was the most common drug-related effect in this species. Higher doses (10 and 30 mg/kg) caused moderate to severe dose-related hypotension, which persisted for up to 3.5 hours and was accompanied by slight tachycardia. Although the pre-clinical acute toxicity studies did not indicate major risks, hypotension and tachycardia were the most frequent adverse events also in man.

Alemtuzumab binding was observed in lymphoid tissues and the mononuclear phagocyte system. Significant binding was also observed in the male reproductive tract (epididymis, sperm, seminal vesicle) and the skin. This information has been included in the SPC. No other findings, from toxicity studies, provide information of significant relevance to clinical use.

Ongoing studies include a Phase II study on pharmacokinetics and efficacy (CAM213) and, a randomised crossover pharmacokinetics and pharmacodynamics study investigating the IV and SC route of administration (CAM002). The results will be reported to the CPMP on an ongoing basis.

MabCampath is associated with an outstanding response rate and substantial reduction in disease burden in all sites of involvement in the majority of patients. Meaningful clinical benefits are realised for many patients including both responders and non-responders according to the NCIWG criteria.

The applicant has complied with the CPMP advice given in 1998. It was considered that a comparative Phase III prior to approval was not feasible or necessary since an acceptable comparator cannot be identified in this population and best supportive care is considered unethical.

The applicant has committed, as part of the specific obligations, to perform a randomised trial (CAM307) to investigate MabCampath vs chlorambucil as front-line therapy in patients with progressive B-CLL as measured by progression-free survival. Safety and efficacy will be assessed by an independent data safety monitoring board on a regular basis. Particular attention will be given to infection and bone marrow toxicity. It is anticipated that this will elucidate the position of MabCampath in the treatment of CLL.

Benefit-risk assessment

In a population of heavily pre-treated patients with CLL, MabCampath has shown outstanding anti-leukaemia activity. The response rate and duration was independent of previous treatment as the molecule has a completely different mechanism of action. The response rate was higher in earlier stages of the disease.

The main safety issue with MabCampath is the risk of infections in the context of the general immunosuppression, which is inherent in the disease and worsened by the cytostatic treatment.

The majority of infusion related reactions were mild to moderate in severity and appropriate recommendations on premedication and dose escalation in order to avoid or ameliorate these events, are included in the SPC.
Based on the CPMP review of data on quality, safety and efficacy, the CPMP considered by consensus that the benefit/risk profile was favourable for MabCampath in 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.